Update on Acute Kidney Injury: What Works, What Doesn’t

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Director, Acute and Home Dialysis Programs
University of Colorado Hospital
Denver, Colorado
Demographics of AKI

• AKI is very common

• It complicates up to 5% of hospital admissions and up to 30% of ICU admissions

• AKI still associated with very high mortality of 30-80%
AKI is an Independent Risk Factor of Mortality

<table>
<thead>
<tr>
<th>AKI characteristics</th>
<th>Adjusted OR</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital acquired</td>
<td>6.2</td>
<td>Shusterman, 1987</td>
</tr>
<tr>
<td>Radiocontrast</td>
<td>5.5</td>
<td>Lewy, 1996</td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>9.1</td>
<td>Kashyap, 1997</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>7.9</td>
<td>Chertow, 1998</td>
</tr>
<tr>
<td>ICU</td>
<td>1.6</td>
<td>De Mendonca, 2000</td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>2.5</td>
<td>Obialo, 2000</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>6.6</td>
<td>Bates, 2000</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>4.3</td>
<td>Agarwal, 2001</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>6.8</td>
<td>Parikh, 2005</td>
</tr>
</tbody>
</table>
Overview of Talk

• What’s this Acute Kidney Injury (AKI)? What happened to Acute Renal Failure (ARF)?

• Biomarkers

• Pharmacologic Interventions

• Renal Replacement Therapy (RRT)
A decrease in the glomerular filtration rate (GFR) occurring over hours to days resulting in the failure of the kidney to excrete nitrogenous waste products and maintain fluid and electrolyte homeostasis.
Problem Areas

• How is GFR assessed?
• How severe a decline in GFR?
• How many “hours to days”?
• Lacking uniform definitions we…
  - can’t design and perform studies- RCT, observational, or retrospective.
  - are unable to “talk to each other” to compare data and outcomes.
• Renal vs. Kidney
Acute Kidney Injury Network

• “The purpose of this network is to facilitate international, interdisciplinary, and intersociety collaborations to ensure progress in the field of acute kidney injury.”

• The fundamental goal is “to improve best outcomes for patients who are at risk” for or from kidney injury.

• First meeting held in September, 2005
Acute Kidney Injury - Definition

“An abrupt increase in serum creatinine over 48 hours resulting from injury or insult that causes a functional or structural change in the kidney”.

Problem Areas

- How is GFR assessed? Scr
- How severe a decline in GFR? \( \geq 0.3 \text{ mg}\% \)
- How many “hours to days”? 48 hours
- Renal vs. Kidney Kidney
# RIFLE Classification of AKI

<table>
<thead>
<tr>
<th>Risk</th>
<th>GFR Criteria</th>
<th>Urine Output Criteria</th>
<th>High sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss</td>
<td>Persistent Kidney Injury</td>
<td>Loss of function &gt; 4w</td>
<td>End Stage</td>
</tr>
<tr>
<td>ESKD</td>
<td>End Stage</td>
<td>Kidney disease</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>SCr x 2</td>
<td>GFR decrease &gt; 50%</td>
<td>UO &lt; 0.5 ml/hr/kg x 12 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>SCr x 3</td>
<td>GFR decrease &gt; 75%</td>
<td>UO &lt; 0.3 ml/hr/kg x 24hr (=oliguria)</td>
</tr>
<tr>
<td></td>
<td>SCr &gt; 4 mg%</td>
<td></td>
<td>Anuria x 12 hr</td>
</tr>
<tr>
<td></td>
<td>SCr x 1.5; GFR decrease &gt; 25%</td>
<td></td>
<td>UO &lt; 0.5 ml/hr/kg x 6 hr</td>
</tr>
<tr>
<td></td>
<td>Absolute increase in SCr of 0.3 mg%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADQI Curr Opin Crit Care, 2002
“Acute Kidney Injury” (AKI) is/ will be replacing “Acute Renal Failure” (ARF). Some people feel it should also replace “Acute Tubular Necrosis” (ATN). I do not agree.
Differential Diagnosis of AKI

- Pre-Renal
- Post-Renal
- Intra-Renal
Pre-Renal AKI

• The problem may lie anywhere between the heart and the glomerulus:
  - LV failure
  - Tamponade (hemomediastinum), constrictive pericarditis
  - Coarctation
  - Renal artery disease (all of renal mass)
  - Renal vasoconstriction (e.g. HRS)
  - Volume depletion
Pre-Renal AKI

- GFR is poor but tubules function normally. Therefore, characterized by:
  - Avid Na reabsorption ($U_\text{Na} < 20$, $FE_\text{Na} < 1\%$)
    - Diuretics or significant metabolic alkalosis will confound use of $FE_\text{Na}$; may use $FE_\text{urea}$ instead.
  - Concentrated urine ($SG \geq 1.020$)
  - High BUN/creatinine ratio (> 20)
  - Bland sediment (may have granular casts)
Treatment for Pre-Renal AKI

Fix the underlying problem.
Post-Renal AKI

- Should always be considered, even if just to dismiss it.
- Won’t cause increased Scr unless all renal mass is involved:
  - Bladder outlet obstruction
  - Solitary kidney
  - Big stones
  - Women with pelvic malignancy
- There’s not much easier or less invasive than an ultrasound!
Intra-Renal AKI

The kidney is comprised of:

- Vessels
- Glomeruli
- Tubules
- Interstitium
Urinalysis in Vasculitis & GN

- Characterized by hematuria and RBC casts
- Proteinuria variable
Surgeons don’t commonly encounter these except for:

- Immune complex GN in patients with bacterial endocarditis.
- Atheroembolic Disease- sometimes spontaneous, more commonly seen after manipulation of the aorta or in anticoagulated patients. Look for livedo reticularis, evidence of emboli in fingers and toes, or Hollenhorst plaques on fundoscopy.
Hollenhorst Plaques
Acute Interstitial Nephritis

- Classic presentation: rash (15%), fever (27%), eosinophilia (23%). Triad is very rare.
- Modest proteinuria (< 1 gram/day)
- Most commonly drug-induced (70%)
- Other causes include autoimmune diseases, infections (legionella, leptospirosis, streptococcal, CMV)
- Hyperkalemia and/or acidosis may be disproportionately severe relative to GFR
Urine Microscopy in AIN

Characterized by WBCs and WBC casts.

May have RTE cells, alone or in casts.
Drugs Commonly Causing AIN

• NSAIDs
• Penicillins and Cephalosporins
• Rifampin
• Sulfonamides (TMP/SMX, furosemide, thiazides)
• Quinolones (predominantly ciprofloxacin)
• H2 receptor blockers (cimetidine, ranitidine)
• PPIs (omeprazole, lansoprazole)
• Others- indinavir, allopurinol, mesalamine
Acute Tubular Necrosis (ATN)

• ATN is the most common cause of AKI in the hospital and ICU settings

• Sepsis and ischemia are the most common causes of ATN
Clinical Manifestations of ATN

• Urine output may vary from complete anuria to non-oliguric state or polyuria

• Characterized by high $U_{Na} (>40)$ and $FE_{Na} (> 2\%)$ with isosmotic urine

• Urinalysis classically demonstrates broad deeply pigmented granular casts and renal tubular epithelial cells.
Urine Microscopy in ATN
Markers of Acute Kidney Injury

Creatinine is the most commonly used marker but the least sensitive. Increase of 50% or 0.5 mg/ dL generally used clinically. May not occur for 24-72 hours after injury.
Cystatin C

- 13 kDa cysteine protease inhibitor.
- Produced by nucleated cells at a constant rate that is not affected by race, sex, or inflammation.
- Freely filtered by glomerulus, reabsorbed and catalyzed.
- Not secreted by tubules.
- Easy to measure by immunonephelometry.
Early Detection of AKI by Cystatin C

85 patients at high risk of AKI. Patients classified by RIFLE criteria: Risk (50% increase in SCr), Injury, Failure, Loss, ESRD

<table>
<thead>
<tr>
<th></th>
<th>AKI (n=44)</th>
<th>Control (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-Day-3</td>
<td>R-Day-2</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.81</td>
<td>0.88</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.13*</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>1.45*</td>
<td>1.0*</td>
</tr>
<tr>
<td></td>
<td>1.79*</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 vs. R-Day-3

Herget-Rosenthal et al. Kid Int 66: 1115, 2004
Cystatin C- Summary

• Superior to serum creatinine in detecting small changes in GFR.

