Acute Kidney Injury
Bench to Bedside

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During the bombing of London in World War II, Bywaters described cases of acute loss of kidney function in severely injured crush victims. Histological evidence for patchy necrosis of renal tubules at autopsy, suggested him to use the term Acute Tubular Necrosis (ATN) to describe this clinical entity.
AKI: historical notices

ARF mortality approached 100% in World War II (no treatment available). Acute hemodialysis was first used clinically during the Korean War in 1950 to treat military casualties, decreasing ARF mortality to about 50%.
Courtesy of Coll. Dr: Paul Teschan
Fluid resuscitation on the battlefield with the rapid evacuation of the casualties to hospitals by helicopter was optimized further during the Vietnam War. For seriously injured casualties the incidence of ischemic ARF was one in 200 in the Korean War and one in 600 in the Vietnam War. This historical sequence of events suggested that early intervention could prevent the occurrence of ARF, at least in military casualties.
In the last half century, much has been learned about the pathogenesis of ischemic and nephrotoxic ARF in experimental models, but there has been very little improvement in mortality. This may be explained by changing demographics: age and comorbidity of patients with ARF continue to rise, possibly obscuring any increased survival related to improved critical care.

Vicenza Database 1974 – 1979
Total number of incident cases = 48

- Ward 85%
- ICU 15%

Mortality 54 %

Vicenza Database 1995 – 2000
Total number of incident cases = 525

- Ward 8%
- ICU 92%

Mortality 53 %
ARF/AKI and Critical Care Nephrology

From speciality-oriented to patient-oriented

Severity of illness

专项

重症

特殊

临床

互动

高

中

低

从专病到患者导向
AKI Incidence

<table>
<thead>
<tr>
<th>ICU Patients</th>
<th>Hospital Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.2%</td>
<td>57.3%</td>
</tr>
<tr>
<td>11.6%</td>
<td>6.4%</td>
</tr>
<tr>
<td>8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>5.3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>18.2%</td>
<td>12%</td>
</tr>
<tr>
<td>2.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Salahudeen et al (2013)</td>
<td>Cancer</td>
</tr>
<tr>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Murungan et al (2010)</td>
<td>Non severe Pneumonia</td>
</tr>
<tr>
<td>16%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Community-based incidence rates of AKI

**AKI non requiring dialysisis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number per 100,000 per years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996–1997</td>
<td>322.7</td>
</tr>
<tr>
<td>1998–1999</td>
<td>388.3</td>
</tr>
<tr>
<td>2000–2001</td>
<td>453.6</td>
</tr>
<tr>
<td>2002–2003</td>
<td>522.4</td>
</tr>
</tbody>
</table>

**AKI requiring dialysisis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number per 100,000 per years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996–1997</td>
<td>19.5</td>
</tr>
<tr>
<td>2000–2001</td>
<td>26.7</td>
</tr>
<tr>
<td>2002–2003</td>
<td>29.5</td>
</tr>
</tbody>
</table>

- The number of cases of AKI is progressively increasing
- The demand for renal replacement therapy is increasing
- The cost for patients requiring RRT is higher than average
Increasing incidence of AKI

PATIENT → comorbidities → AKI

PATIENT → iatrogenicity → AKI

PATIENT → aging kidney → AKI
Incidence: AKI in Sepsis

Rangel-Frausto et al JAMA 1995
AKI severity correlates with hospital mortality.
Outcome in patients with conservative treatment and RRT.

Elseviers et al. Critical Care 2010
Epidemiology: AKI

• Incidence: 5-7% hospitalised patients

• Incidence: 5-25% ICU patients

• Incidence varies greatly according to
  – specific population studied
  – definition used

The growth of acute kidney injury: a rising tide or just closer attention to detail?

Edward D. Siew¹ and Andrew Davenport²
Incidence of AKI (Definition/Reporting Issues)

- ≥0.3 mg/dL: 31%
- ≥0.5 mg/dL: 13%
- ≥0.5 mg/dL or ≥1.0 mg/dL*: 13%
- ≥1.0 mg/dL: 4%
- ≥2.0 mg/dL: 1%
- 25% AND creatinine≥2.0 mg/dL: 44%
- 50%: 21%
- 100%: 8%
- 50% AND creatinine≥2.0 mg/dL: 4%
Over 30 definitions of AKI/ ARF exist 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 >= 177µmol/L Δ>62µmol/L
9. Creat > 200µmol/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 >0µmol/L
17. ΔCr72h >25µmol/L
18. ΔCr72h >44µmol/L
19. ΔCr72h >50µmol/L
20. ΔCr72h >100µmol/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. U α1-microglob
30. U β2- microglobulin
31. U N-acetyl- β-D-glucosaminidase
32. U glutation transferase-π
33. U glutation transferase- α
34. NGAL
35. RRT
36.…. 
Mr John Doo in the ward has ARF…

