Preventing Contrast Induced Nephropathy (CIN)

First, some renal board questions:

1. Which opioid is recommended for treatment of chronic pain in a patient with renal failure currently receiving dialysis?
   - A. Long acting morphine
   - B. Long acting oxycodone
   - C. Tramadol
   - D. Hydrocodone
   - E. Fentanyl patch

Renal Board Review

2. What drug combination is most likely to cause acute renal failure in the elderly?
   - A. Metformin and an ACE
   - B. An ACE and an ARB
   - C. An ACE and an NSAID
   - D. An ACE and a beta blocker
   - E. Methotrexate and HCTZ

Renal Board Review

3. According to JNC 8, what should be the blood pressure goal for a 65 yo AA male diabetic with stage 3a CKD? Less than:
   - A. 150/90
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   - C. 130/85
   - D. 130/80
   - E. None of the above is correct

Renal Board Review

4. After initiating an ACE inhibitor for HTN in a 50 yo female diabetic, you note a rise in creatinine from 1.0 to 1.3. This rise predicts:
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   - B. Impending acute renal failure
   - C. A positive microalbumin test
   - D. The future need for dialysis
   - E. The need for at least 2 agents for BP control

Renal Board Review

5. Which anticoagulant does not need a dosing adjustment for CKD when used for thromboembolism prophylaxis?
   - A. Rivaroxaban (Xarelto)
   - B. Apixaban (Eliquis)
   - C. Enoxaparin (lovenox)
   - D. Dabigatran (Pradaxa)
   - E. Heparin
Case Study

- Mr. Peters, a 52 yo WM, presents with symptoms consistent with a ureteral stone. His plain abdominal film, however, fails to show any calcifications within the urinary tract. You decide to order a CT – Stone protocol.

- Mr. Peters baseline creatinine is 1.3 with an eGFR of 58. He is not a diabetic. He has a 10 yr h/o treated HTN and no h/o CAD or heart failure.

- Would any measures to decrease Mr. Peters risk of Contrast Induced Nephropathy (CIN) be warranted?

- If so, what would you order?

Learning Objectives

1. Define CIN
2. Understand pathophysiology of CIN
3. Be able to risk assess patients for CIN
4. Describe various prophylactic strategies for CIN

Definition - CIN

- Most Accepted – research definition
  - A rise in creatinine from baseline of 0.5mg/dl OR a 25% rise in baseline creatinine within 3 days after administration of contrast media.

- Acute Kidney Injury Network – 2009
  - A rise in creatinine of 0.3mg/dl above baseline with oliguria

Risk factors for CIN

- Preexisting renal insufficiency
  - Most important risk factor
  - In 3232 patients undergoing contrast study:\n    - 5.3% incidence in those with creatinine <1.2
    - 15.7% incidence in those with creatinine > 1.2
  - In Minnesota Registry of Cardiac Procedures
    - 22% for creatinine 2-3, 30% for creatinine > 3

- Diabetes
  - Risk varies from 5.7 to 29.4%. Correlates with renal function

Risk factors for CIN

- Age
  - > 75 is an independent risk factor
- Anemia
- Congestive Heart Failure
- Contrast media
  - Osmolality
  - Volume
- Hypotension

Creating a risk calculator

- Roxana Mehran, et al\(^1\): “A simple risk score for prediction of Contrast Induced Nephropathy after percutaneous coronary intervention”
  - 8,357 consecutive patients undergoing PCI at Columbia University Medical Center
  - 16 variables showed a significant association with CIN occurrence
  - 8 variables chosen for risk tool

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportion (%)</th>
<th>ODDS</th>
<th>99% CI</th>
<th>p-value</th>
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<td>0.69-0.72</td>
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<td>1.9</td>
<td>1.05</td>
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Renal Physiology (The Glorious Kidney)
Little known fact #1

- 90% of total renal blood flow normally goes to cortex – 10% to medulla
- 80% of renal O₂ consumption supports Na⁺K⁺ATPase in the medulla
- “Remote from the vasa recta, the outer medulla always operates on the verge of hypoxia”¹


Pathophysiology of CIN

- Unknown, but thought to be multifactorial
- Related to
  - Contrast osmolality
  - Shifts in renal blood flow
  - Release of adenosine by macula densa
  - Increased renal interstitial pressure
  - Increased reactive oxygen species
  - Inflammation
- All leading to medullary ischemia
Strategies for preventing CIN

• What DOESN'T work:
  ▫ Calcium channel blockers
  ▫ Diuretics (lasix worsens risk)
  ▫ Atrial natriuretic peptide
  ▫ Theophylline
  ▫ Dopamine
  ▫ Fenoldapam

• Type of contrast media
• Withholding renal risky drugs
• Hydration
• Alkalization of urine
• Ascorbic acid
• N-acetylcysteine
• Statins
• Ischemic preconditioning

Contrast Characteristics

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<tr>
<th>Type of contrast media</th>
<th>Chemical name</th>
<th>Injection volume</th>
<th>Dosage at 1°C</th>
<th>Volume at 25°C</th>
<th>Max. injection rate</th>
<th>Reaction time</th>
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Withholding renal risky drugs

• NSAIDS
• Metformin
• Vancomycin
• Aminoglycosides
• Amphotericin B
• Chemotherapeutic agents

Hydration

• Consistent randomized data document benefit
  ▫ IV superior to oral
  ▫ Isotonic superior to half normal

• Optimum regimen not determined
  ▫ Standard suggested regimen is isotonic fluids at 1ml/kg/hr for 12 to 24 hrs before procedure, carried through to 12 to 24 hrs after procedure

Urine alkalinization

• Sodium bicarbonate
  ▫ May decrease generation of free radicals
  ▫ May scavenge peroxynitrate, a potent oxidant
  ▫ Isotonic bicarb shown to be effective in most studies
    ▫ Systematic review – 23 studies
    ▫ Pooled RR 0.62 for CIN
  ▫ No clear benefit on dialysis, heart failure, mortality

Ascorbic Acid

- Potent antioxidant
- Initial RCT noted sig protection from CIN\(^1\)
- 2007 RCT comparing 3 prevention strategies noted no benefit with added AA\(^2\)
- 2009 RCT comparing AA to NAC reported latter significantly more beneficial\(^3\)

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N-Acetylcysteine

- Antioxidant and vasodilator
- Initial study in 2000 noted “amazing” protection
  - 83 patients with renal insuff (mean creatinine 2.4) randomized to either 600mg NAC bid or placebo
  - Patients undergoing CT with low molecular contrast
  - RR 0.1 – 1 patient in treatment group vs 9 patients in control

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Tepel, et al. 2000

- **Little known fact #2**
  - N-Acetylcysteine increases tubular secretion of creatinine\(^4\)
  - **Implications**
    - Changes in serum creatinine measurements may not reflect changes in GFR
    - Thus trials that do not measure outcomes may overstate NACs renal protection

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NAC meta-analyses

- As of 2012, 11 meta-analyses have been conducted
  - 7 out of 11 have found a net benefit.
  - Mean RR of 0.62

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2006 Meta Analysis - NAC vs placebo
Statins

- Anti-inflammatory, improve endothelial function, anti-apoptotic
- Between 2002 and 2005, 5 cohort studies showed patients on long term statins had lower rates of CIN than non-users
- 2005-2008 – 9 RCT’s explored peri-procedure administration of statins
  - 3 showed protection vs placebo
  - 3 showed high dose protection vs low dose
  - 3 showed no protection

PRATO-ACS

- Results
  - CIN RR – 0.43, p=0.003
  - 30 day death or MI – RR 0.5
  - 30 day persistent renal damage – RR 0.42
  - At 6 months, those who developed CIN had a higher rate of death or MI (12.7% vs 4.5%, p=0.02)
  - Those in statin group had trend toward decreased death and nMI (3.6% vs 7.2%, p=0.07)

Ischemic preconditioning

- What is it?
  - Deliberate induction of transient, nonlethal ischemia in a remote organ prior to contrast
- How does it work? (Theory)
  - Vasodilatory factors as well as those protecting cells from oxidative stress are released into the blood stream which protect the renal medulla
  - 2 recent trials, 2012 and 2013, showed RR’s of 0.2 to 0.3. Both showed less death or rehospitalization at 30 days.
  - Intriguing. No one’s ready to jump on this ship yet.

Summary/Guidelines

1. Risk assess all patients who will be receiving IV contrast
2. Use iso or low osmolality contrast
3. Consider alternative imaging for those at highest risk of CIN (>50% risk)
4. For those at increased risk (>7.5%), hydrate with isotonic saline (INS) or isotonic bicarb (uptodate)
5. For those at increased risk, Consider NAC at 1200mg bid 24 hrs before and 24 hrs after imaging (INS, uptodate – Yes; ACC/AHA – No)
6. Consider starting rosuvastatin, 40mg prior to procedure, 20mg daily until d/c, or beyond
Back to our Board questions

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