ACUTE KIDNEY INJURY

• Acute kidney injury (AKI) is a global public health concern associated with high morbidity, mortality, and healthcare costs.

• AKI often has a very rapid onset in hours or days, in contrast with chronic kidney disease (CKD) which takes months or years to develop.

• In the developed world, AKI tends to manifest in older patients in the Intensive Care Unit (ICU).

• In lower- to middle-income countries, which represent 85% of cases of AKI, young adults and women are particularly prone and at risk of death.

• Among those patients who survive, long-term outcomes of AKI can include the development of CKD and end-stage renal disease (ESRD), or exacerbation of pre-existing CKD accelerating the progression to ESRD.

• Although previously thought to have a benign course in patients who recovered, AKI can lead to poor quality of life and high long-term costs.

• Early detection is important as some 20-30% of cases of AKI may be partially or fully preventable.

CAUSES OF AKI

AKI may be caused by a variety of conditions including disease, injury, toxins, drugs or major surgery (especially cardiac surgery). It is common for patients developing AKI to have multiple etiologies at once.

Common conditions leading to AKI:
- Severe infections: sepsis, malaria, COVID-19
- Critical illness
- Circulatory shock
- Burns
- Trauma
- Cardiac surgery (especially with cardiopulmonary bypass)
- Major non-cardiac surgery
- Nephotoxic drugs
- Radiocontrast agents
- Poisonous plants and animals

In patients with critical illness:
- Sepsis and hypovolemia are the most frequent reported etiologies for AKI.
- Nephrotoxic drugs were reported as the etiology for AKI in 14.4% of patients.
- At the time of AKI diagnosis, one-third of patients were treated with diuretics and 11.9% with non-steroidal anti-inflammatory drugs.
- Aminoglycosides, glycopeptides and contrast media were administered in less than 10% of AKI patients.
- Half of AKI patients were treated with vasoactive therapy at the time of AKI diagnosis.
- One-third were mechanically ventilated.
STAGES OF AKI

AKI is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) consensus classification and is staged for severity according to the following criteria.

KDIGO staging of AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 µmol/L) increase</td>
<td>&lt;0.5 mL/kg/h for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>&lt;0.5 mL/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR Initiation of renal replacement therapy OR In patient &lt;18 years, decrease in eGFR to &lt;35 mL/min per 1.73 m²</td>
<td>&lt;0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>

eGFR: estimated Glomerular Filtration Rate

Conceptual framework and targeted approach for raising awareness of AKI


CLINICAL PRESENTATION

- AKI is a process that evolves from early injury through severe damage, resulting in kidney failure and the need for RRT. The natural course can vary from complete renal recovery to dialysis dependency or death.
- Unlike myocardial infarction and stroke, kidney disease is largely asymptomatic, and kidney injury may be discovered only late in the course.
- For this reason, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline begins with patients at high risk of AKI, and not with patients who already have the condition.
- Although a number of susceptibilities (e.g. advanced age, underlying chronic disease) and exposures (e.g. sepsis, critical illness, shock, burns, trauma, cardiac surgery, major non-cardiac surgery, nephrotoxic drugs, radiocontrast agents) for AKI have been identified, there is no reliable way for a clinician to use this information to establish a clear risk profile.

Risk groups for AKI

- Dehydration or volume depletion
- Advanced age
- Female gender
- Black race
- Chronic kidney disease (CKD)
- Chronic diseases (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anemia
Opportunities for timed and targeted therapy in AKI³³

Surveillance could be initiated for high-risk individuals on the basis of clinical and biomarker criteria. Sequential assessment of biomarkers may permit identification of a window of opportunity in which kidney injury has been initiated but has not progressed to renal functional change. The duration of this window is inherently dependent on the type and site of injury and the nature and specificity of the biomarkers to determine the targets for intervention. Progression of kidney injury would be determined by development of functional changes staged on the basis of the severity of kidney injury. Biomarkers could further define progression, determine need for additional interventions, and predict prognosis. GFR, glomerular filtration rate.

