Contrast Induced Nephropathy

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Contrast Induced Nephropathy

- CIN is the development of acute renal failure after the administration of intravenous contrast
- It is defined as an absolute increase in serum creatinine of ≥ 0.5 mg/dL or a relative increase of ≥ 25% above baseline within 2 to 7 days after contrast exposure
- CIN is the third most common cause of hospital-acquired acute renal failure

Contrast Induced Nephropathy

- CIN increases morbidity, mortality and length of hospital stay
- Patients who developed a relative increase in serum creatinine of only 25 to 50% within 3 days after cardiac catheterization had a 1.4 fold increase in odds for death, while those who doubled their serum creatinine had a 3.6 fold increase in odds for death

CIN and Mortality

Weisbord et al; J Am Soc Nephr 2006
Risk Factors for CIN

### Patient Related
- Preexisting renal dysfunction with an estimated GFR of less than 60 mL/min or serum creatinine of ≥ 1.5 mg/dL
- Patients with DM
- Hypovolemia
- Cardiovascular disease
- Intra-aortic balloon pump
- Advanced age
- Exposure to nephrotoxins (NSAID, CSA)

### Procedure Related
- High volume of contrast
- Type of intravenous contrast – ionic vs nonionic, iso-osmolar/low-osmolar vs high-osmolar
- Multiple exposures to contrast agents

Risk Score for CIN after PCI

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Points</th>
<th>Risk for CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP &lt; 80</td>
<td>5</td>
<td>&lt; 6</td>
<td>7.5%</td>
</tr>
<tr>
<td>IABP</td>
<td>5</td>
<td>6-10</td>
<td>14%</td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
<td>11-16</td>
<td>26.1%</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>4</td>
<td>&gt; 16</td>
<td>57.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Contrast Vol</td>
<td>1/100 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR 40-60</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR 40-20</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR &lt; 20</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Iodinated Contrast Agents

- Ionic high-osmolar agents
- Nonionic low-osmolar agents
- Nonionic iso-osmolar agent
- Iso-osmolar/low-osmolar agents are less nephrotoxic than high-osmolar agents
### Iodinated Contrast Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Ionic</th>
<th>Non-ionic low-osmolar</th>
<th>Non-ionic iso-osmolar</th>
<th>Osmolality (mosm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metrizoate (Isopaque)</td>
<td>+</td>
<td></td>
<td></td>
<td>2100</td>
</tr>
<tr>
<td>Diatrizoate (Hypaque)</td>
<td>+</td>
<td></td>
<td></td>
<td>1530</td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td>+</td>
<td></td>
<td></td>
<td>580</td>
</tr>
<tr>
<td>Iopamidol (Isovue)</td>
<td>+</td>
<td></td>
<td></td>
<td>616</td>
</tr>
<tr>
<td>Iohexol (Omnipaque)</td>
<td>+</td>
<td></td>
<td></td>
<td>640</td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td>+</td>
<td></td>
<td></td>
<td>290</td>
</tr>
</tbody>
</table>

### Pathogenesis

- **Contrast Agent**
  - ↑Endothelin/Adenosine
  - ↓NO and Prostaglandines
  - Direct cytotoxic effect
  - Increase interstitial pressure
  - Vasoconstriction
  - ↓Medullary Blood flow
  - ARF/Acute Tubular Necrosis

### Risk of CIN in patients with and without renal insufficiency (RI) and Diabetes (DM)

- **RI(-) DM(-)**
- **RI (+) DM(-)**
- **RI(+)DM(+)**

N=1196

### Drugs to hold prior to IV contrast administration

- Metformin - ↑risk of lactic acidosis
- NSAIDS - ↑risk of CIN
- Diuretics - ↑risk of CIN
- Mannitol - ↑risk of intravascular volume contraction
- Cyclosporin - ↑risk of CIN

ACE inhibitors and ARB may be continued in stable patients on long term therapy.
### Clinical Manifestations

- Incidence ranges from less than 2% in the general population to more than 50% depending on risk factors and various definitions.
- The risk is negligible with normal renal function.
- Nephrotoxicity ranges from a nonoliguric transient mild renal failure to severe renal failure requiring hemodialysis.

### Clinical Manifestations

- Urinalysis shows muddy brown casts typical for acute tubular necrosis.
- Differential diagnosis includes atheroembolic disease, interstitial nephritis, different etiologies of acute tubular necrosis including sepsis and other nephrotoxins, and prerenal acute kidney injury.

### Clinical Manifestations

- In the majority of cases the renal failure is mild and improves within 3 to 5 days.
- Persistent renal dysfunction may develop in some patients.
- End stage renal disease may develop especially in patients with advanced chronic kidney disease and diabetes.

### Management of Contrast Induced Nephropathy

- The main issues are detection of risk factors and prevention.
- Treatment is not effective in established CIN.
- Diuretics are used for volume control and do not expedite the recovery of renal function.
- Renal replacement therapy is required if renal function worsens and/or volume status deteriorates.
Contrast Induced Nephropathy: Prevention

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The Ohio State University

Strategies for Prevention of CIN

1. Volume Expansion
2. Bicarbonate
3. N-acetylcysteine
4. Choice of contrast agent
5. Hemodialysis and Hemofiltration

Outline

1. Strategies for prevention of CIN
2. Consensus panel recommendations
3. Algorithm for patients receiving contrast

Prevention of CIN
Volume Expansion

**Prevention of CIN**

**Volume expansion – Oral vs IV**

- IV fluid administration is superior to oral hydration.
- Isotonic saline is superior to hypotonic fluid.
- Both Lasix and Mannitol – increase the risk for CIN.

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**Prevention of CIN**

**Bicarbonate**

- Merten: JAMA 291; 2328-2334: 2004

<table>
<thead>
<tr>
<th></th>
<th>IV saline (n=59)</th>
<th>Bicarbonate (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN %</td>
<td>13.6 (8)</td>
<td>1.7 (1)</td>
</tr>
</tbody>
</table>

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**Prevention of CIN**

**Bicarbonate (REMEDIAL trial)**

<table>
<thead>
<tr>
<th></th>
<th>Saline + NAC</th>
<th>Bicarbonate + NAC</th>
<th>Saline + Ascorbic acid + NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>CIN</td>
<td>11 (9.9%)</td>
<td>2 (1.9%)*</td>
<td>10 (10.3%)</td>
</tr>
</tbody>
</table>

*Relatively small study size. If 1 patient less in Saline group and 1 more patient in Bicarb group had developed CIN – results would be NS.*
**Prevention of CIN**

**Bicarbonate (RENO trial)**

<table>
<thead>
<tr>
<th>Group A: n=56</th>
<th>Group B: n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre procedure</td>
<td>Post procedure IV</td>
</tr>
<tr>
<td>Bicarbonate + NAC</td>
<td>Saline + NAC</td>
</tr>
<tr>
<td>CIN</td>
<td>1/56 (1.8%)</td>
</tr>
</tbody>
</table>

- Rates of fluid different in both groups
- Difference in outcome could be due to difference of fluid given pre procedure rather than due to Bicarbonate


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**Prevention of CIN**

**N-Acetylcysteine**

- Subject of numerous clinical trials and intense debate
- First study in NEJM 2000, Tepel
- Since then 25 RCT and 17 meta-analyses with conflicting results

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**Prevention of CIN**

**Bicarbonate**

- Insufficient Data to make firm recommendation for prevention of CIN

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**Prevention of CIN**

**N-Acetylcysteine**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ACETYL-CYSTEINE GROUP (N=41)</th>
<th>CONTROL GROUP (N=42)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine concentration — mg/dl</td>
<td>2.5±1.3</td>
<td>2.4±1.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Change 48 hr after administration of contrast agent</td>
<td>-0.4±0.4</td>
<td>+0.2±0.6</td>
<td>-0.001†</td>
</tr>
<tr>
<td>Incidence of acute reductions in renal function — no. (%)</td>
<td>1 (2)</td>
<td>9 (21)</td>
<td>0.01‡</td>
</tr>
</tbody>
</table>

Tepel, NEJM 2000
Prevention of CIN
Intravenous N-Acetylcysteine

<table>
<thead>
<tr>
<th>End point</th>
<th>N-Acetylcysteine (n = 220)</th>
<th>Placebo (n = 227)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>23.3%</td>
<td>20.7%</td>
<td>.51</td>
</tr>
<tr>
<td>Secondary end points</td>
<td>24.5%</td>
<td>20.0%</td>
<td>.58</td>
</tr>
<tr>
<td>≥ 5 mL/min decline in creatinine clearance (Cockcroft-Gault formula)</td>
<td>7.3%</td>
<td>5.7%</td>
<td>.57</td>
</tr>
<tr>
<td>≥ 44 μmol/L increase in serum creatinine</td>
<td>11.4%</td>
<td>10.6%</td>
<td>.88</td>
</tr>
</tbody>
</table>

*Limitation: Rate of CIN in control group significantly high

Marenzi; NEJM 2006;354:2773-82

Prevention of CIN
N-Acetylcysteine

• Despite large number of studies, literature is inadequate to resolve the question of NAC’s effectiveness at preventing CIN

Bagshaw; Arch Int Med 166:161-166, 2006

Prevention of CIN
Choice of Contrast Agent

• Low-osmolar/Iso-osmolar contrast agents substantially decrease CIN in high risk patients as compared to high-osmolar contrast agent

• Low-osmolar vs Iso-osmolar?

Standard-Dose N-Acetylcysteine Group

Control Group (N=113) | N-Acetylcysteine Group (N=113) | High-Dose N-Acetylcysteine Group (N=110) | P Value |

Contrast-medium-induced nephropathy (≥25% increase in serum creatinine concentration) | 10 (9) 9% | 17 (15) 15% | 10 (9) 9% | <0.001 |

*Marenzi; NEJM 2006;354:2773-82
Prevention of CIN
Choice of Contrast Agent

"NEPHRIC study"

Aspelin; NEJM 2003

N=129
Iodixanol: Iso-osmolar
Iohexol: Low-osmolar

Differences in Nephrotoxicity between Iodixanol and Iohexol

Prevention of CIN
Choice of Contrast Agent

General Consensus:

- In high risk patients – an iso-osmolar or low-osmolar contrast agent should be used
- Minimize volume of contrast agent
- Avoid repetitive exposure to contrast in short period of time

Prevention of CIN
Hemodialysis and Hemofiltration

Cruz; Am J Kid Dis 2006

Prevention of CIN
Hemofiltration- CVVH

Marenzi; Am J Med 2006
Prevention of CIN
Hemodialysis and Hemofiltration

- Studies of Hemodialysis after contrast have suggested the potential for harm
- The relative risk for CIN associated with HD was 1.35
- Prophylactic CVVH not recommended

Prevention of CIN
Consensus Panel Recommendations

1. All patients must be evaluated for CIN risk. Presence of multiple risk factors can create a risk of 50% for CIN and risk of 15% ARF requiring dialysis
2. All patients should be in optimal volume status. Intravenous Normal saline 1 to 1.5 ml/kg for 3 to 12 hrs before and 6 to 24 hr after the procedure. Data on oral fluid is insufficient
3. High risk patients considered for pharmacologic prophylaxis with therapies supported by clinical evidence
4. Non ionic, iso-osmolar contrast medium is associated with lowest risk for CIN

Prevention of CIN
Consensus Panel Recommendations

- Consensus Panel for CIN
- CIN Consensus Working Panel

5. Intra-arterial administration of contrast pose a greater risk than intravenous
6. High contrast volume associated with higher rates of CIN in patients at risk
7. Drugs that adversely affect renal functions should be withheld
8. Follow up creatinine in 24-72 hrs after exposure
9. Prophylactic Hemodialysis and Hemofiltration have not been validated as effective
## Prevention of CIN Recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Details</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous saline</td>
<td>IV 0.9% saline 1-2 ml/kg/hr for 24 hrs, beginning 4-6 hrs before procedure</td>
<td>Generally recommended Maintain euvoemia</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>600 mg PO Q 12 hrs for 4 doses, begin the day before procedure</td>
<td>Not generally recommended pending more data on efficacy</td>
</tr>
<tr>
<td>IV Sod Bicarbonate</td>
<td>154 mmol/L at 3 ml/kg/hr before and 1 ml/kg/hr for 6 hrs after procedure</td>
<td>Not generally recommended unless efficacy confirmed by further trials</td>
</tr>
</tbody>
</table>

Barrett. NEJM 2006

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## Algorithm for patients receiving contrast

- Calculate eGFR
- Assess CIN risk
- eGFR >90 mL/min
- Hospitalization
- Nephrology consultation
- Dietary planning
- Other strategies as for eGFR 30–90 mL/min
- Intravenous volume expansion
- Renal, arterial
- Intravenous volume expansion
- Total volume: 600 mL
- Consult cardiology
- Serum Cr on discharge or within 24–72 hrs