He needs RRT…

↑25% in Crea…
Definitions of AKI and mortality

\[ R^2 = 0.3962 \]
\[ p = 0.007 \]

Kellum et al. Current Opin in Crit Care 2002
Application of AKI Definitions

Consensus Needed
RIFLE Criteria for Acute Kidney Injury

**Cr/ GFR Criteria**

- Increased creatinine x1.5 or GFR decrease > 25%
- Increased creatinine x2 or GFR decrease > 50%
- Increase creatinine x3 or GFR dec >75% or creatinine ≥4mg/dl (Acute rise of ≥0.5 mg/dl)

**Urine Output Criteria**

- UO < .5ml/kg/h x 6 hr
- UO < .5ml/kg/h x 12 hr
- UO < .3ml/kg/h x 24 hr or Anuria x 12 hrs

**Risk**

- Describes high sensitivity

**Injury**

- Describes high specificity

**Failure**

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

**Loss**

- End Stage Renal Disease

**ESRD**

- Describe outcome of AKI
The RIFLE criteria and mortality in acute kidney injury: A systematic review

Z Ricci\(^1\), D Cruz\(^2,3\) and C Ronco\(^2,3\)

\(^1\)Department of Pediatric Cardiosurgery, Bambino Gesù Hospital, Rome, Italy; \(^2\)Department of Nephrology, Dialysis and Transplantation, S Bortolo Hospital, Vicenza, Italy and \(^3\)International Renal Research Institute Vicenza (IRRIV), Vicenza, Italy

Increase in All-Cause Mortality with worse RIFLE Class

<table>
<thead>
<tr>
<th>Risk</th>
<th>Failure vs NonAKI</th>
<th>Injury vs NonAKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs NonAKI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N= 1.500,000 patients

Relative Risk

\[1\] 2.4 4.15 6.37 10

Mortality
H-LOS
ICU-LOS
Costs
R. Recovery
AKIN

- 

- Increased creatinine x1.5 OR > 0.3mg/dl

- Increased creatinine x2

- Increase creatinine x3 or creatinine ≥4mg/dl (Acute rise of ≥0.5 mg/dl)

- UO < .5ml/kg/h x 6 hr

- UO < .5ml/kg/h x 12 hr

- UO < .3ml/kg/h x 24 hr or Anuria x 12 hrs

- RRT Started

- GFR criteria removed

- RRT = Stage 3

- AKI diagnosis based on 2 creatinine levels within 48 hr period
Creatinine-based Definitions

Baseline Creatinine

1. MDRD-back estimation
2. Admission SCr
3. Nadir
4. Pre-admission SCr

Malnourishment & Muscle Wasting

Fluid Overload

TRUE SCr
Acute Dialysis Quality Initiative
Consensus Conference on Acute Kidney Injury Biomarkers
Clinical Phases Of AKI And Organ Function
Clinical Phases Of AKI And Organ Function

- Ischemia
- GFR (%)
- Days
- Initiation
- BBM loss
- Exfoliation
- Tubular Obstruction

Basile et al. Compr Physiol 2012
Clinical Phases Of AKI And Organ Function

- **Ischemia**
  - Cell Injury → Tubular Obstruction
  - BBM loss
  - Exfoliation

- **Initiation**
  - CMJ Hypoxia
  - Microvascular injury with obstruction, coagulopathy & inflammation

- **Extension**

- **GFR (%)**
- **Days**

Basile et al. *Compr Physiol* 2012
Clinical Phases Of AKI And Organ Function

Basile et al. Compr Physiol 2012
Clinical Phases Of AKI And Organ Function

Basile et al. Compr Physiol 2012
Clinical Phases Of AKI And Organ Function

Basile et al. Compr Physiol 2012
Generation of biomarkers in AKI

1. Increased synthesis in extrarenal tissues
2. Release from circulating immune cells
3. Glomerular filtration
4. Impaired reabsorption in the proximal tubule
5. Increased synthesis in tubular cells
6. Release from infiltrating immune cells

Increased biomarker levels in urine
Increased biomarker levels in plasma
Structural VS Functional Biomarkers

