Pathogenesis of Acute Kidney Injury

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Intrinsic renal failure

RBF regulation

Cellular response

molecular level response

mitochondrial response

Biomarkers

Post-renal

Pre-renal

Intrinsic renal failure

From the pathogenesis point of view

Definition

Epidemiology

Causes

AKI in special conditions

AKI and extra-renal organ dysfunction
The Problematic Definition of AKI

- Over **30** published AKI definitions
- All based on increased serum creatinine levels
- Pediatric AKI definition: a moving target
- Infants Cr in the first few weeks of life may reflect maternal values
- Children Low baseline Cr makes 0.2-0.3 changes in Cr significant
- Varying muscle mass
- Changes in SCr may lag changes in GFR and may be a very late indicator of renal injury
Definition

- Sudden interruption of kidney function results in retention of toxins, fluids, and end products of metabolism. Usually reversible with medical treatment. May progress to ESRD, uremic syndrome, and death without treatment.

Earlier diagnosis of AKI represents an important area in treating patients with AKI.
**GFR criteria**

- Risk
  - Increased creatinine $\times 1.5$ or GFR decrease $>25\%$
  - Increased creatinine $\times 2$ or GFR decrease $>50\%$
  - Increased creatinine $\times 3$ or GFR decrease $>75\%$ or creatinine $\geq 4$ mg per 100 ml (acute rise of $\geq 0.5$ mg per 100 ml dl)

**Urine output criteria**

- High sensitivity
  - UO $< 0.5$ ml kg$^{-1}$ h$^{-1}$ $\times 6$ h
  - UO $< 0.5$ ml kg$^{-1}$ h$^{-1}$ $\times 12$ h

- Oliguria (High specificity)
  - UO $< 0.3$ ml kg$^{-1}$ h$^{-1}$ $\times 24$ h or anuria $\times 12$ h

**Loss**

- Persistent ARF = complete loss of renal function $> 4$ weeks

**ESRD**

- End-stage renal disease
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The largest epidemiological study of pediatric AKI encompassing both general and critical care populations in hospitals throughout the USA, and reported an AKI incidence of **3.9 cases per 1000 admissions**.

### Renal Function at Hospital Discharge

(66%) survivors completely **recovered**

(29%) had improved renal function or **chronic renal insufficiency**

(5%) required **RRT**
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CAUSES of AKI

Acute renal failure

Pre-renal causes
- Glomerular disease
  - Inflammation (glomerulonephritis)
  - Thrombosis
- Tubular injury
- Interstitial nephritis
- Vascular disease
  - Inflammation (vasculitis)
  - Occlusion (thrombosis or embolism)

Intrinsic renal causes
- Ischaemia
- Toxins

Post-renal causes

Hilton: BMJ 2006; 333: 786-790
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AKI and extra-renal organ dysfunction
Characterized by **acute obstruction** to urinary flow.

Increases **intra-tubular pressure** and thus decreases GFR

In addition, it can lead to **impaired renal blood flow and inflammatory processes** that also contribute to diminished GFR
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Prerenal azotemia

25% of the cardiac output, a **decrease in GFR** due to a **decrease in renal perfusion pressure without** damage to the renal parenchyma.

The normal response of the kidney to prerenal conditions is to **concentrate** the urine maximally and **avidly reabsorb sodium** in an effort **to maintain/increase intravascular volume and normalize renal perfusion**.

It is important to appreciate that **prolonged** or **profound** prerenal azotemia can result in **ischemic** damage to the kidney and thus there is spectrum from prerenal azotemia to ischemic AKI.
Pathophysiology of Prerenal AKI

Response to decrease in renal blood flow by increase in vasodilating prostaglandins
Blunted by NSAIDS that inhibit prostaglandin production

Response to decrease in renal blood flow by preferential constriction of efferent arteriole by Angiotensin II
Blunted by ACE Inhibitors/ARBs that inhibit Angiotensin II production

Both mechanisms of compensation work together to increase glomerular blood flow and maintain intraglomerular hydrostatic pressure required for proper filtration

Both mechanisms may be overcome by severe hypovolemia
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Pathophysiology

