Acute Kidney Injury

From Galenus to KDIGO

Norbert Lameire, MD, PhD
Em Prof of Medicine & Nephrology
University Hospital, Gent

The Eberhard Ritz lecture
Heidelberg, April 4, 2019
Claudius Galenus (AD 129 – Pergamon c. 200/c. 216, Pergamon.

Galenus, the personal physician of 3 emperors Marcus Aurelius, Commodus, and Septimus Severus) was (according to Marcus Aurelius), the first under the physicians and the most prominent of the philosophers; he learned his skills on trauma and wound care in the sanctuary of Aesclepius, the god of cure, but mainly as physician of the gladiators of Pergamon. He continued his studies of medicine in Alexandria.

He is the most accomplished of all medical researchers of antiquity, Galenus influenced the development of various scientific disciplines, including anatomy, physiology and pathology, as well as philosophy.

He was the first to definitely demonstrate that the urine did not originate in the bladder but in the kidneys
Differential diagnosis and work-up of oliguria according to Galenus.

Aphorisms

All who drink of this remedy recover in a short time, except those in whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.

Galenus of Pergamon, 131-201 AD
Impact of Galenus on Medieval Medicine

• Galenus believed in the Aristotelian doctrine that, in Nature (God), form follows function. “If we want to understand the function of an organ, tissue or body part, we must first study its form”.

• Galenus was a monotheist and his monotheism greatly enhanced the acceptance of his medical theories and teachings by later Muslim and Christian scholars and physicians.

• For over a 1200 years after his death, Galenus was considered to be the “gospel truth”, the ultimate authority on all matters medical.

• Medieval medical authorities dogmatically agreed: If Galenus figured it all out, why look any further? It wasn't until the Renaissance that Galen was finally questioned and his errors uncovered.
De humani corporis fabrica, Libri septem (1543)
Andreas Vesalius, Basel

Brussel 31/12/1514-Zakynthos 15/10/1564

Later personal physician of Charles V and Philips II.
Giovanni Battista MORGAGNI (1682-1771)

1755

ISCHURIA

ischuria urethralis
ischuria ureterica
ischuria vesicalis
ischuria renalis
Crush Syndrome History

First described in German literature in victims of Messina earthquake 28/12/1908

Franz Colbers-Coburg 1909 “acute muscle necrosis and oliguria”

WW I German authors noted traumatic rhabdomyolysis
- Frankenthal (army-surgeon) 1916
- Hackradt 1917 “vasomotorische nephrose” working in prof Max Borst’s systematic “war pathology” service
- Lewin student of Ludwig Pick 1919
- Siego Minami 1923 (working with Pick)

Bajema, Rotmans, NDT (2018) 33: 2113–2114

Abb. 3. Schnitt aus Nierenrinde (Fall 1159). Tod nach Verschüttung am 7. Tag. Hämalaunfärbung. Leitz, Oc. 1, Obj. 6, Tub. 155. \( pgr \) = Pigmentgranula in dichter Lagerung innerhalb von Tubuli contorti; \( pb \) = Pigmentstreifen und -bänder; \( e \) = Epithelen der Tubuli contorti; \( bl \) = geschrumpfte rote Blutkörperchen in Blutcapillaren.
“Victim buried several hours with pressure on a limb...good condition on admission... later shock... diminution of arterial pulsations in affected limb... incipient gangrene... signs of renal damage... blood urea and potassium become progressively higher... death usually within a week.”