Biomarkers

Normal epithelium → Ischemia/reperfusion → Toxicity → Damage → Cell death

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

GFR ↓

Delayed biomarkers for kidney injury:
- ↑ Serum creatinine
- ↑ Blood urea nitrogen
Clinical Continuum of AKI

Devarajan, Biomarkers Med 4:265-80, 2010
Established AKI

Early AKI

Severity of AKI

830 citations identified

715 excluded because not a study of AKI and biomarkers

115 articles

87 excluded because did not meet inclusion criteria

31 articles of biomarkers for AKI included

Differential diagnosis in established AKI (n=14)

Early detection (n=14)

Prognosis (n=9)

Serum (studies)

Urine (studies)

Serum (studies)

Urine (studies)

Serum (studies)

Urine (studies)

Cystatin C
Carb Hb
NGAL

NGAL
IL-18
GST
NAG
α-1 microglobulin
KIM-1
NHE3
MMP-9

Cystatin C
Pro-ANP
NGAL
Neutrophil-CD11b

NGAL
IL-18
KIM-1
GST
γ-GT
π-GST
α-GST
AP
NAG
LDH
MMP-9

RRT
Cystatin C
NGAL

RRT
NGAL
Cystatin C
α-1 microglobulin
RBP
β-2 microglobulin
NAG
α-GST
GGT
LDH
KIM-1

Death
IL-6
IL-8
IL-10

Death
NGAL
IL-18
NAG
KIM-1

RRT = renal replacement therapy

Numbers of studies of biomarkers do not add up to 31 because some studies tested multiple biomarkers

Coca SG et al, Kidney Int, 2007
Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra*, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Morí, Jonathan Barasch, Prasad Devarajan

71 children undergoing cardiopulmonary bypass surgery
Urinary KIM-1 concentration is significantly higher in patients with ischemic ATN compared to other forms of AKI or CKD. KIM-1 is expressed in ischemic tubuli.
KIM-1 co-localizes with markers for dedifferentiation and proliferation

Secreted ectodomain in lumen - Biomarker
Protective protein – Role in Regeneration?
Changes in AKI biomarker concentration over time after renal injury

Initiation

Extension

Maintenance and Repair

Biomarker Concentration (% of maximum)

Time After Renal Injury (hours post-op)

0.0
20.0
40.0
60.0
80.0
100.0

Pre-op 0-6 6-12 12-18 24 48 72 96

uNGAL
pNGAL
uIL-18
uKIM-1
uL-FABP

Alge JL, Arthur JM. CJASN. 2015 Jan 7;10(1)
Cell Cycle Arrest Biomarkers
(Sapphyre Study)

[TIMP-2]-[IGFBP7]
Urine TIMP-2
Urine IGFBP7
Urine NGAL
Plasma Cystatin C
Urine KIM-1
Plasma NGAL
Urine IL-18
Urine pi-GST
Urine L-FABP

AUC (with 95% CI)
AKI outcomes

NGAL (-) Crea (-) n=1,296
NGAL (+) Crea (-) n=445
NGAL (-) Crea (+) n=107
NGAL (+) Crea (+) n=474

Dialysis Mortality combined

Incidence [%]

Haase, Ronco, Kellum: nneph 2012, in press
No functional change | Damage
---|---
No AKI | Subclinical AKI
Functional AKI | Established AKI

Progression | Resolution
**New ADQI diagnostic criteria for AKI**

<table>
<thead>
<tr>
<th>FUNCTIONAL CRITERIA</th>
<th>DAMAGE CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGE 1</strong></td>
<td>+</td>
</tr>
<tr>
<td>Increased serum creatinine ≥ 0.3 mg/dl or 150% ≤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>++</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>Biomarkers positive</td>
</tr>
<tr>
<td><strong>STAGE 3</strong></td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum creatinine by 300% (or ≥ 4.0 mg/dl with an acute increase of ≥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>
</tbody>
</table>

**FUNCTIONAL CRITERIA**

- Increased serum creatinine
- ≥ 0.3 mg/dl or 150% ≤ 48 hours
- Urine output < 0.5 ml/kg/h for > 6 hours
- Mildly decreased GFR

**STAGE 1**

- Increased serum creatinine by 200% or urine output < 0.5 ml/kg/h for > 12 hours
- Moderately decreased GFR

**STAGE 2**

- Increased serum creatinine by 300% (or ≥ 4.0 mg/dl with an acute increase of ≥0.5 mg/dl) or urine output < 0.3 ml/kg/h for > 24 hours or anuria for > 12 hours or acute RRT, or severely decreased GFR

