Update on Contrast Material Use in Children

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  – **Bracco Diagnostics, Inc.**
  – **Siemens Medical Systems USA, Inc.**

• Member of ACR Committee on Drugs and Contrast Media
Outline/Objectives

1. Review commonly used intravascular iodinated & gadolinium-based contrast materials (ICMs & GBCMs)

2. Review clinical presentation & management of physiologic/allergic-like contrast material reactions

3. Present up-to-date reviews of contrast-induced nephrotoxicity (CIN) & nephrogenic systemic fibrosis (NSF) for the pediatric radiologist
IV Iodinated Contrast Materials (ICMs)

• Very safe
• Nonionic agents = standard of care in U.S.
• Low-osmolar (monomer) > iso-osmolar (dimer)
• Ionic/high-osmolar agents no longer used due to side-effect profile
  – Non-allergic-like/physiologic
  – Allergic-like
  – Contrast-induced nephrotoxicity (CIN)
ICMs – Monomeric vs. Dimeric

- Iohexol (Omnipaque)
- Iopamidol (Iovue)
- Iopromide (Ultravist)
- Ioversol (Optiray)

Osmolality ≈ 600-800 mOsm/kg H₂O

- Iodixanol

Osmolality ≈ 290 mOsm/kg H₂O
Pediatric IV ICM Usage in U.S.

- 2011 *SCORCH* member survey (66% response rate)
  - Ioversol (52%)
  - Iohexol (38%)
  - Iodixanol (29%)
  - Iopamidol (26%)
  - Iopromide (5%)

- Dosing: 2 ml/kg (88%)

- Iodine concentration: 300-320 mg/l (81%)

- Iodine load to patient: range, 270-740 mg l/kg

IV Gadolinium-Based Contrast Materials (GBCMs)

- Also very safe!

- Major GBCM groups:
  - Linear agents —
    - OptiMARK, OmniScan, Magnevist, MultiHance
  - Macrocyclic agents —
    - ProHance, Gadovist, Dotarem
  - Other agents —
    - Eovist – hepatocyte uptake/excretion
    - Ablavar – blood pool agent
Pediatric IV GBCM Usage in U.S.

- 2011 SCORCH member survey (66% response rate)
  - Magnevist (88%)
  - MultiHance (38%)
  - ProHance (14%)
  - OmniScan (10%)
  - Eovist (10%)
  - Ablavar (5%)
  - OptiMARK (2%)

- Dosing: 0.1 mmol/kg most common

Non-Allergic-Like Reactions to IV ICMs & GBCMs

- **Mechanism:** Due to variety of *physiologic* responses
  - Direct chemotoxicity, osmotoxicity?
  - Vasodilation, brainstem stimulation, etc.
- **Dose-dependent**
- **More common than allergic-like reactions**
- **Countless listed in package inserts**
  - e.g., nausea/emesis, headache, flushing
- **Treatment:** Reassurance
- **Prevention strategy:** None
Allergic-Like Reactions to IV ICMs & GBCMs

• **Mechanism**: Likely anaphylactoid ("idiosyncratic")
  
  – Cause: direct histamine release, other mediators (complement, kinin system)
  
  – No prior exposure required!

• Rarely anaphylactic?
  
  – Requires identification of antigen-antibody response (e.g., positive skin test)

• Primarily dose/concentration independent
Allergic-Like Reaction Severity

• Spectrum of manifestations:
  – **Mild**: no medical management or only anti-H (e.g., diphenhydramine)
    • Overwhelming majority of reactions
  – **Moderate**: medical management > than anti-H (e.g., albuterol, epinephrine)
  – **Severe**: life-threatening
    • Generally require epinephrine ± hospitalization
Management of Pediatric Allergic-Like Reactions to IV ICMs & GBCMs

• **Treatment**: identical to that of similar allergic reaction (food, bee sting, etc.)

• **Key medications**:
  
  – Diphenhydramine
  
  – Albuterol
  
  – Epinephrine
• Diphenhydramine (Benadryl):
  – Nonselective anti-histamine
  – 1-2 mg/kg (up to 50 mg); PO, IM, or IV
  – Only firm indication is severe pruritis/cutaneous reaction (urticaria)
  – Can cause hypotension
  – **DOES NOT** effectively treat bronchospasm, laryngeal edema, or anaphylaxis (hypotension/tachycardia)
Management of Pediatric Allergic-Like Reactions to IV ICMs & GBCMs

• Albuterol:
  – Inhaled β-agonist
  – Bronchodilator – treats bronchospasm/wheezing
  – 2 puffs from MDI --- use spacer
  – Repeat as indicated
  – WILL NOT effectively treat laryngeal edema or anaphylaxis (hypotension/tachycardia)
Management of Pediatric Allergic-Like Reactions to IV ICMs & GBCMs

• Epinephrine:
  – α-agonist
  – 0.01 mg/kg IV slow push over 2-5 min
    [1:10,000 concentration – 10 ml vial]
    • up to 0.3 mg (3 ml) per dose
  – ALTERNATIVE: 0.15 mg (EpiPen Jr)/0.3 mg (EpiPen) IM [1:1,000 concentration]
  – Treats **ALL** allergic-like reactions:
    • urticaria, laryngeal edema, bronchospasm, & anaphylaxis (hypotension/tachycardia)

http://www.epipen.com/about-epipen/overview
GOOD NEWS

- Pediatric allergic-like reactions to ICMs are rare!
  - Dillman et al. *(AJR 2007)*: 0-18 years-old
    - 20 rxns/11,306 injections = 0.18% (1.8 rxn/1000 injections)
      - 16 mild, 1 moderate, 3 severe
  - Callahan et al. *(Radiology 2009)*: 0-21 years-old
    - 57 rxns/12,494 injections = 0.46% (4.6 rxn/1000 injections)
      - 47 mild, 10 moderate, 0 severe
  - Gooding et al. *(AJR 1975)*: “children”
    - 5 “major” rxns/12,419 injections = 0.04%
More GOOD NEWS

- Pediatric allergic-like reactions to GBCMs are even rarer!
  - Dillman JR, et al. (AJR 2007):
    - 6 rxns/13,344 injections = 0.04% (0.4 rxn/1000 injections)
      - 5 mild, 1 severe
  - Davenport MS, Dillman JR, et al. (Radiology 2012):
    - 8 rxns/15,706 injections = 0.05% (0.5 rxn/1000 injections)
      - 7 mild, 1 moderate
Management of Pediatric Allergic-Like Reactions to IV ICMs & GBCMs

- DON'T FORGET SUPPORTIVE MEASURES!!
  - Maintain airway/IV access
  - Check vitals
  - Consider oxygen (high flow)
  - Isotonic IV fluids if hypotensive

- Call 911 (or other phone #) if deterioration

- GOOGLE: "ACR Contrast Manual"
Allergic-Like Reaction Abatement

- Efficacy of “adult” premedication regimens never studied in children (neither ICMs nor GBCM)
- We **ASSUME** adult premedication protocols give children at least some protection
Allergic-Like Reaction Abatement

• Landmark premedication study:
  – Lasser et al. (AJR 1994)
    • LOCM; 1155 subjects/controls --- 3 institutions
    • METHYLПREDNISOLONE – 12 & 2 hr prior to contrast
    • 4.9% → 1.7% reaction frequency
    • No significant ↓ in moderate/severe reactions

• Allergic-like reactions can occur despite premedication (“breakthrough” reactions)
  – Frequency unknown

Dillman JR, et al. AJR 2007; 188:1643-1647
### Table A: Sample Pediatric Corticosteroid and Antihistamine Premedication Regimen

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<tr>
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<th>Dosage</th>
<th>Timing</th>
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<tr>
<td><strong>Prednisone</strong></td>
<td>0.5–0.7 mg/kg PO (up to 50 mg)</td>
<td>13, 7, and 1 hrs prior to contrast injection</td>
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<tr>
<td><strong>Diphenhydramine</strong></td>
<td>1.25 mg/kg PO (up to 50 mg)</td>
<td>1 hr prior to contrast injection</td>
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**Note:** Appropriate intravenous doses may be substituted for patients who cannot ingest PO medications.
Allergic-Like Reaction Abatement

• Current (2013) University of Michigan indications for premedication (intravascular ICM)*:

1. Prior allergic-like reaction to ICM
2. Ongoing asthma attack (wheezing)
3. Prior severe allergic-like reaction to 2 or more categories of substances
   • e.g., penicillin & food allergy

*Adults & Children
ICM & Contrast-Induced Nephrotoxicity (CIN) in Children

- Acute kidney injury (AKI) occurring 48-72 hr after intravascular ICM
- Etiology – osmotoxicity, viscosity, other?

