AKI Risk Assessment, Prevention & Early Detection

Dr Lui G Forni Worthing Hospital, Brighton & Sussex Medical School

Western Sussex Hospitals NHS Trust
Where Do We Begin?

In 25 Minutes…
What Do we Mean By Risk Assessment?
Five steps to risk assessment
Step 1
Identify the hazards
So Who Is At Risk?

Where Do We Go For Guidance?

Step 1
Identify the hazards

Step 2
Decide who might be harmed and how
KDIGO Clinical Practice Guideline for Acute Kidney Injury
Conceptual Model for Acute Kidney Injury (AKI)

- Normal
- Increased risk
- Damage
- ↓ GFR
- Kidney failure
- Death

Complications

Kidney Disease: Improving Global Outcomes
Risk Factors for Developing AKI

Shared (patient specific):
- Volume Depletion
- Age
- Female Gender
- CKD
- Previous AKI
- Comorbidities
  - CHF
  - COPD
  - Hypertension
  - Diabetes
- Premedication
  - ACE/ARB
  - Devil’s Medicine

Disease specific:
- Genetics
- Pathophysiology

Intervention Specific:
- Medication
- Procedures
Revised Risk factors for AKI

Shared (patient specific):
- Old Age
- Female Gender
- CKD
- Previous AKI
- Comorbidities
  - CHF
  - Liver Disease
  - Proteinuria
- Premedication
  - ACE/ARB
  - NSAIDS

Disease specific:
- Genetics
- Pathophysiology

Intervention specific:
- Medication
- Procedures
- Weekend Admission
- Surgery

Examples?
Weekends: AKI On Admission

Small = 1-249 Beds
Medium = 25-374 Beds
Large = 50->450 Beds

Mortality (%)
Weekends: AKI During Admission

Small = 1-249 Beds
Medium = 25-374 Beds
Large = 50->450 Beds

![Bar graph showing mortality rates for different hospital sizes during weekends and weekdays.](image-url)
Revised Risk factors for AKI

Shared (patient specific):
- Old Age
- Female Gender
- CKD
- Previous AKI
- Comorbidities
  - CHF
  - Liver Disease
  - Proteinuria
- Premedication
  - ACE/ARB
  - NSAIDS

Disease specific:
- Genetics
- Pathophysiology

Intervention specific:
- Medication
- Procedures
- Weekend Admission
- Surgery

Why Proteinuria & Not Diabetes?

*Kidney Disease: Improving Global Outcomes*
Surgery & AKI: Influence of DM

Over 1000 Surgical Patients
AKI as defined by AKIN
Major determinants of AKI?

Critical Care 2009 13:R79
BUT NOT DIABETES
Diabetes & ICU Outcomes

- Is this a surprise??

- In fact conflicting results in the literature......

What We Need Is A Meta-Analysis!!!
### Table 1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Diabetic</th>
<th>Non-diabetic</th>
<th>Log(Odds Ratio)</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brit 2006</td>
<td>1.15</td>
<td>1.05</td>
<td>-1.51</td>
<td>2.09</td>
<td>0.56</td>
<td>(0.92, 3.00)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ongkoro 2009</td>
<td>1.06</td>
<td>0.96</td>
<td>-0.06</td>
<td>1.06</td>
<td>0.24</td>
<td>(0.74, 1.51)</td>
<td>0.19</td>
</tr>
<tr>
<td>Wu 2008</td>
<td>1.00</td>
<td>0.95</td>
<td>-0.05</td>
<td>1.06</td>
<td>0.24</td>
<td>(0.74, 1.51)</td>
<td>0.19</td>
</tr>
<tr>
<td>Zhao 2008</td>
<td>1.00</td>
<td>0.95</td>
<td>-0.05</td>
<td>1.06</td>
<td>0.24</td>
<td>(0.74, 1.51)</td>
<td>0.19</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.00</td>
<td>1.00</td>
<td>-0.05</td>
<td>1.00</td>
<td>0</td>
<td>(0.74, 1.51)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

### Figure 2

Forest plots showing odds ratios (ORs) and 95% confidence intervals (95% CI) of ICU mortality risk for patients with or without diabetes. The "0" indicating the number of diabetic or non-diabetic patients means the information was not available. SE: standard error, IV: inverse variance.
**Summary**

