Past, Present and Future

Claudio Ronco
University of Padova – Chair of Nephrology
Department of Nephrology Dialysis and Transplantation
International Renal Research Institute
St. Bortolo Hospital, Vicenza - Italy
Targeting Endogenous Repair Pathways after AKI

Benjamin D. Humphreys,* Vincenzo Cantaluppi,† Didier Portilla,‡ Kai Singbartl,§ Li Yang,‖ Mitchell H. Rosner,‡ John A. Kellum,§ and Claudio Ronco,‖ for the Acute Dialysis Quality Initiative (ADQI) XIII Work Group


KDIGO
Glomerular and Tubular Kidney Stress Test: New Tools for a Deeper Evaluation of Kidney Function
Ronco C, Chawla L.

- Measure baseline GFR
- Count glomeruli
- What else?

Kidney stress test

Renal Functional Reserve
Baseline GFR

Furosemide Stress Test

Ronco C and Chawla L. Nephron 2016
Renal Functional Reserve

GFR (ml/min/1.73 m²)

Functioning Renal Mass (%)

Insult

Subclinical AKI

Renal functional reserve

Normal creatinine domain

Elevated creatinine domain


KDIGO
Pre-surgical RFR in patients with non-AKI vs. each type of AKI

Biomarkers and RFR identify kidney frailty

<table>
<thead>
<tr>
<th>Condition</th>
<th>RFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no AKI</td>
<td>15.3 ± 13.6*</td>
</tr>
<tr>
<td>subclinical AKI</td>
<td>15.5 ± 5.9*</td>
</tr>
<tr>
<td>AKI stage 1</td>
<td>26.3 ± 8.8</td>
</tr>
<tr>
<td>AKI stage 2 and 3</td>
<td>27.00 ± 8.57</td>
</tr>
</tbody>
</table>
RFR loss in patients with AKI and subclinical AKI (3 months follow up)

- No AKI: RFR loss of -1.2 (-2.5%) *
- Subclinical AKI: RFR loss of -6.4 (-25.6%) †
- AKI stage 1: RFR loss of -3.7 (-23.9%) ‡
- AKI stages 2-3: RFR loss of -16.2 (-90.1%) †

*Kp=0.07
†p=0.02
‡p<0.001
Acute Kidney Disease (3 months)

Highly Susceptible Kidney
(Baseline GFR > 90 ml/min and RFR < 30 ml/min) or Established CKD

Creatinine Domain
(sCr KDIGO Clinical)

Biomarker Domain
(Subclinical)

Increased Risk Acute Kidney Stress (AKS)

Acute Kidney Injury (AKI) with Damage

Acute Kidney Injury (AKI) with dysfunction

Kidney Recovery (GFR > 60 ml/min)

Adaptive Repair

Maladaptive Repair

Sclerosis
Fibrosis

Organ Death
Dialysis

Apparent Full Recovery
(Baseline GFR > 90 ml/min and RFR < 30 ml/min)

Full Recovery
(Baseline GFR > 90 ml/min and RFR > 30 ml/min)

Partial Recovery (GFR < 60 ml/min)

Organ Death
Dialysis

Normal Kidney
Normal Baseline GFR and intact RFR (>30 ml/min)

Recovery Patterns:
a) Early sustained reversal
b) Late reversal
c) Relapsing AKI with recovery
d) Relapsing AKI without recovery
e) Non reversal
Renal Recovery

**Kidney Recovery (GFR >60 ml/min)**

- Adaptative repair
- Organ Death
- Dialysis

**Full Recovery**
(Baseline GFR >90 ml/min & RFR >30 ml/min)

**Apparent Full Recovery**
(Baseline GFR >90 ml/min & RFR <30 ml/min)

**Maladaptive repair**

**Non-Recovery**
(GFR <60 ml/min & RFR <30 ml/min)

**Ion-Recovery**
(GFR <60 ml/min & RFR <30 ml/min)

**CKD**
(GFR <60 ml/min)

Ronco C et al. Am J Respir Crit Care Med 2017
AKI: the myth of inevitability is finally shattered

John A. Kellum

Acute kidney injury continues to challenge physicians, researchers and patients. To date, there is no efficient treatment for acute kidney injury and its occurrence in many critically ill patients seems inevitable. However, a new study might just change the way we approach this seemingly intractable problem.
AKI: the myth of inevitability is finally shattered

John A. Kellum

Acute kidney injury continues to challenge physicians, researchers and patients. To date, there is no efficient treatment for acute kidney injury and its occurrence in many critically ill patients seems inevitable. However, a new study might just change the way we approach this seemingly intractable problem.

"Now that evidence demonstrates that AKI can be prevented, it is our duty to find more ways to do it."

