Objectives

- Define contrast-induced nephropathy (CIN) and discuss its importance
- Discuss risk factors for contrast-induced nephropathy
- Identify at-risk patients
- Discuss use of preventative measures
Scope of Problem

- There are now tens of thousands of CT scanners worldwide.
- The number of CT examinations performed annually has increased steadily as improvements in technology have created new indications for CT and CT angiography.
- In the United States alone, 50 million CT procedures are performed annually, and approximately 50% of CT examinations use contrast.
Scope of the Problem

- The expansion in the use of contrast media has not been limited to radiology procedures.
- Cardiac catheterization and percutaneous coronary intervention (PCI) increased 390% between 1979 and 2002; more than 1.4 million cardiac catheterizations were performed in 2000 in the United States.
Scope of the Problem

- Contrast media have changed over time to become increasingly safe and well tolerated, but the indications for use of contrast media have greatly expanded.
- In addition, the number of patients with risk factors for CIN has also increased.
- The result is that CIN has become an increasing burden on our patient population and health care resources.
Many different definitions of contrast-induced nephropathy (CIN) appear in the literature, but it is broadly defined as an acute decline in renal function following the administration of intravenous contrast in the absence of other causes.
Current Definitions

1. Solomon et al: an acute decrease in renal function manifested by an increase in baseline SCr of at least 0.5 mg/dl within 48 hours of contrast injection.

2. Porter: Within 72 hrs of contrast injection, a SCr increase of:
   1. >25% if baseline SCr is <1.5 mg/dl
   2. >1.0 mg/dl if baseline SCr is >1.5 mg/dl

3. AKIN: an abrupt (w/in 48hrs) reduction in kidney function, evidenced by an increase of the SCr concentration of at least 0.2 mg/dL or at least 50% from baseline or a reduction in urine output (oliguria of <0.5 mL/kg/h for >6hrs).
Current Definitions

- The most commonly used definition is an increase from baseline SCr of at least 0.5 mg/dL or at least 25% within 48-72 hours after exposure to contrast media.
Pathogenesis of CIN

- The precise cause(s) of CIN are still up for debate.
- Contrast media is postulated to harm the kidneys in two ways:
  - Renal hemodynamic changes producing tubular ischemia
  - Direct toxic effect on the tubular epithelium
Clinical Outcome of CIN

- The SCr increase usually peaks between days 3-5, with levels returning to baseline w/in 1-3 wks. Renal failure (if it develops) is usually apparent w/in 12-24 hrs after contrast administration.
- Most cases are nonoliguric and self limited.
- However, in some cases patients will go on to need dialysis (most likely to occur when the baseline SCr exceeds 4 mg/dL)
Clinical Outcome of CIN

- The patient who develops CIN is at risk for a number of adverse events.
- Data derived from experience in treating cardiac patients indicate that there is a twofold-to-fivefold increase in mortality while patients are in the hospital.
Clinical Outcome of CIN

- Hospital resource consumption is increased, as well.
  - Hospital lengths of stay increase from 5 to 10 days for CIN patients and use of dialysis facilities increases 10% to 15%.
- Long-term mortality (at 1 year) also increases threefold.
Diagnosis

- Many contrast agents induce false positive results when dipsticks are used to detect proteinuria, so this is not a good measurement to use for at least 24 hrs after a study.
- SCr currently remains the best measurement to obtain to monitor renal function.
Differential Considerations

- When a rise in SCr is noted following contrast administration, the differential diagnosis should include:
  - CIN
  - Acute tubular necrosis
  - Acute interstitial nephritis
  - Renal atheroemboli
    - Particularly if the contrast was administered during a vascular intervention
In spite of the preponderance of data, the incidence of CIN is difficult to determine due to:

- Poor study design
- Conflicting conclusions
- Data based upon:
  - Older contrast agents
  - Various modalities (e.g. CT scans vs. cardiac cath)
- Widely variant practice patterns
Incidence Rates of CIN

- Rates may vary from 0% to 90%, depending on the presence of risk factors, most notably chronic renal insufficiency, diabetes mellitus, and high contrast volume administered.

- Incidence among patients with diabetes has been reported to be 9–40% in patients with mild-to-moderate chronic renal insufficiency and 50–90% in those with severe chronic renal insufficiency.

- In contrast, the incidence in the general population is much lower and has been calculated to be less than 2%.
Risk Factors for Developing CIN

- Renal insufficiency (Plasma Cr >1.5 mg/dL or GFR <60mL/min per 1.73m)
- Diabetes
- Dehydration
- Nephrotoxic drug use (such as NSAIDs)
- Advanced age
- Multiple Myeloma
Risk Factors for Developing CIN

- Collagen vascular disease
- Renal transplant
- Congestive heart failure
- Contrast dose
- Metabolic syndrome, hyperuricemia, hypertriglyceridemia and impaired fasting glucose
Combating the Risk

- Most of the risk factors on that list we can do nothing about.

- Three things can be done for prevention CIN:
  - Reducing contrast dose
  - Identifying at risk patients
  - Addressing hydration status
Contrast Dose

- Regardless of the type of iodinated contrast agent (low osmolar vs. iso-osmolar), the risk for CIN is reduced with lower contrast volumes and a greater amount of time in between contrast-enhanced studies.

- If the particular question can be answered with a non-contrastated study, then eliminate the IV contrast.

- If you aren’t sure, ask.
Identifying At Risk Patients

- Who needs a creatinine?
- What is the best measurement of renal dysfunction?
- What level of renal dysfunction should prevent IV contrast administration?
Are screening serum creatinine levels necessary prior to outpatient examinations?

- Tippins. Radiology 2000; 216: 481
- 2,034 outpatients undergoing contrast-enhanced CT
- All patients took questionnaire and had serum creatinine.
- 3.2% had elevated creatinine (Cr > 2.0 mg/dL)
- Questionnaire identified 97% of patients with elevated creatinine.
Are screening serum creatinine levels necessary prior to outpatient examinations?

- 640 patients undergoing contrast-enhanced CT
- All patients took questionnaire and had serum creatinine.
- 5.5% had abnormal creatinine (>1.6 mg/dL)
- Questionnaire identified 97% of patients with elevated creatinine.
Routine creatinine is not necessary in most outpatients who have no risk factors on screening questionnaire.
Typical Questionnaire

- Screens for:
  - Age >60
  - HTN
  - Personal or family H/O renal disease
  - Paraproteinemia syndromes
  - Collagen vascular disease
  - Solid organ transplantation

- Yes to any one of these requires a SCr be drawn prior to the study
What numbers should you use?

- The dose of IV contrast that at risk patients receive has traditionally been determined by their SCr.
- Example: At KU Med Center, SCr <1.5 mg/dL full dose; SCr >1.5 to <2.0 half dose; SCr >2.0 no IV contrast
What numbers should you use?

- A growing body of evidence indicates that using estimated GFR (eGFR) does a better job of diagnosing patients with moderate renal impairment.

- Normal SCr levels are maintained until the GFR is reduced by nearly 50%; therefore impaired renal function may exist even when SCr levels are normal.
Creatinine vs. eGFR

- Herts. Radiology 2008; 248; 106
- 5,138 outpatients
- SCr $>$1.4 = 6.2%
- eGFR $<$60 = 15.3%
- 59.7% of patients with moderate renal disease missed using SCr alone.
The KDOQI stages of kidney disease are:

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR*</th>
<th>Description</th>
<th>Treatment stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease</td>
<td>Observation, control of blood pressure. More on management of Stages 1 and 2 CKD.</td>
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<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease</td>
<td>Observation, control of blood pressure and risk factors. More on management of Stages 1 and 2 CKD.</td>
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<tr>
<td>3A 3B</td>
<td>45-59</td>
<td>Moderately reduced kidney function</td>
<td>Observation, control of blood pressure and risk factors. More on management of Stage 3 CKD.</td>
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<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
<td>Planning for endstage renal failure. More on management of Stages 4 and 5 CKD.</td>
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<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td>Very severe, or endstage kidney failure (sometimes call established renal failure)</td>
<td>Treatment choices. More on management of Stages 4 and 5 CKD.</td>
</tr>
</tbody>
</table>
eGFR

- The eGFR can be calculated using the following equations:

  - **MDRD (Modification of diet in renal disease) formula**
    
    $$eGFR = 186 \times SCr^{-1.154} \times Age^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

  - **Cockcroft-Gault formula**
    
    $$eGFR =\frac{[(140 - \text{Age}) \times \text{(Wt in kg)} \times (0.85 \text{ if female})]}{(72 \times \text{Cr})}$$
GFR MDRD Calculator for Adults
(Conventional units)

Serum creatinine: (mg/dL)

Age:

African American: Yes/No

Gender: Male/Female

Calculate/Reset

GFR value: mL/min/1.73 m²

*This equation should only be used for patients 18 and older.

**The US National Kidney Disease Education Program presently recommends reporting estimated GFR values greater than or equal to 60 mL/min/1.73 m² simply as "≥60 mL/min/1.73 m²", not an exact number.
Preventative Measures

- There is currently no way to reverse or ameliorate CIN, but many types of prevention and prophylaxis are currently being utilized, including:
  - Hydration
  - N-Acetylcysteine
  - Bicarbonate
  - Use of iso-osmolar contrast agents
Hydration

- In the dehydrated state, renal blood flow and GFR are decreased leading to prolonged tubular exposure to contrast media due to low tubular flow rates.

- Numerous studies have demonstrated that hydration can reduce the risk of CIN.
  - Solomon et al: the incidence of CIN was decreased in patients with chronic renal insufficiency who underwent cardiac angiography by administering 0.45% saline or 0.9% saline at a rate of 1mL/kg/hr starting 12 hrs before angiography and continuing 12 hours after the procedure.
N-Acetylcysteine (NAC) is a known antioxidant that is thought to help protect the renal tubular epithelium by scavenging free oxygen radicals.

The drug is usually well tolerated and is relatively inexpensive.

But does it work?
N-Acetylcysteine (Mucomyst)

- Tepel. NEJM 2000; 343: 180
- 83 patients with average SCr of 2.4 mg/dL
- CT with iopromide (Ultravist)
- Randomized
  - NAC 600 mg PO Q12 x 4
  - Saline hydration
- >=0.5 mg/dL increase in SCr
  - 2% NAC group
  - 21% hydration group
## Acetylcysteine clinical trials

<table>
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<tr>
<th>First Author</th>
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<th>Controls</th>
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<td>14%</td>
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<td>10%</td>
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<td>N</td>
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<tr>
<td>Briguori</td>
<td>2002</td>
<td>183</td>
<td>7%</td>
<td>11%</td>
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</table>
N-Acetylcysteine (Mucomyst)

- Cystatin C is a low molecular weight protein which is filtered by the kidneys.
  - Thus, it serves as a marker for renal function in addition to SCr.
- A recent study has demonstrated that often serum cystatin C levels rise in patients who received NAC prior to contrast administration even though their SCr remained stable.
- NAC may only impact creatinine production/clearance and not protect the kidneys.
N-Acetylcysteine Bottom Line

- NAC is a relatively benign, inexpensive drug which may have little to no positive impact on reducing CIN.
Sodium Bicarbonate

- Alkalizing renal tubular fluid with bicarbonate may reduce free radical formation and thus reduce epithelial injury.
- Merten. JAMA 2004; 291: 2328
- 119 randomized patients
  - Hydration with NaCl
  - Hydration with sodium bicarbonate
- Incidence of CIN
  - 13.6% NaCl
  - 1.7% sodium bicarbonate
Sodium Bicarbonate

- Brar. CJASN 2009; 41
- Meta-analysis of 12 sodium bicarbonate vs. NaCl hydration studies.
- No evidence of benefit for hydration with sodium bicarbonate compared with NaCl for the prevention of CIN.
Sodium bicarbonate administration demonstrates little or no positive impact in reducing CIN relative to other forms of IV hydration.
Iso-Osmolal Contrast Media (IOCM)

- Part of the toxicity of the iodinated contrast is felt to be related to its increased osmolality relative to blood.
- Most contrast-enhanced CT scan are now performed with low-osmolality agents.
- There is one agent, iodixanol (Visipaque), which is iso-osmolal to blood.
- This is the most expensive iodinated contrast agent.
Iso-Osmolal Contrast Media (IOCM)

  - Increase in SCr
    - Visipaque: 0.06 mg/dL
    - LOCM: 0.10 mg/dL
  - Incidence of CIN
    - Visipaque: 1.4%
    - LOCM: 3.5%

- Heinrch. Radiology 2009; 250: 68-86
  - Overall relative risk: 0.80
  - Intra-venous relative risk: 1.08
  - Intra-arterial + renal dysfunction relative risk: 0.38
IOCM Bottom Line

- IOCM may reduce the risk of CIN in patients who undergoing arterial interventions.
- However, IOCM does not significantly alter the risk of CIN in patients undergoing intra-venous administration of contrast material for CT.
- Given its higher cost, IOCM should not be used in CT examinations.
Other prophylactic agents that have been studied:

**May Work:**
- Calcium Channel Blockers
- Theophylline
- Hemofiltration
- Ascorbic acid
- Prostaglandins

**Don’t Work:**
- Mannitol
- Furosemide
- Dopamine
- Atrial natriuretic factor
- Fenoldopam
- Hemodialysis
What about Dialysis patients?

- Contrast agents are not protein-bound and have low molecular weights, therefore they are readily cleared by dialysis.

- There is often concern about the osmotic load of the media, however unless there is underlying cardiac dysfunction or a high volume of contrast is needed there is no reason for immediate dialysis following contrast use.

- Patients with renal insufficiency who are only undergoing occasional/intermittent dialysis should NOT be given contrast agents; alternative imaging studies that do not require contrast should be done.
Summary

- Increasing use of contrast-enhanced procedures, aging of our populace, and increased prevalence chronic health conditions is placing our patients at greater risk for CIN.

- CIN is associated with much greater patient morbidity/mortality and health care costs.
Summary

- The incidence of CIN varies based upon the patient population but is most common in those with pre-existing renal dysfunction.
- Routine outpatients with no major risk factors for renal insufficiency do not need SCr testing.
- eGFR superior to SCr for diagnosing moderate renal insufficiency.
Summary

- Hydration and contrast dose reduction are **still** the only proven means to reduce the incidence of CIN.
  - 1 mL/kg/hr NaCl x 12 hrs before and after contrast administration
- N-acetylcysteine and sodium bicarbonate will not harm the patient, though probably only have a minimal impact on reducing CIN.
- Use of Visipaque should be restricted to the cath lab.
11. Poleti. IV NAC and Emergency C: Use of Creatinine and Cystatin C as Markers of Radiocontrast Nephrotoxicity AJR 2007; 189: 687