**Results:** We included 141 studies containing 12,489,574 patients, including 2,705,624 deaths (21.7%). Of these patients at least 2,327,178 (18.6%) had diabetes. Overall no association between the presence of diabetes and mortality risk was found. Analysis for ICU type showed a significant disadvantage for patients with diabetes for all mortality definitions when admitted at the surgical ICU (ICU mortality: OR [CI] 1.48 [1.04-2.11]; hospital mortality: 1.59 [1.28-1.97]; 30-day mortality: 1.62 [1.13-2.34]). In medical and mixed ICU’s no effect of diabetes was seen for all outcomes. Sensitivity analysis showed that the disadvantage in the diabetic surgical population was attributable to cardiac surgery (1.77 [1.45-2.16], \( P<0.00001 \)) and not to general surgery patients (1.21 [0.96-1.53], \( P=0.11 \)).
Conclusions: This meta-analysis showed that diabetes was not associated with increased mortality risk in any ICU population except for those who underwent cardiac surgery.
No obvious problem with DM here....
Meta Analysis Did Tell Us That Cardiac Surgery & DM Was Bad…

Table 4. Factors associated with postoperative acute kidney injury defined by the Acute Kidney Injury Network Criteria (n = 1052)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>DM</td>
<td>1.66 (1.14 to 2.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent MI</td>
<td>1.78 (1.16 to 2.72)</td>
<td>0.009</td>
</tr>
<tr>
<td>IABP</td>
<td>3.56 (1.83 to 6.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonelective surgery</td>
<td>3.66 (2.15 to 6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no proteinuria</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>mild proteinuria</td>
<td>1.66 (1.09 to 2.52)</td>
<td>0.018</td>
</tr>
<tr>
<td>heavy proteinuria</td>
<td>2.30 (1.35 to 3.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>preserved eGFR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>stage 3</td>
<td>1.68 (1.12 to 2.52)</td>
<td>0.012</td>
</tr>
<tr>
<td>stage 4</td>
<td>3.01 (1.57 to 6.03)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Tao-Min Huang J Am Soc Nephrol 2010 22:
Table 5. Factors associated with postoperative AKI needing RRT ($n = 1052$)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.06 (1.02 to 1.10)</td>
<td>0.003</td>
</tr>
<tr>
<td>Low LVEF</td>
<td>3.31 (1.36 to 8.79)</td>
<td>0.009</td>
</tr>
<tr>
<td>ECMO</td>
<td>15.75 (6.01 to 41.26)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Nonelective surgery</td>
<td>6.49 (2.84 to 14.86)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>3.90 (1.86 to 8.20)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Heavy proteinuria</td>
<td>7.29 (3.00 to 17.73)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>
Evidence Outside the ICU?

Huge Study : 920,985 Patients
All hospital admissions between 2002-2007
Median FU 35 months

0.7% Admitted to hospital with AKI

James etal Lancet 2010 376 2096-103
Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study

Matthew T James, Brenda R Hemmelgarn, Natasha Wiebe, Neesh Pannu, Braden J Manns, Scott W Klarenbach, Marcello Tonelli, for the Alberta Kidney Disease Network

eGFR (>60) : RR of AKI was 4.4 higher in those with proteinuria

In those with heavy proteinuria the risk of AKI and AKI requiring RRT was raised regardless of GFR

James etal Lancet 2010 376 2096-103
So: I Think That Proteinuria Should Be A Prominent Risk Factor For AKI

James et al. Lancet 2010 376 2096-103
Step 1
Identify the hazards

Step 2
Decide who might be harmed and how

Step 3
Evaluate the risks and decide on precautions
Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study

Risk Dependent on Cause

Kidney Disease: Improving Global Outcomes

CV Thakar et al, Crit Care Med 2009
Step 3: Evaluating The Risk

- Causation cannot be ignored
- Can we predict the risk?
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>AKI</th>
<th>Cohort Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candela-Toha 2008</td>
<td>External Validation of Thakar and Wyesundera in 1780 pts with cardiac surgeries at a University Hospital in Madrid, Spain from 2002-2006</td>
<td>AKI</td>
<td>Retrospective cohort Single center</td>
</tr>
<tr>
<td>Mehran 2004</td>
<td>8,357 pts who underwent PCI possibly at Columbia Medical Center, New York, New York, over a period of 6 years (dates unspecified).</td>
<td>CIN</td>
<td>Retrospective cohort Presumed single center</td>
</tr>
<tr>
<td>McCullough 2007</td>
<td>1,826 consecutive pts undergoing coronary intervention at William-Beaumont Hospital, Michigan from December 1993-August 1994.</td>
<td>RRT</td>
<td>Retrospective cohort Single Center</td>
</tr>
<tr>
<td>Skelding 2007</td>
<td>External Validation of William Beaumont score in 3,213 pts from the Mayo Clinic PCI Registry who underwent PCI at the from July 1, 2000 to June 30, 2003</td>
<td>CIN</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Drawz 2008</td>
<td>540 hospitalized patients in 3 hospitals in Cleveland, Ohio since January 1, 2003</td>
<td>Hospital-acquired AKI</td>
<td>Case-controlled</td>
</tr>
<tr>
<td>Ghani 2009</td>
<td>247 pts undergoing PCI in Kuwait from March to May 2005</td>
<td>CIN</td>
<td>Prospective cohort Single-center</td>
</tr>
</tbody>
</table>
Predicting Acute Renal Failure after Cardiac Surgery: External Validation of Two Clinical Scores

Table 1. Risk factors and points in Cleveland and SRI (Toronto) scores^a

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cleveland Points</th>
<th>SRI Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>History of CHF</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>LVEF&lt;35%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LVEF&lt;40%</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Preoperative IABP</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>COPD treated with bronchodilators</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes that required treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with insulin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>with any medication</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type of surgery^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>valvular</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>combined (CABG + valvular)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>other surgeries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Preoperative renal function^c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCr (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 to 2.09</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>≥2.1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to 60</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Operative status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>emergent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>nonelective</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Score range</td>
<td>0 to 17</td>
<td>0 to 8</td>
</tr>
</tbody>
</table>
Predicting Acute Renal Failure after Cardiac Surgery: External Validation of Two New Clinical Scores

Cleveland

Toronto

Kidney Disease: Improving Global Outcomes

Candela-Toha, CJASN 2008

WWW.KDIGO.ORG
What About Non-Surgical Patients?
# Risk Factors for CIN

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Procedure-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>Multiple contrast media injection within 72 hrs</td>
</tr>
<tr>
<td>Diabetes mellitus with</td>
<td>Intra-arterial injection site</td>
</tr>
<tr>
<td>renal insufficiency</td>
<td>High volume of contrast media</td>
</tr>
<tr>
<td>Age</td>
<td>High osmolality of contrast media</td>
</tr>
<tr>
<td>Volume depletion</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Low cardiac output</td>
<td></td>
</tr>
<tr>
<td>Class IV CHF</td>
<td></td>
</tr>
<tr>
<td>Other nephrotoxins</td>
<td></td>
</tr>
<tr>
<td>Renal transplant</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia (&lt;35 g/L)</td>
<td></td>
</tr>
</tbody>
</table>


*Kidney Disease: Improving Global Outcomes*
Contrast-nephropathy Risk Score

- **Risk Factors**
  - Hypotension: 5
  - IABP: 5
  - CHF: 5
  - Age >75 years: 4
  - Anemia: 3
  - Diabetes: 3
  - Contrast media volume: 1 for each 100 cc³
  - Serum creatinine >1.5 mg/dl: 4
  - eGFR <60 ml/min/1.73 m²: 2 for 40 - 60, 4 for 20 - 40, 6 for <20

- **Integer Score**

- **Calculate**

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Risk of CIN</th>
<th>Risk of Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5</td>
<td>7.5%</td>
<td>0.04%</td>
</tr>
<tr>
<td>6 to 10</td>
<td>14.0%</td>
<td>0.12%</td>
</tr>
<tr>
<td>11 to 16</td>
<td>26.1%</td>
<td>1.09%</td>
</tr>
<tr>
<td>≥ 16</td>
<td>57.3%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

*Mehran, JACC 2004*
So What Does This Tell Us?
We recommend that patients be stratified for risk of AKI according to their susceptibility and in context with the exposure whenever possible. (1B)
It is reasonable to manage patients according to their susceptibilities and exposures to reduce the risk of AKI.
It is reasonable to test patients at increased risk for AKI with measurements of serum creatinine and urine output to detect AKI. Individualize frequency and duration of monitoring based on patient risk and clinical course. 

---

Andrew Davenport

Clinical guidelines for the protection of kidney function and prevention of acute kidney injury in the intensive care unit: common sense rather than magic bullets?
Step 1
Identify the hazards

Step 2
Decide who might be harmed and how

Step 3
Evaluate the risks and decide on precautions

Prevention?
How Do We Prevent AKI??
Don’t Get Admitted to Hospital...
4. Acute Kidney Injury (AKI) (Guidelines AKI 4.1 – 4.5)

Guideline 4.1 – AKI : Management; General Management

We recommend that general supportive measures include optimisation of haemodynamic status by appropriate fluid therapy, administration of vasopressors and/or inotropes and treatment of any underlying sepsis. Nephrotoxic medications should be stopped. (1A)

Guideline 4.2 – AKI : Management; Pharmacological Therapy

We recommend that therapeutic drug dosing must be adapted to altered kinetics in AKI. (1B)

Guideline 4.3 – AKI : Management; Pharmacological Therapy

We recommend that there is no specific pharmacological therapy proven to effectively treat AKI secondary to hypoperfusion injury and/or sepsis. (1B)
Management of Patients According to their Susceptibilities

- **Hypovolemia** -> Volume Expansion
- **Hypotension** -> Volume Expansion, Vasopressors
- **CHF** -> Inotropes, Inodilators (e.g. levosimendan)
- **Nephrotoxins** -> Stop them
- **ACE/ARB** -> Stop them

- **Age** -> ?
- **Gender** -> ?

