ACUTE KIDNEY INJURY

Stuart Linas
U. Colorado SOM
Marked increases in incidence of dialysis-requiring AKI in last decade
Question 1

Of patients who recover from an episode of AKI, what percentage have CKD Stage 3-5 at 10 years?

A) 2%
B) 5%
C) 10%
D) 20%
AKI: Change in Outcomes over last 60 years
Outline of Presentation

- Classification
- Diagnosis of AKI
- Epidemiology of ATN
- Prevention and Treatment of ATN
- Specific Conditions
  - Cardiorenal syndrome
  - Contrast-induced nephropathy
## Classification of AKI: KDIGO

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screat increase (mg/dl)</th>
<th>Urine Output ml/kg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>1.5-1.9x base &gt;0.3 mg/dl base</td>
<td>&lt;.5 6-12 hrs</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2-2.9 x base</td>
<td>&lt;.5 &gt;12hrs</td>
</tr>
<tr>
<td>Stage 3</td>
<td>3x base &gt;4mg/dl</td>
<td>&lt;.3 &gt;24 hrs or anuria &gt;12hrs</td>
</tr>
</tbody>
</table>
Value of KIDIGO: Short term survival in AKI
AKI: Etiology—U Colorado vs. Literature

- **Prerenal**: Literature - 20, U of Colorado - 10
- **Postrenal**: Literature - 15, U of Colorado - 15
- **Renal: ATN**: Literature - 50, U of Colorado - 50
- **AIN**: Literature - 5, U of Colorado - 5
- **AGN**: Literature - 5, U of Colorado - 5
- **Other: HRS/CRS**: Literature - 10, U of Colorado - 10
AKI: Diagnosis
## AKI: Urinalysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abnormality</th>
<th>NPV(%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGN</td>
<td>Casts</td>
<td>80</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Abnl RBC</td>
<td></td>
<td>&gt;95</td>
<td>90</td>
</tr>
<tr>
<td>AIN</td>
<td>WBC</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>Eosin</td>
<td></td>
<td>&lt;10</td>
<td>&gt;95</td>
</tr>
<tr>
<td>ATN</td>
<td>RTEC</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>Muddy Casts</td>
<td></td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>
# AKI: FE Sodium and Urea

<table>
<thead>
<tr>
<th></th>
<th>No Diuretics</th>
<th>Diuretics</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Fx Ex Urea</td>
<td>Fx Ex Sodium</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>43</td>
<td>64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Urea</th>
<th>Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV (%)</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>33</td>
<td>49</td>
</tr>
</tbody>
</table>

AJKD50 566 2007
Summary

- Urinalysis and urine chemistries aren’t perfect markers for establishing the diagnosis of AKI or the specific causes of AKI
Why can’t Nephrology find a ‘troponin’ for the kidney?
Kidney Biomarkers

Proximal tubules:
- Kim-1
- Clusterin
- NGAL
- GST-\(\alpha\)
- \(\beta_2\)-microglobulin
- \(\alpha_1\)-microglobulin
- NAG
- Osteopontin
- Cystatin C (urinary)
- Netrin-1
- RBP
- IL-18
- HGF
- Cyr61
- NHE-3
- Exosomal fetuin-A
- L-FABP
- Albumin

Distal tubules:
- Osteopontin
- Clusterin
- GST-\(\mu/\pi\)
- NGAL
- H-FABP
- Calbindin D28

Collecting duct:
- Calbindin D28

Loop of Henle:
- Osteopontin
- NHE-3

Glomerulus:
- Total protein
- Cystatin C (urinary)
- \(\beta_2\)-microglobulin
- \(\alpha_1\)-microglobulin
- Albumin

Thomas L. Nicholas, M.D., M.S; Matthew J. O’Rourke, B.S; Jen Yang, M.D, PhD; Meghan E. Sise, B.S; Pietro A. Canetta, M.D; Nicholas Barouch, B.S; Charles Buchen; Fattah Khan, M.D; Kiyoshi Mori, M.D, PhD; James Giglio, M.D; Prasad Devanjan, M.D; and Jonathan Barouch, M.D, PhD

