Consultant: Astute, Baxter, OCD, Medtronic, Asahi Medical, Jaffron, Biomerieux

Advisory Board: GE, Kaneka, Cytosorbents,

Speaker Bureau: Toray, Estor, FMC, B.Braun
AKI
Past, Present and Future

PAST
1900 1960 1990
Middle Age Wold War II

PRESEN

FUTURE
2020

KDIGO
AKI in 1900: the clinical diagnosis

ARF was diagnosed from signs and symptoms such as oliguria, fatigue, vomiting, GI bleeding.

«Disorders of the Renal Glands»
Acute Peritoneal Dialysis

Diagrammatic Representation of Intermittent Peritoneal Irrigation with Flexible Sump Drain

To fill pelvis—clamps A & B closed, clamp C open.

To empty pelvis—clamps A & B open, clamp C closed.

Clamp B may be left open at all times if air column is at least 4-5 feet high.

Continuous suction

Negative pressure regulator

20 liter bottle

Filtered air inflow

Alkaline cresol solution

20 liters irrigation fluid

Scale graduated in 500 cc

Flexible sump drain

Semi-erect position of patient

KDIGO
AKI: Changing Pattern

1970-1980
Total number of incident cases = 156

- Ward 85%
- ICU 15%

Mortality 58%

1980-1990
Total number of incident cases = 925

- ICU 92%
- Ward 8%

Mortality 54%
Critical Care Nephrology

FROM SPECIALITY-ORIENTED TO PATIENT-ORIENTED

Severity of illness

Ultra Specialistic

Clinically Specific

Common but low interaction

Clinically Specific

Ultra Specialistic

Specialistic

Moderate Interaction

High Interaction

Specialistic

Moderate Interaction
Claudio Ronco and Rinaldo Bellomo

Critical Care Nephrology: The time has come

Editorial entitled “Critical Care Nephrology: the time has come”. It was not so long ago that the term “critical care nephrology” was unknown or at least obscure to most physicians both in the nephrological and in the intensive care community; a push was definitely needed to move forward. Today, a few years later, a simple internet query on critical care nephrology leads to more than 157,000 references. For this reason I have decided to dedicate this acquired expertise and training in both areas.

In either case, by the late nineties, the formal development of a specialty field called Critical Care Nephrology was seen as something whose time had come.

Why had this conceptually simple and effective approach not been developed before? Several issues were raised on the occasion of the First International Course on Critical Care Nephrology held in Vicenza in
Arterio-venöse Hämodialyse
Nieren-(Ersatz)-Therapie im Intensivpflegebereich

Herausgeber: Peter Kramer

University Hospital
Department of Internal Medicine
Division of Nephrology
Göttingen, Federal Republic of Germany

Vandenhoeye & Ruprecht Göttingen - Zürich

HD-o
Beginning of CRRT

1977
First CAVH in Gottingen
First CAVH in Vicenza

1983
Fluid Balance systems

1986
CVVH
CVVHD
Adoptive Technology

1990
First generation CRRT machines
CVVH
CVVHD
CVVHDF

1995
Second generation CRRT machines
CVVH
CVVHD
CVVHDF

KDIGO
Creatinine Kinetics

Urine Output
Accurate Real-Time Continuous RIFLE Critical Monitoring
90 Kg Patient
Over 30 definitions of AKI/ARF existed in the literature

1. Creat Δ 0.1 mg/dL
2. Creat increase > 0.5 mg/dL
3. Creat >= 0.5 mg/dL
4. Creat >= 1.7 mg/dL
5. Creat >= 1.5 mg/dL
6. Creat >= 2 mg/dL
7. Creat >= 2.1 mg/dL and x 2
8. Creat >= 177 µmol/L Δ > 62 µmol/L
9. Creat > 200 µmol/L (2.36 mg/dL)
10. Creat > 3.2 mg/dL or x 2
11. Creat > 5 mg/dL or K > 5.5
12. RIFLE
13. Creat increase >= 25%
14. Creat increase >= 50%
15. Creat increase >= 100%
16. ΔCr72h > 0 µmol/L
17. ΔCr72h > 25 µmol/L
18. ΔCr72h > 44 µmol/L
19. ΔCr72h > 50 µmol/L
20. ΔCr72h > 100 µmol/L
21. Cockcroft-Gault Cr Cl < 30 mL/min
22. Cockcroft-Gault Cr Cl 30–60 mL/min
23. ΔCockcroft-Gault72hr < 0%
24. ΔCockcroft-Gault72hr < -15%
25. ΔCockcroft-Gault72hr < -25%
26. ΔCockcroft-Gault72hr < -50%
27. MDRD: 50% change in GFR
28. UO < 100 q 8hr
29. α1-microglob
30. U β2 - microglobulin
31. U N-acetyl- β-D-glucosaminidase
32. U glutathion transferase-π
33. U glutathion transferase- α
34. NGAL
35. RRT

KDIGO
AKI situation in Y2K

**Epidemiology:** Uncertain or even unknown

**Definition:** Multiple discordant definitions

**Diagnosis:** Urine output and Serum Creatinine

**Case mix:** Patients with multiple organ involvement

**Mechanisms:** Undefined for most clinical conditions

**Therapy:** CRRT/IRRT, Dose, Timing, Modality, undefined

**Outcome:** Basically unchanged compared to the past
Beginning of CRRT

1977
First CAVH
In Gottingen
and
First CAVH
in Vicenza

1983
CAVHD
CAVHDF
Fluid
Balance
systems

1986
CVVH
CVVHD
and
Adoptive
Technology

1990
First
generation
CRRT
machines
CVVH
CVVHD
CVVHDF

1995
Second
generation
CRRT
machines
CVVH
CVVHD
CVVHDF

2000
Study on
Dose &
Adequacy
35 ml/Kg/
h.

2000
The Birth
of
ADQI

 KDIGO
The first international consensus conference on continuous renal replacement therapy

John A. Kellum, Ravindra L. Mehta, Derek C. Angus, Paul Palevsky, and Claudio Ronco, for the ADQI Workgroup

Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; Department of Medicine, University of California, San Diego, CA; Veterans Administration Pittsburgh Healthcare System, Pittsburgh, PA; Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; and Renal Research Institute, New York, NY, USA

The first international consensus conference on continuous renal replacement therapy.

Background. Management of acute renal failure (ARF) in the critically ill is extremely variable and there are no published standards for the provision of renal replacement therapy in this population. We sought to review the available evidence, make evidence-based practice recommendations, and delineate key questions for future study.

Methods. We undertook an evidence-based review of the replacement therapy (CRRT) [3] and use of this therapy is increasing worldwide. However, there are no standard guidelines for the application of CRRT and practice patterns vary widely between individual centers. Results from recent clinical trials on selection of dialysis membranes [4-7] and dialysis dose [8, 9] provide important evidence to guide therapy. Yet important questions re-
AKI and CRRT

Dose of Dialysis (ml/Kg/hr)

Survival


Saudan et Al, KI 2006

Ronco et Al, Lancet 2000

Bellomo et Al, NEJM 2009

Tolwani et Al, JASN 2008 - Palewsky et Al, NEJM 2008

Presence of Sepsis Early Intervention
Honoré et Al. CCM, 2002

KDIGO
DoReMi Database (N=865)

Median delivered = 27 mL/kg/h
Median prescribed = 34 mL/kg/h

- Delivered dose
- Prescribed dose

Dose of CRRT (mL/kg/h)

Patients (%)
Delivered dose of CRRT

<table>
<thead>
<tr>
<th>Method</th>
<th>Delta ml/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVHD</td>
<td>25</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>40</td>
</tr>
<tr>
<td>CVVH</td>
<td>32</td>
</tr>
</tbody>
</table>

Delivery VS Prescription

KDIGO
Relationship between fluid accumulation and predicted probability of death

Predicted Probabilities for icu_death
With 95% Confidence Limits

Predicted Probabilities for icu_death_12=1
With 95% Confidence Limits

ITALY

KDIGO
May 10-12, 2002 Vicenza

Research
Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group
Rinaldo Bellomo1, Claudio Ronco2, John A Kellum3, Ravindra L Mehta4, Paul Palevsky5 and and the ADQI workgroup6

1Department of Intensive Care and Medicine, Austin Health, Melbourne, Australia
2Department of Nephrology, San Bortolo Hospital, Vicenza, Italy
3Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, and Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA
4Department of Medicine, University of California, San Diego, California, USA
5Department of Medicine, University of Pittsburgh Medical Center, and Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA
6For a complete list of authors, see Appendix 1

Corresponding author: Rinaldo Bellomo, rinaldo.bellomo@austin.org.au
From lab results to an organic classification

Over 30 definitions of AKI/ ARF in the literature

1. Creat Δ 0.1 mg/dL
2. Creat increase >0.5 mg/dL
3. Creat>= 0.5 mg/dL
4. Creat >= 1.7 mg/dL
5. Creat >= 1.5 mg/dL
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29. U α1-microglob
30. U β2- microglobulin
31. U N-acetyl- β-D-glucosaminidase
32. U glutathion transferase-β
33. U glutathion transferase-α
34. NGAL
35. RRT
36. ESRD
37. ESRD >3 months

Non-oliguria

Abrupt (1–7) days decrease (>25% in GFR, or serum creatinine x 1.5 sustained
Decreased UO relative to fluid input UO <0.5 mg/kg/h x 6 h

Oliguria

Adjust creatinine or GFR decrease >50% serum creatinine x 1.5
Decreased UO relative to fluid input UO <0.5 mg/kg/h x 12 h

Adjust creatinine or GFR decrease >75% serum creatinine x 3 or serum creatinine <4 mg%
when acute increase >0.5 mg%
Decreased UO relative to fluid input UO <0.5 mg/kg/h x 12 h
Anuria x 12 h

Irreversible AKI or persistent AKI >4 weeks

ESRD

ESRD >3 months

Risk
Injury
Failure
Loss
Reversibility
Irreversibility
KDIGO
The “Vicenza Retreat”
An independent Group

Acute Kidney Injury Network

The “Vicenza retreat” has been organized as an independent body, supported by the participating societies and completely free from industrial funding.

The absolute freedom from any external input represents a warranty for the quality and the meaning of the decisional process.

The Birth of AKIN

Vicenza - Italy
Hotel Michelangelo-Arcugnano
September 22-23, 2004
From lab results to an organic classification

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Definition of AKI</strong></td>
<td><strong>Definition of AKI</strong></td>
<td><strong>Definition of AKI</strong></td>
</tr>
<tr>
<td>Abrupt (1-7 days) ↓ in renal function from base line</td>
<td>Abrupt (within 48 h) ↓ in renal function from base line</td>
<td>Abrupt (hours days) ↓ in renal function from base line</td>
</tr>
</tbody>
</table>

**Definition of decrease in renal function**
- ↑ in Scr of **0.5 mg/dL** or more
  - or
    - ↑ in Scr **1.5-fold from baseline**
    - or
      - ↓ UO < 0.5 mL/kg/h for >6 h
      - or
        - ↓ GFR > 25%
Altered Cell metabolism

Migration of integrins

Loss of cell polarization

Loss of cell-to-cell adhesion

Oliguria

Multiple Timezones of AKI and Organ Damage Clock

KDIGO

The sCreatinine clock is always late
Editorial Review

A basic science view of acute kidney injury biomarkers

Jennifer R. Charlton¹², Didier Portilla³ and Mark D. Okusa²⁴
Biomarkers

Ischemia/reperfusion → Toxicity → Damage → Cell death

Normal epithelium

Necrosis

Apoptosis

Potential urinary biomarkers for early diagnosis of AKI

- NAG
- β2M
- α1M
- RBP
- Cystatin C
- KIM-1
- Clusterin
- Microalbumin
- NGAL
- CYR-61
- IL-18
- OPN
- FABP
- NHE3
- Fetuin A

Delayed biomarkers for kidney injury

↑ Serum creatinine
↑ Blood urea nitrogen
AKI Biomarkers

NGAL  
KIM - 1  
Nephrocheck

KDIGO
KDIGO – Kidney Disease: Improving Global Outcomes

No damage

No functional change

No AKI
Bm – sCr –

Subclinical AKI
Bm + sCr –

Functional change

Functional AKI
Bm – sCr +

Established AKI
Bm + sCr +

Progression
Resolution
**New diagnostic criteria for AKI?**

<table>
<thead>
<tr>
<th>FUNCTIONAL CRITERIA</th>
<th>DAMAGE CRITERIA</th>
</tr>
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<tbody>
<tr>
<td><strong>STAGE 1</strong></td>
<td></td>
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<tr>
<td>Increased serum creatinine $\geq 0.3$ mg/dl or 150% $\leq 48$ hours or urine output $&lt; 0.5$ ml/kg/h for $&gt; 6$ hours, or mildly decreased GFR</td>
<td>+</td>
</tr>
<tr>
<td><strong>STAGE 2</strong></td>
<td>Biomarkers positive</td>
</tr>
<tr>
<td>Increased serum creatinine by 200% or urine output $&lt; 0.5$ ml/kg/h for $&gt; 12$ hours, or moderately decreased GFR</td>
<td>++</td>
</tr>
<tr>
<td><strong>STAGE 3</strong></td>
<td></td>
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<tr>
<td>Increased serum creatinine by 300% (or $\geq 4.0$ mg/dl with an acute increase of $\geq 0.5$ mg/dl) or urine output $&lt; 0.3$ ml/kg/h for $&gt; 24$ hours or anuria for $&gt; 12$ h or acute RRT, or severely decreased GFR</td>
<td>+++</td>
</tr>
<tr>
<td>Biomarker Domain</td>
<td>Creatinine/Urine Output Domain</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Sub-Clinical AKI</td>
<td>Clinical AKI</td>
</tr>
</tbody>
</table>

- **Biomarker + (trend)**
- **Biomarker +++ (Cut off)**
- **Renal Angina**
- **Rifle R / AKIN Stage I**
- **Rifle I / AKIN Stage II**
- **Rifle F / AKIN Stage III**

**Delta Biomarker Domain**

<table>
<thead>
<tr>
<th>Serum Creatinine increase in mg/dl or from baseline (B)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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</table>
Cellular and Molecular Mechanisms of AKI

Anupam Agarwal,* Zheng Dong,† Raymond Harris,‡ Patrick Murray,§ Samir M. Parikh,¶ Mitchell H. Rosner,‖ John A. Kellum,** and Claudio Ronco,††
for the Acute Dialysis Quality Initiative XIII Working Group

Figure 1. Involvement of mitochondria in ischemic AKI: Healthy mitochondria generate the ATP necessary for cellular health and, in the renal tubule, the energy needed for the movement of solute and water against gradients. Ischemia-reperfusion injury leads to rapid fragmentation of mitochondrial networks through a dynamic process termed fission regulated by proteins such as dynamin-related protein 1 (Drp1) and mitochondrial fission 1 protein (Fis1). The mitochondrial fusion machinery includes mitofusin 1 (Mfn1), Mfn2 and optic atrophy 1. Fragmented mitochondria appear to be a less efficient source of ATP and can undergo the MPT. MPT results in mitochondrial swelling from the influx of water, and it promotes cell death through the release of calcium (Ca^{++}), cytochrome c (Cyt c), and other proapoptotic proteins. Damaged mitochondria can be cleared and recycled through mitophagy, the first step of which is envelopment of the injured mitochondrion by a double-membrane structure termed the autophagosome (shown in green). Finally, in surviving cells, mitochondrial biogenesis results in an expansion of mitochondrial mass through regulated gene expression of structural and enzymatic components of mitochondria. Reprinted from www.adqi.net, with permission.
The Role of Inflammation in the Cardio-Renal Syndrome: A Focus on Cytokines and Inflammatory Mediators

Mitchell H. Rosner, MD,* Claudio Ronco, MD,† and Mark D. Okusa, MD*

[Diagram showing innate immunity and inflammation, with keywords like KDIGO highlighted]
Lung–Kidney Crosstalk in the Critically Ill Patient

Faeq Husain-Syed\textsuperscript{1,2}, Arthur S. Slutsky\textsuperscript{3,4}, and Claudio Ronco\textsuperscript{1}

KDIGO
CKD and ESRD after AKI

AKI to CKD

HR = 8.8
(95%CI 3.1-25.5)

AKI to ESRD

HR = 3.1
(95%CI 1.9-5.0)

Coca, et al.
Kidney Int 2012
Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup

Lakhmir S. Chawla1, Rinaldo Bellomo2, Azra Bihorac3, Stuart L. Goldstein4, Edward D. Siew5, Sean M. Bogshaw6, David Bittleman7, Dinna Cruz8, Zoltan Endre9, Robert L. Fitzgerald1, Lui Fornil10, Sandra L. Kane-Gill11, Eric Hoste12, Jay Koyner13, Kathleen D. Liu14, Etienne Macedo15, Ravindra Mehta16, Patrick Murray17, Mitra Nadim18, Marlies Ostermann19, Paul M. Palevsky18,19, Neesh Pannu20, Mitchell Rosner21, Ron Wald22, Alexander Zarbock23, Claudio Ronco24 and John A. Kellum25 on behalf of the Acute Disease Quality Initiative Workgroup 16.