Contrast Media-Induced Nephropathy: What you’re DYEing to know about!!

Stephen M. Korbet, M.D.
Professor of Medicine
Cases

FP is a 78 yo WF with a long history of DM and HTN was admitted for evaluation of chest pain, nausea and vomiting. Her SCr was 1.0, Urinalysis- Normal.

CB is an 81 yo WM with a history of HTN, renal cell CA s/p right nephrectomy in 2002 and metastatic prostate CA was admitted for evaluation of low back pain.

His SCr was 1.2 mg/dl, urinalysis- Normal, and Renal US-L kidney 14.6 cm, no hydrenephrosis.
In both cases a contrast CT of abdomen and pelvis was performed using 125 ml of iopamidol (Isovue)
Days
Contrast Study
Contrast Study
FP
CB
FP UO
CB UO
SCr [mg/dl]
Urine Vol [L/day]
What is the incidence of hospital acquired acute renal failure and what are the causes?
Hospital Acquired ARF: The Rush Experience

- Prospective study from Feb to June 1996 (4 mo)
- 4,622 consecutive medical and surgical admissions
- Acute renal failure during the hospitalization
- ARF defined by an increase in SCr of $\geq 0.5$ mg/dl
- ARF developed in 332 (7%) patients

Nash et al. AJKD 2002
<table>
<thead>
<tr>
<th>Cause</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased renal perfusion</td>
<td>147 (44%)</td>
</tr>
<tr>
<td>Medications</td>
<td>61 (18%)</td>
</tr>
<tr>
<td>Radiographic contrast media</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>35</td>
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<td>Sepsis</td>
<td>25</td>
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Nash et al. AJKD 2002
## Hospital Acquired ARF: The Rush Experience

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Nash et al. AJKD 2002
### Hospital Acquired ARF: The Rush Experience

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>61</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>18</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>13</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>7</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>6</td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>6</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>2</td>
</tr>
<tr>
<td>Multiple nephrotoxins (&gt;3)</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin, cis-platinum, acyclovir, ceftazidime</td>
<td>1</td>
</tr>
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Nash et al. AJKD 2002
### Hospital Acquired ARF: The Rush Experience

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Nash et al. AJKD 2002
## Hospital Acquired ARF: The Rush Experience

### Type of Contrast Study Resulting in ARF

<table>
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<tr>
<th>Study</th>
<th>Result</th>
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<tbody>
<tr>
<td>Cardiac cath and coronary angioplasty</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>CT scan</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Peripheral angiogram</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (12%)</td>
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<tr>
<td>TOTAL</td>
<td>43</td>
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Proportion of Contrast Studies Resulting in ARF
(Overall, 750 Cardiac Caths and 825 CTs done in 4 mo)

Cardiac cath and coronary angioplasty 2.8%
CT scan 1.7%

Nash et al. AJKD 2002
Contrast media-induced nephropathy
Dermatologists at the Mayo Clinic studying the use of iodine-containing compounds in the treatment of syphilis

They recognized the value of the known radiopacity and renal excretion of iodine in rendering the urinary tract opaque to x-ray
ROENTGENOGRAPHY OF URINARY TRACT DURING EXCRETION OF SODIUM IODID*

EARL D. OSBORNE, M.D.
CHARLES G. SUTHERLAND, M.B. (Tor.)
ALBERT J. SCHOLL, JR., M.D.
AND
LEONARD G. ROWNTREE, M.D.
ROCHESTER, MINN.

Jour. A.M.A.
Feb 10, 1923
1930, proposed using an organic nucleus as iodine carrier
Benzoic acid is metabolized to hippuran
Hippuran is excreted by the kidneys
Lead to the development of sodium diatrozoate in 1950s

Moses Swick, MD
“father of intravenous urography”
• Sodium salt of tri-iodinated benzoic acid
• Ionic with high osmolarity (>1500 mOsm/kg)
• Water soluble, not protein bound, mol wt- 636
• 99% excreted by glomerular filtration
• Renal clearance of 50% by 30-60 minutes
BRIEF RECORDING

Acute Renal Failure after Drip-Infusion Pyelography*

LAWRENCE A. BERGMAN, M.B., B.Sc., M.R.C.P. (Lond.),
MACEO R. ELLISON, M.D., and
GEORGE DUNEA, M.B., M.R.C.P. (Lond. & Ed.)

*From the Hemodialysis Unit and the Department of Medicine, Mount Sinai Hospital Medical Center and Chicago Medical School (address reprint requests to Dr. Dunea at 2750 W. 15 Pl., Chicago, Ill. 60608).
A 52-year-old normotensive diabetic man was known to have had proteinuria and diabetic retinopathy for several years. Elevation of blood urea nitrogen was first recorded some 12 months earlier, and further deterioration in renal function occasioned admission to the hospital (with a blood urea nitrogen of 63 mg and serum creatinine of 4.5 mg per 100 ml). His general condition was good. The urine volume was about 2000 ml, and protein excretion 1.3 gm per 24 hours.

Shortly after admission drip-infusion pyelography was done with the use of 150 ml of meglumine diatrizoate† in 150 ml of 3 per cent sodium chloride, the infusion being completed in 10 minutes. There were no immediate adverse reactions, but severe oliguria (excretion of less than 400 ml per day) developed within several hours after the procedure was completed. An attempt to induce diuresis with mannitol failed. Oliguria persisted for three days, after which a spontaneous diuresis ensued. Subsequent progress has been uneventful.
Osmolarity (mOsm/kg)

High (>1500)

Ionicity

Ionic

Diatrizoate

6 mPa.S

Benzine rings

Monomer

Iohexol

5-10 mPa.S

Name

Dimer

Iodixanol

11 mPa.S

Viscosity at 98.6°F

Iso (280)

Nonionic

Iso
What is the definition and presentation of contrast media-induced nephropathy?
Contrast media-induced nephropathy:

An increase in serum creatinine within up to 48-72 hours of a contrast procedure

Increase in serum creatinine

Absolute: 0.5 mg/dl

Relative: 25%
• Overall incidence of ARF from contrast is 3%

• The incidence is 0.6% in patients with normal renal function

In 2010, 3.3 million Cardiac Angio & 70 million CTs
0.03 x 73 = 2.2 million

Rudnick et al, KI 1995
Contrast Media-induced Nephropathy

- Usually non-oliguric
Contrast Media-induced Nephropathy

- Usually non-oliguric
- Urinalysis has minimal or no proteinuria and bland sediment with granular casts
Contrast Media-induced Nephropathy

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- Urinalysis has minimal or no proteinuria and bland sediment with granular casts
- Fractional excretion of sodium is low
Contrast Media-induced Nephropathy

- Usually non-oliguric
- Urinalysis has minimal or no proteinuria and bland sediment with granular casts
- Fractional excretion of sodium is low
- Serum creatinine peaks by 4 to 5 days
What are the proposed mechanisms for contrast media-induced nephropathy?
Contrast media induces CYTOTOXIC and HEMODYNAMIC insults.

Idee et al. Invest Radiol 2004
Contrast Media

Cellular effects
- vacuolization
- necrosis
- apoptosis
- effects mesangial cells
- inhibits protein reabsorption

Acute Renal Failure

Idee et al. Invest Radiol 2004
Altered Mitochondrial Function in Porcine Proximal Tubule Cell Line

MTT reduction, percent of control

Contrast media, mg/L/mL

Low- Iso- Hyper-
Contrast Media

Cellular effects
- vacuolization
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Hemodynamic effects

Acute Renal Failure

Idee et al. Invest Radiol 2004
Contrast Media

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Hemodynamic effects

Osmolality related

Osmolality unrelated

Acute Renal Failure

Idee et al. Invest Radiol 2004
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- Osmolality related
  - adenosine release ↑
- Osmolality unrelated

Acute Renal Failure

Idee et al. Invest Radiol 2004
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Acute Renal Failure

Idee et al. Invest Radiol 2004
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Medullary hypoxia + Free radicals

Acute Renal Failure

Idee et al. Invest Radiol 2004
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Medullary hypoxia + Free radicals

Acute Renal Failure

Idee et al. Invest Radiol 2004
Effect of Contrast on pO$_2$ in the Cortex

Effect of Contrast on pO₂ in the Outer Medulla

[Graph showing the effect of contrast on pO₂ over time.]

Osmolarity (mOsm/kg)
- High (>1500)

Ionicity
- Ionic

Benzine rings
- Monomer

Name
- Diatrizoate

Viscosity at 98.6F
- 6 mPa.S
Osmolarity (mOsm/kg) → Ionicity

- **High (>1500)**: Ionic
  - Monomer: Diatrizoate (6 mPa.S)
  - Monomer: Iopamidal (5-10 mPa.S)
- **Low (600-1000)**: Nonionic
  - Monomer: Iohexol

**Viscosity at 98.6°F**
- Diatrizoate: 6 mPa.S
- Iopamidal: 5-10 mPa.S
<table>
<thead>
<tr>
<th>Name</th>
<th>Osmolarity (mOsm/kg)</th>
<th>Ionicity</th>
<th>Benzine rings</th>
<th>Viscosity at 98.6°F</th>
</tr>
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<tbody>
<tr>
<td>Diatrizoate</td>
<td>&gt;1500</td>
<td>High</td>
<td>Monomer</td>
<td>6 mPa.S</td>
</tr>
<tr>
<td>Iopamidal</td>
<td>(600-1000)</td>
<td>Low</td>
<td>Dimer</td>
<td>5-10 mPa.S</td>
</tr>
<tr>
<td>Iohexol</td>
<td>(280)</td>
<td>Iso</td>
<td>Nonionic Dimer</td>
<td>11 mPa.S</td>
</tr>
<tr>
<td>Iodixanol</td>
<td></td>
<td></td>
<td>Nonionic</td>
<td></td>
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</table>
Effect of Contrast on $pO_2$ in the Outer Medulla

![Graph showing the effect of contrast on $pO_2$ over time. The graph indicates a decrease in $pO_2$ after injection, with different lines representing iso-osmolar and low-osmolar conditions.](image-url)

Liss et al. KI 1998
Iso-osmolar compounds have greater viscosity
Contrast Media

Cellular effects
- vacuolization
- necrosis
- apoptosis
- effects mesangial cells
- inhibits protein reabsorption

Hemodynamic effects
- Osmolality related
- Osmotic diuresis
- adenosine release ↑
- Medullary hypoxia + Free radicals
- Acute Renal Failure

Osmolality unrelated
- vasoconstriction

Idee et al. Invest Radiol 2004
Contrast Media

Cellular effects
- vacuolization
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Hemodynamic effects

Osmolality
- related
  - Osmotic diuresis
    - ↑Na⁺ delivery
      - Medullary hypoxia
        - Free radicals
          - Acute Renal Failure
  - adenosine release ↑

Osmolality
- unrelated
  - vasoconstriction

Idee et al. Invest Radiol 2004
Contrast Media

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Osmolality related
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- Medullary hypoxia + Free radicals
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Osmolality unrelated
- adenosine release ↑
- vasoconstriction

Ideé et al. Invest Radiol 2004
Contrast Media

Cellular effects

- vacuolization
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Hemodynamic effects

Osmolality

- related
  - Osmotic diuresis
  - Na\(^+\) delivery
  - Medullary hypoxia + Free radicals
  - Acute Renal Failure

- unrelated
  - adenosine release \(\uparrow\)
  - vasoconstriction

Idee et al. Invest Radiol 2004
Contrast Media

Cellular effects
- vacuolization
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Hemodynamic effects
- Osmolality related
  - Osmotic diuresis
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- Osmolality unrelated
  - ↑endothelin release
  - vasoconstriction

Ideé et al. Invest Radiol 2004
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- Osmolality unrelated
  - adenosine release ↑
  - endothelin release ↑
  - vasoconstriction

Acute Renal Failure

Idee et al. Invest Radiol 2004
Increased In-Vivo Plasma Endothelin Levels are Not Related to Contrast Osmolarity

Saline
Isohalenate
Ioxaglate
Iohexol
Hypertonic saline
Hypertonic glucose
Hypertonic mannitol

Plasma endothelin, fmol/ml

Solomon: KI 1998
Contrast Media

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Hemodynamic effects
- Osmolality related
  - Osmotic diuresis
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- Osmolality unrelated
  - ↑endothelin release

↑Na⁺ delivery + vasoconstriction

Medullary hypoxia + Free radicals

Acute Renal Failure

Idee et al. Invest Radiol 2004
What is the course and outcome in contrast media-induced nephropathy?
Contrast Media-induced Nephropathy

- Serum creatinine peaks by 4 to 5 days and returns to baseline over 7 to 10 days
Morbidity of Contrast Media-induced Nephropathy

- Increases length of hospital stay
- Need for dialysis (10-25%)
- Failure of SCr to return to baseline (30%)
- Associated with increased patient mortality (34%)

Solomon: KI 1998
Increased Mortality Associated with Contrast Media-induced Nephropathy

- 16,248 hospitalized pts having contrast studies
- Contrast induced ARF - 1.1%
- ARF requiring dialysis - 12%

<table>
<thead>
<tr>
<th>Mortality rate:</th>
<th>Yes</th>
<th>No</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF</td>
<td>34%</td>
<td>7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>60%</td>
<td>31%</td>
<td>&lt;0.01</td>
</tr>
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- CMIN increased the risk of severe non-renal causes of death (sepsis, bleeding, resp failure, delerium)

Levy et al, JAMA 1996
## Hospital Acquired ARF: The Rush Experience

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<td>3 (37.5)</td>
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<td>Obstruction</td>
<td>7</td>
<td>2 (28.6)</td>
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<td>Hepatorenal</td>
<td>7</td>
<td>5 (71.4)</td>
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Nash et al. AJKD 2002
What are the risk factors for contrast media-induced nephropathy?
## Risk Factors for Contrast Nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td><strong>Patient Related</strong></td>
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</tr>
<tr>
<td>SCr level (mg/dl):</td>
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<tr>
<td>1.2-1.9</td>
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<tr>
<td>Diabetes mellitus</td>
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Goldenberg & Matetzky  
CMAJ 2005
Renal Function Predicts Risk of Contrast Nephropathy

 MCCULLOUGH, APPLICATIONS IN IMAGING 2003

Calculated CrCl (mL/min)

Renal Event Rate

Diabetic
Non-diabetic

CMIN
Dialysis

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

0 1 2 3 4 5 6 7 8 9 10

McCullough, Applications in Imaging 2003
# Risk Factors for Contrast Nephropathy

**Goldenberg & Matetzky**  
*CMAJ* 2005

### Risk Factor Odds ratio

#### Patient Related

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</tr>
<tr>
<td>Age (per yr increase)</td>
<td>1.02</td>
</tr>
<tr>
<td>CHF</td>
<td>1.5</td>
</tr>
<tr>
<td>HTN</td>
<td>1.2</td>
</tr>
<tr>
<td>Low effective circulatory volume</td>
<td>1.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.9</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>1.9</td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Low vs high osmolar in CRI</td>
<td>0.5</td>
</tr>
<tr>
<td>Volume of contrast (per 100 mL)</td>
<td>1.12</td>
</tr>
</tbody>
</table>

Goldenberg & Matetzky
CMAJ 2005
The increased risk in patients with DM, HTN or vascular disease may be a result of “endothelial dysfunction” with decreased release of vasodilatory substances such as nitric oxide.
## Risk Assessment to Predict Contrast Nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</tr>
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<tbody>
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</tr>
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</tr>
<tr>
<td>CHF</td>
<td>5</td>
</tr>
<tr>
<td>SCr &gt;1.5 mg/dl</td>
<td>4</td>
</tr>
<tr>
<td>Age &gt;75 yrs</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Volume of contrast (per 100 mL)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Risk categories

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>ARF (%)</th>
<th>HD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ≤5</td>
<td>8%</td>
<td>0.04%</td>
</tr>
<tr>
<td>Moderate 6-10</td>
<td>14%</td>
<td>0.1%</td>
</tr>
<tr>
<td>High 11-15</td>
<td>26%</td>
<td>1%</td>
</tr>
<tr>
<td>Very High ≥16</td>
<td>57%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Mehran et al, J Am Coll Cardiol 2004
## Risk Assessment to Predict Contrast Nephropathy

### Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<th>FP</th>
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</tr>
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Mehran et al, J Am Coll Cardiol 2004
## Risk Assessment to Predict Contrast Nephropathy

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</table>

Mehran et al, J Am Coll Cardiol 2004
Defining Chronic Renal Insufficiency

- Serum creatinine >1.5 mg/dl
- Calculated creatinine clearance <60 ml/min

Cockcroft and Gault equation:

\[
\frac{140 - \text{age} \times \text{kg}}{\text{Scr} \times 72} = \text{[x .85 in women]}
\]
Calculated for a 70kg man

Creatinine Clearance
mls/min

Serum Creatinine mg/dl

Age 65

(-15)

Age 85
Calculated Creatinine clearances

<table>
<thead>
<tr>
<th>Pt</th>
<th>SCr</th>
<th>CrCL</th>
</tr>
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<tbody>
<tr>
<td>FP</td>
<td>1.0</td>
<td>54 ml/min</td>
</tr>
<tr>
<td>CB</td>
<td>1.2</td>
<td>55 ml/min</td>
</tr>
</tbody>
</table>
## Risk Assessment to Predict Contrast Nephropathy

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Mehran et al, J Am Coll Cardiol 2004
What prophylactic measure can be taken to reduce the risk of contrast media-induced nephropathy?
Modification of Risk Factors to Prevent CMIN

- Delay exposure in hemodynamically unstable pts
- Avoid repeated exposure
  - 48 hrs in pts with normal renal function
  - 72 hrs in pts with CRI or DM
  - until SCr returns to baseline in ARF
- Discontinue NSAIDs for 1-2 days prior
Prophylaxis of Contrast Media-Induced Nephropathy

- Contrast media
- Hydration
- Pharmacologic agents
- Prophylactic dialysis

Idee et al. Invest Radiol 2004
Prophylaxis of Contrast Media-Induced Nephropathy

- **Contrast media**
  - Minimize the dose
  - Avoid repeated exposure
  - Use the least toxic form of contrast

Idee et al. Invest Radiol 2004
Non-ionic vs Ionic Contrast Media

Rudnick et al, KI 1995
Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial
(Coronary angiography)

MICHAEL R. RUDNICK, STANLEY GOLDFARB, LEWIS WEXLER, PHILIP A. LUDBROOK, MARY J. MURPHY,
ELKAN F. HALPERN, JAMES A. HILL, MICHAEL WINNIFORD, MARTIN B. COHEN,
DOUGLAS B. VANFOSSEN, for the Iohexol Cooperative Study¹
High vs Low Osmolar Contrast Media in Cardiac Angiography

(ARF defined by >0.5 mg/dl increase in SCr at 48-72 h)

Rudnick et al, KI 1995
Non-ionic Low vs Iso-Osmolar Contrast Media

Aspelin et al, NEJM 2003
Randomized, double-blind, prospective study
129 pts with DM and SCr of 1.5 to 3.5 mg/dl or calculated CrCl of ≤60ml/min
Underwent coronary or aorto-femoral angiography
All pts were well hydrated

Aspelin et al, NEJM 2003
Aspelin et al, NEJM 2003

P <0.01

No. of Patients

Iodixanol

Iohexol

290 mOsm/kg

780 mOsm/kg

Peak Increase in Serum Creatinine Concentration

≥0.5 mg/dl

26%

3%
DB-RC Trials of Low vs Iso-Osmolar Contrast in Pts with eGFR <60 Having Coronary Angiography

(ARF defined by ≥0.5 mg/dl increase in SCr at 24-72 hrs)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>eGFR</th>
<th>DM</th>
<th>Hydrated</th>
<th>Low-Osm</th>
<th>Iso-Osm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo et al JACC 2006</td>
<td>275</td>
<td>45</td>
<td>35%</td>
<td>100%</td>
<td>8.9%</td>
<td>3.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Solomon et al Circ 2007</td>
<td>414</td>
<td>50</td>
<td>41%</td>
<td>100%</td>
<td>4.4%</td>
<td>6.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Rudnick et al Am Heart J 2008</td>
<td>299</td>
<td>38</td>
<td>52%</td>
<td>100%</td>
<td>24%</td>
<td>22%</td>
<td>NS</td>
</tr>
<tr>
<td>Laskey et al Am Heart J 2009</td>
<td>418</td>
<td>48</td>
<td>100%</td>
<td>100%</td>
<td>9.8%</td>
<td>11.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>
What is the risk of CIN in CKD pts (eGFR <60) undergoing intravenous contrast enhanced CT?
### DB-RC Trials of Low vs Iso-Osmolar Contrast in CKD Pts Undergoing CT scans

<table>
<thead>
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<tr>
<td>Barrett Invest Radiol 2006</td>
<td>153</td>
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<td>65%</td>
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<td>2.6%</td>
<td>NS</td>
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<tr>
<td>Thomsen Invest Radiol 2008</td>
<td>148</td>
<td>20%</td>
<td>12%</td>
<td>0%</td>
<td>6.9%</td>
<td>&lt;0.05</td>
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<tr>
<td>Kuhn AJR 2008</td>
<td>263</td>
<td>100%</td>
<td>8%</td>
<td>5.6%</td>
<td>4.9%</td>
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### DB-RC Trials of Low vs Iso-Osmolar Contrast in CKD Pts Undergoing CT scans

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</tr>
</tbody>
</table>

Intra-arterial adm delivers greater concentration and/or volume.
Prophylaxis of Contrast Media-Induced Nephropathy

- Contrast media
- Hydration
- Pharmacologic agents
- Prophylactic dialysis
Proposed Beneficial Effects of Hydration

- Increases renal blood flow and GFR in volume contracted patients
- Increases medullary blood flow, enhancing regional $pO_2$
- Reduces concentration of contrast in tubules

Persson et al. KI 2005
What is the most effective form of hydration?
H2O: 1 Liter

Extra-cellular: 330 ml
Intra-cellular: 660 ml
H2O: 1 Liter

<table>
<thead>
<tr>
<th>Extra-cellular</th>
<th>Intra-cellular</th>
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</thead>
<tbody>
<tr>
<td>330 ml</td>
<td>660 ml</td>
</tr>
</tbody>
</table>

0.45-NS: 1 Liter

<table>
<thead>
<tr>
<th>Extra-cellular</th>
<th>Intra-cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ml + 170 ml</td>
<td>330 ml</td>
</tr>
</tbody>
</table>

\[ 670 \text{ ml} \]
<table>
<thead>
<tr>
<th></th>
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<th>Intra-cellular</th>
</tr>
</thead>
<tbody>
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<td>H2O: 1 Liter</td>
<td>330 ml</td>
<td>660 ml</td>
</tr>
<tr>
<td>0.45-NS: 1 Liter</td>
<td>500 ml + 170 ml</td>
<td>330 ml</td>
</tr>
<tr>
<td>NS: 1 Liter</td>
<td>1000 ml</td>
<td>1000 ml</td>
</tr>
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Comparison of Oral vs 0.9% Saline Hydration in Patients Undergoing Coronary Angioplasty

- Prospective, randomized trial in 53 pts
- Unrestricted oral fluids vs 0.9% NS infused at 1 ml/kg/hr for 12 hrs prior to the procedure
- Primary endpoint:
  >0.5 mg/dl increase in SCr within 48 hrs
- Oral: 9/26 (35%) vs NS: 1/27 (3%), p <0.01

Trivedi et al. Nephron Clin Pract 2003
Comparison of 0.9% vs 0.45% NS Hydration in Patients Undergoing Coronary Angioplasty

- Prospective, randomized, controlled trial: 1,383 pts
- Low-osmolar contrast
- N-acetylcysteine was NOT used
- 0.9% vs 0.45% NS infused at 1 ml/kg/hr for 24 hrs
- Primary endpoint:
  - >0.5 mg/dl increase in SCr within 48 hrs

Comparison of 0.9% vs 0.45% NS Hydration in Patients Undergoing Coronary Angioplasty

- **Incidence, %**
  - **CN**: 0.7%
  - **Mortality**: 0.4%

- **P-values**
  - 0.9% Saline: P = .04
  - 0.45% Sodium Chloride: P = .35

## Multivariate Analysis for the Development of Contrast Media-Induced Nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>3.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline SCr</td>
<td>6.6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NS hydration</td>
<td>0.3</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*increase in SCr of 1 mg/dl

Sodium Bicarbonate vs Saline in the Prevention of Contrast-Media Induced Nephropathy
Sodium Bicarbonate vs Saline in the Prevention of Contrast-Media Induced Nephropathy

• Alkalization of urine inhibits free radical formation
• Reducing free radical formation will decrease CIN

Merten et al. JAMA, 2004
Sodium Bicarbonate vs Saline in the Prevention of Contrast-Media Induced Nephropathy

- **SALINE**
  - 0.9% NS

- **SODIUM BICARBONATE**
  - 154 mEq/L sodium bicarb
    - 3 ml/kg/hr for 1 hr prior
    - 1 ml/kg/hr for 6 hrs post
Sodium Bicarbonate vs Saline in the Prevention of Contrast-Media Induced Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Saline</th>
<th>Bicarb</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>119</td>
<td>8/59 (13.6%)</td>
<td>1/60 (1.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac cath</td>
<td>97</td>
<td>8/48 (16.7%)</td>
<td>1/49 (2%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Merten et al. JAMA, 2004
Saline vs Na-Bicarb in the Prevention of CIN in CKD pts undergoing Angiography: PRCTrials

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>NS</th>
<th>Na-Bicarb</th>
<th>p value</th>
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<tbody>
<tr>
<td>Brar JAMA 2008</td>
<td>353</td>
<td>13.3%</td>
<td>8.9%</td>
<td>NS</td>
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<tr>
<td>Farahani AJKD 2006</td>
<td>265</td>
<td>5.9%</td>
<td>7.4%</td>
<td>NS</td>
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</table>
Wiedermann & Joannidis. NDT 2010

<table>
<thead>
<tr>
<th>Study name</th>
<th>Time point</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Odds ratio and 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Addad</td>
<td>2006</td>
<td>0,731</td>
<td>0,297</td>
<td>1,798</td>
<td>Normal: 13 / 70, Sodium Bicarbonate: 10 / 70</td>
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<tr>
<td>Adolph</td>
<td>2008</td>
<td>1,588</td>
<td>0,257</td>
<td>9,799</td>
<td>Normal: 2 / 74, Sodium Bicarbonate: 3 / 71</td>
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<tr>
<td>Assadi</td>
<td>2006</td>
<td>10,694</td>
<td>0,560</td>
<td>204,340</td>
<td>Normal: 0 / 50, Sodium Bicarbonate: 4 / 46</td>
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<tr>
<td>Brar</td>
<td>2008</td>
<td>0,886</td>
<td>0,498</td>
<td>1,579</td>
<td>Normal: 30 / 165, Sodium Bicarbonate: 26 / 158</td>
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<td>Briguori</td>
<td>2007</td>
<td>0,172</td>
<td>0,037</td>
<td>0,793</td>
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<tr>
<td>Chen</td>
<td>2007</td>
<td>0,114</td>
<td>0,013</td>
<td>0,960</td>
<td>Normal: 0 / 50, Sodium Bicarbonate: 1 / 55</td>
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<tr>
<td>Heguilen</td>
<td>2007</td>
<td>1,000</td>
<td>0,053</td>
<td>18,915</td>
<td>Normal: 1 / 9, Sodium Bicarbonate: 1 / 9</td>
</tr>
<tr>
<td>Hengel</td>
<td>2006</td>
<td>0,191</td>
<td>0,020</td>
<td>1,799</td>
<td>Normal: 4 / 33, Sodium Bicarbonate: 1 / 39</td>
</tr>
<tr>
<td>Hill</td>
<td>2005</td>
<td>0,429</td>
<td>0,031</td>
<td>5,985</td>
<td>Normal: 2 / 8, Sodium Bicarbonate: 1 / 8</td>
</tr>
<tr>
<td>Kim</td>
<td>2007</td>
<td>0,978</td>
<td>0,350</td>
<td>2,732</td>
<td>Normal: 8 / 44, Sodium Bicarbonate: 10 / 56</td>
</tr>
<tr>
<td>Lin</td>
<td>2007</td>
<td>0,706</td>
<td>0,169</td>
<td>2,945</td>
<td>Normal: 6 / 24, Sodium Bicarbonate: 4 / 21</td>
</tr>
<tr>
<td>Maioli</td>
<td>2008</td>
<td>0,854</td>
<td>0,485</td>
<td>1,505</td>
<td>Normal: 29 / 252, Sodium Bicarbonate: 25 / 250</td>
</tr>
<tr>
<td>Malpica</td>
<td>2008</td>
<td>0,675</td>
<td>0,249</td>
<td>1,833</td>
<td>Normal: 10 / 46, Sodium Bicarbonate: 9 / 57</td>
</tr>
<tr>
<td>Masuda</td>
<td>2007</td>
<td>0,207</td>
<td>0,042</td>
<td>1,031</td>
<td>Normal: 10 / 39, Sodium Bicarbonate: 2 / 30</td>
</tr>
<tr>
<td>Merten</td>
<td>2004</td>
<td>0,108</td>
<td>0,013</td>
<td>0,893</td>
<td>Normal: 8 / 59, Sodium Bicarbonate: 1 / 60</td>
</tr>
<tr>
<td>Mora</td>
<td>2007</td>
<td>0,038</td>
<td>0,005</td>
<td>0,286</td>
<td>Normal: 21 / 88, Sodium Bicarbonate: 1 / 86</td>
</tr>
<tr>
<td>Ozcan</td>
<td>2007</td>
<td>0,302</td>
<td>0,093</td>
<td>0,975</td>
<td>Normal: 12 / 88, Sodium Bicarbonate: 4 / 88</td>
</tr>
<tr>
<td>Pakfetrat</td>
<td>2009</td>
<td>0,217</td>
<td>0,070</td>
<td>0,677</td>
<td>Normal: 16 / 96, Sodium Bicarbonate: 4 / 96</td>
</tr>
<tr>
<td>Recio-Mayoral</td>
<td>2007</td>
<td>0,065</td>
<td>0,008</td>
<td>0,521</td>
<td>Normal: 12 / 55, Sodium Bicarbonate: 1 / 56</td>
</tr>
<tr>
<td>Tamura</td>
<td>2008</td>
<td>0,099</td>
<td>0,012</td>
<td>0,800</td>
<td>Normal: 9 / 72, Sodium Bicarbonate: 1 / 72</td>
</tr>
<tr>
<td>Shaikh</td>
<td>2007</td>
<td>0,722</td>
<td>0,348</td>
<td>1,495</td>
<td>Normal: 19 / 161, Sodium Bicarbonate: 14 / 159</td>
</tr>
<tr>
<td>Shavit</td>
<td>2008</td>
<td>1,196</td>
<td>0,267</td>
<td>5,356</td>
<td>Normal: 3 / 36, Sodium Bicarbonate: 5 / 51</td>
</tr>
<tr>
<td>Vasheghani-Farahani</td>
<td>2009</td>
<td>1,255</td>
<td>0,453</td>
<td>3,475</td>
<td>Normal: 7 / 130, Sodium Bicarbonate: 9 / 135</td>
</tr>
</tbody>
</table>

Total (95% CI): 244 / 1788, 148 / 1810

Heterogeneity:
$T^2 = 0.37; \ Chi^2 = 46.0; df = 23 (p = 0.003); I^2 = 50\%$

Favours Bicarbonate | Favours Control

Wiedermann & Joannidis. NDT 2010
Prophylaxis of Contrast Media-Induced Nephropathy

- Contrast media
- Hydration
- Pharmacologic agents
- Prophylactic dialysis

Idee et al. Invest Radiol 2004
Pharmacologic Prophylaxis of Contrast Media-Induced Nephropathy

- Furosemide and/or mannitol
- Calcium channel blockers
- Adenosine blockers
- Dopaminergic agonists (fenoldopam)
- Endothelin receptor antagonists
- Atrial natriuretic peptide
- N-Acetylcysteine

Idee et al. Invest Radiol 2004
Contrast Media

Cellular effects
- vacuolization
- necrosis
- apoptosis
- effects mesangial cells
- inhibits protein reabsorption

Hemodynamic effects
- Osmolality related
  - Osmotic diuresis
  - adenosine release ↑
- Osmolality unrelated
  - ↑endothelin release

Theophylline
- ↑Na⁺ delivery
- vasoconstriction

N-Acetylcysteine
- Medullary hypoxia + Free radicals
- Acute Renal Failure

ET receptor antagonists
- Diuretics, ANP, CCB
  - Dopa-1 agonist

Idee et al. Invest Radiol 2004
Contrast Media

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  - ET receptor antagonists
  - Diuretics, ANP, CCB
  - Dopa 1 agonist

Idee et al. Invest Radiol 2004
N-Acetylcysteine Prophylaxis for Contrast Media-Induced Nephropathy

- Stimulates the synthesis of glutathione
  - Reduces Oxidative stress
- At high dose promotes vasodilatation
- Decreases medullary vascular resistance

Idee et al. Invest Radiol 2004
N-Acetylcysteine Prophylaxis for Contrast Media-Induced Nephropathy

- All patients had stable CRI
- GFR <60 ml/min, SCr 2.4 to 2.8 mg/dl

NAC dose:
- 400 to 600 mg PO BID
- The day before and the day of the procedure
Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)

- 2,308 pts having coronary or peripheral angio
- 1 risk factor (>70yo, CKD, DM, CHF, low BP)
- NAC 1200 mg BID Pre & Post vs Placebo
- Hydration: NS- 1 ml/kg/hr 6-12 hr pre/post-study

End point: ≥25% increase in SCr at 48-96 hrs
13% placebo vs 13% NAC (p =0.97)

End point: ≥0.5 mg/dl increase in SCr at 48-96 hrs
4% placebo vs 4% NAC (p =0.85)

ACT Investigators. Circulation 2011
Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)

Death or need for dialysis

P value = 0.92

Days after randomization
**Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Active</th>
<th>Placebo</th>
<th>Relative Risk</th>
<th>P Value for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated glomerular filtration rate - eGFR (ml/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>6/56</td>
<td>3/48</td>
<td>1.71 (0.45; 6.49)</td>
<td>0.73</td>
</tr>
<tr>
<td>30 - 60</td>
<td>30/425</td>
<td>27/398</td>
<td>1.04 (0.63; 1.72)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>111/672</td>
<td>112/673</td>
<td>0.99 (0.78; 1.26)</td>
<td></td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min/1.73m² and diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>122/889</td>
<td>122/905</td>
<td>1.02 (0.81; 1.29)</td>
<td>0.92</td>
</tr>
<tr>
<td>Yes</td>
<td>24/260</td>
<td>20/214</td>
<td>0.99 (0.56; 1.74)</td>
<td></td>
</tr>
</tbody>
</table>

ACT Investigators. Circulation 2011
Efficacy of Short-Term High Dose Statin in Preventing CIN

- Statins: ↑ nitric oxide, ↓ endothelin-1, anti-inflammatory, and anti-oxidative
- Meta-analysis of 7 PRCT comparing high-dose statin (40-80 mg) v. low-dose or no statin
- Short-term statin use lead to a 49% RR of CIN
- But statin use was not protective in studies of patients with ↓ GFR or those receiving NAC

Li et al. PLoS ONE 2012; 7:e34450
Prophylaxis of Contrast Media-Induced Nephropathy

- Contrast media
- Hydration
- Pharmacologic agents
- Prophylactic dialysis
Statement 10:
Prophylactic hemodialysis or hemofiltration has not been proven to be efficacious in reducing the risk of AKI after exposure to iodinated contrast.

CIN Consensus Working Panel, Am J Cardiology, 2006

Statement 4.5:
We suggest NOT USING prophylactic HD or hemofiltration for contrast-media removal in patients at increased risk for CI-AKI.

KDIGO AKI Work Group, Kidney Int, 2012
Approach to Patients Receiving IV Contrast

**Low risk**
- Oral Hydration

**High risk**
- Avoid contrast
  - DC NSAIDs/Metformin 24-48 hrs prior
  - Check SCr pre-prophylaxis
  - Intravenous saline/bicarb hydration
  - Low dose, non-ionic, low osmolar contrast
  - Check SCr 24-48 hrs post-procedure

1 ml/kg/h (0.5 ml/kg/hr in CHF pts) for 6-12 hrs pre- and post-procedure

Consensus Panel for CIN, KI 2007/2012
Statement 4:

In the setting of emergency procedures, where the benefit of very early imaging outweighs the risk of waiting, the procedure can be performed without knowledge of serum creatinine or eGFR.