Description by Bywaters of trapped victims in the London Blitz, 1941

More than one million London houses were destroyed or damaged, and more than 40,000 civilians died.
History of dialysis


Willem Kolff

Kolff rotating drum kidney (1943)
Sophia Schafstadt (1945)
The first patient, owing her life to dialysis after having suffered from ARF. She was Kolff’s patient n° 17 at age 67 yrs. Picture taken in the Kampen hospital garden 4 weeks after her „recovery“ (october 1945)
She died in 1951.
THE „ROTATING DRUM“ IN 1945 CLINICAL-BIOCHEMICAL REPORT OF PATIENT 17

A case report of patient 17......
Characteristics of the initial dialysis

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<td>Treatment time</td>
<td>690 min</td>
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<td>Blood flow</td>
<td>116 ml/min</td>
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<td>Urea clearance</td>
<td>87 ml/min</td>
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<td>Pre-post urea</td>
<td>396/121 mg%</td>
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<td>URR</td>
<td>69%</td>
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<td>Kt/V</td>
<td>1.40</td>
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<td>Vurea DDQ</td>
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Colonel med Paul Teschan performing acute dialysis during the Korean War (1952) with the Kollf-Brigham rotating drum at the 11th Evacuation hospital, 8th US Army. The mortality rate in ARF in military casualties was 80% – 90% (like in WW2). The use of this dialyzer decreased mortality to 53%.
Developing a consensus classification system for acute renal failure

John A. Kellum, MD,* Nathan Levin, MD,† Catherine Bouman, MD,‡ and Norbert Lameire, MD§

A biochemical definition and classification system for acute renal dysfunction is long overdue. Its absence has impeded progress in clinical and even basic research concerning a syndrome associated with mortality rates of 30 to 80%. No definition of acute renal dysfunction will be perfect, but the absence of a definition or, worse, more than 35 separate definitions, as found in the literature, is unacceptable. Many of the challenges, considerations, and controversies associated with achieving consensus and developing a classification for acute renal dysfunction are addressed. Recommendations for validating a classification system are also considered. Curr Opin Crit Care 2002, 8:509–514 © 2002 Lippincott Williams & Wilkins, Inc.

Definitions are easy

Acute renal failure (ARF) is easily defined. It is an “abrupt and sustained decrease in renal function,” although most might argue that function should be clarified because the kidney has numerous functions (eg, fluid and solute excretion, electrolyte and acid–base regulation, endocrine functions, and so forth). However, in clinical practice, the argument is accepted that the only functions that are routinely and easily measured and that are unique to the kidney are the production of urine and the excretion of waste products of nitrogen metabolism [1•]. This is not to say that the other functions of the kidney are less important, only that they are less verifiable, at least for now. Thus, for clinical research, ARF can be defined as an “abrupt and sustained decrease in glomerular filtration, urine output, or both.”

Of course, this is only a qualitative definition and therefore is not very useful for the purposes of standardizing entry criteria or endpoints for clinical trials [1•]. To do this, a quantitative definition of ARF is needed, and there are three terms that require quantification: abrupt, sustained, and decrease. For ARF, abrupt appears to be a

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Correspondence to John A. Kellum, MD, Department of Critical Care Medicine, University of Pittsburgh Medical Center, 3550 Terrace St, Pittsburgh, PA 15261, USA; e-mail: Kellumja@ccm.upmc.edu

Current Opinion in Critical Care 2002, 8:509–514
Evolving definition and classification of AKI

- **AKI proposed**
  - September 2004: The term AKI is proposed to reflect the entire spectrum of ARF

- **AKIN classification of AKI**
  - AKIN develops uniform standards for defining and classifying AKI

- **1941**
  - ARF described
  - ARF is described by E.G. Bywaters in his observations of patients after crush injuries from the London bombings in WWII

- **2004**
  - Introduction of RIFLE staging for ARF
  - May 2004: To address the lack of a consensus definition for ARF, the ADQI devises the RIFLE definition and staging system for ARF

- **2005**

- **2006**

- **2007**

- **2008**

- **2009**

- **2010**

- **2011**

- **2012**

- **2013**

- **KDIGO unifies definitions of AKI**
  - Kidney Disease: Improving Global Outcomes (KDIGO) recognizes the need for a single unifying definition of AKI using RIFLE and AKIN criteria as the basis

KDIGO definition and classification of AKI

Diagnostic criteria for AKI:
- Serum-creatinine increase ≥ 0.3 mg/dl within 48h OR
- Serum-creatinine increase ≥ 1.5 times baseline, which is known or presumed to have occurred within the last 7 days OR
- Urine volume < 0.5 ml/kg for 6 h

Scatter plot showing the relationship between serum-creatinine, KDIGO stage, and urine volume.
Time to reach AKI diagnosis by sCr and UO criteria in non-oliguric, and oliguric AKI with sCr and without sCr change oliguric patients

Clinical ICU outcomes by AKI diagnosis criteria

Further categorizing AKI KDIGO stage 1

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<th>Modification of KDIGO criteria (KDIGO-4)</th>
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<tr>
<td>No AKI</td>
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<td>No AKI criteria were met</td>
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<tr>
<td>Stage 1a (new)</td>
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<tr>
<td>≥0.3 absolute SCr increase over 48-hour window of observation</td>
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<td>Stage 1b (new)</td>
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<td>≥50% relative SCr increase over a 7-day window of observation</td>
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<td>Stage 2</td>
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<tr>
<td>≥100% relative SCr increase over a 7-day window of observation</td>
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<td>Stage 3</td>
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<tr>
<td>≥200% relative SCr increase over a 7-day window of observation</td>
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Impact of new categorization on hospital days and odds ratio of in-hospital mortality

Limitations of SCr-based AKI definition

**Structural Kidney Injury**

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<th>No Damage</th>
<th>Damage</th>
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<tr>
<td>No</td>
<td>No kidney injury</td>
<td>“Subclinical AKI”</td>
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<tr>
<td>Yes</td>
<td>“Hemodynamic AKI”</td>
<td>Clinical AKI</td>
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**Renal Reserve**
- SCr Kinetics
- Decreased Production

**Lack on information on AKI Phenotypes**
- Etiology
- Molecular Pathways
- Therapy
- Prognosis

**Pre-renal Azotemia**
- Hepatorenal Syndrome
- Cardiorenal Syndrome
- RAAS Inhibition

Moledina, Parikh, Semin Nephrol 38:3-11, 2017
Idealized GFR vs SCr showing renal reserve in a patient with normal kidney function

For SCr to rise 67% of total functions must be lost

Baseline GFR = Fasting GFR
Total GFR = Baseline + Renal Reserve

Detection Zones
Sensitive Transition Insensitive

Detection

Baseline
Total

Renal Reserve

Preoperative Renal Functional Reserve Predicts Risk of AKI Post Cardiac Surgery


Patients with preoperative RFR \( \leq 15 \text{ml/min/1.73m}^2 \) were 11.8 times more likely to develop AKI.
Potential SCr trajectories and AKI misclassification

What the AKI KDIGO guideline has accomplished

- AKI is Common Harmful
- Increased awareness
- Standardized AKI definition
- Educational tool
- Diagnostic and therapeutic care bundles
- E-alerts
- New Biomarkers

A selection of remaining uncertainties in AKI

- Should management be individualized on a better phenotyping of AKI by etiology, severity of injury, and ability to recover?
- Can we predict/detect AKI early enough to modify outcome?
- Should biomarkers be incorporated in the diagnosis and result in earlier intervention and improvement of prognosis?
- What determines the long-term outcome of AKI?
- How can recovery be defined and can it be optimized?
- How do we optimize RRT and what parameters can be used for correct timing for initiation and stopping RRT?
- Does RRT modality affect long-term outcome?
# KDIGO Controversies Conference on Acute Kidney Injury

**Conference Co-Chairs**
John Kellum (US)  
Marlies Ostermann (UK)

## Nomenclature & Diagnostic Criteria

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## Renal Replacement Therapy

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First they ignore, then they laugh, then they resist until they accept, and finally they use it

Mahatma Gandhi
1869-1948