Use of Intravenous Contrast Media in Imaging: Attributes and Safety Concerns

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Learning Objectives

- Identify emerging safety concerns associated with the use of intravenous (IV) contrast media in clinical settings
- Evaluate and select appropriate IV contrast media by considering clinical attributes and ability to produce optimal image quality
- Decrease the incidence of adverse events (AEs) in IV contrast media use by following practices suggested by the American College of Radiology (ACR)
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Arlington Medical Resources Database. Imaging Market Guide. 2006.
## Periodic Table of Elements

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* Lanthanide Series
  | 58 Ce  | 59 Pr | 60 Nd | 61 Pm | 62 Sm | 63 Eu | 64 Gd | 65 Tb | 66 Dy | 67 Ho | 68 Er | 69 Tm | 70 Yb | 71 Lu |

+ Actinide Series
  | 90 Th  | 91 Pa | 92 U  | 93 Np | 94 Pu | 95 Am | 96 Cm | 97 Bk | 98 Cf  | 99 Es | 100 Fm | 101 Md | 102 No | 103 Lr |

### Legend - click to find out more...

- **H** - gas
- **Li** - solid
- **Br** - liquid
- **Tc** - synthetic

- **Non-Metals**
- **Transition Metals**
- **Rare Earth Metals**
- **Halogens**
- **Alkali Metals**
- **Alkali Earth Metals**
- **Other Metals**
- **Inert Elements**

IV Contrast: Gd-Containing Agents

- The most commonly used agents for MR procedures
  - T1 shortening

- Examples (in order of FDA approval)
  - Gd-DTPA; gadopentetate dimeglumine (Magnevist®; 6/88)
  - Gd-HP-DO3A; gadoteridol (ProHance®; 11/92)
  - Gd-DTPA-BMA; gadodiamide (Omniscan™; 1/93)
  - Gd-DTPA-BMEA; gadoversetamide (OptiMARK®; 12/99)
  - Gd-BOPTA; gadobenate dimeglumine (MultiHance®; 12/04)
### IV Contrast: Formulations of Gd Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Gd-Ligand Complex</th>
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<tr>
<td>Gd-DTPA (gadopentetate dimeglumine; Magnevist)</td>
<td><img src="image1" alt="Structure" /></td>
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<td>Gd-HP-DO3A (gadoteridol; ProHance)</td>
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<td>Gd-DTPA-BMA (gadodiamide; Omniscan)</td>
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<td>Gd-DTPA-BMEA (gadoversetamide; OptiMARK)</td>
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<tr>
<td>Gd-BOPTA (gadobenate dimeglumine; MultiHance)</td>
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Gd Chelates: Linearity and Ionicity

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<td>[Macrocyclic Structure]</td>
</tr>
<tr>
<td>Non-Ionic</td>
<td>[Non-Ionic Linear Structure]</td>
<td>[Non-Ionic Macrocyclic Structure]</td>
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Comparison of Commonly Used Gd Contrast Agents

<table>
<thead>
<tr>
<th></th>
<th>R1 Relaxivity (plasma @ 37°C, 1.5 T)</th>
<th>Structure</th>
<th>Osmolality³ (mOsm/kg @ 37°C)</th>
<th>Viscosity³ (cP @ 37°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Magnevist)</td>
<td>3.9¹ (4.1²)</td>
<td>Linear ionic</td>
<td>1960</td>
<td>2.9</td>
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<tr>
<td>Gadoteridol (ProHance)</td>
<td>4.1²</td>
<td>Cyclic nonionic</td>
<td>630</td>
<td>1.3</td>
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<tr>
<td>Gadodiamide (Omniscan)</td>
<td>4.3²</td>
<td>Linear nonionic</td>
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<td>1.4</td>
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<tr>
<td>Gadoversetamide (OptiMARK)</td>
<td>4.7²</td>
<td>Linear nonionic</td>
<td>1110</td>
<td>2.0</td>
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<tr>
<td>Gadobenate dimeglumine* (MultiHance)</td>
<td>8.1¹ (6.3²)</td>
<td>Linear ionic</td>
<td>1970⁴</td>
<td>5.4⁴</td>
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</tbody>
</table>

*Prolonged hepatic enhancement despite relatively small (2%-4%) hepatocyte uptake.

Factors Affecting Image Quality

- **Contrast factors**
  - Degree of T1 weighting
  - Specific contrast agent
  - Contrast dose

- **Patient factors**
  - Cardiac output
  - Patient size

- **Protocol factors**
  - Duration
  - Flow rate
Ionicity and Osmolality of Gd Agents

- Ionicity
  - Ionic
    - Divides into charged particles in solution (blood)
  - Nonionic
    - Does not divide

- Osmolality
  - Concentration of a solution measured in moles or millimoles per kilogram of solvent

- MR contrast has a lower osmotic load per dose than CT contrast
  - Ionic vs nonionic
    - Nonionic is perceived to be safer
Viscosity of Gd Agents

- Higher viscosity with larger molecules
- Warming the contrast reduces viscosity
- Higher-viscosity agents
  - Are harder to inject
  - May require a larger-bore needle
  - Are typically ionic
Dosing for MR Agents

- A standard dose is 0.1 mmol/kg
  - Other applications may require a larger dose (eg, CE-MRA)
  - Can safely readminister, if necessary (up to a triple dose)\(^1-3\)

- 3 T scans
  - May result in increased T1 contrast compared with 1.5 T scans
  - T1 weighting: \(1 - e^{-\text{Tr}/T1}\)

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Administration of MR Agents

- IV injection rate (1-5 mL/s) and dose (0.1-0.3 mmol/kg) depend on specific application/area of enhancement
  - Brain
    - Slow; no bolus effect
  - Angiography
    - 1 to 3 mL/s
  - Brain and cardiac perfusion
    - 4 to 5 mL/s

- Power injectors are often used
Administration of MR Agents (cont)

- Initially circulate in intravascular space
- Leak through pores of vessels into extracellular/interstitial space\(^1\)
- Do not cross the normal blood-brain barrier
- Are excreted primarily through the kidneys by glomerular filtration\(^1\)
  - Cleared with half-life of about 90 minutes\(^1\) to 2 hours in patients with normal renal function
  - Over 75% excreted within 3 hours\(^1\); 98% eliminated in 1 day
  - Half-life prolonged in chronic renal failure

Gd Contrast Agents: “Off-Label” Use

- In the US, no Gd contrast agent is FDA approved for the following uses:
  - Cardiac
  - Breast
  - Musculoskeletal system
  - MR angiography
  - Intra-articular or intra-arterial procedures

- Some are not approved for higher doses, faster injection rates, or pediatric patients

- “Off-label” use is permitted with no legal ramifications if
  - There are no explicit warnings or contraindications
  - Use meets “community standard” of care
Safety of Gd Agents

- Overall incidence of AEs for MR is less than that for CT
  - Contrast-induced nephropathy (CIN)
  - Contrast extravasation

- The risk of an AE is higher in patients with
  - History of reaction to iodinated contrast media
  - History of reaction to Gd contrast media
  - Allergies
  - Asthma
  - Severe or end-stage renal disease (ESRD)
    - From 3% to 5% may develop nephrogenic systemic fibrosis (NSF)

Contrast-Induced Nephropathy

- **Cause**
  - Not well understood
  - Thought to be through direct toxicity to tubular cells and renal medullary ischemia

- **Fewer cases of CIN in MR than CT at approved doses**
  - CIN can be induced when injecting large doses of contrast for MR procedures
  - Incidence may increase when used intra-arterially during MR procedures
  - More prevalent with use of iodine-containing contrast

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Contrast-Induced Nephropathy (cont)

- **Impairment of renal function**¹
  - Occurring within 48 hours after administration of contrast media
  - Manifested by¹,²
    - An absolute increase in serum creatinine (Cr) of at least 0.5 mg/dL (44.2 μmol/L)
    - OR
    - A relative increase in serum Cr of at least 25% from the baseline value

- **Risk factor**³,⁴
  - Preexisting renal failure

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Contrast-Induced Nephropathy (cont)

Reduction of risk
- Minimize volume
- Prevent repetitive exposure to contrast media in a short period of time
- Avoid use of high-osmolar contrast media