Multiple Timezone Organ Damage Clock Display

The clinical clock is always late
• **Functional** alterations lead to injury
  
  Failure of autoregulation

• **Injury** precedes functional change
  
  Direct Nephrotoxicity 30%
  
  Ischemia Reperfusion 60%
  
  Inflammation, AKI Related Sepsis

• **Injury** and **functional** change are **concurrent**
  
  Complete vascular occlusion

• **Extension** phase represents an area potential of treatment with the greatest possible impact
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AKI and extra-renal organ dysfunction
• Suggested AKI be replaced with **vasomotor nephropathy**
• In adults auto-regulated over a range of MAP’s **80-160**
• Developmental changes
  – Doubling of RBF in first **2 weeks** of life
  – Triples by **1 year**
  – Approaches adult levels by **preschool**
• **Hypo-perfusion**
  
  – Well perfused kidney – 90% of blood to cortex
  – Ischemia – *increased* blood flow to *medulla*
  – Profound reduction of the blood flow to the *outer stripe of the outer medulla*
  – Outcome may be able to be influenced by restoration of energy/supply demands
    
    • Lasix example
    
    – Leads to *tubular* damage
Renal blood flow regulation is complex. No one system accounts for everything.

Insult to tubular epithelium causes release of vasoactive molecules which cause the constriction Angiotensin II, endothelin, NO, adenosine, prostaglandins, etc.
Renin Angiotensin Axis

- Renin’s role in pathogenesis of AKI
  - **Hyperplasia** of JGA with increased renin granules seen in patients and experimental models of AKI
  - Increased plasma renin activity in AKI patients
  - Changing intra-renal renin content modifies degree of damage
Prostaglandins

PGE 2 and PGI

Very important for renal vasodilation, especially in the injured kidney

Act as a buffer against uncontrolled A2 mediated constriction

The RAS and Prostaglandin pathways account for ~60% of RBF auto-regulation...
Adenosine

- Potent *renal vasoconstrictor*
  - Peripheral vasodilator
- Infusion of *methylxanthines* (adenosine receptor blockers) *inhibits* the *decrease* in GFR that is seen with *tubular damage*

- But.... Likely not a major factor in AKI
  - Methylxanthines have lots of *other actions* besides adenosine blockade
  - Adenosine is *rapidly degraded* after production
  - *Intra-renal* adenosine levels diminish *very rapidly* after reperfusion, but the *vasocontraction* remains for a *longer* period
Endothelin

• 21 amino acid peptide that is one of the most potent vasoconstrictors
• Can be used as a pressor
• Its role is unclear in normal state
• In AKI, overproduction by cells (both in and outside of the kidney) leads to decreased afferent flow and thus decreased RBF and GFR
  – Endothelin increases mesangial cell contraction which reduces glomerular ultrafiltration
• Anti-endothelin antibodies or endothelin receptor antagonists decrease AKI in experimental models
nitric oxide

- Produced by multiple isoenzymes of NOS
- In addition to its role in **vasodilation**, likely has a role in **sodium reabsorption**
  - Give a NOS **blocker** and you get **naturesis**
- Exact mechanisms not worked out completely...

- Confusing results
  - Ischemic rat kidney model – inducing **NOS causes increasing injury**
  - But if you **block NOS production**, you get **worsening** of renal function and severe **vasoconstriction**
Dopamine

- Dopamine receptors in the **afferent** arteriole
- **Dilation** of renal vasculature at **low** doses, **constriction** at **higher** doses
- Also causes naturesis (? Reason for increased UOP after starting)
- Renal dose dopamine controversy........
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The continuum of renal cell damage

Pathophysiology of AKI on the cellular level

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Repair
- Damage to **mitochondrial** membrane and change of xanthine **dehydrogenase** (NAD carrier) to xanthine **oxidase** (produces O2 radicals)
- Profound utilization of ATP → **5-10 minutes of ischemia** use ~90% of ATP
Especially during reperfusion injuries
- Main players
  - Super-oxide anion, hydroxyl radical – highly ionizing
  - Hydrogen peroxide, hypochlorous acid – not as reactive, but because of that have a longer half life and can travel farther and cause injury distal to the site of production
- Amount of damage depends on ability to replete ATP stores
  - Continued low ATP leads to disruption of cell cytoskeleton, increased intracellular Ca, activation of phospholipases and subsequently the apoptotic pathways
- This endothelial cell injury sparks an immune response....that can’t be good....
Alterations of the interstitium, vasculature, and glomeruli have also been documented in ATN