WG Nephrology of ESICM (Joannidis et al, Intensive Care Med 2009)
**Stage-Based Management**

<table>
<thead>
<tr>
<th>AKI Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
</tr>
<tr>
<td>Discontinue all nephrotoxic agents when possible</td>
</tr>
<tr>
<td>Ensure volume status and perfusion pressure</td>
</tr>
<tr>
<td>Consider functional hemodynamic monitoring</td>
</tr>
<tr>
<td>Monitoring Serum creatinine and urine output</td>
</tr>
<tr>
<td>Avoid hyperglycemia</td>
</tr>
<tr>
<td>Consider alternatives to radiocontrast procedures</td>
</tr>
<tr>
<td>Non-invasive diagnostic workup</td>
</tr>
<tr>
<td>Consider invasive diagnostic workup</td>
</tr>
<tr>
<td>Check for changes in drug dosing</td>
</tr>
<tr>
<td>Consider Renal Replacement Therapy</td>
</tr>
<tr>
<td>Consider ICU admission</td>
</tr>
<tr>
<td>Avoid subclavian catheters if possible</td>
</tr>
</tbody>
</table>

**Stage-based management of AKI:** Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.

*Kidney Disease: Improving Global Outcomes*
Preventing AKI

• Often (always) multifactorial
• Can we expect to find a ‘cure-all’?

• What has been Tried?
Vasoactive Drugs

Diuretics

NAc, Statins, Ascorbate

EPO, IgF-1, Insulin

Renal Vasodilators
No Evidence In Patients of Any Benefit

MESNA
Statins
Retinoic Acid
Carvedilol
Spironolactone
Pentoxifyline
Statins
Urodilatin
AND MANY OTHERS
Fluid replacement: Must be a good thing

Despite the recognition of volume depletion as an important risk factor for AKI, there are no randomized controlled trials (RCTs) that have directly evaluated the role of fluids vs. placebo in the prevention of AKI. However, RCTs mostly in the field of CI-AKI have...

Not entirely surprising...
CONCLUSIONS

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy. (Funded by the National Health and Medical Research Council of Australia and others; CHEST ClinicalTrials.gov number, NCT00935168.)

Evidence that colloids increase the need for RRT...
Key messages

- It has been hypothesized that hyperoncotic colloid solutions may damage the kidney. A meta-analysis of randomized controlled trials was performed to test this hypothesis.
  - Hyperoncotic albumin decreased the odds of acute kidney injury by 76% and of death by 48%.
  - Hyperoncotic hydroxyethyl starch increased the odds of acute kidney injury by 92% and of death by 41%.
  - Hyperoncotic colloids *per se* do not appear to be harmful to the kidney.
  - Renal effects may be specific to the particular colloid molecule.
FLUIDS

3.1.1: In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI. (2B)
Diuretics

- Rationale
  - Reduced $O_2$ Consumption
  - Increased Tubular Flow
  - Increased Urea Excretion
  - Volume Management
High-dose Furosemide in patients with Established AKI

Cantarovic F, Am J Kidney Dis 2004

<table>
<thead>
<tr>
<th></th>
<th>Furosemide (n = 166)</th>
<th>Placebo (n = 164)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients alive at the end of the study (n = 221)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS ≤15</td>
<td>60</td>
<td>67</td>
<td>0.36*</td>
</tr>
<tr>
<td>SAPS &gt;15</td>
<td>47</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Deaths (n = 109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS ≤15</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SAPS &gt;15</td>
<td>43</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>No. of RRT sessions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS ≤15</td>
<td>5.6 ± 5.5</td>
<td>5.7 ± 4.5</td>
<td>0.37†</td>
</tr>
<tr>
<td>SAPS &gt;15</td>
<td>7.3 ± 5.3</td>
<td>7.9 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.5 ± 5.4</td>
<td>6.9 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Time on RRT (d)</td>
<td>11.4 ± 8.6</td>
<td>12.4 ± 8.7</td>
<td>0.21†</td>
</tr>
<tr>
<td>Time to achieve a serum creatinine level &lt;2.26 mg/dL without RRT (d)</td>
<td>19.7 ± 40.6</td>
<td>21.4 ± 65.1</td>
<td>0.99†</td>
</tr>
<tr>
<td>Time to achieve a 2-L/d diuresis (d)</td>
<td>5.7 ± 5.8</td>
<td>7.8 ± 6.8</td>
<td>0.004†</td>
</tr>
</tbody>
</table>
Results. Renal recovery, the need for dialysis, and death were no different in the three groups. Patients given a loop diuretic had a significant rise in urine flow rate in the first 24 h compared to placebo ($P = 0.02$). Based on the urine flow rate during the first post-medication day patients were divided into two groups—oliguric ($<50 \text{ ml/h}$) and non-oliguric ($\geq 50 \text{ ml/h}$). Non-oliguric patients had a significantly lower mortality than oliguric patients ($43\%$ vs $69\%, P = 0.01$). However, they were less ill (APACHE II score $17.2$ vs $20.6, P = 0.008$) and had less severe renal failure at entry (creatinine clearance $14 \text{ ml/min}$ vs $4 \text{ ml/min}, P < 0.0001$).

