Can gadolinium be Used Safely for Imaging in Stage 4/5 CKD Patients?

Pro

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Agenda

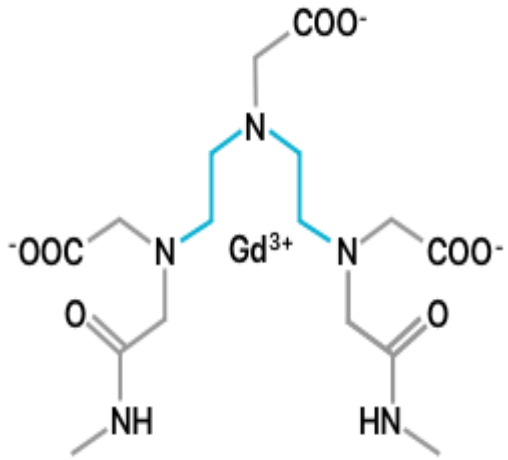
- Gadolinium based contrast agents (GBCA) types.
- Long term outcomes of GBCA.
- Risk factors for poor outcome for GBCA.
- Pro concept.

Gadolinium

- Gadolinium is a **heavy metal of the lanthanide group** with a molecular weight of **157 Daltons** and known **paramagnetic properties.**
- **Free Gadolinium ion is highly toxic** in humans (Gd3+) as it competes with Ca2+ in all biological processes because of similar ionic radius.
- This competition can lead to an **inhibition of calcium channels**, with inhibition of nerve impulse transmission and **blockage of all Ca2+ dependent enzymes** such as de-hydrogenases, kinases, and ATPases. This inhibition may affect mitochondrial function and **impair cellular survival.**

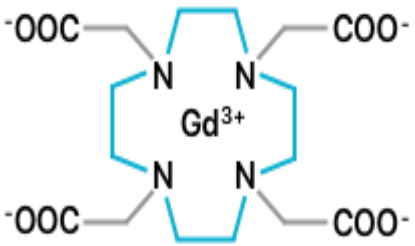
Gadolinium based contrast agents (GBCA)

- GBCA is categorized depending upon the structure of chelate carrier (**linear versus macrocyclic**) and on their charge (**ionic versus non-ionic**).
- **Macrocyclic and ionic carriers** bind more strongly to Gd3+ with less toxicity.
- All GBCA are **excreted** through kidneys except gadobenate and gadoxetate have dual excretion (renal and hepatobiliary)



Linear Agents

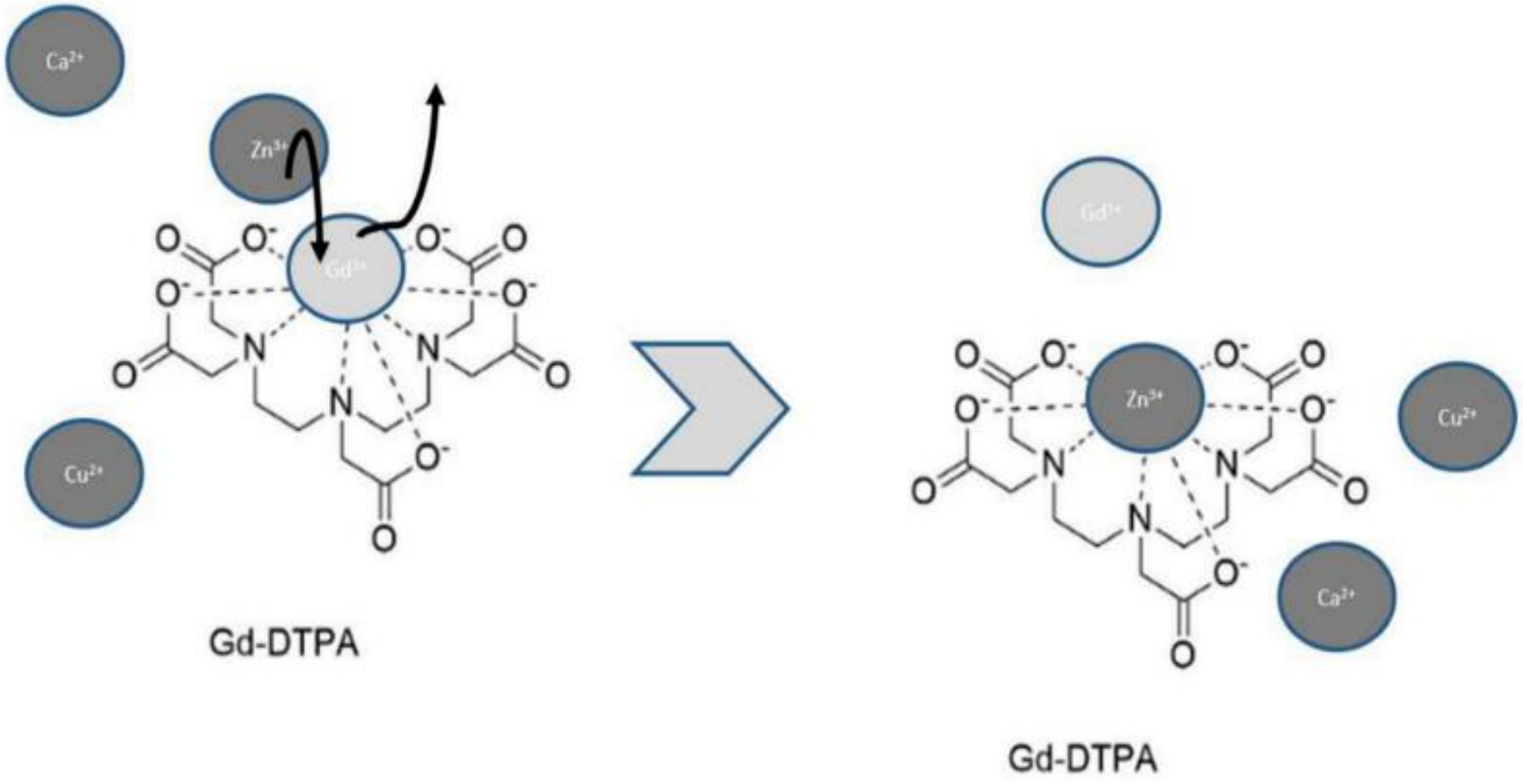
Linear agents do not fully surround the gadolinium (Gd) ions.