- **Interstitial edema** is often observed and may develop from leakage of fluid from increased microvascular permeability or back-leak of tubular filtrate
- Peritubular accumulation of *leukocytes* in the interstitium
  - Congestion of the *peritubular capillaries* in the outer medullary region is a salient feature of ATN that may play an important role in regional alterations of blood flow and exacerbating tubular injury during the extension phase.
- Additionally the accumulation of *leukocytes in the vasa recta*,
  - As may be expected, the most noted *glomerular* alteration in ATN is collapse of the glomerular tuft due to hypoperfusion.
  - Alterations in glomerular *foot processes* have also been described, but this has not been a consistent finding.
contradiction between the degree of histological abnormalities on human biopsy samples and the extent of GFR depression has served as a one of the main paradoxes in AKI.

Outside of rare frankly necrotic tubular cells that occur, the prominent findings in human biopsies include detachment of renal tubular epithelial cells from the basement membrane, sloughing of cells into the tubular lumen, effacement and loss of brush border in proximal tubular segments, and the formation of tubular casts derived from sloughed cells, tubular debris, and protein.

While evidence of tubular injury is apparent, evidence of tubular cell regeneration can also been seen alongside the injury.

Tubular cells with basophilic cytoplasm and hyperchromatic nuclei consistent with regenerating epithelial cells and even tubular cells undergoing active mitosis have been observed in many human biopsies of patients with ATN.
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mammalian kidney has no portal blood supply (unlike fish). The proximal tubule is particularly sensitive to ischemia because it relies predominantly on aerobic adenosine triphosphate production (mitochondrial Krebs cycle) and it cannot use the ischemic salvage pathway of glycolysis. The proximal tubule reabsorbs most of the filtered substances including toxins, in part by endocytosis. For example, gentamycin is taken up by the cubilin megalin complex and gentamycin toxicity is increased in a water-retaining kidney.

Tubules have a remarkable capacity to regenerate lost cells, usually within less than a week.
the role of a recently discovered subpopulation of tubule cells is discussed: 
**scattered tubular cells (STCs).** These cells become abundant in response to AKI and likely play a major role in the regenerative process.

In **2011**, a novel subpopulation of proximal tubular cells was described. Because these cells showed a distinct morphology and were scattered as single cells among fully differentiated inconspicuous tubular cells throughout the entire proximal tubule, these cells were termed scattered tubular cells.

It is an open question whether the STC phenotype reflects cellular **dedifferentiation** or an **alternative cellular program** that is activated specifically upon injury.

**STCs are not a fixed** progenitor population and that STCs can arise from any surviving proximal tubular cell.
STCs show very characteristic morphologic and ultrastructural features. They generally are smaller than fully differentiated tubular cells and may have different shapes. In the normal kidney, they occur as single cells or, less often, as doublets or triplets. They are surrounded by fully differentiated tubular cells, mostly with an abrupt transition. In this setting, STCs often show an arrow flask-like shape. Importantly, STCs show a dramatic decrease in mitochondria compared with neighboring proximal tubule cells.

STCs do not have pronounced apical brush border.

STCs also express only very low levels of the classic multitarget protein endocytic transporter megalin. STCs also lack the basolateral labyrinth of extensive membrane infoldings.
Because Kim-1 is expressed by STCs, it may be regarded as a marker for kidney regeneration rather than kidney injury.

Several observations support this notion: STCs become more numerous after AKI, they express similar antigens as hematopoietic stem cells (eg, glyCD133, CD24, and vimentin), and they show a higher proliferation index.

**STCs MAY RENDER THE KIDNEY MORE RESISTANT TO INJURY**

STCs may be more resistant to ischemia because they contain significantly fewer mitochondria. This suggests that STCs may be able to derive their adenosine triphosphate also from glycolysis, but this still needs further investigation.