**STAGE 3**

- Biomarkers positive

**DAMAGE CRITERIA**

- +
- ++
- +++

**Biomarkers positive**
NGAL Score in CSa-AKI

Cardiac surgery associated (CSA) acute kidney tubular damage - \( \text{NGAL}_{\text{CSA}} \) Score

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Delta (( \Delta )) NGAL at following measurement</th>
<th>( \text{NGAL}_{\text{CSA}} ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{uNGAL} ) 50 - &lt;150</td>
<td>&gt;100 + second value ( \geq 125 )</td>
<td>2 Tubular damage</td>
</tr>
<tr>
<td>( \text{pNGAL} ) 100 - &lt;200</td>
<td>&gt;100 + second value ( \geq 150 )</td>
<td>2 Tubular damage</td>
</tr>
<tr>
<td>( \text{uNGAL} ) &lt;50</td>
<td>0</td>
<td>Tubular damage unlikely</td>
</tr>
<tr>
<td>( \text{pNGAL} ) &lt;100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{uNGAL} ) 150 - &lt;1000 or</td>
<td></td>
<td>3 Severe tubular damage</td>
</tr>
<tr>
<td>( \text{pNGAL} ) 200 - &lt;1000 or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{uNGAL} &gt;1000 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{pNGAL} &gt;1000 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nephrocheck Quantum Thresholds
**Biomarker Domain**

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

**Creatinine/Urine Output Domain**

- Serum Creatinine increase in mg/dl or from baseline (B)
  - Delta Biomarker Domain:
    - 0
    - < 0.3
    - > 0.3
    - B x 1.5
    - > 0.3
    - B x 2.0
    - > 4.0
    - B x 3.0 or Dialysis

---

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

---

**Delta Biomarker Domain**

- 0
- < 0.3
- > 0.3
- B x 1.5
- > 4.0
- B x 3.0 or Dialysis
Diagnosis and Biomarkers

• Acute Kidney Injury is a severe condition that may significantly worsen patients clinical outcomes.

• Its incidence depends on definition and diagnostic criteria utilized

• Kidney damage and kidney dysfunction may coexist or represent two separate entities in the clinical syndrome

• New Biomarkers may contribute to discriminate between acute injury and acute dysfunction and to uncover conditions of subclinical AKI

• Because…………………………
Subclinical AKI is still AKI

Claudio Ronco†, John A Kellum2 and Michael Haase3

Abstract
The concept of acute kidney syndromes has shifted in recent years from acute renal failure to acute kidney injury (AKI). AKI implies injury or damage but not necessarily dysfunction. The human kidney has an important glomerular function reserve, and dysfunction becomes evident only when more than 50% of the renal mass is compromised. Recent AKI classifications include even slight changes in serum creatinine, acknowledging that this condition is associated with worse outcomes. This, however, still represents a functional criterion for AKI and implies a glomerular filtration rate alteration that may be a late phenomenon in the time course of the syndrome. An early diagnosis of AKI by using tubular damage biomarkers preceding filtration function loss is

Many terms have been used to describe acute events occurring to or involving the kidneys, such as acute renal failure, acute kidney diseases, acute kidney syndromes, or acute kidney injury (AKI). Indeed, the spectrum of such disorders has been expanding over the last decades. The diagnosis and management of acute syndromes involving the kidneys has become a multidisciplinary field concerning not only nephrology and urology but also critical care medicine, cardiology, radiology, and other fields. With this evolution, the term acute renal failure, used for many years in clinical practice, has been replaced with the term AKI. The new term implies potentially reversible kidney injury or damage occurring in a time frame of hours or days and characterizing the disorder as ‘acute’. Although the term ‘injury’ would not necessarily encompass kidney dysfunction without damage, the diagnosis of AKI syndrome is still made on
Risk Factors

- Anemia
- 
- Na + H₂O retention
- Uremic solute retention
- Ca and Phos abnormalities
- Hypertension
- Genetic risk factors
  - Acquired risk factors
  - Low cardiac output (CO)
- Chronic hypoperfusion
- Increased renal vascular resistance
- Increased venous pressure
- Embolism
- Anemia, hypoxia
- RAA and sympathetic activation
- Na + H₂O retention
- Ca and Phos abnormalities
- Hypertension, LVH

Kidney Attack

- Increased susceptibility to insults
- Chronic hypoperfusion
- Apoptosis
- Insult and initiation of kidney damage
- Sclerosis - Fibrosis
- Progression of CKD
- Partial Recovery
- Complete Recovery