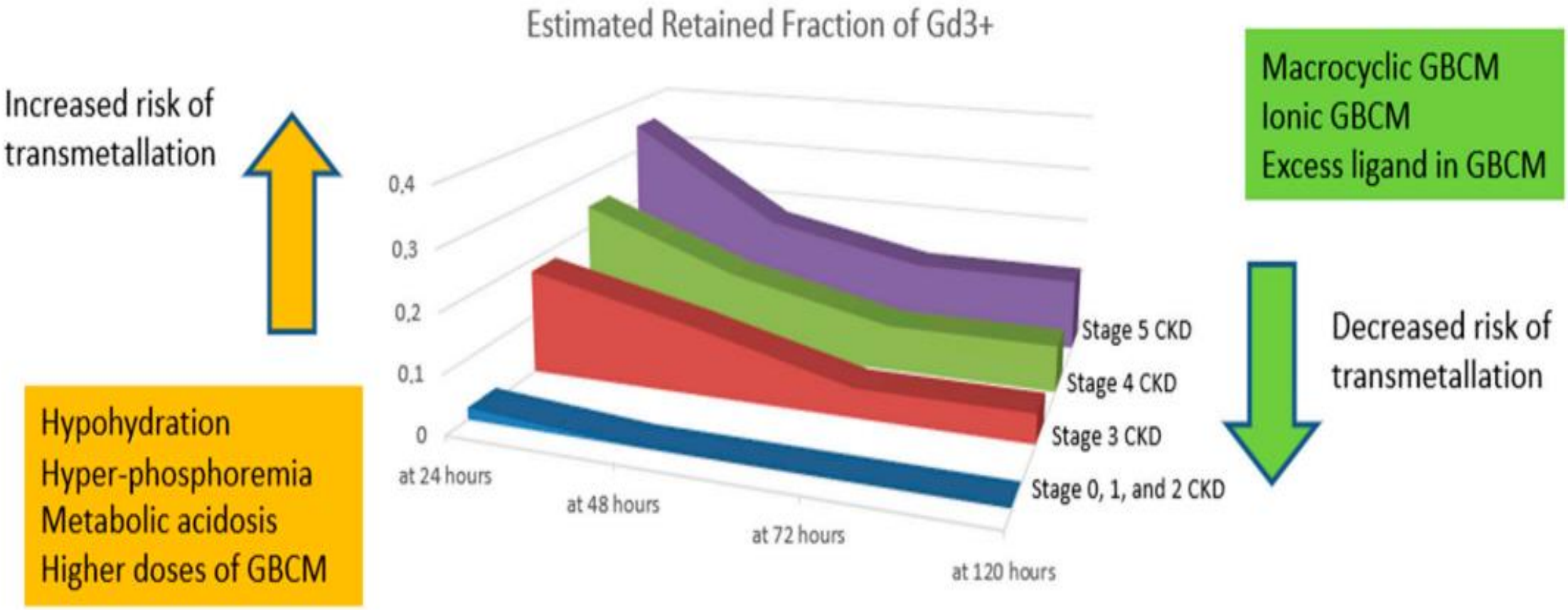
Macrocyclic Agents

Macrocyclic molecules fully enclose gadolinium (Gd) ions with nitrogen (N).

Transmetallation



Gadolinium and CKD



Long term poor outcomes of GBCA

- Nephrogenic systemic fibrosis (NSF).
- Gadolinium deposition disease.
- Nephrotoxicity by GBCA.

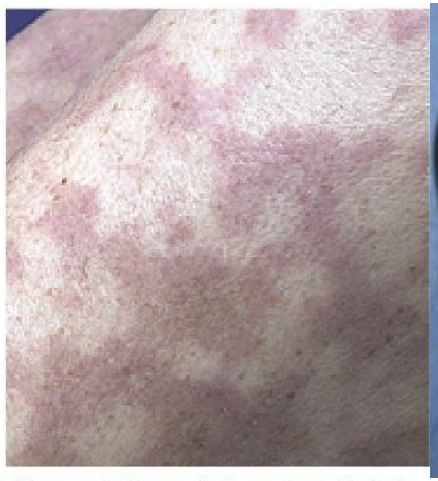
Nephrogenic systemic fibrosis (NSF)

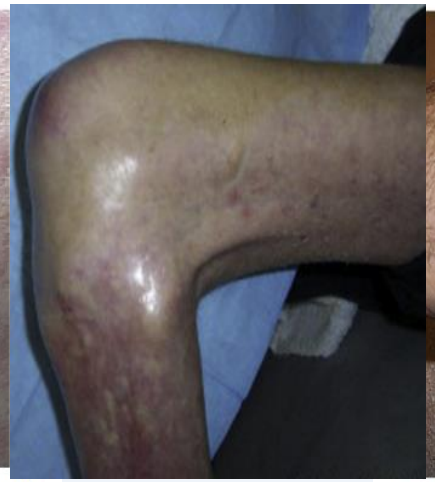
- At 2007, the Food and Drug Administration (FDA) issued a “black-box warning” for patients with severe kidney insufficiency using GBCA of group I. From that time the **incidence of NSF become very low 0-0.07%.**
- It is devastating condition characterized by **extensive thickening and hardening of the skin** with histopathologic features of haphazardly arranged dermal collagen bundles and abundant fibroblasts.

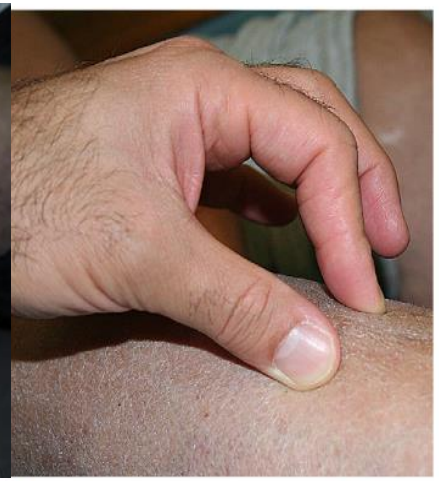
Nephrogenic systemic fibrosis (NSF)

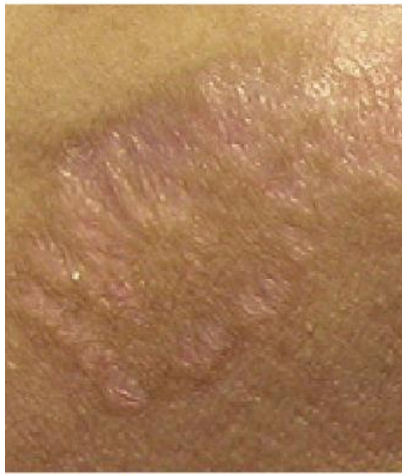
- Usually **symmetrical**, develop on the limbs and trunk, and begin as a **papule** that transitions to erythematous **plaques with a peau d'orange** appearance.
- **Contractures over joints** are common.
- **Systemic involvement** in heart, lung, muscles, CNS, GIT, Kidneys may occur.

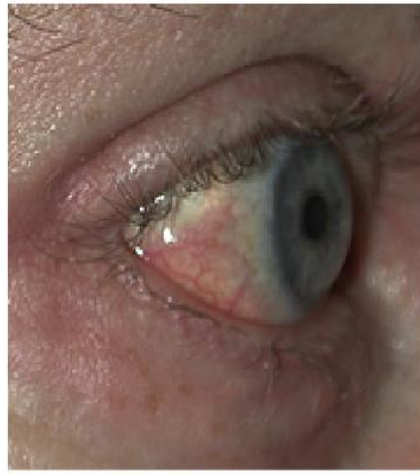
Major clinical criteria	Minor clinical criteria
Patterned plaques	Puckering/linear banding
Joint contractures	Superficial NSF (plaque/patch)
Cobblestoning	Dermal papules
Marked induration/peau d'orange	Scleral Plaques (pt <45yo)











1. Patterned plaques (major criterion). Red to vio

. Joint contractures. Image

9. Marked induration (major criterion). There may

Superficial plaque/patch (minor criterion)

6. Dermal papules (minor criterion). Slightly br

0. Scleral plaques (minor criterion). There ar

Histologic findings

- Increased dermal cellularity (score +1)
- $CD34^+$ cells with tram-tracking (score +1)
- Thick and thin collagen bundles (score +1)
- Preserved elastic fibers (score −1 if *absent*)
- Septal involvement (score +1)
- Osseous metaplasia (score +3)

Table IX. Histopathological score*

Score	Histologic interpretation
4	Highly consistent with NSF
3	Consistent with NSF
2	Suggestive of NSF
1	Inconsistent with NSF
0	NSF excluded (diagnostic of another entity)

Clinical score	Histological score
4=Consistent with NSF (> 1 major criteria)	4=Consistent with NSF (4 or 5 criteria)
3=Suggestive of NSF (1 major criteria)	3=Suggestive of NSF (3 criteria)
2=Inconsistent with NSF (>1 minor criteria)	2=Inconsistent with NSF (2 criteria)
1=NSF ruled out (0–1 minor criteria)	1=NSF ruled out (1 criteria)

Gadolinium deposition disease

- There is **brain deposition** mainly in dentate nucleus and globus pallidus in patients with multiple GBCA exposures especially with linear compounds.
- There is also **bone deposition** of GBCA especially linear compounds.
- Gadolinium-associated plaques are **skin plaques**, but who did not have classic NSF findings, after GBCA exposure.

Gadolinium and nephrotoxicity

Journal of
Clinical Medicine

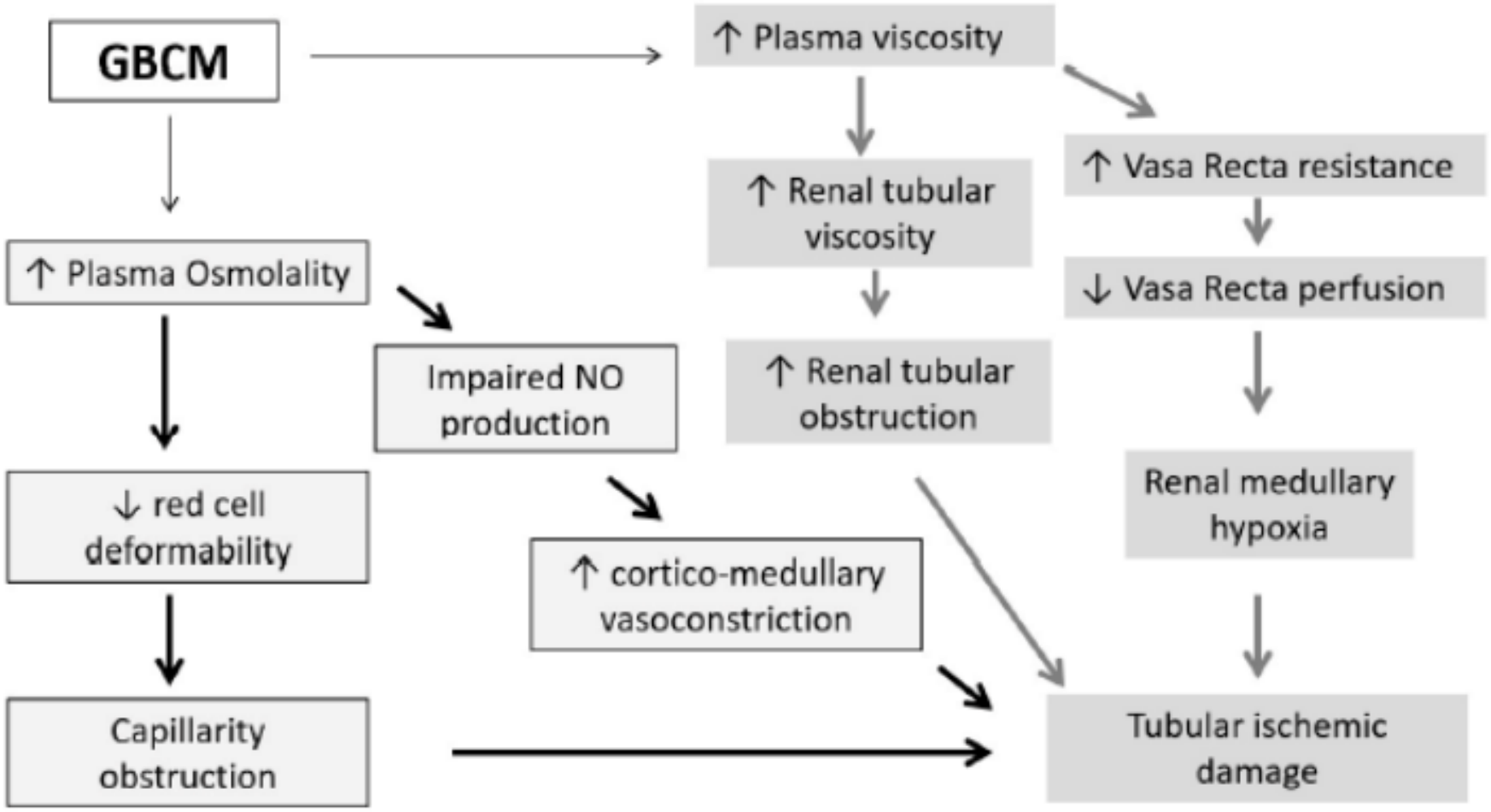
MDPI

Review

Gadolinium-Based Contrast Media Nephrotoxicity in Kidney Impairment: The Physio-Pathological Conditions for the Perfect Murder

Francesca Martino [1,2,*], Gianpaolo Amici [3], Mitchell Rosner [4], Claudio Ronco [1,2] and Giacomo Novara [5,*]

Mechanism of Gadolinium nephrotoxicity



Presentations of Gadolinium nephrotoxicity

- **Subclinical cases of AKI** are more common.
- Manifest cases occur with **risk factors** (severe kidney impairment, diabetes, high dose of GBCM, or use of linear GBCM)
- **Biomarkers of Tubular injury** as NAG,KIM1, NGAL, IL18, insulin-like growth factor binding protein 7 (IGFBP7), and Tissue inhibitor of metalloprotease-2 (TIMP2).

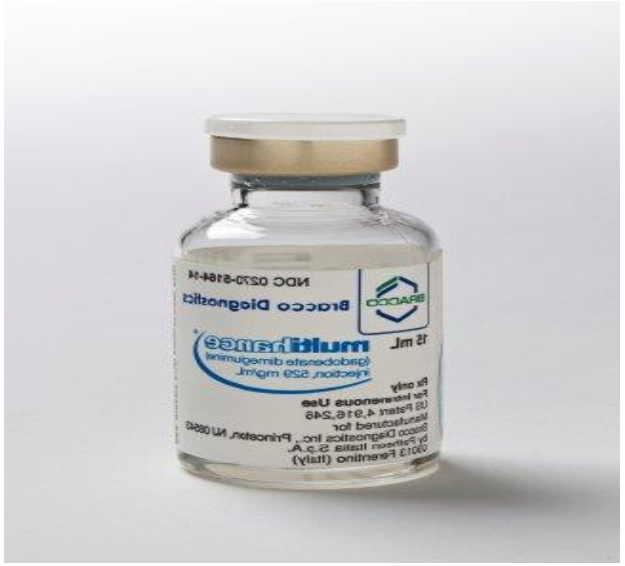
Long term poor outcomes of GBCA

- **Nephrogenic systemic fibrosis (NSF).**
- Gadolinium deposition disease.
- Nephrotoxicity by GBCA.

Risk Factors for NSF

- Patient-related factors

- GBCA related factors



Patient-related factors

- CKD stage 4,5.
- Acute kidney injury.
- A **proinflammatory state** in a patient with impaired renal function.
- **Renal immaturity** in fetuses, neonates, and infants, and consequently pregnant women (because of the risk to the fetus)

GBCA related factors

- **Higher doses** above standard doses
- **Multiple administrations**, especially within a short time.
- **Type of GBCA** (structure of the organic chelating ligand (linear or macrocytic) and net charge (ionic or non-ionic)and hence, stability).
- **Mode of excretion of GBCA**, all have renal excretion except gadobenate and gadoxetate which have both renal and hepatobiliary.

Box 1. ACR Manual Classification of GBCA Relative to NSF

Group I: Agents associated with the greatest number of NSF cases
- Gadodiamide (Omniscan, GE Healthcare)
- Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals)
- Gadoversetamide (OpiMARK, Guerbet)

Group II: Agents associated with few, if any, unconfounded cases of NSF
- