Acute Kidney Injury – New Insights

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Outline

- Epidemiology
- AKIN Criteria
- AKI Concepts
- Diagnostics
- Management Strategies
Acute Kidney Injury

- AKI prevalence in hospital 5-7%
- Mortality 10-80% dependent on patient population
- Patients with AKI and
  - multiorgan failure – 50% mortality
  - if requiring renal replacement therapy – up to 80% mortality
- Independent risk factor for mortality

Table 3. Period Prevalence of Acute Renal Failure and Mortality by Country*

<table>
<thead>
<tr>
<th>No. of Participating Centers (N = 54)</th>
<th>No. of Patients (N = 1738)</th>
<th>Period Prevalence (95% CI), %</th>
<th>Predicted Mortality, %†</th>
<th>Hospital Mortality (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>6</td>
<td>6.3 (5.6-7.0)</td>
<td>47.0</td>
<td>53.4 (47.7-59.1)</td>
</tr>
<tr>
<td>Belgium</td>
<td>3</td>
<td>8.8 (7.5-10.1)</td>
<td>43.2</td>
<td>57.7 (50.1-65.3)</td>
</tr>
<tr>
<td>Brazil</td>
<td>4</td>
<td>4.8 (4.0-5.5)</td>
<td>43.6</td>
<td>76.8 (70.1-83.6)</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
<td>4.6 (3.7-5.6)</td>
<td>56.8</td>
<td>59.8 (49.8-69.8)</td>
</tr>
<tr>
<td>China</td>
<td>2</td>
<td>8.8 (6.9-10.7)</td>
<td>48.5</td>
<td>61.0 (50.1-71.9)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
<td>16.8 (10.2-23.4)</td>
<td>44.6</td>
<td>61.9 (41.1-82.7)</td>
</tr>
<tr>
<td>Germany</td>
<td>2</td>
<td>3.3 (2.7-3.8)</td>
<td>39.4</td>
<td>61.9 (53.4-70.4)</td>
</tr>
<tr>
<td>Greece</td>
<td>1</td>
<td>2.4 (0.3-4.5)</td>
<td>62.2</td>
<td>80.0 (44.9-100.0)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1</td>
<td>4.4 (2.7-6.1)</td>
<td>41.4</td>
<td>72.0 (54.4-89.6)</td>
</tr>
<tr>
<td>Israel</td>
<td>1</td>
<td>2.1 (0.8-3.4)</td>
<td>61.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Italy</td>
<td>6</td>
<td>5.4 (4.4-6.4)</td>
<td>32.0</td>
<td>50.5 (41.1-59.8)</td>
</tr>
<tr>
<td>Japan</td>
<td>4</td>
<td>5.5 (4.4-6.6)</td>
<td>40.8</td>
<td>64.0 (54.1-74.0)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2</td>
<td>6.1 (5.0-7.2)</td>
<td>49.5</td>
<td>62.5 (53.5-71.5)</td>
</tr>
<tr>
<td>Norway</td>
<td>2</td>
<td>3.7 (2.7-4.7)</td>
<td>46.6</td>
<td>62.0 (48.5-75.5)</td>
</tr>
<tr>
<td>Portugal</td>
<td>2</td>
<td>22.1 (15.7-28.5)</td>
<td>53.7</td>
<td>63.9 (48.2-79.6)</td>
</tr>
<tr>
<td>Russia</td>
<td>1</td>
<td>2.6 (1.3-3.9)</td>
<td>82.6</td>
<td>61.5 (35.1-88.0)</td>
</tr>
<tr>
<td>Singapore</td>
<td>2</td>
<td>6.3 (4.2-8.4)</td>
<td>59.3</td>
<td>74.2 (58.8-89.6)</td>
</tr>
<tr>
<td>Spain</td>
<td>2</td>
<td>10.5 (5.6-15.3)</td>
<td>32.2</td>
<td>43.8 (19.4-68.1)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1</td>
<td>4.7 (1.7-7.7)</td>
<td>25.7</td>
<td>22.2 (0-49.4)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>3.2 (2.0-4.4)</td>
<td>44.3</td>
<td>65.4 (47.1-83.7)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1</td>
<td>20.6 (15.6-25.5)</td>
<td>63.7</td>
<td>73.1 (61.0-85.1)</td>
</tr>
<tr>
<td>United States</td>
<td>6</td>
<td>8.0 (6.8-9.3)</td>
<td>44.2</td>
<td>52.1 (45.0-59.2)</td>
</tr>
<tr>
<td>Uruguay</td>
<td>1</td>
<td>12.9 (8.5-17.3)</td>
<td>35.6</td>
<td>65.5 (48.2-82.8)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>5.7 (5.5-6.0)</td>
<td>45.6</td>
<td>60.3 (58.0-62.6)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Countries are provided for illustrative purposes only because sampling was not representative of any given country.
†Calculated with Simplified Acute Physiology Score II.
Revised AKIN Criteria