Targeting the STC subpopulation of proximal tubule cells therapeutically is a promising novel approach to develop a specific therapy for prevention and amelioration of AKI.
The fact that PECs and STCs have a similar protein expression pattern. STCs AS THERAPEUTIC TARGET: WHAT MAY BE GOOD FOR THE TUBULE MAY BE BAD FOR THE GLOMERULUS AND VICE VERSA e.g. doxycycline
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Biomarkers for Acute Kidney Injury

- Ideally AKI would have a biomarkers like myocardial infarction
  - (i.e. troponin-1)

- Currently no Troponin-I like marker to identify the site or severity of injury, although various markers are being evaluated
  - (KIM-1)
  - (NGAL)
  - IL-18
  - Cystatin C
Conceptual Model for AKI

Kidney Injury Continuum


a Kidney injury continuum

Biomarkers (predictors) → Biomarkers (prevention protection) → Complications → Biomarkers (therapy)

Normal ← Increased risk ← Damage ← ↓ GFR ← Kidney failure ← Death

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Three hypothetical receiver-operating characteristic (ROC) curves are shown. The blue (straight) line represents a biomarker with an area under the curve (AUC) of 0.5, which indicates a result that is no better than expected by random chance. The red (middle) curve yields an AUC of about 0.75, which is generally considered a good biomarker. The green (top) curve gives an AUC of approximately 0.9, which would represent an excellent biomarker.
## Current status of promising (AKI) biomarkers in various clinical situations

<table>
<thead>
<tr>
<th>Biomarker Name</th>
<th>Sample Source</th>
<th>Cardiac Surgery</th>
<th>Contrast Nephropathy</th>
<th>Sepsis or ICU</th>
<th>Kidney Transplant</th>
<th>Commercial Test?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>Plasma</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Biosite^a</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Plasma</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Dade-Behring</td>
</tr>
<tr>
<td>NGAL</td>
<td>Urine</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Abbott^a</td>
</tr>
<tr>
<td>IL-18</td>
<td>Urine</td>
<td>Intermediate</td>
<td>Absent</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>None</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Urine</td>
<td>Intermediate</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not Tested</td>
<td>None</td>
</tr>
</tbody>
</table>

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Special clinical scenarios

AKI Pathophysiology: As the injury/repair process progresses, several markers are expressed/released and can be identified and measured.
Rhabdomyolysis

- the breakdown and necrosis of damaged skeletal muscle and subsequent release of its contents (i.e. myoglobin, sarcoplasmic proteins) into extracellular fluid and circulation.
- These products may be filtered through the glomeruli, leading to AKI via different mechanisms,
  - such as intratubular obstruction secondary to protein precipitation,
  - renal vasoconstriction,
  - inflammation and
  - tubular damage associated with reactive oxygen species production.
- Rhabdomyolys is usually develops in the setting of one or more of the following situations:
  - disruption of the substrates and/or oxygen for metabolism (i.e. ischaemia, hypoxia, crush injuries),
  - excessive metabolic demand (i.e. strenuous exercise),
  - impaired cellular energy production (i.e. hereditary enzymatic disorders, toxins),
  - and/or increased intracellular calcium influx
Medications frequently show toxic effects on the kidney as **glomerular**, **interstitial** and **tubular** cells encounter significant concentrations of medications and their metabolites, which can induce changes in kidney **function** and **structure**.

**Renal tubular cells** are particularly vulnerable to the toxic effects of drugs because of their role in concentrating and reabsorbing glomerular filtrate, which exposes them to high levels of circulating toxins.

**Renal toxicity can be a result of**
- hemodynamic changes,
- direct injury to cells and tissue,
- inflammatory tissue injury and
- obstruction of renal excretion.
Contrast agents are used widely for diagnostic and therapeutic purposes.

Their nephrotoxic potential was first suggested at least 50 years ago and today are considered one of the most common causes of AKI among hospitalised patients. The risk of CIN has long been assumed to be proportional to the degree of preexisting renal dysfunction

and it is associated with extended length of hospital stay, accelerated onset of end stage renal disease, need for dialysis, increased mortality and increased costs.