• More sensitive than creatinine but timeframe still days, not hours, after injury.
Biomarkers in AKI: The Search for a Kidney Troponin
Potential Biomarkers of Kidney Damage

• Markers of Impaired GFR
  - Plasma Granzyme B

• Markers of Tubular Injury
  - Urinary IL-18
  - Urinary IL-6
  - Urinary TNF
  - Urinary Kidney Injury Molecule-1 (KIM-1)
  - Urinary tubular enzymes e.g. γGT, Alk Phos, NAG
  - Urinary proteases e.g. CYR61
  - Urinary NGAL (Neutrophil gelatinase- associated lipocalin)
Urine NGAL 2 Hrs After CPB Predicts Subsequent Development of AKI

Mishra et al. Lancet 365: 1231, 2005
Urinary NGAL as a Predictor of ARF

Urine NGAL > 25 ug/L
Sensitivity  100%
Specificity  98%

Mishra et al. Lancet 365: 1231, 2005
Urine IL-18 is Increased in Patients With ATN

Urine IL-18 (pg/mg creatinine)

* P <0.0001

Urine IL-18 Four Hrs After CPB Predicts Subsequent Development of AKI

Parikh et al. Kid Int 70:199, 2006
Use of Multiple Biomarkers

- Cross-sectional study of AKI (n= 29) vs. control (n= 45; 15 CKD and 30 normal)
- Also examined 10 patients with UTI
- Studied utility of 3 biomarkers- MMP-9, NAG, and KIM-1- alone and in combination

Han WK et al. Kid Int 73: 863, 2008
Use of Multiple Biomarkers

Han WK et al. Kid Int 73: 863, 2008
Receiver Operating Curves for Urinary Biomarkers Alone and in Combination

AUC

MMP-9 0.74
NAG 0.97
KIM-1 0.90
Combination 1.00

Han WK et al. Kid Int 73: 863, 2008
Biomarkers: Summary

• Serum creatinine is a very insensitive marker for AKI
• Cystatin C offers modest improvement
• The use of biomarkers - more likely combinations of biomarkers - is likely to improve the early diagnosis of AKI though further study is needed
• But does that matter?
Update on Pharmacologic Interventions in AKI
Diuretics in AKI

- Cohort study of 552 patients at 4 University of California Hospitals
- AKI defined as BUN $\geq 40$ mg% or Scr $\geq 2$ mg%, or (in patients with prior kidney disease) increase Scr $\geq 1$ mg%
- Patients stratified by use of diuretics (n= 326) or not (n=226) at time of nephrology consultation
- As compared to patients not treated with diuretics those who did receive diuretics were older, were more likely to have CHF or respiratory failure, and were more likely to have non-ischemic or septic causes for ARF.

Mehta et al. JAMA 288: 2547, 2002
## Diuretics in ARF

<table>
<thead>
<tr>
<th>Diuretic group</th>
<th>Odds-ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>1.65 (1.05-2.58)</td>
</tr>
<tr>
<td>Non-recovery of renal function</td>
<td>1.70 (1.14-2.53)</td>
</tr>
<tr>
<td>Death</td>
<td>1.74 (1.12-2.65)</td>
</tr>
</tbody>
</table>

*Covariate- adjusted

Mehta et al. JAMA 288: 2547, 2002
“Renal Dose” Dopamine in Early AKI

- Randomized prospective controlled trial
- n=328 in 23 ICUs
- Dopamine (2ug/kg/min) vs. placebo (saline)
- Baseline characteristics were similar in 2 groups.

ANZICS. Lancet 356: 2139, 2000
“Renal Dose” Dopamine in Early AKI

Max Scr (mg/dl)  Mortality (%)

p =NS  p =NS

ANZICS. Lancet 356: 2139, 2000
Time to Renal Recovery

ANZICS. Lancet 356: 2139, 2000
Dopamine or Furosemide in Cardiac Surgery

- Double-blind randomized control trial
- n=126; single center (University of Vienna)
- Dopamine (2µg/kg/min), furosemide (0.5 mg/kg/hr), placebo (saline)
- Baseline characteristics, fluid intake, MAP, PCWP, CVP the same in the 3 groups.