- Acute Kidney Injury
  - Abrupt (within 48 hours)
  - Reduction in renal function:
    - Increased in serum creatinine by more than 26.4 µmol/L (0.3 mg/dL), or
    - relative increase in creatinine of ≥50%, or
    - a reduction in urine output to < 0.5 ml/kg per hour for more than 6 hours
### Revised AKIN Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥0.3mg/dl [26.4μmol/L] or ≥1.5 – 2x increase</td>
<td>&lt;0.5ml/kg/h for &gt;6hrs</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2 – 3x increase</td>
<td>&lt;0.5ml/kg/h for &gt;12hrs</td>
</tr>
<tr>
<td>3</td>
<td>&gt;0.5mg/dl [44.0μmol/L] &amp; Creat ≥4.0mg/dl [354μmol] or &gt;3x increase</td>
<td>&lt;0.3ml/kg/h for &gt;24hrs or Anuria &gt;12hrs</td>
</tr>
</tbody>
</table>

Higher stage associated with higher chance of mortality.

Pathophysiology of AKI

CELL INJURY

Ischaemia

Anoxia

Toxic

Inflammatory

Defective Function

Concentrating Defect

Reduced GFR
Phases of Ischaemic AKI

<table>
<thead>
<tr>
<th>Pre renal</th>
<th>Initiation</th>
<th>Extension</th>
<th>Maintenance</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early phase (0–48h)</td>
<td>Late phase (&gt;48h)</td>
<td>Inflammation</td>
<td>Dedifferentiation Migration Proliferation</td>
<td>Redifferentiation Repolarization</td>
</tr>
</tbody>
</table>

Days after insult

GFR (%)

Vasomotor Nephropathy
ATP depletion Endothelium Epithelium
Microvascular injury Obstruction Inflammation Coagulation

Adapted from Sutton et al KI 2002;62:1539-1549
Therapeutic targets aimed at (A) preventing, (B) limiting extension phase (C) treating established AKI

Molitoris B et al JASN 2003;14:265-267
Diagnosing AKI
# Role of urinary indices in AKI

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Prerenal Azotemia</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional excretion of sodium (%)</td>
<td>&lt;1</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Fractional excretion of urea (%)</td>
<td>&lt;35</td>
<td>&gt;35</td>
</tr>
</tbody>
</table>

\[
FE_{\text{Urea}} = \frac{\text{Urine Urea}}{\text{Serum Urea}} \times \frac{\text{Serum creatinine}}{\text{Urine creatinine}} \times 100
\]

Normal \( FE_{\text{Urea}} >45\% \)

If on diuretics
- prerenal Azotemia : \( FE_{\text{Na}} >2\% \) and low \( FE_{\text{Urea}} \)
- ATN : \( FE_{\text{Na}} \) high and \( FE_{\text{Urea}} \) high

\( FE_{\text{Urea}} \) - sensitivity 90% and specificity 96% (with or without diuretics)
- positive predictive value 99% in prerenal cases

Carvounis et al KI 2002;62:2223-2229
Markers of renal injury being studied

- **NGAL** (Neutrophil Gelatinase Associated Lipocalin)
- **KIM1** (Kidney Injury Molecule 1)
- **Cystatin C**
- **NAG** (N-acetyl-beta-D-glucosaminidase)
- **NHE3** (Isoform 3 of Na-H Exchanger)
- **IL18**
NGAL

- Most promising emerging biomarker for detection of AKI
- 25 kDa protein produced in renal tubules in response to structural kidney injury and secreted into the urine

Role in
- Emergency Department – discriminates intrinsic AKI Vs prerenal AKI, CKD and normal renal function\(^1\)
- Hospitalised patients – discriminates intrinsic and prerenal AKI (area under ROC curve of 0.87)\(^2\)
  - NGAL level <47g/L – unlikely to have intrinsic AKI (LR 0.2)
  - NGAL level >104 g/L – likely to have intrinsic AKI (LR 5.97)

However, more studies using standardised assays across various patient groups still required to validate this biomarker

1. General Measures
   - Avoid further nephrotoxic insults
   - Remove causative factors
   - Glycaemic control

2. Haemodynamic Management
   - Early Goal Directed Therapy
   - Maintain CO & ECV

3. Renal Replacement Therapy
   - Timing
   - Dose
   - Type
   - Intensity
AKI Management

- Fluid management
- Electrolytes
- Drugs titration
- Nutritional support
- Dialysis / CRRT
Early Goal-Directed Therapy

CVP: central venous pressure; MAP: mean arterial pressure; ScvO2: central venous oxygen saturation.

