Radiocontrast Agents: Risks in Kidney Disease

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Charlottesville, Virginia
Session Overview

1. Overview of contrast nephropathy and risks of gadolinium with focus on patients with kidney disease
2. Emerging functional MRI techniques
3. Specific populations
   - Oncology patients
Key Questions

• Patients with underlying kidney disease have multiple co-morbidities that require imaging
• Many imaging procedures require a “contrast” agent to enhance the images
• Certain types of “contrast” are toxic in patients with underlying kidney disease
• Complete avoidance of contrast-enhanced imaging may lead to missed diagnoses and other important consequences
• It is critical for physicians to utilize imaging modalities that obtain critical information with doing little or preferably no harm
• How do we accomplish these goals?
What are the Major “Toxic” Concerns?

• AKI due to iodinated radiocontrast exposure (AKA)
  – Radiocontrast-induced nephropathy (RCIN)
• Systemic fibrosing disorder associated with gadolinium-based contrast agent (GBCA) administration
  – Nephrogenic systemic fibrosis (NSF)
What are the “Other” Concerns?

- Consequences of excluding the appropriate imaging test to make a diagnosis
  - Metastatic cancer (due to missed/delayed diagnosis)
- Exposing young patients to ionizing radiation
  - Increased solid cancer risk
- Exposing patients to increased risk of dangerous reactions (i.e., anaphylactoid reactions)
  - Increased morbidity and mortality
Radiocontrast-induced Nephropathy
What is it?

• AKI defined as an increase in serum Cr of 25%-50% (0.5 mg/dl) or decrease in GFR of 25%
• 3rd most common cause of hospital-acquired AKI
• AKI incidence ranges from 5-40%, depending on AKI definition and underlying patient risk factors
  – Underlying kidney disease (CKD, AKI)
  – Older age, DM, CHF, volume depletion, nephrotoxins, volume/type of contrast
• Dialysis requiring AKI incidence is relatively rare, with range of 0-35%, weighted mean incidence of 3.1%
Controversies

• **Post-contrast AKI**: general term to describe sudden deterioration in kidney function following IV administration of iodinated contrast: *Correlative diagnosis*

• **Contrast-induced nephropathy**: sudden decrease in kidney function caused by iodinated contrast medium: *Causative diagnosis*

American College of Radiology: “CIN is a real, albeit rare, entity. Published studies on CIN have been heavily contaminated by bias and conflation.”
Controversies

- Much of the literature investigating the incidence of CIN has failed to include a control group of patients not receiving contrast medium.
- This is problematic because several studies have shown that the frequency and magnitude of serum creatinine change in patients who have not received contrast medium is similar to the changes in patients who have received it.
- In more than 30,000 patients at a single institution who did not receive any contrast medium, more than half showed a change in serum creatinine of at least 25%, and more than 40% showed a change of at least 0.4 mg/dL.
- The authors noted that had some of these patients received iodinated contrast medium temporally related to the rise in serum creatinine, the rise would have been undoubtedly attributed to it, rather than to physiologic variation or another etiology.

Controversies

• Since 2007, an increasing number of published studies have included control groups of patients not exposed to iodinated contrast medium.

• Most have found no evidence of CIN, but most also utilized non-randomized non-matched controls who happened to receive unenhanced CT as part of routine clinical care.

• The clinical population of patients imaged with unenhanced CT is enriched with patients who are at risk for AKI and therefore is contaminated by selection bias.

Controversies

• Four large studies released in 2013 and 2014 (each with >10,000 patients) have addressed selection bias in the unenhanced CT population through use of propensity score adjustment and propensity score matching

• Conclusions remain contradictory and not clear:
  – Stable eGFR ≥45 mL / min/1.73m², IV iodinated contrast media are not an independent nephrotoxic risk factor
  – eGFR 30-44 mL / min/1.73m², IV iodinated contrast media are either not nephrotoxic or rarely so
  – IV iodinated contrast material is an independent nephrotoxic risk factor in patients with Stage IV and Stage V chronic kidney disease

ACR Manual on Contrast Media Version 10.3 May 31, 2017
Classic Risk Factors Associated with RCIN

- Underlying kidney disease
  - Acute kidney injury
  - Chronic kidney disease
- Diabetes mellitus (with or without kidney disease)
- Intravascular volume depletion
- Hypercalcemia
- Multiple myeloma (with kidney disease)
- Drugs
  - NSAIDs
  - Calcineurin inhibitors
  - Vasoconstrictors
  - Nephrotoxins (aminoglycosides, etc)
- Radiocontrast media
  - High osmolar, iodinated radiocontrast
  - Increased viscosity radiocontrast
  - Large volumes of radiocontrast
  - Intra-arterial injection of radiocontrast
Risk Thresholds in AKI

• In patients with AKI, the administration of iodinated contrast medium should only be undertaken with appropriate caution, and only if the benefit to the patient outweighs the risk.

• There have been no published series demonstrating that IV iodinated contrast medium administration to patients with AKI leads to worse or prolonged renal dysfunction than would occur in a control group.

• However, patients with AKI are particularly susceptible to nephrotoxin exposure and therefore it is probably prudent to avoid intravascular iodinated contrast medium in these patients when possible.
Pathophysiology of RCIN

<table>
<thead>
<tr>
<th>Ischemic acute tubular injury</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adenosine</td>
<td></td>
</tr>
<tr>
<td>• Endothelin</td>
<td></td>
</tr>
<tr>
<td>• Angiotensin II</td>
<td></td>
</tr>
<tr>
<td>• Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>• Tubuloglomerular feedback (osmotic effects)</td>
<td></td>
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<tr>
<td>• Viscosity-induced medullary hypoxia</td>
<td></td>
</tr>
<tr>
<td>• Direct endothelial damage</td>
<td></td>
</tr>
<tr>
<td>• Smooth muscle injury</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Direct tubular toxicity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tubular cell dysfunction and swelling due to hyperosmolarity</td>
<td></td>
</tr>
<tr>
<td>• Tubular injury from increased viscosity</td>
<td></td>
</tr>
<tr>
<td>• Reduced tubular cell ATP</td>
<td></td>
</tr>
<tr>
<td>• Increased intracellular calcium concentration</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxidative stress and lipid peroxidation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Generation of reactive oxygen species</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apoptosis of tubular cells</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tubular cell injury from osmotic stress</td>
<td></td>
</tr>
<tr>
<td>• Hypoxia of tubular cells</td>
<td></td>
</tr>
</tbody>
</table>
• On the surface, a reversible (usually) decline in kidney function is benign

• However, data are accumulating that the AKI event is not so benign

• RCIN is associated with:
  – Increased complications (infection, bleeding, etc)
  – Increased hospital length of stay (and costs)
  – Possible development of CKD and all of its consequences (CVD, dialysis, death)
  – Increased mortality
Radiocontrast-induced Nephropathy Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>In Hospital Mortality</th>
<th>1 Year Mortality</th>
<th>5 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AKI</td>
<td>AKI</td>
<td>AKI + HD</td>
</tr>
<tr>
<td>McCullough 1997</td>
<td>1.1%</td>
<td>7.1%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Levy 1996</td>
<td>7%</td>
<td>34%</td>
<td>62%</td>
</tr>
<tr>
<td>Gruberg 2000</td>
<td>4.9%</td>
<td>14.9%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Rihal 2002</td>
<td>1.4%</td>
<td>22%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Perazella MA. Minerva Urol Nefrol 2009
Radiocontrast-Induced Nephropathy Adverse Events

- CARE trial-randomized study of low osmolar vs iso-osmolar contrast
- Follow-up data were obtained at least 1 yr after contrast exposure on 294 patients of the original 414 participants
- Major AEs- Death, CVA, MI, ESRD requiring dialysis

<table>
<thead>
<tr>
<th>Definition of CIN</th>
<th>Overall CIN Incidence (%)</th>
<th>CIN Group</th>
<th>Non-CIN Group</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCysC increase ≥15%</td>
<td>24.8</td>
<td>25/60 (42%)</td>
<td>47/182 (26%)</td>
<td>0.02</td>
</tr>
<tr>
<td>ScysC increase ≥20%</td>
<td>19.4</td>
<td>20/47 (43%)</td>
<td>52/195 (27%)</td>
<td>0.03</td>
</tr>
<tr>
<td>ScysC increase ≥25%</td>
<td>16.1</td>
<td>18/39 (46%)</td>
<td>54/203 (27%)</td>
<td>0.01</td>
</tr>
<tr>
<td>SCr increase ≥0.3 mg/dl</td>
<td>17.3</td>
<td>22/51 (43%)</td>
<td>70/243 (29%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Solomon RJ. CJASN 2009
Radiocontrast-induced Nephropathy Adverse Events

<table>
<thead>
<tr>
<th>CIN Definition</th>
<th>ScysC Increase</th>
<th>SCR Increase ≥0.3 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥15%</td>
<td>≥20%</td>
</tr>
<tr>
<td>All AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted IRR</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.1 to 3.6</td>
<td>0.9 to 3.3</td>
</tr>
<tr>
<td>$P^b$</td>
<td>0.0291</td>
<td>0.0935</td>
</tr>
<tr>
<td>Major AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted IRR</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.9 to 5.1</td>
<td>0.8 to 4.5</td>
</tr>
<tr>
<td>$P^b$</td>
<td>0.0632</td>
<td>0.1437</td>
</tr>
</tbody>
</table>

IRR - Incidence Rate Ratio

Solomon RJ. CJASN 2009
RCIN Post-PCI

Pre-procedural Clinical Risk Factors for Contrast Induced Nephropathy

• **Modifiable Risk Factors**
  - Contrast volume
  - Hydration status
  - Concomitant nephrotoxic agents
  - Recent contrast administrations

• **Non-modifiable Risk Factors**
  - Diabetes/Chronic kidney disease
  - Shock/hypotension
  - Advanced age (> 75 yrs)
  - Advanced congestive heart failure

## Multi-factorial Predictors of CIN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>2.537</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IABP use</td>
<td>5</td>
<td>2.438</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
<td>2.250</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SCR&gt;1.5</td>
<td>4</td>
<td>2.053</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age.75</td>
<td>4</td>
<td>1.847</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>1.601</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>1.508</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Contrast Volume</td>
<td>1/100ml</td>
<td>1.290</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multi-factorial Predictors of CIN

A Risk Score for Prediction of CIN

Multivariate Predictors

- Hypotension: 5 points
- IABP use: 5 points
- CHF: 5 points
- SCr >1.5 mg/dL: 4 points
- (>132 μmol/L): 4 points
- Age >75 y: 4 points
- Anemia: 3 points
- DM: 3 points
- Contrast volume: 1 point/100 mL

Risk group: Risk score:
- Low ≤5
- Moderate 6 to 10
- High 11 to 15
- Very High ≥16

CIN, contrast-induced nephropathy; DM, diabetes mellitus; IABP, Intra-aortic balloon pump
Radiocontrast-induced Nephropathy
Summary

• RCIN is the 3rd most common cause of hospital-acquired AKI
• AKI develops in patients with underlying risk factors
  – Underlying kidney disease (CKD, AKI)
  – Older age, DM, CHF, volume depletion, nephrotoxins, volume/type of contrast
• Dialysis requiring AKI incidence is relatively rare
• RCIN is associated with untoward outcomes
  – Increased hospital length of stay (and costs)
  – Possible development of CKD and all of its consequences (CVD, dialysis, death)
  – Increased mortality
If imaging with radiocontrast is required
  – Pre-treat with volume expansion
    • Isotonic saline
  – Use low or iso-osmolar chelate contrast
    • Iopamidol, Ioversol, Iomeprol
    • Iodixanol is only better than Iohexal
  – Use lowest dose possible to achieve image
  – Stop nephrotoxic drugs and limit multiple contrast exposure over a short period of time (? 24 hours)
• No data to support hemodialysis after exposure
Contrast Dose

• Maximal Allowable Contrast Dose (MACD)
  – 5 cc contrast x body wgt (kg)/ baseline Cr

• Volume to Creatinine Clearance Ratio
  – Contrast volume/ CrCl
  – Laskey, JACC 2007, unselected population, 3.7 ratio
  – Gurm et al, JACC, 2011, <2 safe; >3 concern
Contrast Type

• Low osmolar or Iso-osmolar better than high osmolar contrast
  – Iso-osmolar may be better than certain low osmolar contrast (iohexol) but has not consistently been proven for all low osmolar agents.

• Keys
  – Low-osmolar or iso-osmolar
  – Limit dose
  – Repeat studies>72 hrs, if clinically possible
## Radiographic Contrast Media

<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>I Concentration (mgI/mL)</th>
<th>Osmolality (mOsm/kg H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monomers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iohexol (Omnipaque)</td>
<td>non-ionic</td>
<td>350</td>
<td>844</td>
</tr>
<tr>
<td>iopamidol (Isovue)</td>
<td>non-ionic</td>
<td>370</td>
<td>796</td>
</tr>
<tr>
<td>ioxilan (Oxilan)</td>
<td>non-ionic</td>
<td>350</td>
<td>695</td>
</tr>
<tr>
<td>iopromide (Ultravist)</td>
<td>non-ionic</td>
<td>370</td>
<td>774</td>
</tr>
<tr>
<td>ioversol (Optiray)</td>
<td>non-ionic</td>
<td>350</td>
<td>792</td>
</tr>
<tr>
<td><strong>Dimers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iodixanol (Visipaque)</td>
<td>non-ionic</td>
<td>320</td>
<td>290</td>
</tr>
<tr>
<td>ioxaglate (Hexabrix)</td>
<td>ionic</td>
<td>320</td>
<td>600</td>
</tr>
</tbody>
</table>

*Kozak M, Chambers, CE. Cardiac Catheterization Laboratory: In: Kaplan, JA, ed. Kaplan’s Cardiac Anesthesia. 6th ed., 2011*
Contrast Timing

• One purported risk factor for the development of CIN is the administration of multiple doses of intravascular iodinated contrast medium within a short period of time.

• Most low-osmolality iodinated contrast media have a half-life of approximately two hours. Therefore, it takes approximately 20 hours for one administered dose of contrast medium to be eliminated in a patient with normal renal function.

• Therefore, it has long been suggested that dosing intervals shorter than 24 hours be avoided except in urgent situations.

• However, in patients with CKD the risk and clearance of the contrast is different and should be treated with greater caution.
No benefit of IV sodium bicarbonate over IV sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis or persistent decline in kidney function at 90 days. Routine use of sodium bicarbonate and/or n-acetylcysteine can no longer be recommended among high-risk patients undergoing angiography.
• High-risk patients undergoing angiography with contrast dye were randomized to intravenous 1.26% sodium bicarbonate versus 0.9% sodium chloride and to oral n-acetylcysteine versus placebo.

• Study fluids were given pre-angiography 1-3 cc/kg/hr over 1-12 hours, intra-angiography 1-1.5 cc/kg/hr, and post-angiography 1-3 cc/kg/hr over 2-12 hours. N-acetylcysteine was given as 1200 mg twice daily for 5 days, starting 1 hour before angiography.
PRESERVE TRIAL

- Total number of enrollees: 4,993 (the trial was stopped early after a prespecified interim analysis)
- Duration of follow-up: 90 days
- Mean patient age: 70 years
- Percentage female: 6.5%
- Percentage with diabetes: 81%
- Patients undergoing coronary or noncoronary angiography
- Chronic kidney disease; estimated glomerular filtration rate (eGFR) 45-60 cc/min plus diabetes or 15-45 with cc/min ± diabetes
The primary outcome, incidence of death, need for dialysis, or persistent ≥50% increase in serum creatinine at 90 days, occurred in 4.4% of the sodium bicarbonate group versus 4.7% of the sodium chloride group (p = 0.62).

The primary outcome, incidence of death, need for dialysis, or persistent ≥50% increase in serum creatinine at 90 days, occurred in 4.6% of the n-acetylcysteine group versus 4.5% of the placebo group (p = 0.88).
PRESERVE: Secondary Outcomes

- Contrast-induced nephropathy: 9.5% of the sodium bicarbonate group versus 8.3% of the sodium chloride group ($p = 0.13$)
- Contrast-induced nephropathy: 9.1% of the n-acetylcysteine group versus 8.7% of the placebo group ($p = 0.58$)
Nephrogenic Systemic Fibrosis
What is it?

• First patients noted in 1997 in San Diego, CA
• Systemic fibrosing disorder of patients with advanced kidney disease
  – Patients with failed kidney transplants on hemodialysis
• Predominant manifestation in the skin
  – Thickening, non-pitting, woody, plaque forming, cobble-stoning
  – Similar clinically to scleroderma, lipodermatosclerosis, myositis
  – Similar histologically to scleromyxedema, morphea (scleroderma), and eosinophilia-myalgia
• CDC & California DOH unable to determine cause but noted kidney disease was a common thread
• Described as a “new disease” by Cowper and Leboit with publication in the Lancet (2000)
Nephrogenic Systemic Fibrosis

Clinical signs

Early edema of fingers
“Sausaging”
Edema that is non-pitting and “unpinchable”
Nephrogenic Systemic Fibrosis

Clinical signs

Peau d’orange surface skin changes
Nephrogenic Systemic Fibrosis

Clinical signs

Flexion and extension contractures of hands and feet
Skin Biopsy

Collagen bundles with surrounding clefts

Dermal spindle cells apposed to collagen bundles

Mucin is identified by alcian blue staining (early)

Deposition of gadolinium in skin lesions

Mass spectrometry (Quantification)
- Total Gd in tissue (+ & - controls)
- Significant Gd in skin/tissues of NSF
  - 5-106 ppm (~70 ppm)
- Gd in bone tissue of healthy subjects exposed to 0.1 mmol/kg of gadodiamide or gadoteridol
  - 1.77 ppm for gadodiamide
  - 0.477 ppm for gadoteridol

Gd in NSF 35-150 fold higher than healthy controls exposed to Gd
Deposition of gadolinium in skin lesions
Energy Filtering Transmission Electron Microscopy

Electron Spectroscopic imaging (ESI)

Electron Energy Loss Spectroscopy (EELS) Spectrum

Schroder et al. CJASN 2008
Molecular mass (~550 Da)
- Distributed in ECF (Vd ~ 0.6 L/kg)
- No biotransformation
- No protein binding
- Excreted unchanged by GFR
  - > 90% excreted in one day
- Half life ~1.3-1.6 hours
  - prolonged with reduced GFR

Gadolinium-based Contrast Agents
Pharmacokinetics

Perazella & Rodby. Sem Dialysis 2007

Schuhmann-Giampieri. Invest Radiol 1991
Nephrogenic Systemic Fibrosis: What’s the Big Deal?

- NSF is associated with severe morbidity & increased mortality
- Severe dermal manifestations associated with debilitating pain, joint immobility, & bed-confining contractures occur
- 5% of cases have a rapid & severe course to wheelchair or bed bound state from severe contractures
Nephrogenic Systemic Fibrosis: What’s the Big Deal?

• Systemic manifestations are severe and include lung, heart, muscle, dura, kidney and other end organ involvement.

• Many patients die from these systemic manifestations, bed sores or hip fractures.

• No therapy is currently available, although anecdotal benefit from various treatments have been noted
  – Kidney transplant, extra-corporeal photopheresis, imatinib, sodium thiosulfate.
Nephrogenic Systemic Fibrosis
Patients and GBC Risks

• **Risk of patients exposed to GBC**
  – **High Risk:**
    • CKD Stage V & ESRD (PD > HD) is highest risk
    • Acute Kidney Injury (esp. HRS, liver transplant)
  – **Medium/Lower Risk:**
    • CKD Stage IV
  – **Very Low/No Risk:**
    • CKD stages I-III
  – **No Risk:**
    • Normal kidney function

• **Risk of Gadolinium-based contrast agents**
  – **High Risk:**
    • Nonionic linear chelates (gadodiamide > gadoversetamide?)
  – **Medium Risk:**
    • Ionic linear chelates (gadopentetate > gadobenate?)
  – **Low Risk:**
    • Macrocyclic chelates (gadoteridol)
In EU, linear GBCAs have recently been restricted or removed from the market due to concerns related to tissue retention

McDonald RJ, et al. Radiology 2018; 289: 517
GBCAs and NSF

Patients with CKD Stage 4 or 5 have a 1-7% chance of developing NSF after one or more exposures to group 1 GBCAs

Between 12-20% of cases of NSF have occurred in patients with AKI often with CKD

TABLE 1. ACR Manual Classification of Gadolinium-Based agents Relative to Nephrogenic Systemic Fibrosis

<table>
<thead>
<tr>
<th>Group I: Agents associated with the greatest number of NSF cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide (Omniscan® – GE Healthcare)</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMARK® – Guerbet)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group II: Agents associated with few, if any, unconfounded cases of NSF:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)</td>
</tr>
<tr>
<td>Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals; Gadovist in many countries)</td>
</tr>
<tr>
<td>Gadoterate acid (Dotarem® – Guerbet)</td>
</tr>
<tr>
<td>Gadoteridol (ProHance® – Bracco Diagnostics)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any, unconfounded cases of NSF have been reported:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoxetate disodium (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries)</td>
</tr>
</tbody>
</table>
Incidence of NSF with Group II Agent

Nephrogenic Systemic Fibrosis Guidelines/Recommendations for Prevention

- If MR imaging with gadolinium-based contrast is required
  - Use macrocyclic chelate contrast
    - Gadoteridol (non-ionic macrocyclic chelate)
  - Use lowest dose possible to achieve image
  - Consider hemodialysis after exposure and the next day in ESRD/AKI patients already on hemodialysis (*theoretical*)
    - 6 hours of high flux hemodialysis
    - Limited data with conflicting results
Use of GBCA in patients with category G4 or G5 CKD (eGFR less than 30 mL/min/1.73 m2) or dialysis dependent patients.

Alternative diagnostic tests (e.g., unenhanced MRI, CT, ultrasound, biopsy, scintigraphic examinations, etc) should be considered before GBCA are prescribed.

When another diagnostic modality is not available or considered inferior to enhanced MRI, and MRI is deemed necessary for patient care, then gadolinium enhanced examinations using macrocyclic or newer linear GBCA may be performed with patient informed consent citing an exceedingly low risk (much less than 1%) of NSF based on available literature.

Repeat dosing is to be avoided.

For patients on dialysis; HD efficiently removes GBCA with about 70% clearance in 1 session and > 95% clearance after 3 sessions and HD should be scheduled soon after exposure, ideally within 2 to 3 hours after GBCA-enhanced MRI.

NSF and RCIN
Guidelines/Recommendations for Prevention
Identify high risk patients

**NSF**
- ESRD (PD > HD)
- Acute Kidney Injury
  - HRS, liver transplant
- CKD Stage 5 > Stage 4
- Patients with known or suspected NSF
- Patients with other co-factors (inflammation, infection, metabolic disturbances)

**RCIN**
- ESRD (PD, HD) with RRF
- Acute Kidney Injury
- CKD Stage 5 > Stage 4 > Stage 3
  - In particular Diabetic Nephropathy
- Patients with CHF, Myeloma Kidney, Volume Depleted
• Use alternative imaging modalities when possible & appropriate
  – Ultrasound (Color, Power, Spectral Doppler)
  – PET, CO\textsubscript{2} angiography
  – CT scan without radiocontrast
  – MR without gadolinium contrast
    • Non-contrast MR techniques
    • Ultrasmall paramagnetic iron oxide- USPIOs

• Factor in the following:
  – Importance of the imaging information
  – Exposure to ionizing radiation
  – Potential for anaphylactoid reactions
    • Iodinated radiocontrast >> gadolinium-based contrast
Summary

• A thoughtful approach to the use of radiocontrast agents is needed in order to balance risks and benefits.

• In most cases, either risk mitigating or alternative radiological procedures can be utilized.

• Controversies regarding the exact risk of iodinated contrast agents continues and it is likely that “truth” regarding the risks of these agents will continue to be a source of disagreement.