### Characteristics of acute kidney injury biomarkers³

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sample type</th>
<th>Class</th>
<th>Appearance or peak after injury</th>
<th>Functional role in the kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue inhibitor of metalloproteinases-2 (TIMP-2) and Insulin-like growth factor-binding protein 7 (IGFBP-7)</td>
<td>Urine</td>
<td>Stress</td>
<td>Immediately after cardiopulmonary bypass; peaks at 6-24 h</td>
<td>Cell-cycle arrest: can induce cell-cycle arrest - thought to be a protective mechanism</td>
</tr>
<tr>
<td>Neutrophil gelatinase associated lipocalin (NGAL)</td>
<td>Urine or plasma</td>
<td>Damage</td>
<td>&lt;4 h after cardiopulmonary bypass; peaks at 4-6 h</td>
<td>Iron trafficking: binds to iron-siderophore complexes in renal tubular epithelial cells; tubular epithelial genesis: forms an iron-siderophore complex (holo-neutrophil gelatinase associated lipocalin), which is secreted by the ureteric bud, and can induce the genesis of tubular epithelium; anti-inflammatory and anti-apoptotic</td>
</tr>
<tr>
<td>Kidney injury molecule-1 (KIM-1)</td>
<td>Urine</td>
<td>Damage</td>
<td>12-24 h; peaks at 2-3 days</td>
<td>Renal recovery and tubular regeneration: clearance of apoptotic bodies; anti-inflammatory effect</td>
</tr>
<tr>
<td>Liver-type fatty acid binding protein (L-FABP)</td>
<td>Urine</td>
<td>Damage</td>
<td>Unknown</td>
<td>Fatty acid uptake and intracellular transport: mobilises lipid peroxides from cytoplasm of tubular epithelial cells to tubular lumen; L-FABP gene expression is increased by peroxisome proliferator activated receptor-α and hypoxaemia</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Serum or urine</td>
<td>Function</td>
<td>NA</td>
<td>None, filtration marker: cystatin C is normally taken up by renal tubular epithelial cells; as such its appearance in the urine indicates tubular dysfunction</td>
</tr>
<tr>
<td>Pro-enkephalin</td>
<td>Urine</td>
<td>Function</td>
<td>NA</td>
<td>None, filtration marker</td>
</tr>
</tbody>
</table>

NA: not applicable.

* Available evidence for the time from injury to detection of the marker. Filtration markers have a variable relationship to injury so specific times are not possible to establish.
PROPOSED NEW DEFINITION OF ACUTE KIDNEY INJURY\textsuperscript{12,14,15}

The 23\textsuperscript{rd} Acute Disease Quality Initiative (ADQI) recently developed consensus statements for biomarker use. The ADQI expert panel suggested that a combination of damage and functional biomarkers, along with clinical information, be used to:

- Identify high-risk patient groups
- Improve the diagnostic accuracy of AKI
- Recognize the different pathophysiological processes
- Discriminate AKI etiology
- Assess AKI severity
- Improve processes of care
- Assist the management of AKI

In addition, the 23\textsuperscript{rd} ADQI recommends using validated biomarkers to identify patient populations for whom preventive interventions have been shown to improve outcomes. This recommendation received a grade of A, strong. Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, i.e. tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7), were effective at preventing AKI.

In the table below, stage 1S identifies an early stage when there is evidence of kidney injury that is not detected by creatinine and urine output and insulin-like growth factor-binding protein 7 (IGFBP-7), were effective at preventing AKI. TIMP-2 and IGFBP-7 have been shown to improve risk stratification in critically ill patients with AKI stage 1.

Proposed new definition of Acute Kidney Injury\textsuperscript{12}

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<table>
<thead>
<tr>
<th>Functional criteria</th>
<th>Stage</th>
<th>Damage criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change or Scr level increase &lt;0.3 mg/dL and no UO criteria</td>
<td>1S</td>
<td>Biomarker positive</td>
</tr>
<tr>
<td>Increase of Scr level by ≥0.3 mg/dL, for ≥48 h or ≥150% for ≤7 days and/or UO &lt;0.5 mL/kg/h for &gt;6 h</td>
<td>1A</td>
<td>Biomarker negative</td>
</tr>
<tr>
<td>Increase of Scr level by &gt;200% and/or UO &lt;0.5 mL/kg/h for &gt;12 h</td>
<td>2A</td>
<td>Biomarker negative</td>
</tr>
<tr>
<td>Increase of Scr level by &gt;300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO &lt;0.3 mL/kg/h for &gt;24 h or anuria for &gt;12 h and/or acute KRT</td>
<td>3A</td>
<td>Biomarker negative</td>
</tr>
</tbody>
</table>

KRT: kidney replacement therapy.

MANAGEMENT OF AKI\textsuperscript{6}

- Early detection of AKI is critical as up to one-third of cases may be partially or fully preventable.
- There is no definitive treatment for AKI. Treatment will be based on addressing the cause of the kidney injury.
- Other than dialysis, no therapeutic interventions reliably improve survival, limit injury, or speed recovery.
- Supportive care is the main management, regardless of AKI etiology.

References: