ACUTE KIDNEY INJURY & RENAL REPLACEMENT THERAPY IN THE ICU

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Discussion topics and other stuff:

• **BACKGROUND:**
• **Definitions**: AKIN, RIFLE, CRS: Key concepts
• **CRS**: pathophysiology
• **Biomarkers in AKI**
• **THE WAY FORWARD:**
• **Treatment modalities**: 
  • Role of loop diuretics in oliguric AKI
  • CRRT
Definitions and diagnostic criteria: Risk stratification

- Acute Kidney Injury Network: AKI is an abrupt deterioration in renal function in response to surgery, sepsis or cardiogenic shock within a 48 hour period and staged as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Crea:</th>
<th>U-output:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in s-Crea &gt; 150-200% from baseline</td>
<td>&lt; 0,5 ml/kg/hr for more than 6 consecutive hours</td>
</tr>
<tr>
<td>2</td>
<td>Increase in s-Crea &gt; 200-300% from baseline</td>
<td>&lt; 0,5 ml/kg/hr for more than 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>Increase in s-Crea &gt; 300% from baseline or S-Crea &gt; 365 μmol/l or acute increase in S-Crea &gt; 44μmol/l</td>
<td>&lt; 0,3 ml/kg/hr for 24 hrs or anuria for 12 hours</td>
</tr>
</tbody>
</table>
RIFLE CRITERIA:

- R = Risk
- I = Injury
- F = Failure
- L = Loss of function
- E = Endstage renal disease

### Severity Grading in AKI

<table>
<thead>
<tr>
<th>RIFLE</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>x1.5 serum creatinine or urine production of less than 0.5 ml/kg for 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>x2.0 serum creatinine or urine production of less than 0.5 ml/kg for 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>x3.0 serum creatinine or creatinine more than 355 μmol/l or urine output below 0.3 ml/kg for 24 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent AKI or complete loss of kidney function for more than 4 weeks</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Complete loss of kidney function for more than 3 months</td>
</tr>
</tbody>
</table>

### AKIN

<table>
<thead>
<tr>
<th>AKIN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>(1) Kidney damage within a 48 h window.</td>
</tr>
<tr>
<td></td>
<td>(2) Increase in serum creatinine of at least 0.3 mg/dl (at least 26.4 μmol/l).</td>
</tr>
<tr>
<td></td>
<td>(3) Increase in serum creatinine of at least 50%.</td>
</tr>
<tr>
<td></td>
<td>(4) Reduction in urine output of less than 0.5 ml/kg/h for more than 6 h.</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; RIFLE, Risk, injury, failure, loss, end-stage. Adapted from [13,53,4].
### Table 1. Classification of Cardiorenal Syndrome

<table>
<thead>
<tr>
<th>CLASS</th>
<th>TYPE</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute cardiorenal syndrome</td>
<td>Abrupt worsening of cardiac function leading to acute kidney injury (AKI)</td>
<td>Hemodynamically mediated AKI secondary to acute heart failure or acute coronary syndrome in patients with chronic heart failure</td>
</tr>
<tr>
<td>II</td>
<td>Chronic cardiorenal syndrome</td>
<td>Chronic abnormalities of cardiac function leading to chronic kidney disease (CKD)</td>
<td>CKD in patients with chronic heart failure</td>
</tr>
<tr>
<td>III</td>
<td>Acute renocardiac syndrome</td>
<td>Abrupt worsening of kidney function leading to acute cardiac dysfunction</td>
<td>Arrhythmias or acute pulmonary edema in patients with AKI</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic renocardiac syndrome</td>
<td>CKD leading to chronic cardiac dysfunction</td>
<td>Cardiac hypertrophy and adverse cardiovascular events in patients with CKD</td>
</tr>
<tr>
<td>V</td>
<td>Secondary cardiorenal syndrome</td>
<td>Systemic disorders causing both cardiac and renal dysfunction</td>
<td>Sepsis, leukemia, amyloidosis, etc</td>
</tr>
</tbody>
</table>
Pathophysiological Pillars:

I: Neurohormonal Adaptations:

- Impaired LV function leads to a number of hemodynamic derangements: ↓ stroke volume and Q, arterial underfilling, elevated atrial pressures and venous congestion.
- This leads to triggering of the RAAS system, sympathetic nervous system, ↑ ADH & endothelin-1.
- This leads to ↑ in H2O and salt retention and systemic arterial vasoconstriction: although the aim is to preserve perfusion of the vital organs, this leads to ↑ afterload and ↓ Q and decreased renal perfusion.
Pathophysiological Pillar 2:

• **II: Reduced renal perfusion:**
  - Worsening renal function in patients with HF not solely due to decreased renal perfusion due to ↓ Q.
  - Hypotension can reduce GFR independent of renal blood flow
  - ESCAPE TRIAL: PAC in AHF: results showed no correlation between CI and baseline GFR/ worsening renal function. Improving the CI did not improve renal function after discharge.
  - Although reductions in CI can lead to ↓ renal blood flow, GFR initially maintained by increased filtration fraction.
Pathophysiological Pillar 3:

III: **Increased renal venous pressure:**

- Renal venous pressure is ↑ by ↑ intra-abdominal pressure or CVP
- Reduction GFR
- Studies have shown that intra-abdominal pressures up to 20 mmHg led to an average decrease in GFR of 28%.
- The degree of reduction of IAP with therapy directly proportional to improvement of GFR
- Increased RVP also implicated in the linear relationship between the severity of TR and the degree of GFR impairment
- Mechanisms as yet unclear
Pathophysiological Pillar 4:

**IV: Right ventricular dysfunction:**
- RV dilation impairs LV filling via the ventricular interdependence,
- In the presence of an intact pericardium, Increased RV pressure leads to reduced LV transmural pressure for any given intracavitatory LV pressure, thereby decreasing LV preload and distensibility and reducing forward flow
- Reduction in RV filling pressure during treatment may lead to an increase in GFR by reducing renal venous pressure and decreasing effects of ventricular interdependence.
Cardiorenal syndrome: type 3

Acute kidney injury:
- Glomerular diseases
- Interstitial diseases
- Acute tubular necrosis
- Acute pyelonephritis
- Acute urinary obstruction

Acute heart dysfunction:
- Acute decompensation
- Acute heart failure
  - Ischemic insult
  - Arrhythmias
  - Decreased CO

Humoral signalling:
- Caspase activation
  - Apoptosis
- Monocyte activation
- Endothelial activation

Cytokine secretion:
- Caspase activation
  - Apoptosis

Sympathetic activation:
- RAA activation, vasoconstriction
- Electrolyte, acid-base and coagulation imbalances

Hypertension:
- Volume expansion
- Increased preload

Decreased GFR

Decreased Na+ and H2O retention

Cardiorenal syndrome: type 3

Acute kidney injury

Acute heart dysfunction
Cardiorenal syndrome: type 5

Heart failure

Sympathetic system activation
- Neurohumoral stress
- Inflammation

Hemodynamic changes
- Hypoperfusion
- Perfusion pressure ↓, RVR ↑
- Ischemia/reperfusion

Systemic diseases
- Diabetes
- Amyloidosis
- Vasculitis
- Sepsis

Hypoxia
- Oxidative stress
- Toxemia

Exogenous toxins
- Heme proteins
- Antibiotics, contrast media

LPS / endotoxin
- Monocyte activation
- Cytokines

Renal insufficiency

Organ damage/dysfunction
Summary:

Sick heart ⇔ Sick kidney
Biomarkers of AKI:

- Common clinical scenarios for CRS / AKI include cardiac surgery, acute decompensated HF and CIN.
- Established functional biomarkers of GFR: s-Crea, Ur and diuresis delay Dx of AKI by 24 – 48 hrs.
- Novel biomarkers have emerged as early indicators of renal injury as early as 2 hrs after an insult.
- Serum and urinary panels are advocated for screening purposes.
## Biomarkers of AKI

### Table II. Criteria for an Ideal Biomarker

<table>
<thead>
<tr>
<th>Criteria</th>
<th>An Ideal Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Must be generated from the damaged cells and exhibit the organ specificity</td>
</tr>
<tr>
<td>2</td>
<td>Its concentration in the body fluid must be proportional to the damaging event</td>
</tr>
<tr>
<td>3</td>
<td>Should be expressed early after the occurrence of the organ damage, when such damage is still potentially reversible</td>
</tr>
<tr>
<td>4</td>
<td>Its concentration should drop quickly following the end of the acute injury episode to enable it as a therapeutic monitoring tool</td>
</tr>
<tr>
<td>5</td>
<td>Should be rapidly and reliably measurable</td>
</tr>
</tbody>
</table>
Figure 1 Structural representations of kidney biomarkers

(a) Cys C
(b) IL-18
(c) KIM-1
(d) NGAL

Structural representations of kidney markers. (a) Cystatin C, (b) interleukin-18, (c) kidney injury molecule-1, and (d) neutrophil gelatinase-associated lipocalin.
Figure 3: Potential use of a kidney marker panel as a diagnostic tool in assessing kidney failure.

Antecedents
intermediate stage
AKI
outcomes

Normal
Increased risk
Damage
↓ GFR
Kidney failure
Death

Complications

Early detection (n = 14)
- Serum (studies)
  - Cystatin C
  - Pro-ANP
  - NGAL
  - Neutrophil-CD11b
- Urine (studies)
  - NGAL
  - IL-18
  - KIM-1
  - GST
  - γ-GT
  - α-GST
  - AP
  - LDH
  - MMP-9

Differential diagnosis in established AKI (n = 14)
- Serum (studies)
  - Cystatin C
  - Carb Hb
- Urine (studies)
  - NGAL
  - IL-18
  - GST
  - NAG
  - α-1 microglobulin
  - KIM-1
  - NHE3
  - MMP-9

Prognosis (n = 9)
- Serum (studies)
  - RRT Cystatin C
  - NGAL
- Urine (studies)
  - Cystatin C
  - α-1 microglobulin
  - β 2 microglobulin
  - RBP
  - IL-6
  - IL-8
  - IL-10

Death
- NAG
- α-GST
- GGT
- LDH
- KIM-1

Death
NGAL
• Contribution by:
• Werner Henri
Biomarkers cont:

**Neutrophil Gelatinase- Associated Lipocalin (NGAL):**
- 25kDa protease-resistant polypeptide bound to gelatinase in specific granules of neutrophils, involved in ischaemic renal injury and repair processes.
- Transporter function of lipophilic substances (eg. Vitamin E and arachidonic acid), regulates intrarenal iron trafficking and is involved in the diffusion of renal tubular cells and nephrons.
- Following an ischaemic insult it was detectable in the urine within 2 hours.
- In CSA-AKI, NGAL showed excellent predictive value for AKI as early as 2 hrs post-op: ROC in urine: 0.99, ROC in serum: 0.90.
- S-Crea: the clinical diagnosis of AKI- 24-48hrs later.
Biomarkers: cont

• **Cystatin C:**
  - Is a 13-kDa endogenous proteinase inhibitor constantly produced by nucleated cells
  - Filtered by the glomerulus and reabsorbed & completely catabolized by the intact renal tubules
  - Levels are unaffected by age, sex, race, muscle mass, steroid therapy, infection, liver disease or inflammation
  - Detect early changes in GFR and AKI
  - Peaks 8-10 hrs after NGAL
Biomarkers cont:

- **Kidney injury molecule -1 (KIM-1):**
  - Transmembrane glycoprotein from the IG –gene superfamily
  - Differentiation of T helper cells and expressed on the proximal tubule apical membrane cilia with injury; NOT IN THE NORMAL KIDNEY.
  - Peaks 24-48 hrs after insult (cardiac catheterisation)

- **IL-18:**
  - Pro-inflammatory cytokine produced by renal tubular cells and by macrophages
  - Active role in renal disease processes e.g. apoptosis, ischaemia / reperfusion, infx, autoimmune conditions and malignancy
  - Peaks 24 hrs after insult
Biomarkers cont:

• **Fatty Acid-Binding Proteins:**
  • Abundantly expressed in tissues with an active FAB metabolism
  • 2 types isolated in human kidney (L-FABP and H-FABP)
  • L-FABP is reabsorbed in proximal tubular cells, increased urinary levels leads to early and accurate detection of ischaemia-type AKI
  • H-FABP is present in the distal tubules and the heart
  • U- L-FABP increased 4 hrs post insult and remained elevated for up to 24 hrs post cardiac catheterisation.
All forms of AKI can potentially result in:
- Volume overload
- AB disorders
- Electrolyte disorders
- Uraemia
- Oliguria

In the absence of mechanical obstruction, the therapeutic options to restore urine flow are limited:
- Options include: additional fluid therapy, improved hemodynamics with vasoactive drugs, diuretics and RRT.
Oliguria and fluid dynamics:

• RESUSCITATIVE PHASE:
  • Fluids should be targeted acc to phys end points e.g. MAP, Q, CVP and urine output
  • Patients with AKI remain oliguric/ develop oliguria despite being in the post – resus phase
  • Fluid challenge in oliguric patient only appropriate for AKI where volume depletion is suspected
  • “Fluid responsiveness”- temporary increase in output after bolus – NOT an indication for ↑ fluids
In patients with optimal and restored haemodynamics (restored IV volume), already on diuretics, indiscriminate and liberal fluid therapy failed to improve renal function. 

Led to Grossly positive fluid balance, significant reduction in lung functions and oxygenation, oedema related complications.

Positive fluid balance in several studies = increased hospital mortality.

- **Pinsky MR**: Goals of resuscitation from circulatory shock. *Contr Neph 2004:14494-104*
Loop diuretics:

- **Theoretical basis for use:**
  - Recent studies in rat models of ischaemia/reperfusion induced AKI showed that low-dose furosemide can reduce injury by improving renal haemodynamics, attenuate ischaemia-induced apoptosis and related gene transcription.
  - In Vitro studies have shown that peripheral PMNC stimulated with LPS show that high dose furosemide immunosuppressive and cytotoxic properties: ↓expression TNF-α IL-6 and IL-8.
  - Management of fluid overload, augmenting diuresis and natriuresis and maintaining AB and K balance, also aiding in the delivery of adequate nutritional support.
  - Generally dosage is titrated to 0.5-1.0 ml/kg/hr.
  - Some studies have alluded that administration of loop diuretics might increase risk of death.
  - As yet no high-quality trial that has answered questions relating to survival, renal recovery.
  - Loop diuretics limited if no role in established oliguric AKI.
RRT: Indications and timing in AKI:

- Indications:
- Refractory fluid overload
- Hyperkalemia
- Uremic complications
- Refractory metabolic acidosis (pH < 7.1)
- Certain drug and toxins
- EARLY Please: grade 2 B
## Renal Replacement Therapy:

<table>
<thead>
<tr>
<th></th>
<th>CRRT</th>
<th>IHD</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elimination of uremic toxins</strong></td>
<td>convective</td>
<td>diffusive</td>
<td>diffusive</td>
</tr>
<tr>
<td><strong>Membranes</strong></td>
<td>High-flux</td>
<td>LF/HF</td>
<td>HF</td>
</tr>
<tr>
<td><strong>Dialysate flow</strong></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Ultrafiltration and solute elimination</strong></td>
<td>continuous</td>
<td>Intermittant 3-5 hrs</td>
<td>Intermittant 8-18 hrs</td>
</tr>
<tr>
<td><strong>Citrate AC</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dialysis nursing staff</strong></td>
<td>Not required</td>
<td>required</td>
<td>required</td>
</tr>
<tr>
<td><strong>Mobilization/dx procedures</strong></td>
<td>Not possible</td>
<td>possible</td>
<td>possible</td>
</tr>
</tbody>
</table>
### Renal Replacement Therapy:

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<tr>
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<th>CRRT</th>
<th>IHD</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating costs</td>
<td>high</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Physical workload</td>
<td>high</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Risk of microbial contamination</td>
<td>high</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Use of std machines</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
<td>excellent</td>
<td>poor</td>
<td>excellent</td>
</tr>
<tr>
<td>Proven survival benefit if compared to other methods</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
What is the method of choice in AKI

- CVVH was long thought to be the superior mode in offering CV stability
- This opinion recently challenged: IHD performed with low blood flow and UF rates, reduced dialysate temperature, procedural morbidity comparable with CRRT
- Early RRT rather than late: patients that received RRT before they met the AKIN stage III criteria had lower ICU mortality rates than patients that were started on the day they met the AKIN III criteria (49.8% vs 64.6%)
- **BEST TRIAL:**
  - CRRT is the preferred choice over IRRT (80% vs 20%) since patients are likely to be hypotensive and ill.
  - Median dose 20 ml/kg/hr, cost for CRRT was higher
  - No technical feature (e.g. dose, modality, type of filter or anticoagulation technique) seemed to influence mortality.
  - Late CRRT: higher mortality
DO-RE-MI

- **DO-RE-MI (Dose Response Multicentre International) Collaboration:**
  - Dose was categorized as more intensive (CRRT 35ml/kg/hr, IRRT six sessions per week)
  - Less intensive (CRRT < 35ml/kg/hr, IRRT < 6 sessions per week)
  - No survival benefit for higher dose RRT
  - Overall crude mortality rates were less for IRRT than for CRRT
  - When clinicians prescribe RRT, consider 25% safety margin: targeting 25-30ml/kg/hr to meet actual delivered dose of 19-22ml/kg/hr

553 patients enrolled with AKI

- CRRT: 338
- IRRT: 87
- Both Modalities: 128
CRRT: rationale behind it as preferred choice

- Enhanced hemodynamic stability
- Increased net salt and water removal
- Enhanced clearance of inflammatory mediators
- Better preservation of cerebral perfusion in patients with acute brain injury or fulminant hepatic failure
- Effluent rate of 25ml/kg/hr to get flow rate of 20ml/kg/hr (Grade 1B)
Can Dialysis delay recovery of renal function?

- **Fall in urine output:**
  - Increased tubular reabsorption in remaining functioning nephrons

- **Repeated episodes of hypotension:**
  - Impaired autoregulatory response to ischaemia

- **Complement activation:**
  - Complement activation due to blood-dialyzer interaction leads to granulocyte infiltration in the kidney with upregulation of adhesion molecules that can prolong AKI

- **Other complications:**
  - Arrhythmias
  - Hypoxemia: loss of CO2 through dialyzer with decreased respiratory drive, “first-use syndrome”: rapid activation of complement, leucoagglutination in lungs with bronchospasm
  - Haemorrhage
  - Dialysis dysequilibrium
  - Sepsis
Water movement during standard hemodialysis:

- **Step 1**: Loss of urea and water
- **Step 2**: Osmolality 320 mosmol/kg falling to 290 mosmol/kg as diffusion occurs
- **Step 3**: Water movement from extracellular fluid to intracellular fluid

Osmolality:
- Intracellular fluid: 320 mosmol/kg
- Extracellular fluid: 320 mosmol/kg
Water movement during isolated ultrafiltration:

- **Intracellular fluid**
  - Osmolality: 320 mosmol/kg

- **Extracellular fluid**
  - Osmolality: 320 mosmol/kg
  - With rising plasma oncotic pressure
  - Water movement

- **Dialyzer**
  - Step 1: Isosmotic loss of solutes and water
  - Step 2
  - Step 3
What about PD?

- Option in patients where it is difficult to obtain venous access
- CI: recent / previous abdominal surgery, vascular grafts
- 2 L exchanges every 2 hrs with 2 hrs dwell time (even to consider exchanges every 4-6 hrs)
- Option in resource limited settings?

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anticoagulation needed</td>
<td>Protein loss</td>
</tr>
<tr>
<td></td>
<td>peritonitis</td>
</tr>
<tr>
<td></td>
<td>Drainage difficulties</td>
</tr>
<tr>
<td></td>
<td>Compromised pulmonary function</td>
</tr>
<tr>
<td></td>
<td>hydrothorax</td>
</tr>
<tr>
<td></td>
<td>Complications related to catheter placement</td>
</tr>
<tr>
<td></td>
<td>Glucose and electrolyte AN</td>
</tr>
</tbody>
</table>
That’s all folks!
Bibliography:

• Available on request