Conclusion. The use of loop diuretics in oliguric patients with ARF can result in a diuresis. There is no evidence that these drugs can alter outcome.
Diuretics and AKI

Despite Repeated Trials...

They must work...

The SPARK Study: a phase II randomized blinded controlled trial of the effect of furosemide in critically ill patients with early acute kidney injury

Sean M Bagshaw¹, RT Noel Gibney¹, Finlay A McAlister², Rinaldo Bellomo³
3.4.1: We recommend not using diuretics to prevent AKI. (1B)

3.4.2: We suggest not using diuretics to treat AKI, except in the management of volume overload. (2C)
Dopamine

- Rationale
- ? Preferential Renal Vasodilatation
- ? Evidence
Effect of ‘low-dose’ dopamine on Renal Resistive Index

In conclusion ‘low-dose’ dopamine can worsen renal perfusion in patients with ARF, which adds to the rationale for abandoning the routine use of ‘low-dose’ dopamine in critically ill patients.


Figure 5 | Effect of dopamine on RI values in patients with and without norepinephrine (NE) infusion.
DOPAMINE DOES NOT PREVENT AKI

RCT - dopamine 2µg/kg/min throughout ITU stay

...And No Effect on the development of AKI

Lancet 2000;356:2139
3.5.1: We recommend not using low-dose dopamine to prevent or treat AKI. (1A)
What of Vasoconstrictors?

Rifle R

P=0.007

NAd
VASOPRESSORS

3.1.2: We recommend the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for, AKI. (1C)

PROTOCOLIZED HEMODYNAMIC MANAGEMENT

3.1.3: We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (2C) or in patients with septic shock (2C).
• IGF-1
• ANP
• Fenoldapam
• NAc
• EPO

• Not Recommended
• Not Recommended
• Not Recommended
• Not Recommended
• Not Recommended
Pooled analysis failed to confirm early beneficial effects of IIT.

NICE-Sugar the largest randomized trial to date found that IIT increased mortality.

- BG target 4.5-6.0 higher mortality than ≤ 9.99.

The end for IIT?
Insulin

- Further analysis of the original studies on IIT
- Renal end-points combined using a modified version of RIFLE:
  - Tight glycemic control reduced the incidence of severe AKI from 7.6% to 4.5% ($P = 0.0006$)
  - Need for RRT was not decreased in overall population/medical ICU population
  - But significantly lower in the surgical ICU patients (4% vs. 7.4%, $P = 0.008$).

M. Schetz, JASN 2008
Intensive Insulin Therapy and AKI

Balance of Risk

? Curse of the RCT?

M. Schetz, JASN 2008
GLYCEMIC CONTROL IN CRITICAL ILLNESS: RENAL EFFECTS AND OUTCOMES

3.3.1: In critically ill patients, we suggest insulin therapy targeting plasma glucose 110–149 mg/dl (6.1–8.3 mmol/l). (2C)
What About Well Defined Conditions?

- Cellular breakdown
- Kidney obstruction or compression or renal vascular thrombosis in solid tumors
- Uric acid crystals obstruct tubules and collecting ducts
- Uric acid and phosphate
- ARF
- Acidic pH
- Chemotherapeutic, antibiotics, antiviral and antifungal drugs
Rhabdomyolysis

- Should be easy
- Identifiable (mostly)
- Biomarker (of sorts)
- Bicarbonate/Mannitol/Frusemide
- ?Evidence
Therapy for Rhabdomyolysis