Prevention
- Evaluate risk
- Maintain optimal volume status (hydration)
- Use low-osmolar contrast media in all patients
- Withhold drugs that adversely affect renal function
- Perform a follow-up Cr test on all high-risk patients

Solomon et al. Kidney Int. 2006;69(suppl 100S):S51-S53.
Executive Summary: NSF

- Scleromyxedema-like illness seen in patients with severe renal failure receiving Gd
  - 3% to 5% of patients (GFR <30) develop NSF (no cure)
  - 5% of NSF patients develop fulminant disease

- Gd is cleared by the kidneys
  - Possible prolonged circulation time leads to increased exposure to Gd chelate or free Gd

- Nonionic linear chelates have lower stability constants
  - Approximately 90% of cases involve gadodiamide (Omniscan)

- Mechanism unknown
  - 95% of renal failure patients receiving Gd don’t get NSF
NFD to NSF

- 1989
  - Epoetin alfa (Procrit®)\textsuperscript{a} marketed in the chronic kidney disease population
- 1997
  - First cases of NSF seen
- 1998
  - Paricalcitol (Zemlpar\textsuperscript{b})\textsuperscript{b} approved
  - Sevelamer (Renagel\textsuperscript{c})\textsuperscript{c} approved
- 2000
  - Cowper report in *Lancet*
  - Condition named NFD
- 2001
  - Darbepoetin alfa (Aranesp\textsuperscript{d})\textsuperscript{a} approved in the dialysis population
- 2001 (cont)
  - First NFD case in a patient who had never required dialysis
- 2001-2004
  - Approximately 100 cases reported
- 2004
  - Skeletal muscle involvement reported
  - First NFD in lupus reported
  - Circulating fibrocytes identified
  - Lanthanium carbonate (Fosrenol\textsuperscript{d})\textsuperscript{d} approved
- 2005
  - First non-Western report (India)
- 2006
  - Suggested name change to NSF
Nephrogenic Systemic Fibrosis

- Occurs in acute or chronic severe renal dysfunction
- Most prominent and visible effects are in the skin
- Diagnosis is confirmed on skin biopsy by specific histopathologic features

Clinical Characteristics

- Hardened papules/plaques
- Symmetrical
- Involve limbs and trunk
- Advancing edge of lesions described as “amoeboid”
- Gradual restriction of range of motion
Symptoms of NSF

- Early: pruritis, pain, swelling, and erythema of lower extremities
- Later: thickening of skin and subcutaneous tissues, with “woody” texture and brawny plaques
- Internal organ failure (lungs, heart, skeletal muscle)
NSF Distribution

- NSF lesions usually on upper and lower extremities
- Accumulation of the Gd chelate or free Gd in these dependent, edematous subcutaneous tissues may be the reason the disease normally manifests there
Nephrogenic Systemic Fibrosis

- Natural history and prognosis not well established
  - May develop over days to weeks
  - Approximately 5% of patients have a rapidly progressive course
  - Several documented deaths

- Development not related to either the duration or underlying cause of kidney disease

- Currently, an NSF Registry is maintained at Yale University
  - http://www.icnfdr.org
  - http://www.pathmax.com/dermweb/

Epidemiology of NSF

- Male:Female 1:1
- Age range: 8 to 87 years
- Mean age: 46.4 years
- No race predilection
- All have renal failure
- 90% on dialysis
- All received Gd

Epidemiology of NSF (cont)

- **Association with surgical procedures**
  - Approximately 15% of patients had a nontransplant, nonvascular surgery preceding the onset of NSF symptoms
  - Rises to approximately 48% with the inclusion of transplant surgery (renal or hepatic)
  - Climbs to 90% with the inclusion of vascular access procedures (fistulas, grafts, central catheters)\(^1\)

Epidemiology of NSF (cont)

- Association with renal disease
  - All patients have some form of impaired renal function
  - Can be acute or chronic
  - Dialysis is not a requirement
  - Acidosis common

<table>
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<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
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<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
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<td>4</td>
<td>Severe ↓ GFR</td>
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<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
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</table>