Using biomarker enrichment the authors were able to achieve an effect with a number needed to treat of only 6. Without biomarkers it would have been >33.
Meersch M, ICM 2017

Measuring [TIMP2]*[IGFBP7] 4h after cardiac surgery: if [TIMP2]*[IGFBP7] is ≥ 0.3

Randomization

Control group (Standard)  Intervention group (KDIGO)

KDIGO

 Patients with AKI [%]

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>all AKI</td>
<td>71.7%</td>
<td>55.1%</td>
</tr>
<tr>
<td>moderate and severe AKI</td>
<td>44.9%</td>
<td>29.7%</td>
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</table>
Number of Patients with AKI

<table>
<thead>
<tr>
<th>Year</th>
<th>ICU</th>
<th>CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>169</td>
<td>145</td>
</tr>
<tr>
<td>2016</td>
<td>152</td>
<td>127</td>
</tr>
</tbody>
</table>
19.8% Reduction of need for CRRT
Controversies in Acute Kidney Injury

Editors
J.A. Kellum
C. Ronco
J.-L. Vincent

Achieving Consensus in Acute Kidney Injury

RRT Indications
Time of Initiation
Modality of RRT
Prescription, dose, Fluid Management
Quality Control
KDIGO Understanding and managing kidney disease burden through demand-capacity modeling.

- **Demand**
  - Disease burden
  - Solute load
  - Volume load

- **Capacity**
  - Normal function
  - Reduced function

- **Demand-capacity balance**
  - Gap
  - Capacity
  - Demand

KDIGO framework helps in assessing the balance between demand and capacity in kidney disease management.
About timing

- No consensus on “When” to initiate RRT (controv. studies)
- Early initiation probably improves outcomes (but early means what? Admission? Creatinine? Other?)
- RIFLE/AKIN Stage stratification may represent a surrogate of timing (severity)
- There is a rationale for early initiation
- There are draw backs for early initiation
- An objective algorithm has been proposed for RRT initiation

Do we need additional clinical studies?
About Modality

• The process of decision making is linked to indications leading to therapy initiation

  – Classic Blood Purification

  – Alternative

    • Fluid overload   Ultrafiltration
    • Sepsis           HVHF - CPFA
Recent multicenter RCTs have failed to confirm earlier trials suggesting a benefit of higher CRRT dose in critically ill patients.

Several differences (total effluent dose, convective contribution, timing of treatment initiation) exist among the various CRRT dose/outcome trials, making it difficult to establish a “standard” dose.

Based on standard practice in chronic dialysis, routine assessment of delivered CRRT dose should be an integral aspect of AKI patient management in the future.

For the time being, 30 to 35 mL/kg/hr is a reasonable target for prescription to make sure no less than 20-25 mL/kg/hr is effectively delivered.
Technology in CRRT

RISK Assessment
- Scores Biomarkers
  - IT - EMR
- Biochemistry
  - Physical
  - E-Alerts
- Relative Absolute Non Renal

Clinical Diagnosis

Indications
- Dose Volume
  - Homeostasis
- Organ support

Identification of Therapy Targets

Prescription
- Decision to modify prescription
  - Integrated Data Evaluation
  - (CRRT + EMR)

Monitoring
- Automated Data Collection
  - Training
  - Logistics Finance Staffing
- Technique Machine/filter
  - Dose/fluids
  - Settings Anticoagulation

Delivery
- Decision to start prescription
Evolution of CRRT

Third generation CRRT machines, Tr. of Sepsis HVHF & HCO Membr. 2002

2002

2005 Liver support MOST, CPFA

Lung support ECCO2R Citrate anticoagulation Sorbents

2010

Pediatric CRRT

2017

Fourth generation CRRT machines

1995 Second generation CRRT machines CVVH, CVVHDF and studies on Dose & Adequacy 35 ml/Kg/h

2002

2005

2005

2010

2017

2017

2018-2019

Pediatric CRRT

New generation of CRRT machines

2017

Fourth generation CRRT machines
Biomarker Type & Magnitude at different AKI Stage

AKI CLINICAL SYNDROME STAGE

- AKI Risk
- Acute Kidney Stress
- Damage
- Dysfunction
- Fibrosis

Biomarkers:
- IGFBP-7
- TIMP-2
- NGAL – IL-18 - NAG
- KIM-1 – L-FABP
- sCr – Cystatin-C
- Galectin-3 – TGF-β

KDIGO
Biomarkers for CRS detection

Diuretics-Ultrafiltration

BNP

BM+

Creatinine

Arbitrary Units

STOP HARMFUL INTERVENTION

KDIGO
Biomarker for Recovery (CRRT discontinuation)

- Successful discontinuation
- Restart CRRT

KDIGO
Nephrocheck Curve Study
(Vicenza 2017-2018)

KDIGO
Novel Biomarkers indicating repair or progression after AKI

Kellum J, Kashani K

Injury markers quantify damage

Markers of regeneration/repair

Absence markers not detected when normal

Injury markers for new or ongoing damage

Markers of fibrosis or maladaptive repair

Markers assessing overall environment affecting recovery (e.g., inflammation)
Is there a molecular signature for different types of AKI?