No Difference in:
- % Renal Failure
- % Dialysis
- % Mortality

Brown C et al.
*J Trauma* 2004; 30 : 1191-96
Therapy for Rhabdomyolysis

Table 4. Comparative Studies on Preventive and Therapeutic Regimens in Rhabdomyolysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Patient Group</th>
<th>No. in Sample</th>
<th>Therapeutic Strategy</th>
<th>Outcome in Patients with Acute Kidney Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shimazu et al.34</td>
<td>Retrospective</td>
<td>Patients with the crush syndrome</td>
<td>14</td>
<td>Late vs. early initiation of therapy; high (&gt;10 liters for 48 hours) vs. low volume of hydration</td>
<td>Better if therapy initiated early; high volume of hydration better</td>
</tr>
<tr>
<td>Gunal et al.35</td>
<td>Retrospective</td>
<td>Patients with the crush syndrome</td>
<td>16</td>
<td>Early vs. late treatment with normal saline followed immediately by bicarbonate</td>
<td>Better if treatment initiated early</td>
</tr>
<tr>
<td>Hornsi et al.36</td>
<td>Retrospective</td>
<td>Patients in the intensive care unit</td>
<td>24</td>
<td>Normal saline vs. normal saline plus bicarbonate and mannitol</td>
<td>No difference</td>
</tr>
<tr>
<td>Brown et al.37</td>
<td>Retrospective</td>
<td>Patients with trauma</td>
<td>2083</td>
<td>Normal saline vs. bicarbonate plus mannitol</td>
<td>No difference</td>
</tr>
<tr>
<td>Cho et al.38</td>
<td>Prospective, randomized</td>
<td>Patients with intoxication from doxylamine</td>
<td>28</td>
<td>Ringer’s lactate vs. normal saline; bicarbonate if urine pH is &lt;6.5</td>
<td>No effect on peak creatinine kinase level or recovery with Ringer’s lactate as compared with normal saline; more bicarbonate needed with normal saline than with Ringer’s lactate</td>
</tr>
</tbody>
</table>
Tumour Lysis Syndrome

- TLS characterized by Severe
  - Hyperuricemia
  - Hyperphosphatemia
  - Hyperkalemia
  - Hypocalcemia
  - Acute Kidney Injury
Rasburicase

Allopurinol

Rasburicase

Goldman Blood 2001 97; 2998-3003
Rasburicase

- Rasburicase Group
  - Adjusted SCr fell from 144% to 102%

- Allopurinol Group
  - Adjusted SCr rose from 132% to 147%

- No difference in need for RRT
- Peak Uric Acid reduced (p<.0001)
- Mean Uric acid AUC less (p <.0001)

Goldman Blood 2001 97; 2998-3003
Preventing AKI…..

■ Beset by Problems:

■ An incomplete understanding of the underlying pathophysiologic mechanisms

■ The lack of robust early markers for AKI, and hence an unacceptable delay in initiating therapy
Conclusions

- Limited therapeutic options
- Early initiation of treatment may be key

At Present... Is this the best we can hope for?
Early Detection?
AKI Biomarkers

Glomerular filtration:
- Cystatin C
- NGAL

Prox tubule:
- Cystatin C
- NAG
- α-GST
- γ-GT
- NGAL
- KIM–1
- IL-18
- RBP
- L-FABP

Distal tubule:
- π-GST
- NAG
- NGAL

Loop of Henle:
- RAP (in rats)
What Is A Biomarker?

NIH Definition:
“…a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention…”
The Rise of the Biomarker

Approaching 250 Papers to-date.....

...and counting...
<table>
<thead>
<tr>
<th>AKI biomarker</th>
<th>Production / origin</th>
<th>Handling by the kidney</th>
<th>Sample sources</th>
<th>Detection time after renal injury</th>
<th>Confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil gelatinase-associated lipocalin (NGAL)</td>
<td>25 kDa glycoprotein produced by epithelial tissues throughout the body</td>
<td>plasma NGAL is excreted via glomerular filtration and undergoes complete reabsorption in healthy tubular cells</td>
<td>plasma and urine</td>
<td>2-4 hours post AKI</td>
<td>sepsis, malignancy, chronic kidney disease, pancreatitis, COPD, endometrial hyperplasia</td>
</tr>
<tr>
<td>also known as oncogene 24p3</td>
<td></td>
<td>NGAL is also produced in distal tubular segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>13 kDa cysteine protease inhibitor produced by all nucleated human cells and released into plasma at constant rate independent of gender, race, muscle mass and hydration level</td>
<td>freely filtered in glomeruli and completely reabsorbed and catabolized by proximal tubular cells; no tubular secretion (not detectable in urine in healthy subjects)</td>
<td>plasma and urine (plasma cystatin C may be a marker of GFR; cystatin C only detectable in urine after tubular injury)</td>
<td>12-24 hours post renal injury</td>
<td>systemic inflammation, malignancy, thyroid disorders, glucocorticoid deficiency and excess smoking</td>
</tr>
<tr>
<td>Interleukin-18 (IL-18)</td>
<td>18 kDa proinflammatory cytokine</td>
<td>released from proximal tubular cells following injury</td>
<td>plasma and urine</td>
<td>6-24 hours after renal injury</td>
<td>inflammation, sepsis, heart failure</td>
</tr>
<tr>
<td>Kidney Injury Molecule – 1 (KIM-1)</td>
<td>Transmembrane glycoprotein produced by proximal tubular cells after ischaemic or nephrotoxic injury; no systemic source</td>
<td>present in urine after ischaemic or nephrotoxic damage of proximal tubular cells</td>
<td>urine</td>
<td>12-24 hours after renal injury</td>
<td>renal cell carcinoma, chronic proteinuria, chronic kidney disease, sickle cell nephropathy</td>
</tr>
<tr>
<td>Liver-type fatty acid-binding protein (L-FABP)</td>
<td>14 kDa intracellular lipid chaperone produced in liver, intestine, pancreas, lung, nervous system, stomach and proximal tubular cells</td>
<td>freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage</td>
<td>plasma and urine</td>
<td>1 hour after ischaemic tubular injury</td>
<td>chronic kidney disease, polycystic kidney disease, liver disease, sepsis</td>
</tr>
</tbody>
</table>
NGAL