Normal Serum Cre Increases with Age

- More recent definition – AKIN criteria
  - Increase serum Cre by 0.3 mg/ml
  - Probably most appropriate for pediatric population
ICM & CIN in Children

- Rarely occurs in isolation – frequently associated with:
  - Concomitant insult
    - e.g., nephrotoxic meds, hypotension, dehydration, sepsis
  - Underlying risk factor(s)
    - e.g., CKD, DM, CHF
- Difficult to establish actual incidence
  - IA >>> IV?
  - Extremely rare in patients with NL eGFR
  - Pediatric incidence unknown
CIN Prevention

- Efficacy of adult CIN prevention strategies have not been studied in children
- We **ASSUME** adult prevention strategies provide some protection (*and* do no harm)
- Recommendations for at-risk children:
  1. Consider noncontrast CT/MRI, US, etc.
  2. Consider nephrology consult prior to CT
  3. Consider hydration
  4. **STOP** other nephrotoxic agents
  5. ↓ volume of IV contrast material
ICM & CIN – Prevention

• Other preventive medical strategies?
  – N-acetylcysteine (NAC):
      – 83 pts with CKD undergoing CE-CT
      – Randomized, prospective, control group
      – 21% (control) vs. 2% (NAC) CIN (p<0.01)
      – NAC: ↓ serum Cre mean 2.5 to 2.1 mg/dl

![Chemical Structure of NAC]
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ICM & CIN – NAC Actually Renoprotective?

  – In normal volunteers (*no IV contrast*), NAC reduced serum Cre without changing cystatin C

• ACT Trial (*Circulation* 2011)
  – 2308 pts; only high-risk pts undergoing coronary or peripheral arteriography
  – Randomized, prospective, control group, intent-to-treat
  – AKI 12.7% in both NAC & control groups
  – **Conclusion**: NAC provides no reduction in risk
ICM & CIN – Prevention

• Other medical prevention strategies?
  – Sodium bicarbonate

• Marten et al. (JAMA 2004):
  – 119 pts; labs only on days 1 and 2 postcontrast
  – Prospective, randomized, single-center
  – CIN: 14% (w/o bicarb) → 2% (w/ bicarb)
### ICM, CIN & Bicarb – Review of the Literature

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<td>Lee ^</td>
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^ With NAC
ICM & CIN – Prevention

• Other medical prevention strategies?
  – Iodixanol (Visipaque; iso-osmolar agent)
  
    – 129 high-risk angiography pts
    – Serum Cre at baseline & 72 hours
    – Mean serum Cre increase: 0.1 (iodixanol) vs. 0.6 (iohexol)
    – CIN: 3% (iodixanol) vs. 26% (iohexol)
## ICM, CIN & Iodixanol – the Meta-Analyses

<table>
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<td>McCullough(^1)</td>
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\(^1\)Meta-analysis of 16 trials, all (cardio)angiography

\(^2\)Meta-analysis of 25 trials (7 IV)

\(^3\)Meta-analysis of 16 trials (5 IV)

\(^4\)Meta-analysis of 36 trials (10 IV)
CIN – is it Always the Contrast?

- Newhouse JH, et al. (AJR 2008):
  - 32,161 adult pts with serum Cre on 5 consecutive days
  - No prior IV contrast within 10 days
  - 15% “CIN rate” (actually “hospital-induced nephropathy”)
  - Rate of CIN OVERESTIMATED in literature?
  - Emphasized need for CONTROLS in CIN studies
Davenport MS, Dillman JR, et al. (Radiology 2013):

- 10,121 noncontrast & 10,121 enhanced CT exams analyzed using 1:1 propensity-matching
- IV LOCM had a significant effect on the development of post-CT AKI for patients with pre-CT serum Cre ≥1.6 mg/dl (p=0.007, OR 1.45)
  - Relationship strengthened as serum Cre increased
- Patients with stable serum Cre <1.5 mg/dl were at NO RISK for CIN (p=0.25, power >95%)
GBCM & Nephrogenic Systemic Fibrosis (NSF)

• First described ≈2000 ("NFD")

• Almost all cases in setting of acute or chronic kidney disease & IV GBCM

• **Mechanism(?)**:  
  - Increased GBCM circulation time → "transmetallation" (Ca, Fe, Zn?)  
  - Free Gad in blood binds with anions (e.g., \(\text{PO}_4\)), deposits in skin/viscera & incites fibrosis (CD34+ fibrocytes)

• Most often affects skin  
  - erythema, induration/plaque-like thickening, contractures
# NSF – Does the GBCM Matter?

## Table 1

**Group I: Agents associated with the greatest number of NSF cases:**

- Gadodiamide (Omniscan® – GE Healthcare)
- Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
- Gadoversetamide (OptiMARK® – Covidien)

**Group II: Agents associated with few, if any, unconfounded cases of NSF:**

- Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
- Gadoteridol (ProHance® – Bracco Diagnostics)
- Gadoteric acid (Dotarem® – Guerbet – as of this writing not FDA-approved for use in the U.S.)
- Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)

**Group III: Agents which have only recently appeared on the market in the US:**

- Gadofosveset (Ablavar® – Lantheus Medical Imaging)
- Gadoxetic acid (Eovist® – Bayer HealthCare Pharmaceuticals)
NSF – ACR Recommendations

• eGFR <30 ml/min:
  – Avoid GBCM if possible ("black box" warning)
  – Avoid Group I agents
  – Lowest dose possible

• eGFR <40 ml/min:
  – Avoid GBCM if possible
  – Avoid Group I agents
  – Lowest dose possible

• eGFR ≥40 ml/min: No special precautions
NSF & Children

- Very rare – ≈20 reported cases (Saddleton, et al. SUR scientific session 2011)
  - Youngest known pt → 8 years-old
  - All had significant renal dysfunction
- No pediatric-specific EBM guidelines for prevention
- **Recommendation:** Follow ACR & FDA “black box” recommendations for identifying at-risk patients & administering GBCMs
NSF & Children

- Judicious use of GBCM in preemies/neonates, as GFR may be <30 ml/min
- Avoid GBCM in CKD and eGFR <30 ml/min (including dialysis pts) or AKI, if possible
- Pediatric eGFR calculation = Bedside Schwartz equation (not adult MDRD equation):
  \[ \text{GFR (mL/min/1.73 m}^2\text{)} = 0.41 \times \frac{\text{height (cm)}}{\text{serum Cre (mg/dL)}} \]
Conclusions

• Wide variety of IV ICMs and GBCMs can be safely administered to children of all ages

• Contrast material-related adverse events are rarer in children than adults
  – We must still know how to manage allergic-like reactions

• Pediatric radiologists should consider renal function when administering IV ICMs & GBCMs to mitigate CIN/NSF risks
A 15 year-old boy undergoes a CT examination with intravenous iodinated contrast material. The patient becomes unresponsive two minutes after the scan and is noted to have diffuse skin erythema. Initial vital signs confirm a blood pressure of 68/42 and a heart rate of 125. After calling for help, what is the next most appropriate step in the medical management of this patient?

A. Administer IV diphenhydramine (Benadryl) and IV corticosteroid (e.g., hydrocortisone)

B. Administer inhaled B-agonist medication (e.g., albuterol)

C. Administer IV atropine

D. Administer IM epinephrine
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D. Administer IM epinephrine
Regarding nephrogenic systemic fibrosis (NSF) in the pediatric population, which of the following is TRUE?

A. NSF has been documented mostly in children with normal renal function.

B. Patients with an estimated glomerular filtration rate (eGFR) between 45 and 60 ml/min are considered to be at-risk for NSF.

C. Macrocyclic gadolinium chelates are less likely to be associated with the development of NSF than linear gadolinium chelates.

D. Macrocyclic gadolinium chelates absolutely must be avoided in children determined to be at-risk for NSF, even if the benefits of imaging outweigh the risk of NSF.
Question #2

Regarding nephrogenic systemic fibrosis (NSF) in the pediatric population, which of the following is TRUE?

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