CONTRAST INDUCED NEPHROPATHY
KIDNEY KILLER OR MEDICAL MYTH

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OBJECTIVES:
• Explain current controversies regarding contrast-induced nephropathy, including its diagnosis, estimation of frequency and causality.
• Explain the limitations of using serum creatinine and the benefits of using estimated GFR as determinants of renal function.
• Explain rationales for the ACR recommendations regarding which patients should be screened for renal insufficiency.
• List measures that can be employed to protect patients from contrast-induced nephropathy.

IMPORTANT DEFINITIONS:
• POST-CONTRAST ACUTE KIDNEY INJURY (PC-AKI)
  • A general term used to describe a sudden deterioration in renal function that occurs within 48 hours following the intravascular administration of iodinated contrast medium
  • It may occur regardless of whether the contrast medium was the cause of the deterioration
  • PC-AKI is a correlative diagnosis

• CONTRAST-INDUCED NEPHROPATHY (CIN)
  • A specific term used to describe a sudden deterioration in renal function that is caused by the intravenous administration of iodinated contrast medium
  • Synonymous with Contrast Induced Acute Kidney Injury
  • CIN is a subgroup of PC-AKI
  • CIN is a causative diagnosis

ACUTE KIDNEY INJURY
Definition is arbitrary!
The Acute Kidney Injury Network (AKIN) proposed the following in 2007:
Diagnosis of AKI is made according to AKIN criteria if one of the following occurs within 48 hours after a nephrotoxic event:
- Increase by ≥ 50% (≥ 1.5-fold increase)
- Absolute increase of ≥ 0.3 mg/dL
- Urine output reduced to ≤ 0.5 mL/kg/hour for at least 6 hours

How frequent is contrast induced nephropathy?
• More recent prospective investigations have shown low rates of CIN with use of low- and iso-osmolar contrast medium for contrast enhanced CT, approximating an overall rate of 5.4%, even in patients with baseline renal insufficiency.
• On the other hand, in the cardiology literature, overall rates of CIN in patients with chronic kidney disease and diabetes are around 3.0%, as noted by Frishman et al in the Interheart Cooperative Study, a large randomized trial.

IS CONTRAST INDUCED NEPHROPATHY CLINICALLY SIGNIFICANT?
• Again, CIN related to contrast enhanced CT is less common than we thought, in particular when compared with the incidence after intra-arterial administration
• It is mostly self-limited and not associated with increased morbidity in most patients
• Hospitalized patients experience random variations in serum creatinine, and this is more common in patients who already have renal insufficiency
WHY DO WE ASSESS KIDNEY FUNCTION?

- Even though the risk is relatively small, we have an obligation to protect our patients from the possibility of contrast induced acute kidney injury
- Screening guidelines have been established in different parts of the world to help detect the patients at higher risk for AKI
- In the United States, the ACR Manual on Contrast Media (currently in version 10.3) is the most complete source on anything you ever wanted to know about contrast media including contrast induced nephropathy

RISK FACTORS FOR THE DEVELOPMENT OF CONTRAST INDUCED AKI

<table>
<thead>
<tr>
<th>Fixed (non-modifiable) risk factors</th>
<th>Modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing renal failure (most important)</td>
<td>Volume and type of contrast medium</td>
</tr>
<tr>
<td>Advanced congestive heart failure</td>
<td>Multiple contrast injections within 72 hours</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Advanced congestive heart failure</td>
</tr>
<tr>
<td>Reduced left ventricular ejection fraction</td>
<td>Contrast-induced diuresis</td>
</tr>
<tr>
<td>Reduced glomerular filtration rate</td>
<td>Confusion state</td>
</tr>
<tr>
<td>Intravenous vs. intraarterial administration</td>
<td>Diabetes, obesity</td>
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<tr>
<td>Nephrotoxic drugs (nonsteroidal anti-inflammatory agents, some antibiotics, cyclosporine, etc.)</td>
<td>Intensive care unit, surgical state</td>
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PATHOPHYSIOLOGY OF CONTRAST INDUCED NEPHROPATHY

- Contrast Administration
  - Intravascular
  - Hypo-osmolality
  - Osmotic load
  - Vasoconstriction
  - Direct cytotoxicity
- Medullary Hypoxia
- CIN
- ROS = Reactive Oxygen Species (free radicals, etc.)

PATHOPHYSIOLOGY OF CONTRAST INDUCED ACUTE KIDNEY INJURY

- The main mechanisms thought to underlie Contrast-induced renal vasocostriction, tubule toxicity, generation of reactive oxygen species, and medullary hypoxia
- Contrast viscosity and osmolality also determine the likelihood of CIN
- Interventions that decrease the concentration of iodinated contrast within the kidney, and within the renal tubules more specifically, appear to reduce the risk of CIN. Therefore, emphasis is on pre-and post-procedural hydration to prevent CIN

WHY DO WE ASSESS KIDNEY FUNCTION?

- Screening for patients with diminished function allows us to minimize kidney injury by finding patients who would potentially benefit from:
  - Deciding if the same diagnosis can be obtained without IV contrast or with a different modality (MRI, US)
  - Obtaining hydration before the study
  - Decreasing the volume of contrast
  - Contrast selection

HOW DO WE ASSESS KIDNEY FUNCTION?

- Serum creatinine
  - Used for many years.
  - Limitations as an accurate measure of kidney function because it depends greatly on:
    - Gender
    - Muscle mass
    - Nutritional status
    - Age
- Glomerular filtration rate (GFR) is a better measure of kidney function
HOW DO WE ASSESS KIDNEY FUNCTION?

• Since direct measurement of GFR is cumbersome and impractical, one alternative, recommended by the National Kidney Foundation and many other organizations involved in the care of patients with renal dysfunction, is to use a formula to calculate GFR (estimated GFR).

**Formulas:***

- **MDRD (Modification of Diet in Renal Disease) Study equation:**
  
  \[
  \text{eGFR, ml/min/1.73 m}^2 = \frac{186 \times \text{Serum Creatinine [mg/dL]}^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})}{(1.580)^{1.235} \times \text{body weight [kg]}}
  \]

- **Cockcroft-Gault equation:**
  
  \[
  \text{Serum Creatinine [mg/dL]} \times 72 \times \frac{1}{\text{age} \times \text{body weight [kg]}}
  \]

- **CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation:**
  
  \[
  \text{eGFR, ml/min/1.73 m}^2 = \frac{141 \times \text{min} \left( \frac{\text{Serum Creatinine [mg/dL]}}{\text{KT}} \right) \times (0.993)^{\alpha} \times \text{sex} \times (1.018 \text{ if female}) \times (1.159 \text{ if African American})}{\text{max} \left( \frac{\text{Serum Creatinine [mg/dL]}}{\text{KT}} \right) - 1.209}
  \]

  Where:
  
  - KT = 0.7 if female
  - KT = 0.9 if male
  - \( \alpha = -0.329 \) if female
  - \( \alpha = -0.411 \) if male

**Notes:**

- MDRD and CKD-EPI equations are the most thoroughly validated equations.
- MDRD: Caucasian and African American populations ages 20 to 79 with estimated GFR between 60 and 190.
- CKD-EPI: Caucasian and African American populations with normal and impaired kidney function (average GFR 68).
- Considered superior to other methods of approximating GFR.
**KIDNEY FUNCTION**

- **eGFR is a more accurate representation of renal function than serum creatinine.**

  - [Website](http://www.kidney.org/professionals/tools/pdf/CystatinC.pdf)

**HOW DO WE ASSESS KIDNEY FUNCTION?**

- Calculators are available in several websites.
- At BMC, the lab always calculates the eGFR for all adults.
- This is an easy one to use and we recommend it:
  - [Website](https://www.niddk.nih.gov/health-information/health-communication-programs/ Kidney/lab-evaluation/gfr-calculators/adults-conventional-unit-ckd-epi/Pages/default.aspx)
  - eGFR > 60 is considered normal.

**SCREENING ALGORITHM**

- **What needs help?**
  - Hypertension
  - Single kidney
  - Diabetes
  - Hemodialysis
  - Hemofiltration

- **When?**
  - Within 30 days for inpatients and 7 days for outpatients

**IV CONTRAST SCREENING FORM**

**SO, WHAT CAN WE DO TO MINIMIZE KIDNEY INJURY?**

- **Dose reduction or elimination**
- **Pharmaceutical premedication**
  - Mucomyst may help protect the kidneys or more likely just decreases serum creatinine levels.
- **Hydration**
  - Proven on multiple studies to help reduce the risk.
- **Iodine based contrast**
  - Some but not all studies have shown contrast is safer than CT without contrast.
  - We only use nonionic contrast.
- **Procedures**
  - Frequently clinician will decide to do exam without IV contrast, or do US or MRI if possible.
  - Vascular stents have made contrast procedures safer.
  - Consent form may need to be signed.
  - ctRenalGraft and ShuntGraft valves. We no longer do this.

- **Gentamicin**
  - Please ask multiple questions to help reduce the risk.

- **Pre-procedural hydration**
  - Patients who may have pre-existing kidney damage are more likely to have decreased serum creatinine levels.

- **Post-progression administration**
  - Not useful prior to IV contrast administration.
**SCREENING ALGORITHM**

### HYDRATION PROTOCOL

**Hydration before the CT**
- Increase water flow to achieve and hold urine output.

**How?**
- Risk factors for AKI
  - Ejection fraction (EF) above 45%
  - History of congestive heart failure (CHF)
  - History of diabetes

**WHAT CAN WE DO TO MINIMIZE KIDNEY INJURY?**

**HYDRATION PROTOCOL**

**All Patients** (requiring IV hydration prior to CT with IV contrast, automatically triggered by eGFR screening):
- IV hydration to be done on nursing unit with same 2 tiers:
  - Mild to moderate
  - Severe

**In-Patients**
- IV hydration to be done on nursing unit with same 2 tiers:
- IV hydration before the CT
- Increase urine flow to achieve and hold urine output.
- High risk patients for pulmonary edema (history of CHF with EF below 45%)

**Exceptions to screening for risk factors for AKI**

- Patients with anuria or sickle cell disease
- Patients with severe liver disease
- Patients with severe renal insufficiency
- Patients with severe congestive heart failure

**Screening Algorithm**

1. **22 yo AA male w/Diabetes**
2. **CT Abdomen and Pelvis w/ IV contrast**
3. **C/v 3.4**
4. **eGFR = 60**

**BMC HYDRATION PROTOCOL**

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SCREENING ALGORITHM

- 50 yo WM w abdominal pain and fever
- CT Abdomen and Pelvis w IV contrast
- Cr = 1.4
- eGFR = 54
- No DM or single kidney

SCREENING ALGORITHM

- 80 yo WF with pneumonia
- CT Chest w IV contrast
- Cr = 1.4
- eGFR = 36

SCREENING ALGORITHM

- 80 yo WF with pneumonia
- CT Abdomen and Pelvis w IV contrast
- Cr = 1.7
- eGFR = 29

DIABETES MELLITUS

- Diabetes treated with Metformin, Glucophage or Glucovance
- Increased risk for metabolic alkalosis if they sustain kidney injury
- Patient directed by ordering physician to hold metformin the morning of IV contrast administration as well as the following day
- If renal function is normal (eGFR ≥ 60), the patient will resume the diabetes medication on the third day without renal recheck
- If renal function is abnormal (eGFR < 60), the patient will recheck serum creatinine on the third day and will resume the diabetes medication only after obtaining approval for this or other physician

- Diabetes treated with Insulin
- Studies best performed in the morning since patients will be asked to eat a very light meal only (NPO 6 hours prior to exam for CT enterography only)
In the last few decades, as advanced imaging has become pervasive, a few adverse effects relating to its use have been accepted. These include age-dependent harms from radiation exposure, the underestimated harms of overdiagnosis and false-positive results, and the harmful effect on renal function from contrast-induced nephropathy (CIN).

It is not unusual for radiology departments to have a renal function cutoff for the use of intravenous contrast or even a protocol requiring hydration or other preventive therapy for those at risk.

PROBLEMS:

- Regulations have been formulated with CIN in mind.
- Some ED providers think it may still even be a relevant clinical entity in the context of the emergency department.
- While many observational studies have documented the substantial incidence of acute kidney injury (AKI) following intravenous (IV) contrast exposure, per the common general definition of CIN, it has been challenging to find a proper control group.

ARE PATIENTS DEVELOPING SUBSEQUENT AKI BECAUSE OF THE IV CONTRAST OR DUE TO THE MORBIDITY OF THE ACUTE ILLNESS INDICATING THE NEED FOR THE CT?

In 2013, a group from the Mayo Clinic performed a systematic review and meta-analysis of the evidence published prior to 2011 regarding the association with IV contrast exposure and subsequent AKI.

- These authors identified 13 nonrandomized studies comprising 25,950 patients, most of which were published after 2008. There was no statistically significant difference in incidence of AKI, need for dialysis, or death in their comparison, and any trend, if present, actually favored the IV contrast cohort.

ARE PATIENTS DEVELOPING SUBSEQUENT AKI BECAUSE OF THE IV CONTRAST OR DUE TO THE MORBIDITY OF THE ACUTE ILLNESS INDICATING THE NEED FOR THE CT?


- The authors included not only emergency department patients undergoing CT with and without IV contrast but also ED patients not undergoing any advanced imaging. These authors considered factors such as critical doença, vital signs, potentially nephrotoxic medication exposures, and controlled baseline features. In their analysis, again, no association was found between IV contrast exposure and AKI across all their comparison groups.
Another study tested sodium bicarbonate against sodium chloride as periprocedural hydration to prevent CIN.


- In an intensive care unit (ICU) cohort, the frequency of AKI was similar as was the need for renal replacement therapy, ICU length of stay, and mortality. These data were consistent with multiple previous studies, which were unable to reliably demonstrate a renal protective effect from sodium bicarbonate.


Sodium chloride hydration prior and following IV contrast exposure or to usual care. Approximately 600 patients, the exact same number of patients, eight in each group, developed AKI.

Kidney Killer or Medical Myth?

The real question remains: Are patients developing subsequent AKI because of the IV contrast or due to clinical problem indicating the need for the CT?
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REFERENCES:

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Solomon, R. Contrast-Induced Acute Kidney Injury (CIAKI) Radiol Clin N Am 2009;783-788


ACR Contrast Media Manual, Version 10.3, July 2017


Josh Farkas at PulmCrit (EMCrit): Do CT Scans Cause Contrast Nephropathy


Ryan Radecki at Emergency Literature of Note: Punching Holes in CIN

Richard Sinert on EMDocs: Contrast-Induced Nephropathy – Confounding Causation


Jeremy Faust & Lauren Westafer on FOAMcast: Contrast-Induced Nephropathy and Genitourinary Trauma


Joel Topf at Precious Bodily Fluids Blog: Confirmation Bias, Cognitive Dissonance, and Contrast Nephropathy