Annals 148 810 2008
Background and Methods

- 685 patients with normal renal function or AKI, CKD or prerenal azotemia at one hospital
- Urinary NGAL
Box plot of NGAL and serum creatinine

NGAL

Creatinine
Conclusions

- A single measurement of urinary NGAL helps to distinguish AKI from prerenal azotemia and CKD
But.....not all studies have been positive
Biomarkers are often positive in prerenal AKI

% of patients with 0-5 biomarkers in upper quartile
Conclusions

- Biomarkers aren’t ready for prime time
- But......early diagnosis of AKI is very important because of subsequent management issues
  - Especially fluids
Epidemiology

1) CKD (low GFR or Albuminuria) is associated with AKI

2) AKI is associated with subsequent CKD
CKD (LOW GFR OR ALBUMINURIA) IS ASSOCIATED WITH AKI
Methods

- Prospective cohort from Atherosclerosis Rick in Communities (ARIC)
- 11,200 patients
- Baseline creatinine and alb/creat ratio
Baseline albuminuria is associated with AKI (Ref 10mg/g creatinine)
eGFR less than 75 ml/min strongly associated with AKI
AKI is a strong predictor of subsequent death, CKD and ESRD
Methods

- Meta analysis of 13 cohorts
- Close to 1.5 million patients
- Std definitions of AKI and CKD
After AKI: 10 fold increased risk of CKD
After AKI: 5 fold increase risk of ESRD
Impaired Kidney Function at Hospital Discharge and Long-Term Renal and Overall Survival in Patients Who Received CRRT

Susanne Stads,*† Gijs Fortrie,* Jasper van Bommel,† Robert Zietse,* and Michiel G.H. Betjes*
Objectives

- To determine the relationship between renal function at hospital discharge and long term mortality and ESRD risks in patients undergoing CRRT
Methods

- Retrospective cohort study in 1220 patients undergoing CRRT
- 475 survivors
  - 64% eGFR under 60 ml/min
Striking decreases in long term survival in patients with eGFR < 30 ml/min
Even worse prognosis for Renal survival with eGFR < 30ml/min
Conclusions

- Most critically ill patients who survive CRRT-requiring AKI have decreased renal function at hospital discharge.
- eGFR under 30 ml/min is a strong risk factor for decreased long term survival as well as poor renal survival.
Take Home Messages:

- CKD (eGFR decreases or proteinuria) is a strong predictor of risk for AKI
- AKI is associated with late mortality, CKD and ESRD
  - Non dialysis patients at risk
  - Dialysis-requiring patients at greater risk
Therapies: Prevention

Fluid management

Remote Ischemic Preconditioning
Prevention: Fluid Management
Question 2

- 66 yr old man with ‘lowish’ BP from suspected BPH and pyelonephritis.
- What is the best fluid resuscitation strategy?
  A) NaCl until SBP reaches goal
  B) NaCl until patient can’t tolerate (e.g. falling O2 Sat)
  C) Low volume NaCl independent of BP
  D) Albumin
  E) Hydroxyethyl Starch
AKI in Acute Lung Injury (ALI)

- The Fluid and Catheter Treatment Trial (FACTT) concluded that fluid restrictive therapy was beneficial in ALI.
- What about in the subset of patients with AKI?
Fluid overload is associated with excess mortality in dialyzed as well as nondialyzed patients with AKI.

**AKI:** Dialysis No Dialysis
If a positive fluid balance is bad, would a negative fluid balance be protective?
Perhaps!

- Randomized Evaluation of Normal and Augmented replacement therapy trial (RENAL)
- Observational trial in Australia and New Zealand of ICU patients requiring RRT
Negative fluid balance associated with increased survival
Which fluid is best: Saline, Starch or Albumin?
ASSOCIATION BETWEEN A CHLORIDE-LIBERAL VS CHLORIDE-RESTRICTIVE INTRAVENOUS FLUID ADMINISTRATION STRATEGY AND KIDNEY INJURY IN CRITICALLY ILL ADULTS