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months.
Quantifying Renal Failure

- “Normal” GFR is $>90 \text{ mL/min/1.73 m}^2$
- Mean GFR at age 70 is $70 \text{ mL/min/1.73 m}^2$
- 26% of adults over 70 have GFR $<60 \text{ mL/min/1.73 m}^2$ (stage 3)
- Normal GFR for neonates <8 weeks old is $<65$ (stage 2)
- Almost 8 million Americans have GFR between 30 and 60
Initial Studies

- **Grobner et al (Austria; Jan 2006)**
  - NFD/NSF diagnosed 2 to 4 weeks after administration of Gd in 5 patients
  - All 5 patients had metabolic acidosis

- **Marckmann, Thomsen, et al (Denmark; July 2006)**
  - 13 cases of NSF
  - First sign of NSF
    - 2 to 75 days (median 25 days)
  - Odds ratio for acquiring NSF after Gd exposure
    - 32.5 ($P < 0.0001$)
  - 7 patients (54%) severely disabled; 1 died 21 months after exposure

Sadowski et al (Univ of Wisconsin; Feb 2007)
- 13 biopsy-proven NSF patients vs chronic renal failure (CRF) controls
- NSF patients exposed to gadodiamide
  - Had estimated GFR (eGFR) <60 (included 2 with stage 3 kidney disease)
  - Had lower eGFR ($P = 0.01$)
  - Had more proinflammatory events (eg, surgery, infection, vascular procedure) ($P < 0.001$)
  - Were exposed to more Gd ($P = 0.002$)
- Incidence: 4.6%

Sadowski et al. Radiology. 2007. [Published online before print.] Available at: http://radiology.rsnaajnl.org/cgi/content/pull/2431062144v1.
Recent Studies (cont)

- **Broome et al (Loma Linda Univ; Feb 2007)**
  - 12 patients with biopsy-proven NSF
    - 8 on dialysis
    - 4 with acute hepatorenal syndrome
  - Gadodiamide administered 2 to 11 weeks before onset
  - Dialysis within 2 days did not help
  - 4% prevalence
Recent reports strongly correlate development of NSF/NFD in patients with impaired renal function following exposure to gadolinium-chelate MR contrast agents, but a cause-and-effect relationship has not been established.

Gadolinium-containing Contrast Agents for Magnetic Resonance Imaging (MRI):

- It may be prudent to institute prompt dialysis in patients with advanced kidney dysfunction who receive a gadolinium contrast MRA. Although there are no data to determine the utility of dialysis to prevent or treat NSF/NFD in patients with decreased kidney function, average excretory rates of gadolinium are 78%, 96%, and 99% in the first to third hemodialysis sessions, respectively (Okada et al, Acta Radiologica, vol 42 p. 339, May 2001).

Five gadolinium-containing contrast agents are FDA-approved for use during magnetic resonance imaging (MRI), a test that can look at internal body organs and tissues. The trade names of the U.S. approved gadolinium-containing contrast agents are Omniscan, OptiMARK, Magnavist, ProHance, and MultiHance. None of these drugs are FDA approved for MRA. The dose of gadolinium-containing contrast agent given to patients undergoing an MRA test is often higher (up to three times) than the approved dose for MRI.

NSF/NFD appears to occur in patients with kidney failure along with high levels of acid in body fluids. It is a condition known as acidosis that is common in patients with kidney failure. NSF/NFD may cause skin to become tight and rigid skin making it difficult to bend joints. NSF/NFD may also result in fibrosis, scarring, or hardening of the skin organs resulting in the inability of body organs to work properly and can lead to death. Diagnosis of NSF/NFD is done by looking at a sample of skin under a microscope.
Other NSF Alerts

- **AJR alert December 2006**
  - Posted on the American Roentgen Ray Society (ARRS) web site

- **European Agency for the Evaluation of Medicinal Products (EMEA; Feb 2007)**
  - Gadodiamide “contraindicated” in patients with GFR <30 mL/min/1.73 m² or with liver transplant
  - Caution in children <1 year old (immature kidneys)
  - Caution with any Gd agent