Lassnigg et al. JASN 11: 97, 2000
Dopamine or Furosemide in Cardiac Surgery

Delta Scr max (mg%) first 48 hr

Cr clearance (ml/min) first 48 hr

Lassnigg et al. JASN 11: 97, 2000
Renal Dose Dopamine in AKI

• No proven benefit

• Harmful: arrhythmias, bowel ischemia, increased myocardial $O_2$ consumption, decreased $O_2$ saturation, suppression of pituitary hormones

• Should not be routinely used
Diuretics in AKI

• Unlikely that they are beneficial in critically ill patients with AKI.

• Harmful?
  Direct tubular toxicity
  Delay in institution of dialysis- does that matter?

• Should probably be reserved for those situations in which successful diuresis will prevent- not just delay- need for dialysis.
Other Non-helpful Pharmacologic Agents Include…

- DA-like agents: fenoldopam
- Osmotic diuretics: mannitol
- CCBs: verapamil, gallopamil
- Growth Factors: CTGF, HGF
- Antioxidants: N-acetyl cysteine
- Natriuretic Peptides: ANP
Nesiritide Administered Peri-Anesthesia Trial (NAPA)

• Randomized, prospective, double-blinded, placebo-controlled
• 54 centers in US
• Studied patients with LVEF ≤ 40% undergoing CABG using CPB; ± MVR. No AVR
• Nesiritide 0.01 µg/ kg/ min x 24-96 hours (starting at time of induction) vs. placebo

Change in Serum Creatinine over Time

Placebo
p < 0.05
Nesiritide

Delta Scr modest; no mention of study of change in need for RRT.

Kaplan-Meier Survival Curves to 180 Days: Nesiritide vs. Placebo

Update on Renal Replacement Therapy in AKI
Is there data demonstrating superior outcomes with either IHD or CRRT?
Outcomes with Continuous vs. Intermittent Dialysis

- Meta-analysis of 13 studies (n=1400) (Kellum, Int.Care.Med., 2002):
  - Similar mortality rates: CRRT (68%), IHD (73.5%)
  - Adjusting for study quality and illness severity: CRRT lower mortality
  - Comparisons difficult as mortality ranged from 33%-93%

- Prospective randomized studies are difficult to perform:
  - Hemodynamically unstable patients cannot tolerate IHD
  - Difficult to confine hemodynamically stable patient to bed to do CRRT
Whichever modality one chooses, is there data to tell us whether “more” is better?
### Dose of Ultrafiltration in CVVH

**Inclusion:** ARF in ICU (75% post surgical).

Baseline Scr: 3.6 mg/dl.

**Primary end point:** survival at 15 days after stopping UF.

<table>
<thead>
<tr>
<th>n=</th>
<th>146</th>
<th>139</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mL/kg/hr)</td>
<td>20</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>41</td>
<td>57*</td>
<td>58</td>
</tr>
</tbody>
</table>

* * p<0.001 vs. 20/kg/hr

Kaplan Meier Estimation of Survival Rates in the Three Groups


p = 0.0007
(Group 1 vs. 2)
Adding a Dialysis Dose to CVVH Increases Survival in AKI

Prospective, randomized study of 206 patients. CVVH (1-2.5 L/hr replacement fluid) vs. CVVHDF (1-2.5 L/hr replacement +1-1.5 L/hr dialysate)

<table>
<thead>
<tr>
<th></th>
<th>CVVH</th>
<th>CVVHDF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 d survival (%)</td>
<td>39</td>
<td>59</td>
<td>0.03</td>
</tr>
<tr>
<td>3 month survival (%)</td>
<td>34</td>
<td>59</td>
<td>0.0005</td>
</tr>
<tr>
<td>Renal recovery (%)</td>
<td>71</td>
<td>78</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Saudan P et al. Kid Int 70: 1312, 2006
## Daily Hemodialysis in ARF

<table>
<thead>
<tr>
<th>Metric</th>
<th>Alternate day</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Hypotension/sepsis (%)</td>
<td>58/32</td>
<td>50/41</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>4.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Oliguria (%)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Weekly delivered Kt/V</td>
<td>3.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>

### Outcomes According to Treatment Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alternate-Day Hemodialysis (N = 80)</th>
<th>Daily Hemodialysis (N = 80)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality – no. (%)</td>
<td>37 (46)</td>
<td>22 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Resolution of acute renal failure (days)</td>
<td>16 ± 6</td>
<td>9 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>% HD treatments with a hypotensive episode</td>
<td>25 ± 5</td>
<td>5 ± 2</td>
<td>0.001</td>
</tr>
</tbody>
</table>


Jeffrey M. Drazen, M.D., Julie R. Ingelfinger, M.D., and Gregory D. Curfman, M.D.

In the issue of January 31, 2002, we published a study by Helmut Schiff H, M.D., Susanne M. Lang, M.D., and Rainald Fischer, M.D. It has come to our attention, through communication with Klaus Peter, Dean of the Medical Faculty at Ludwig Maximilians University in Munich, Germany, that


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“This is to inform you that the office of the rector of the university has informed us that the permanent commission of evaluation of scientific misconduct has concluded that

Accordingly, the Journal is officially removing its expression of concern.


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Whichever modality one chooses, is there data that an earlier start is better?
Potential Risks of Starting RRT too Early

- Risks of catheter placement procedure
- Line-associated bacteremia
- Immobilization
- Prolonged ICU stay
- Prolonged renal failure itself
## Timing of Initiation of Dialysis and Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Predial BUN</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Parsons 1961</td>
<td>33</td>
<td>Cohort</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Historical control</td>
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<td></td>
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<tr>
<td>Fischer 1966</td>
<td>162</td>
<td>Cohort</td>
<td>152</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Historical control</td>
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<td></td>
</tr>
<tr>
<td>Kleinknecht 1972</td>
<td>320</td>
<td>Cohort</td>
<td>93</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Historical control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conger 1975</td>
<td>18</td>
<td>Case control</td>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>Gettings 1999</td>
<td>100</td>
<td>Retrospective</td>
<td>43</td>
<td>95</td>
</tr>
<tr>
<td>Bouman 2002</td>
<td>65</td>
<td>Randomized trial</td>
<td>48</td>
<td>105</td>
</tr>
<tr>
<td>Chertow 2006</td>
<td>243</td>
<td>Observational</td>
<td>&lt;76</td>
<td>&gt;76</td>
</tr>
</tbody>
</table>

*RR death 1.85 (1.16-2.96)*

Early CRRT after Cardiac Surgery is Associated with Improved Survival- 1

- Retrospective review of 3413 patients who underwent “open heart surgery” between March, 1992 and September, 2001. Of these, 61 required CRRT.

- 3/92- 6/96 (n= 27): CVVHDF started when Scr = 5 or K > 5.5, regardless of urine output; average of 2.6 d between surgery and CVVHDF (Group 1, late).

- 6/96- 9/01(n= 34): CVVHDF started when UOP <100 mL/ hour x 8 hrs, U_{Na} > 40, no response to furosemide; average of 0.9 d between surgery and CVVHDF (Group 2, early).

Early CRRT after Cardiac Surgery is Associated with Improved Survival - 1

Early CRRT after Cardiac Surgery is Associated with Improved Survival- 2

- Retrospective review of 1264 adult patients who underwent cardiac surgery between January, 2002 and January, 2003. Of these, 64 developed AKI that required CRRT.

- Group 1 (n= 28): CVVH started when Scr $\geq$ 2.8, BUN $\geq$ 84, or $K \geq$ 6.0, regardless of urine output; average of 2.6 d between surgery and CVVH (late).

- Group 2 (n= 36): CVVH started when UOP <100 mL/hour x 8 hrs with no response to furosemide; average of 0.8 d between surgery and CVVH (early).