Study of 396 patients with dialysis requiring AKI (PICARD study) Patients with fluid accumulation >10% at dialysis initiation had OR for death of 2.07 (95% CI 1.27–3.37) after adjustment for severity of illness and dialysis modality
Pharmacologic Treatment of AKI

- Dopamine
- Fenoldopam
- Loop diuretics
- Atrial natriuretic peptide
- Insulin-like growth factor-1
- Thyroxine

None of these drugs effective in treatment of established AKI
Renal Replacement Therapy (RRT) modalities

- Continuous (CRRT)
  - CVVH/CVVHD/CVVHDF
- Intermittent (IHD)
  - Hemodialysis
  - Hemodiafiltration
  - Slow Low Efficiency Dialysis
Timing

- No conclusive evidence that timing of initiation (early vs late) affects mortality\(^1\)

Modality

- No conclusive evidence on survival benefit of CRRT over IHD in AKI\(^2\)
  - However, CRRT beneficial in pts haemodynamically unstable, need for correction of fluid overload, need for better solute removal

\(^1\)Seabra VF et al. AJKD 2008;52(2):272-284
\(^2\)Lins R et al. Nephrol Dial Transplant 2009;24:512–518
Dose

- CRRT dose – 30-35ml/kg/hr target
- To ensure that >25ml/kg/hr is effectively delivered \(^1,^2\)
- Taking into account time off CRRT

### VA/NIH ATN Study

<table>
<thead>
<tr>
<th></th>
<th>Intensive treatment</th>
<th>Less intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=563</strong></td>
<td>n=561</td>
<td></td>
</tr>
<tr>
<td><strong>Haemodynamically stable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IHD*</td>
<td>6x/week</td>
<td>3x/week</td>
</tr>
<tr>
<td><strong>Haemodynamically unstable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CVVHDF</td>
<td>35ml/kg/hr</td>
<td>20ml/kg/hr</td>
</tr>
<tr>
<td>• SLED*</td>
<td>6x/week</td>
<td>3x/week</td>
</tr>
</tbody>
</table>

*Kt/V 1.2-1.4/treatment

---

No difference in 60 days mortality outcomes for adult patients with AKI secondary to ATN and multiorgan failure requiring less intensive or intensive strategy RRT

## RENAL Study

<table>
<thead>
<tr>
<th></th>
<th>Intensive treatment</th>
<th>Less intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>722</td>
<td>743</td>
</tr>
<tr>
<td>Dose delivered</td>
<td>33.4ml/kg/hr</td>
<td>22ml/kg/hr</td>
</tr>
<tr>
<td>% of prescribed</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>Pts treated with IHD in ICU (%)</td>
<td>7.6</td>
<td>7</td>
</tr>
</tbody>
</table>

Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

### RENAL Vs ATN

<table>
<thead>
<tr>
<th></th>
<th>RENAL</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient numbers</td>
<td>1508</td>
<td>1124</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>64.5</td>
<td>59.7</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>49.5</td>
<td>63</td>
</tr>
<tr>
<td>APACHE II</td>
<td>~26</td>
<td>26.4</td>
</tr>
<tr>
<td>CRRT as initial therapy (%)</td>
<td>100</td>
<td>~50</td>
</tr>
<tr>
<td>ICU days before RRT initiated</td>
<td>2.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Mortality day 90 (%)</td>
<td>44.7</td>
<td>-</td>
</tr>
<tr>
<td>Mortality day 60 (%)</td>
<td>-</td>
<td>52.5</td>
</tr>
<tr>
<td>Dialysis dependence day 28 (%)</td>
<td>13.3</td>
<td>45.2</td>
</tr>
<tr>
<td>Dialysis dependence day 60 (%)</td>
<td>-</td>
<td>24.6</td>
</tr>
<tr>
<td>Dialysis dependence day 90 (%)</td>
<td>5.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Patient with AKI

**Absolute indications for RRT**
1. Serum K > 6.0 mmol/L
2. Serum urea > 30 mmol/L
3. Acidemia pH < 7.15
4. Serum HCO3 < 10 mmol/L
5. Acute pulmonary oedema
6. Uraemic encephalopathy
7. Uraemic pericarditis
8. Physician discretion

Initiate RRT

Vasopressor requirement

- Low
  - Intermittent
- High
  - Continuous
Absence of absolute indications

AKI staging

**AKI stage 1 and 2**
With compelling indications
1. Rapidly worsening AKI
2. Low probability of rapid renal recovery
3. Severe electrolyte disturbances
4. Severe sepsis
5. Severe tumour lysis syndrome
6. Fulminant hepatic failure
7. Hypercatabolic state
8. Burns
9. Selected toxin-induced AKI
10. Physician decision

**AKI stage 3**
Start RRT
Conclusion

- High mortality with AKI
- AKI is usually multifactorial
- Serum Creatinine is a late marker for AKI
- New biomarkers (e.g. NGAL) being validated and looks promising
- FE_{Urea} good to differentiate prerenal states from established AKI (even with diuretics)
- Fluid overload is bad in AKI
- CRRT dose to be given at 35ml/kg/hr if renal support required in ICU
Thank you