Contractures

Skin Discoloration
MRI of NSF

- Subcutaneous tissue thickened
- Increased T2 signal in muscles and fascial planes
- Diagnosis made by dermatologists and pathologists—not radiologists (usually)
NSF and Gd

- Mechanism unknown
- Cases reported to FDA MedWatch (as of 1/17/07)$^1$
  - 85 cases associated with gadodiamide (Omniscan)
  - 21 associated with gadopentetate dimeglumine (Magnevist)
  - 6 associated with gadoversetamide (OptiMARK; 4 of which are known to have also had gadodiamide [Omniscan] exposure)
  - 1 with gadobenate dimeglumine (MultiHance; patient known to have also had gadodiamide [Omniscan])
- FDA believes this is a Gd issue — not an individual agent issue
- Recent reports have demonstrated the presence of gadolinium in the skin biopsies of NSF patients$^{2-4}$

Gd Contrast Agents

- Extracellular Gd chelates have low molecular weights
  - How could this lead to an immunologic disease?
- Millions of exams have been safely performed
- Rate of anaphylactoid reactions is estimated to be 1 in 350,000 to 1 in 450,000 administrations
- One documented fatality in 10 million doses administered

NSF Association With Gd?

- Cause unknown
- Considerations
  - Free Gd\(^{3+}\)
  - Chelate alone
  - Prolonged exposure to high doses of Gd\(^{3+}\) ion or Gd chelate
  - Unique biochemical milieu of the severe renal failure patient
- History of multiple Gd doses associated with increased risk

Early data suggest that elevated levels of the following ions may compete for chelate and increase free Gd (transmetallation)$^{1,2}$:

- Phosphate (or the presence of lanthanum carbonate [Fosrenol])
- Iron
- Zinc
- Copper

Free Gd

- Free Gd$^{3+}$ ion [Gd(III)] solubility is poor and can form in vivo precipitates of salts with anions phosphate, carbonate, or hydroxyl, which are deposited in liver, bone, and muscle.
- In renal failure, the combination of metabolic acidosis and the absence of adequate clearance of the Gd-containing agent may favor clinically significant transmetallation.

Gd\(^{3+}\) and Ca\(^{2+}\)

- **Gd\(^{3+}\) inhibits processes that depend upon influx of calcium (Ca\(^{2+}\))**
  - Cardiac and skeletal muscle
  - Neuronal discharge
  - Coagulation
- **Excess free ligand competes with Ca\(^{2+}\) for laboratory serum test, leading to spurious hypocalcemia**
Stability Constants

\[
\frac{(Gd^{3+}\text{-ligand complex})}{(\text{free Gd}^{3+})}\times\frac{(\text{free ligand})}{=}K
\]

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Log ( K_{eq}\ M^{-1} )</th>
<th>( T_{1/2}, \text{Dissociation} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Magnevist)(^1)</td>
<td>22.1</td>
<td>10 min</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)(^1)</td>
<td>16.9</td>
<td>30 s</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)(^1)</td>
<td>23.8</td>
<td>3 h</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMARK)(^1)</td>
<td>16.6</td>
<td>—</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (MultiHance)</td>
<td>22.6</td>
<td>—</td>
</tr>
</tbody>
</table>

Thermodynamic vs Conditional Stability Constants

- **Thermodynamic Stability Constants** are the measured values, but they do not represent the practical stability under the more physiological conditions of temp and pH (very low pH, high salt).

- **Conditional Stability Constants** are calculated under these “conditions” and are claimed to be a better practical measure of stability (corrected pH 7.4, no salts).
Chelation Characteristics

- In linear, ionic compounds, Gd$^{3+}$ is coordinated to 5 carboxyls, 3 amide nitrogens, and a water molecule.
- In linear, nonionic compounds, the number of carboxyls is reduced from 5 to 3, as the other 2 have been replaced by nonionic methyl amides.
- The amide carbonyls do not bind Gd as tightly as carboxyls.