Early CRRT after Cardiac Surgery is Associated with Improved Survival- 2

## Pooled Effects from RCTs of Various Interventions on Mortality

<table>
<thead>
<tr>
<th>Comparison</th>
<th>References</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous renal replacement therapy vs intermittent hemodialysis</td>
<td>17, 19, 20, 23, 25, 28, 29</td>
<td>293/469</td>
<td>254/449</td>
<td>1.10 (0.99-1.23)</td>
</tr>
<tr>
<td>Continuous renal replacement therapy vs sustained low-efficiency dialysis</td>
<td>23</td>
<td>20/28</td>
<td>14/26</td>
<td>1.33 (0.87-2.03)</td>
</tr>
<tr>
<td>Hemodialfiltration vs hemofiltration</td>
<td>30</td>
<td>43/104</td>
<td>67/102</td>
<td>0.63 (0.48-0.82)</td>
</tr>
<tr>
<td>Early vs late initiation</td>
<td>24, 26</td>
<td>25/49</td>
<td>32/50</td>
<td>0.48 (0.06-3.97)</td>
</tr>
<tr>
<td>Dialysis dose ≥35 vs 20 mL/kg per h</td>
<td>26, 35</td>
<td>138/314</td>
<td>109/181</td>
<td>0.74 (0.63-0.88)</td>
</tr>
<tr>
<td>Bicarbonate vs lactate</td>
<td>33</td>
<td>20/61</td>
<td>24/56</td>
<td>0.77 (0.48-1.22)</td>
</tr>
<tr>
<td>Trisodium citrate vs heparin</td>
<td>18</td>
<td>13/16</td>
<td>10/14</td>
<td>1.14 (0.76-1.71)</td>
</tr>
<tr>
<td>Hirudin vs heparin</td>
<td>21</td>
<td>5/12</td>
<td>7/14</td>
<td>0.83 (0.36-1.95)</td>
</tr>
<tr>
<td>P2SH vs polyamideb</td>
<td>15</td>
<td>11/18</td>
<td>6/10</td>
<td>1.02 (0.54-1.90)</td>
</tr>
<tr>
<td>Polycrionitril vs polysulfone</td>
<td>39</td>
<td>69/97</td>
<td>73/100</td>
<td>0.97 (0.82-1.16)</td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>30</td>
<td>9/21</td>
<td>4/17</td>
<td>1.62 (0.68-4.90)</td>
</tr>
<tr>
<td>Daily vs alternate days</td>
<td>27, 44</td>
<td>32/97</td>
<td>45/97</td>
<td>0.83 (0.40-1.72)</td>
</tr>
<tr>
<td>Acetate-free vs bicarbonate</td>
<td>37</td>
<td>6/16</td>
<td>4/13</td>
<td>1.22 (0.43-3.42)</td>
</tr>
<tr>
<td>High vs low membrane flux</td>
<td>31, 34, 40, 42</td>
<td>76/138</td>
<td>91/149</td>
<td>0.91 (0.74-1.11)</td>
</tr>
<tr>
<td>Biocompatible membrane vs biocompatible membrane</td>
<td>32, 34, 36, 38, 40-42</td>
<td>161/336</td>
<td>173/383</td>
<td>1.11 (0.94-1.31)</td>
</tr>
</tbody>
</table>

Pooled Effects from RCTs of Interventions on Dialysis Dependence in Survivors

<table>
<thead>
<tr>
<th>Comparison</th>
<th>References</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous renal replacement therapy vs intermittent hemodialysis</td>
<td>17, 19, 20, 23, 28</td>
<td>19/155</td>
<td>20/153</td>
<td>0.91 (0.56-1.49)</td>
</tr>
<tr>
<td>Continuous renal replacement therapy vs sustained low-efficiency dialysis</td>
<td>23</td>
<td>2/8</td>
<td>2/10</td>
<td>1.25 (0.22-7.02)</td>
</tr>
<tr>
<td>Continuous renal replacement therapy</td>
<td>16</td>
<td>3/61</td>
<td>10/35</td>
<td>0.75 (0.37-1.52)</td>
</tr>
<tr>
<td>Hemodiafiltration vs hemofiltration</td>
<td>26</td>
<td>1/17</td>
<td>0/22</td>
<td>3.83 (1.17-8.62)</td>
</tr>
<tr>
<td>Early vs late initiation</td>
<td>26, 35</td>
<td>14/182</td>
<td>7/137</td>
<td>1.50 (0.61-3.64)</td>
</tr>
<tr>
<td>Dialysis dose ≥35 vs 20 mL/kg per h</td>
<td>37</td>
<td>3/10</td>
<td>4/9</td>
<td>0.68 (0.20-2.23)</td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>31, 34, 40</td>
<td>34/65</td>
<td>31/54</td>
<td>1.02 (0.75-1.39)</td>
</tr>
<tr>
<td>Acetate-free vs bicarbonate</td>
<td>32, 34, 36, 38, 40-42</td>
<td>43/175</td>
<td>57/210</td>
<td>0.94 (0.67-1.32)</td>
</tr>
</tbody>
</table>
Summary and Conclusions