YUNOS ET AL

JAMA 308 1566 2012
Background

- Administration of solutions high in chloride are associated with renal vasoconstriction in animal models and may precipitate AKI clinically.
Hypothesis

- Chloride-restricted IV fluid therapy will prevent AKI in the medical ICU
Methods

- 1533 patients admitted to the ICU with the usual mix of conditions
- 2 sequential periods of study: Usual therapy (high chloride) followed by “education” and a low chloride arm
- Resuscitation with
  - Phase 1: NaCl high [0.95 NaCl, Gelatin (?), or 4% Albumin]
  - Phase 2: Low Cl (lactate or acetate Ringers or 20% Albumin)
Development of Stage 2 or 3 AKI
RRT in the ICU

![Survival curve for RRT in the ICU with data for 2008 and 2009 showing a statistically significant difference with a Log-rank P = .004.](image-url)
Conclusions

- Use of Chloride restricted therapies in the ICU resulted in a decrease in incidence of AKI and need for RRT
BUT

- Perhaps results are independent of Chloride:
  - More than twice as much lactate Ringers (1840 cc) administered compared to Na Cl (720 cc)
  - 20% Albumin ‘stays’ in the vascular space
  - Could fact that docs were ‘educated’ meant they did a better job of caring for patients independent of volume?

- Not randomized or controlled
Hydroxyethyl Starch

- NEJM
  - Sepsis
  - ICU

- JAMA Review
Conclusions: NEJM Papers

- In ICU patients treated with HES:
  - No differences in 90 day mortality
  - 20% increase in RRT
Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation
A Systematic Review and Meta-analysis

Ryan Zarychanski, MD, MSc
Ahmed M. Abou-Setta, MD, PhD
Alexis F. Turgeon, MD, MSc
Brett L. Houston, BSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Fergusson, PhD, MHA

JAMA 309 678 2013
Methods

- Systematic review and meta-analysis of the use of HES in critically ill patients
- 38 trials
- Over 10,000 patients
HES

- Associated with a 1.27-fold increase in RR of AKI
- Associated with 7% increase in mortality when biased studies excluded
Conclusions

- HES is associated with increases in mortality and in AKI in critically ill patients requiring volume resuscitation.
What about Albumin?
4% Albumin no better than NaCl for resuscitation in the ICU (Saline Vs Albumin Fluid Evaluation)
Bottom Line for Fluid Management:

- Less is best
- Saline still preferred (NEJM paper flawed badly)
Question 3

- A 57 yr old man with CKD is to undergo an elective coronary angiogram and potentially a PCI.
- In addition to NaCl, what HAS BEEN SHOWN to prevent AKI?
  A) Furosemide
  B) NaHCO₃
  C) NAC
  D) Ischemic preconditioning
Prevention: Remote Ischemic Preconditioning

- A potential game changer!!!!
Ischemic Preconditioning for Prevention of Contrast Medium–Induced Nephropathy: Randomized Pilot RenPro Trial (Renal Protection Trial)
Fikret Er, Amir M. Nia, Henning Dopp, Martin Hellmich, Kristina M. Dahlem, Evren Caglayan, Torsten Kubacki, Thomas Benzing, Erland Erdmann, Volker Burst and Natig Gassanov
Background

- In animal models, ischemic preconditioning protects from AKI
- Contrast-induced nephropathy is the most logical condition to test the role of remote ischemic preconditioning in patients

Circulation 126 296 2012
Methods

- 100 patients with eGFR<60 ml/min undergoing elective coronary angiography
  - Standard therapy
  - Preconditioning
    - 5 min of inflation of BP cuff x 4 cycles at least 45 min before angiography
- Primary EP: increase in creatinine by >0.5 mg/dl or 25% at 48 hrs
Incidence of AKI
Conclusions

- Remote ischemic preconditioning was markedly protective in patients with high risk for contrast nephropathy
Renoprotective Effect of Remote Ischemic Post-Conditioning by Intermittent Balloon Inflations in Patients Undergoing Percutaneous Coronary Intervention

Spyridon Deftereos, MD,* Georgios Giannopoulos, MD,*† Vasileios Tzalamouras, MD,* Konstantinos Raisakis, MD,* Charalambos Kossyvakis, MD,* Andreas Kaoukis, MD,* Vasiliki Panagopoulou, MD,* Sofia Karageorgiou,* Dimitrios Avramidis, MD,* Konstantinos Toutouzas, MD,‡ George Hahalis, MD,§ Vlassios Pyrgakis, MD,* Antonis S. Manolis, MD,|| Dimitrios Alexopoulos, MD,§ Christodoulos Stefanadis, MD,‡ Michael W. Cleman, MD†
Methods

- Patients undergoing PCI
  - RIPC: cycles of inflation/deflation (30 sec each × 4) of stent balloon during PCI (N=111)
  - Sham procedure (N=109)

- Primary Endpoint: AKI at 96 hrs after PCI
  - 0.5 mg/dl increase in creatinine or
  - 25% increase in creatinine
50% reduction in AKI with RIPC
More Results

- 30 day rate of death or rehospitalization:
  - Control 22%
  - RIPC 12%
Conclusions

- RIMC during PCI is a simple and effective procedure to prevent AKI
Practical Implications Of Preconditioning

- Why not perform in setting where AKI known risk?
  - Contrast
  - PCI
  - AAA Repair
  - Other
Therapy: What is the best type of renal replacement therapy: Intermittent Hemodialysis (IHD) or Continuous Venovenous hemofiltration (CVVH)?
Options: Ultrafiltration (pressure-dependent convection) vs. Dialysis (concentration-dependent diffusion)

<table>
<thead>
<tr>
<th>Method</th>
<th>BF (ml/min)</th>
<th>UF (ml/hr)</th>
<th>Dialysate Fluid</th>
<th>Replacement Fluid (ml/hr)</th>
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<tr>
<td>SCUF</td>
<td>100</td>
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<tr>
<td>SLED</td>
<td>100</td>
<td>0</td>
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<td>IHD</td>
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<td>0-1000</td>
<td>Yes</td>
<td>0-1000</td>
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Renal Replacement Therapy in Patients With Acute Renal Failure: A Systematic Review

Neesh Pannu; Scott Klarenbach; Natasha Wiebe; et al.
Background and Methods

- Review of randomized controlled trials (n=30) and prospective cohort studies (n=8) of dialytic therapy in AKI
Conclusions

- Intermittent and continuous therapy lead to the same outcomes
What is the correct ‘amount’ of dialysis required?
INTENSITIES OF RENAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

LAMBERS HEERSPINK,* ‡ TOSHIHARU NINOMIYA,* MARTIN GALLAGHER,* RINALDO BELLOMO,‡ JOHN MYBURGH,* § SIMON FINFER,* PAUL M. PALEVSKY,¶** JOHN A. KELLUM,** VLADO PERKOVIC,* AND ALAN CASS*

CJASN 5 956 2010
Background and Objectives

- Systematic review and meta-analysis of 8 large trials
  - 3841 patients
  - 35-48 ml/kg/hr defined as more intense
Conclusions

- Higher intensity RRT does not reduce mortality or improve renal recovery in total cohort or subgroups
SPECIFIC CONDITIONS: CARDIORENOAL SYNDROME (CRS)
CRS: Classification

- **Acute CRS (Type 1, acute worsening of heart function leading to kidney injury)**
- Chronic CRS (Type 2, chronic heart disease leading to kidney injury)
- Acute reno-cardiac syndrome (Type 3, acute kidney injury leading to heart dysfunction)
- Chronic CRS (Type 4, CKD leading to cardiac dysfunction)
- Secondary CRS (Type 5, systemic diseases resulting in heart and kidney injury)
Diuretic (Furosemide) Therapies In Type 1 CRS

- DOSE Trial
- Prospective randomized, blinded trial
- Comparison of:
  - IV bolus q 12hrs
  - Continuous infusion (low dose-prior oral dose)
  - Continuous infusion (high dose-2.5x prior oral dose)