![Amide structure](image)
Diagnosis: Histopathology

- Aberrant fibrocyte activation and proliferation\(^1\)
  - Infiltration of dermis with bone marrow–derived circulating fibrocytes (CD45RO+/CD34+)

- Transforming growth factor-β\(^1\) (profibrotic mediator)
  - Increased in tissues of NSF patients\(^2\)
  - Plays a central role in the development of fibrosis in
    - Scleromyxedema
    - Hepatic fibrosis
    - Glomerulonephritis
    - Other diseases characterized by excessive production of extracellular matrix proteins

Another Potential Mechanism

- Erythropoetin?
NSF Mimicking Inflammatory Breast Carcinoma

- 61-year-old woman with ESRD on hemodialysis
- Presented with tense swelling and “dimpling” of both breasts
- Past medical history
  - Diabetes mellitus
  - Hypertension
  - Asthma
  - Hypercoagulability, recent thrombectomy performed
- Medications
  - Numerous, including epoetin alfa
- Pathologic findings after biopsy
  - Thickening of the dermis
  - Accumulation of thick collagen bundles
  - Increased number of spindled cells resembling fibroblasts (CD68+ and CD34+)

NSF and Patients With No Gd Exposure

- Roditi et al (Glasgow; Mar 2007)¹
  - 6-year, retrospective study
  - 1826 patients on dialysis
    - 425 (23.3%) underwent 583 Gd-enhanced MRI studies
    - For 522 (89.5%), gadodiamide was used
  - 12 patients had confirmed NSF
    - 11 patients received Gd
    - 1 patient had no Gd exposure

  - “More problematic to deducing the cause and mechanism will be cases of NSF in which no exposure to Gd is identified”

---

¹ Roditi et al. Presented at: the European Congress of Radiology; March 9, 2007; Vienna, Austria.
Possible Treatments for NSF

- **Steroids**
  - “Some” efficacy in a subset of NFD patients
  - 1 mg/kg/d

- **Cytoxan**
  - Does not appear to be effective

- **Thalidomide**
  - Slight subjective improvements when used for short durations

- IV immunoglobulin (IVIG)
  - Background: high-dose (hd) IVIG has been used successfully to treat patients with scleromyxedema
  - An NFD patient was treated with hd IVIG (0.4 g/kg QD) x 5 days, repeated at monthly intervals x 3
  - Improvement after the first treatment, none thereafter

Dialysis and NSF

- The role of dialysis in NSF is controversial\(^1,2\)
- Currently, there are few data to determine the utility of dialysis in the prevention or treatment of NSF\(^1,3\)
- Average excretory rates are 78%, 96%, and 99% from original dose in the first to third hemodialysis sessions, respectively\(^3\)

1. Kuo et al. Radiology. 2007. [Published online before print.] Available at: http://radiology.rsna.jnls.org/cgi/content/full/2423061640v1.  
Recent reports strongly correlate development of NSF/NFD in patients with impaired renal function following exposure to gadolinium-chelate MR contrast agents, but a cause-and-effect relationship has not been established.

First published on the American College of Radiology (ACR) website in March 2007.
Recommendations

- Patients with GFR <30 should be referred to a nephrologist
- It is unnecessary to prospectively measure Cr or calculate eGFR for every case
  - Ask about renal failure status
    - Most stage 4 and 5 patients should be detected
- For patients with CRF
  - A radiologist needs to write the order and justification for Gd use, and the patient needs to sign consent

Recommendations (cont)

- Consider using the lowest dose possible that provided diagnostic benefit for renal failure patients.

- For renal failure patients, do not administer the following without a written order from a radiologist:
  - Gd for catheter angiography
  - CT for renal failure patients to avoid CIN from iodine

- Consider not administering Gd to pregnant women because of slow clearance from the fetus.
Executive Summary: NSF

- Scleromyxedema-like illness seen in patients with severe renal failure receiving Gd
  - 3% to 5% of patients (GFR <30) develop NSF (no cure)
  - 5% of NSF patients develop fulminant disease

- Gd is cleared by the kidneys
  - Possible prolonged circulation time leads to increased exposure to Gd chelate or free Gd

- Nonionic linear chelates have lower stability constants
  - Approximately 90% of cases involve gadodiamide (Omniscan)

- Mechanism unknown
  - 95% of renal failure patients receiving Gd don’t get NSF
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Primum non nocere