- There is to date no convincing evidence that either CRRT or IHD is superior to the other; modality selection continues to be driven by clinical judgment.
- For CRRT, a higher dose ($\geq 35\text{ml/kg/hr}$) is associated with improved survival. The same may be true (but I don’t fully believe the data) for intermittent HD.
- Regardless of modality, there is to date no convincing data that early initiation of RRT provides superior outcomes. Patients undergoing major cardiovascular procedures may be the exception; but I wish we RCT data.
Thank You
Relationship Between Serum Creatinine and GFR in ARF

Moran and Myers, Kidney Int, 1985
Factors Affecting Serum Creatinine

- Nutrition
- Hepatic function
- Drugs

Muscle mass

- Protein metabolism

Plasma creatinine

Renal excretion

Infection

Edema

Volume of distribution

Nonlinear

Filtration (GFR)

Adapted from Star RA. Kidney Int, 1998
CVVH PREVENTS CONTRAST ARF

Saline or CVVH 4-8 hr before contrast and continued for 18-24 hr

<table>
<thead>
<tr>
<th></th>
<th>Saline (n=58)</th>
<th>CVVH (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Baseline SCr (mg/dl)</td>
<td>3.0</td>
<td>3.1</td>
</tr>
<tr>
<td>25% increase in SCr (%)</td>
<td>50</td>
<td>5*</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>25</td>
<td>3*</td>
</tr>
<tr>
<td>Event rate (%)</td>
<td>52</td>
<td>9*</td>
</tr>
<tr>
<td>In hospital mortality (%)</td>
<td>14</td>
<td>2*</td>
</tr>
<tr>
<td>1 year mortality (%)</td>
<td>30</td>
<td>10*</td>
</tr>
</tbody>
</table>

Marenzi et al, NEJM, 2003
TIMING OF CRRT IN POST-TRAUMATIC ARF

ARF = CrCl <30ml/min, Renal Recovery in survivors 96%
Dose to keep BUN<70, mix of modalities
Dialysis initiated at BUN<60 or BUN>60

Gettings, Intensive Care Med 1999
DOSE OF ULTRAFILTRATION (UF) IN CVVH

Ronco et al, Lancet, 2000

Survival (%)

No sepsis
sepsis

UF=1.3L/H
UF=2.3L/H
UF= 2.8L/H

20ml/kg/hr
35ml/kg/hr
45ml/kg/hr
## DAILY HEMODIALYSIS IN ARF

<table>
<thead>
<tr>
<th></th>
<th>Alternate day</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Hypotension/sepsis (%)</td>
<td>58/32</td>
<td>50/41</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>4.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Oliguria (%)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Weekly delivered Kt/V</td>
<td>3.0</td>
<td>5.8*</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>46</td>
<td>28*</td>
</tr>
<tr>
<td>Resolution of ARF (days)</td>
<td>16</td>
<td>9*</td>
</tr>
</tbody>
</table>

Schiffl et al, NEJM, 2002
Renal Replacement Therapy
Indications for RRT

- Volume overload (usually with hypoxemia)
- Acidosis (pH < 7.2)
- Hyperkalemia
- "Uremic" symptoms
  - Pericarditis
  - Altered mental status
- Hyperuricemia
Physiology of RRT

- Dialysis (diffusion)
- Ultrafiltration (convection)
Modes of Renal Replacement Therapy

• Intermittent Hemodialysis (IHD): 3-5 hrs, 3-6 times per week

• Continuous renal replacement therapy (CRRT): 24 hr per day (in theory)

• Slow low efficiency daily dialysis (SLEDD): Hybrid IHD and CRRT. 8-12 hrs per day

• Acute peritoneal dialysis: 12-24 hr per day
Hemodialysis

• This is the best modality for achieving rapid changes in solute concentration (e.g. $K^+$, $H^+$).

• May also be used to rapidly remove volume (up to 2.5 L/hr); referred to as acute ultrafiltration.