Neutrophil gelatinase-associated lipocalin

- Neutrophil/epithelial protein – spills into blood and urine
- Released in inflammation from several epithelia
- Released by certain adenocarcinomas
- Released in bacterial infection and sepsis
- Released at higher levels in kidney injury
- Levels increase within <2 hours of kidney injury
<table>
<thead>
<tr>
<th>AKI biomarker</th>
<th>Production / origin</th>
<th>Handling by the kidney</th>
<th>Sample sources</th>
<th>Detection time after renal injury</th>
<th>Confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil gelatinase-associated lipocalin (NGAL) also known as oncogene 24p3</td>
<td>25 kDa glycoprotein produced by epithelial tissues throughout the body NGAL is also produced in distal tubular segments</td>
<td>plasma NGAL is excreted via glomerular filtration and undergoes complete reabsorption in healthy tubular cells</td>
<td>plasma and urine</td>
<td>2-4 hours post AKI</td>
<td>sepsis malignancy chronic kidney disease pancreatitis COPD endometrial hyperplasia</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>13 kDa cysteine protease inhibitor produced by all nucleated human cells and released into plasma at constant rate independent of gender, race, muscle mass and hydration level</td>
<td>freely filtered in glomeruli and completely reabsorbed and catabolized by proximal tubular cells; no tubular secretion (not detectable in urine in healthy subjects)</td>
<td>plasma and urine (plasma cystatin C may be a marker of GFR; cystatin C only detectable in urine after tubular injury)</td>
<td>12-24 hours post renal injury</td>
<td>systemic inflammation malignancy thyroid disorders glucocorticoid deficiency and excess smoking</td>
</tr>
<tr>
<td>Interleukin-18 (IL-18)</td>
<td>18 kDa proinflammatory cytokine</td>
<td>released from proximal tubular cells following injury</td>
<td>plasma and urine</td>
<td>6-24 hours after renal injury</td>
<td>inflammation sepsis heart failure</td>
</tr>
<tr>
<td>Kidney Injury Molecule – 1 (KIM-1)</td>
<td>Transmembrane glycoprotein produced by proximal tubular cells after ischaemic or nephrotoxic injury; no systemic source</td>
<td>present in urine after ischaemic or nephrotoxic damage of proximal tubular cells</td>
<td>urine</td>
<td>12-24 hours after renal injury</td>
<td>renal cell carcinoma chronic proteinuria chronic kidney disease sickle cell nephropathy</td>
</tr>
<tr>
<td>Liver-type fatty acid-binding protein (L-FABP)</td>
<td>14 kDa intracellular lipid chaperone produced in liver, intestine, pancreas, lung, nervous system, stomach and proximal tubular cells</td>
<td>freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage</td>
<td>plasma and urine</td>
<td>1 hour after ischaemic tubular injury</td>
<td>chronic kidney disease polycystic kidney disease liver disease sepsis</td>
</tr>
<tr>
<td>Enzyme/Protein</td>
<td>Molecular Weight</td>
<td>Mode of Action</td>
<td>Sampling Site</td>
<td>Time Frame</td>
<td>Disease</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase (NAG)</td>
<td>&gt;130 kDa lysosomal enzyme; produced in many cells including proximal and distal tubular cells</td>
<td>too large to undergo glomerular filtration; urinary elevations imply tubular origin</td>
<td>plasma and urine</td>
<td>12 hours</td>
<td>diabetic nephropathy</td>
</tr>
<tr>
<td>α glutathione S-transferase (α GST)</td>
<td>47-51 kDa cytoplasmic enzyme produced in proximal tubule</td>
<td>limited glomerular filtration; increased urinary levels following tubular injury</td>
<td>urine</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>n glutathione S-transferase (n GST)</td>
<td>47-51 kDa cytoplasmic enzyme produced in distal tubules</td>
<td>limited glomerular filtration; increased urinary levels following tubular injury</td>
<td>urine</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>Alanine aminopeptidase (AAP)</td>
<td></td>
<td>enzymes located on the brush border villi of the proximal tubular cells</td>
<td>released into urine after tubular injury</td>
<td>urine</td>
<td>?</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-glutamyl transpeptidase (γ-GT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepcidin</td>
<td>2.78 kDa peptide hormone predominantly produced in hepatocytes; some production in kidney, heart and brain</td>
<td>freely filtered with significant tubular uptake and catabolism (fractional excretion 2%)</td>
<td>plasma and urine</td>
<td>?</td>
<td>systemic inflammation</td>
</tr>
<tr>
<td>Hepatocyte growth factor (HGF)</td>
<td></td>
<td>Marker linked to renal tubular epithelial cell regeneration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netrin</td>
<td></td>
<td>Laminin-related molecule, minimally expressed in proximal tubular epithelial cells of normal kidneys</td>
<td>highly expressed in injured proximal tubules</td>
<td>urine</td>
<td>?</td>
</tr>
<tr>
<td>Monocyte chemoattractant peptide-1 (MCP-1)</td>
<td>Peptide expressed in renal mesangial cells and podocytes</td>
<td>detectable in urine</td>
<td>urine</td>
<td>?</td>
<td>variety of primary renal diseases</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>calcium-binding complex of two proteins of the S100 group (S100A8/S100A9); derived from neutrophils and monocytes; acts as activator of the innate immune system</td>
<td>measure of local inflammatory activity; detectable in urine in intrinsic AKI</td>
<td>urine</td>
<td>?</td>
<td>inflammatory bowel disease, urinary tract infection, probably CKD</td>
</tr>
</tbody>
</table>
And is there any evidence...