Biomarkers and the diagnostic process:

- Patient
- Samples of tissues, blood or other bodily liquids
- Analysis and identification of biomarkers
- Choice of personalized medicine according to biomarkers
Different types of diagnosis

- Signs
- Symptoms
- Physical
- Laboratory
- Instrumental
- Imaging
- Biochemical
- Histological
- Molecular
- Computer Aided

KDIGO
Renal Epithelial Cell Polyploidization and Progenitor Proliferation Repair of AKI. The kidney responds to AKI with two separate strategies: local progenitor cells produce new podocytes on the glomerular tuft or new tubular cells depending on the site of injury and epithelial cell loss. In the glomeruli, differentiated podocytes cannot undergo cytokinesis and increase their working capacity by entering the cell cycle to increase their DNA content and become polyploid. At the same time, podocyte progenitors localized among parietal epithelial cells of the Bowman’s capsule differentiate and replace lost podocytes. Tubular epithelial cells that are already fully engaged in essential organ functions increase their working capacity without any interruption by entering the cell cycle to increase their DNA content; a form of alternative cell cycle named endoreplication. This process allows differentiated cells in uninjured S2 segments a compensatory hypertrophy to take over the filtration load of nonfunctioning injured or lost nephrons, while tubular progenitors scattered along the nephron proliferate, completing cell division and drive regeneration in necrotic S3 segments of the proximal tubule of affected nephrons.
Tubulointerstitial fibrosis is considered a hallmark of maladaptive repair processes after tubular injury leading to chronic kidney disease. Upon injury, myofibroblasts promote epithelial repair by producing retinoic acid in place of injured tubular cells. Thus, resident fibroblasts turning into myofibroblasts maintain a cross-talk that protects tubular epithelial cells from injury and can restore tissue integrity and functionality, challenging the concept that fibrosis is only detrimental in nature.
The Future of CRRT

Patients identification
CRRT optimization
MOST and ECOS technology
Integrated Equipment
Patient care and precision CRRT
The Future of AKI & CRRT

PATIENT IDENTIFICATION

- Clear understanding of Capacity and Demand
- Genotype characterization
- Fenotype characterization
- Statistical probability of success evaluation
- Identification of patient’s needs
- Precise definition of therapy targets
- Personalized prescription of the therapy
- Dynamic follow up during and after hospital stay
The Future of CRRT

CRRT TECHNOLOGY

- Vascular Access
- Circuitry
- Filters and membranes
- Anticoagulation
- Machines
- Monitoring
- Biofeedback
### Machine Data Only

**Filter Life**

**Treatment Downtime**

**Prescribed & Delivered Dose**

**Fluid Removal Parameters**

**Alarm Management**

**Summary**

<table>
<thead>
<tr>
<th>Question</th>
<th>This Year</th>
<th>This Month</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q. 1) What is our average filter life?</td>
<td>33</td>
<td>49</td>
<td>48%</td>
</tr>
<tr>
<td>Q. 2) How much treatment time is lost?</td>
<td>14%</td>
<td>12%</td>
<td>-14%</td>
</tr>
<tr>
<td>Q. 3) How are we tracking toward our dosing target?</td>
<td>34</td>
<td>37</td>
<td>9%</td>
</tr>
<tr>
<td>Q. 4) How much fluid was removed per TreatmentDay?</td>
<td>1.4</td>
<td>1.1</td>
<td>-21%</td>
</tr>
<tr>
<td>Q. 5) How many access/return (AR) alarms do we have?</td>
<td>4.2</td>
<td>3.0</td>
<td>-29%</td>
</tr>
</tbody>
</table>

**May at a Glance**

<table>
<thead>
<tr>
<th>Category</th>
<th>This Year</th>
<th>This Month</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>20</td>
<td>2</td>
<td>-71%</td>
</tr>
<tr>
<td>Therapies used</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Filters used</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
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Timing of CRRT Initiation

Fluid Overload and Management, Ventilator and Vasopressor Duration

CRRT Initiation versus KDIGO AKI Stage

Frequency of RRT After CRRT

Summary
Extracorporeal circuits

- Antithrombogenic
- Anti microbial properties
- Temperature self adjusting
- Collapsible (minimum storage volume)
- Biodegradable (minimum wasting)
Water sparing technologies
(Blue Planet Dialysis)

1. Regeneration
2. Double filtration
3. Physical-chemical processes
4. Recirculation
5. Sorbent technologies
Devices, MOST and ECOS

- Fluid Balance control
- New Membranes
- New sorbent devices
- Wearable devices
- Population specific therapies
MOST and ECOS

Sepsis
Organ Crosstalk
The case of Heart, Lungs and Kidney
From Native to Artificial Organ Crosstalk

KDIGO
We need to provide the evidence and the foundations for the next generation KDIGO AKI guidelines, and specifically in the following areas:

• Nomenclature & Diagnostic Criteria
• AKI Risk Stratification & Assessment
• Fluid Management & Hemodynamic Support
• Nephrotoxic Agents & Drugs affecting the Kidney
• Renal Replacement Therapy