The pathophysiology of CI-AKI is not very well defined.
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AKI and extra-renal organ dysfunction
Recent clinical evidence suggests that AKI is not only an indicator for severity of illness, but also leads to earlier onset of multi-organ dysfunction with significant effects on mortality.
AKI hurts other organ systems

Grams ME, Rabb H. Kidney International 2011; advance online publication, 3 August 2011
Proposed mechanism of distal organ injury.
Kidney-lung crosstalk in the critically ill patient
**Kidney-liver interactions: Hepato-renal syndrome**

- **Acute kidney injury**
  - Rise in serum creatinine of ≥ 50% from baseline

- **HRS type 1**
  - A specific form of acute kidney injury

- **Chronic kidney disease**
  - Glomerular filtration rate of <60 ml/min for >3 months
  - Calculated

- **HRS type 2**
  - A specific form of chronic kidney disease

- **Acute-on-chronic kidney disease**
  - Rise in serum creatinine of ≥ 50% from baseline in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months

**Kidney-liver interactions**:
- **Kidney**
  - RAS activation
  - Endothelial dysfunction
  - Glomerulosclerosis
  - Tubulointerstitial fibrosis
  - Increased IL-6
  - Increased AMPK
  - Decreased fetuin-A
  - Increased uric acid synthesis

- **Liver**
  - Insulin Resistance
  - Steatosis
  - Necroinflammation
  - Fibrosis

- **Kidney-liver axis**
  - Increased adiponectin
  - Adipose tissue inflammation
  - Increased ANGII

**Conclusion**
- Kidney-liver interactions are crucial in understanding the progression of kidney disease in liver-related disorders.
## Heart-kidney crosstalk: the cardiorenal syndrome

<table>
<thead>
<tr>
<th>Classification</th>
<th>Abbreviation</th>
<th>Characteristic</th>
<th>Primary Event</th>
<th>Secondary Event</th>
</tr>
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<tr>
<td><strong>Acute cardio-renal syndrome</strong></td>
<td>CRS type1</td>
<td>Abrupt worsening of cardiac function leading to AKI</td>
<td>AHF, ACS cardiogenic shock</td>
<td>AKI</td>
</tr>
<tr>
<td><strong>Chronic cardio-renal syndrome</strong></td>
<td>CRS type2</td>
<td>Chronic worsening of cardiac function leading to progressive and permanent chronic kidney disease</td>
<td>CHD</td>
<td>CKD</td>
</tr>
<tr>
<td><strong>Acute reno-cardiac syndrome</strong></td>
<td>CRS type3</td>
<td>AKI causing acute cardiac dysfunction</td>
<td>AKI</td>
<td>AHF, ACS arrhythmias shock</td>
</tr>
<tr>
<td><strong>Chronic reno-cardiac syndrome</strong></td>
<td>CRS type4</td>
<td>CKD leading to impairment of cardiac function and/or increased risk of adverse cardiovascular events</td>
<td>CKD</td>
<td>CHD, AHF ACS</td>
</tr>
<tr>
<td><strong>Secondary cardio-renal syndrome</strong></td>
<td>CRS type5</td>
<td>Systemic disorders causing both cardiac and renal dysfunction (i.e. septic shock, vasculitis)</td>
<td>Systemic disease (i.e. sepsis)</td>
<td>AKI, CKD AHF, CHD ACS</td>
</tr>
</tbody>
</table>

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Cardiorenal Syndrome Type 1

Heart Failure

- Drug Accumulation ↓Contractility → Metformin → Lactic acidosis Interstitial Damage
- Tumor Lysis, Urate Mediated Dysfunction → Chemotherapy → Urate precipitation Interstitial Damage
- Accumulation → Antibiotics NSAID ← Toxic Damage
- Imaging → Contrast Media ← Transient Ischemia Oxidative Stress
- ↓Afterload ↑Contractility → ACEi - ARB → ↓Filtration Fraction ↓Tubuloglomerular Feedback
- ↑Afterload Arrhythmias V₁/V₂ Imbalance → Aldosterone Receptor Blockers AVP Receptor Blockers
- Overhydration Dehydration → Diuretics
- Diuresis Hypovolemia

Acute Kidney Injury
MCQ

1. With decreases renal perfusion which of the following is right:

A- PGs mediate vasoconstriction on efferent arterioles
B- angiotensin II mediate vasodilatation on afferent arterioles
C- angiotensin II enhances vasoconstriction on afferent arterioles
D- PGs mediates vasodilatation on afferent arterioles
2- the sequence of events in AKI

A- clinical- biochemical- cellular- molecular

B- molecular- cellular- biochemical- clinical

C- molecular- clinical- cellular- biochemical

D- none of the above
3- the most affected part in AKI during ischemia

A- inner side of medulla
B- outer part cortex
C- proximal tubular cells
D- distal tubular cells