NEJM 364 801 2011
Renal function about same with continuous vs continuous therapy BUT clearly worse with high dose continuous therapy.
Composite Endpoints: No differences between bolus and continuous therapy or low vs high dose continuous therapy.
Conclusions

- In Acute CRS (Type 1) no advantages of continuous vs bolus diuretic therapy
- High dose continuous therapy is ‘bad’ for the kidney!
What about Ultrafiltration compared to diuretic therapy?
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O’Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network
Background: CARESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure)

- Acute Cardiorenal syndrome: worsening renal function in patients with acute decompensated heart failure
- Controversy regarding the role of ultrafiltration therapy compared to diuretics
Methods

- Randomized, prospective comparison of UF to aggressive diuretic therapy
- 188 patients with acute cardiorenal syndrome
  - Baseline creatinine 2 mg/dl
- Primary EP: combination of change in creatinine and weight—all results driven by change in creatinine
- UF: 200 ml/hr—4-5l/d
- Diuretics: 4-6l/d urine output
At comparable weight loss, UF associated with greater increases in serum creatinine.
Conclusions

- Diuretic therapy was safer than UF in treating patients with the Acute Cardiorenal Syndrome
- Fewer adverse events with diuretics as well
But......

- Serum creatinine is a poor endpoint marker for eGFR since it may reflect differences in convective removal as well as renal function.
- ‘Who cares’ if there is a transient increase in creatinine if returns to baseline after UF discontinued?
- What about the readmission rate as a more helpful endpoint?
CRS: Therapeutic Conclusions

- Aggressive diuretic therapies not associated with benefits and may injure the kidney
- UF therapies should be reserved for diuretic-resistant patients
Contrast-Induced Nephropathy (CIN)
In addition to AKI, Contrast Nephropathy is associated with:

- Death (in hospital, 30 days and one year)
- MI at one year
- CKD
Contrast nephropathy is not always transient or benign
Persistent Renal Damage After Contrast-Induced Acute Kidney Injury: Incidence, Evolution, Risk Factors, and Prognosis

Mauro Maioli, Anna Toso, Mario Leoncini, Michela Gallopin, Nicola Musilli and Francesco Bellandi
Methods

- Observational study
- 3986 patients at one center
  - coronary angiography
  - 1490 with eGFR<60 ml/min
- Iodixanol (Visipaque*)
- CI-AKI: increase Screat >.5 mg/dl at 3 days
- New CKD: eGFR<75 % baseline at 6 mos
Time course of creatinine:
Overall incidence AKI: 12%
Persistent CKD: 19% of 12%--2.4%
Survival Curves
Conclusions

- CI-induced AKI is not always transient
- CI-AKI is a risk for CKD progression
- CI-induced AKI identifies patients at risk for CV events
Risk Of CIN according to Baseline eGFR
Therapies for Prevention of CIN

- Forced diuresis with mannitol and furosemide------BAD (AJKD 54 602 2009)
- Sodium Bicarbonate---Neutral to BAD (Annals 151 631 2009; CJASN 3 10 2008)
Acetylcysteine

- KDIGO recommendations:
  - 4.4.3: We suggest using oral NAC, together with i.v. iso-tonic crystalloids, in patients at increased risk of AKI (2D)

BUT........after KDIGO recommendations published:
Acetylcysteine: ACT Trial

2308 patients at high risk for CIN
Acetylcysteine vs Placebo
Various Endpoints including mortality, AKI, etc
No differences in death or need for dialysis

P value = 0.92
No differences in AKI in subgroups:

- Elders
- Diabetes
- CKD
- Volume Contrast
- Type of Contrast
- Acute Coronary Syndrome
Bottom line regarding NAC

- Makes little sense not to do it if there is time
Bottom line regarding NAC

- Will probably go better in court if something goes dreadfully wrong!
AKI: Take Home Messages

- **Diagnosis**
  - Urinalysis and FE Na still the best

- **Epidemiology**
  - Recovery from AKI associated with subsequent CKD, ESRD and Mortality

- **Treatment**
  - NaCl but at lower volumes then in past
  - Consider Pre-Ischemic Conditioning