• Can often be performed without anticoagulation.

• Not always feasible hemodynamically
Variants of CRRT

- SCUF (**Slow** **Continuous** **Ultra**Filteration)
- CVVH (**Continuous Veno-Venous Hemofiltration**)
- CVVHD (**Continuous Veno-Venous HemoDialysis**)
- CVVHDF (**Continuous Veno-Venous HemoDiaFiltration**)

Advantages of CRRT over Intermittent Dialysis

- Hemodynamic stability
- Continuous fluid removal
- Minimizes fluid and electrolyte shifts
- Increased alimentation
- Elimination of inflammatory mediators
- Better control of azotemia, fluids, electrolytes and acid base
- Steady state BUN, Scr
- Minimizes shifts in ICP
- No complex machinery
- Relatively simple to perform
Disadvantages of CRRT vs. Intermittent Dialysis

- Immobilization
- Continuous anti-coagulation
- Time and labor intensive for ICU RNs
- Lactate loads (older solutions, easily avoided today)
Urine IL-18 in First 24 Hr after Kidney Transplantation

- High value in first 24 hr predicts development of delayed graft function (DGF)
- Lower in kidneys from cadaveric donor (CD) vs. living donor (LD)
- Lower value predicts faster recovery in DGF

Parikh et al. Am J Kid Dis. 2004
Urinary NGAL as a Predictor of ARF

Urine NGAL > 25 ug/L
Sensitivity 100%
Specificity 98%

Mishra et al. Lancet 365: 1231, 2005
# Percutaneous Venous Dialysis Catheters

<table>
<thead>
<tr>
<th><strong>FEMORAL</strong></th>
<th><strong>IJ</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient must lie flat</td>
<td>Ambulation possible</td>
</tr>
<tr>
<td>For short duration</td>
<td>For long duration</td>
</tr>
<tr>
<td>Easier to insert</td>
<td>More difficult to insert</td>
</tr>
<tr>
<td>Higher infection rate</td>
<td>Lower infection rate</td>
</tr>
<tr>
<td>Higher failure rate</td>
<td>Lower failure rate</td>
</tr>
</tbody>
</table>
# Treatment of ARF

<table>
<thead>
<tr>
<th>EARLY DIAGNOSIS</th>
<th>DRUG THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognize a small increase in Scr</td>
<td>Be careful with diuretics</td>
</tr>
<tr>
<td>TREAT REVERSIBLE CAUSES</td>
<td>Do not use “renal” dopamine</td>
</tr>
<tr>
<td>Prerenal</td>
<td>Specific agents e.g. NAC</td>
</tr>
<tr>
<td>Post renal</td>
<td></td>
</tr>
<tr>
<td>PREVENT FURTHER DAMAGE</td>
<td>DIALYSIS</td>
</tr>
<tr>
<td>Monitor and optimize hemodynamics</td>
<td>Early initiation</td>
</tr>
<tr>
<td>Avoid hypotension and nephrotoxins</td>
<td>Biocompatible membrane</td>
</tr>
</tbody>
</table>

UF dose based on body weight
Higher dose may be better

---

Star, Kidney Int 1998
Urea Clearance - CVVH

- UF rate 2L/hr = 48L/day
- Urea VOD for average person = 40L
- Daily Kt/V = 48/40 = 1.2
- Kt/V can be doubled by using CVVHDF
## Efficacy of Daily IHD and CRRT

<table>
<thead>
<tr>
<th></th>
<th>Daily IHD</th>
<th>24 hr CVVH</th>
<th>24 hr CVVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea clearance (L/day)</td>
<td>40-60</td>
<td>20-50</td>
<td>20-55</td>
</tr>
<tr>
<td>Urea clearance (L/week)</td>
<td>280-420</td>
<td>140-350</td>
<td>140-380</td>
</tr>
</tbody>
</table>
Prevention and Treatment of ARF

NON-DIALYTIC
• Diuretics
• Renal dose dopamine
• Acetylcysteine
• Fenoldopam

DIALYSIS
• When to start? Early vs. late.
• What type of access? Internal jugular vs. femoral
• What mode of dialysis? IHD, CRRT, PD?
• What type of membrane? Biocompatible vs bioincompatible
• What dose of dialysis?