When Might We Use A Biomarker?
Pre-Renal vs Intrinsic

- Nickolas et al. (J Am Coll Cardiol 2012)

- 1635 patients and evaluated
  - NGAL
  - KIM-1
  - L-FABP
  - IL-18
  - Cystatin C

  All Markers Raised

  Only uNGAL & uCysC able to distinguish pre renal from sustained
<table>
<thead>
<tr>
<th>Addition of:</th>
<th>AUC 0.62</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1 :</td>
<td>0.62 to 0.69</td>
</tr>
<tr>
<td>IL-18 :</td>
<td>0.62 to 0.68</td>
</tr>
<tr>
<td>uNGAL :</td>
<td>0.62 to 0.75</td>
</tr>
</tbody>
</table>
Is NGAL Mystic meg?

![Graph showing NGAL (ng/ml) levels over time for No AKI and AKI patients. The graph demonstrates a peak in NGAL levels at 6 hours post AKI onset, followed by a decline.]
15-fold increase in urine NGAL at 2 hours after CPB and 25-fold increase at 4 hours after CPB in children

N = 196

*P < 0.05 comparing patients with or without AKI

Early ‘diagnosis’ of AKI

- Most studies have concentrated on the use of biomarkers to predict rises in serum creatinine……and therefore AKI

- Despite the fact that most proponents of biomarkers for AKI tell us how bad a tool creatinine is…..
Early ‘diagnosis’ of AKI

Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population

Dinna N. Cruz
Massimo de Cal
Francesco Garzotto
Mark A. Perazella
Paolo Lenti
Valentina Corradi
Pasquale Piccinni
Claudio Ronco

Early diagnosis of AKI

- Strong association with disease severity regardless of AKI

Cruz et al. Intensive Care Med 2010;36
Early ‘diagnosis’ of AKI

Cruz et al. Intensive Care Med 2010;36
Fig. 3 Receiver operator characteristic (ROC) curve for plasma NGAL. The area under the ROC is 0.78 (95% CI 0.65–0.90), demonstrating a good performance for the diagnosis of AKI within the next 48 h.
Here’s the but....

301 patients: 133 developed AKI (50% septic)

- Median pNGAL AKI vs Non-AKI (p=0.13)
- 90/133: Had AKI on admission
- ? How many included in the ROC curve
- ? Are We Predicting the obvious
So Where Are We……A Troponin for the Kidney?

■ The Kidney is not the heart
■ AKI is not AMI
■ Is the fault with the biomarkers or the concept of AKI itself?
The Future?

A Personal View

Little role for biomarkers in the ICU at present

May be a role in acute medical units or the deep recesses of orthopaedics…Preferably with a risk assessment tool

This may all change if we can work out how to treat AKI……
Due to the actual financial problems, the light at the end of the tunnel has been turned off.

(We apologize for the inconvenience.)