- Loss of polarity and brush border
- Apoptosis
- Necrosis
- Spreading and dedifferentiation of viable cells
- Sloughing of viable and dead cells, with tubular obstruction
- Phospholipases
- Necrosis
- Integrin
- Na/K - ATPase
- Tubular lumen
- Normal epithelium with brush border
- Calcium
- Reactive oxygen species
- Purine depletion
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
Progression to CKD

ISSUES

• Definition and characterizations of progression
• Pathophysiological mechanisms of progression
• Biochemical pathways (target for therapies)
• Risk identification and prediction of progression
• Treatment strategies to prevent/limit progression
DEFINITION AND FEATURES

• Repair and Adaptive Repair = Normalization of structure and function within few days up to 90 days

• Maladaptive Repair
  - Loss of renal reserve
  - Abnormal tubular repair
  - Impaired vascular repair
  - Alteration in the interstitial architecture (type and activity of cells).
  - Immunological
  - Biomarker studies*

• Progression = Opposite to Recovery, leads to persistent abnormalities in structure or function, detected by biomarkers, imaging, histopathological patterns.
Recovery

Tubular epithelial cell
Endothelial cell
Pericyte
Resident macrophage
Capillary

Repair

Tubular cell proliferation
Pericytes remain in situ

AKI

Injured, adhesive endothelium
Apoptotic tubular cell
Necrotic tubular cell
Reduced vascular NO release
M1 macrophage recruitment
Neutrophil recruitment

Recovery

Full tubular repair
Intact vasculature

Progressive Scarring

Resolution of inflammatory infiltrate
Myofibroblast
Chronic inflammation
Collagen deposition
Secretion of profibrotic factors by G2/M cells
Tubular loss
**Figure 1:** Schematic representation of the different hypotheses proposed to explain tubular regeneration after AKI. (A) After a tubular injury, differentiated tubular cells that survived dedifferentiate and become able to proliferate, migrate and then differentiate, replacing the lost tubular cells. (B) In healthy kidneys, tubular progenitors are scattered among differentiated tubular cells. Tubular progenitors are resistant to death, so they preferentially survive following injury and proliferate, migrate and then differentiate to replace lost tubular cells.

*Romagnani et al, NDT 2015*
Why does AKI progress to CKD?

Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD

Adapted by Ferenbach et al. Nat Rev Nephrol 2015
Cells that are arrested in the G2 phase of cell cycle express profibrotic molecules and promote apoptosis.
Endothelial/Mesenchymal Transition

Stasi A. & Castellano G., Review in preparation

But: Different types of EMT? Beneficial or detrimental?
Complement inhibition prevented fibrosis and EndMT in renal I/R injury

Castellano G., Curci C. Nephrol Dial Transplant. 2014
**Inhibition of EndMT by CPFA treatment**

**Vascular level**

**T9 LPS**

**T9 LPS CPFA**

**Glomerular/interstitial level**

**CD31⁺/α-SMA⁺ cells/HPF**

- **T9 LPS**
- **T9 LPS CPFA**

**p=0.0002**
Treatment of AKI after injury

New therapeutic approaches include:

1) Promotion of renal repair
2) Blockage of maladaptive repair
3) Limitation of profibrotic evolution
4) Reduction of epithelial to mesenchymal transition
When Kidney Attack occurs, the reduction of GFR is compensated by recruitment of nephrons and utilization of renal functional reserve so that creatinine does not increase. If renal functional reserve is lost kidney attack produces an increase in serum creatinine and full repair and return to previous condition is not guaranteed. Repeated Kidney Attacks (heart failure decompensation, ischemia/reperfusion, contrast media, toxic drugs etc) may contribute to the progression to chronic kidney disease.
What end-points for clinical trials? MAKE? A new perspective?
CONCLUSIONS

AKI is an important entity that links the kidney to current epidemiology and population phenotypes.

Pre-existing or concomitant pathological conditions represent important risk factors for developing AKI.

The intensity of the insult and the susceptibility of the kidney play a pivotal role in the development of the syndrome and its characteristics of severity.
CONCLUSIONS

- Recognize patient subsets and risk factors
- Use biomarkers for risk prediction and AKI detection
- Understand precipitating factors
  - Medications
  - Procedures
- Explore new avenues for AKI prevention and organ protection based on pathophysiological mechanisms.
- Optimize extracorporeal therapies and use them to support also other organ besides the kidney
Vicenza Course on AKI & CRRT
June 7-10, 2016
Fiera di Vicenza Convention Center
Vicenza, Italy
www.irriv.com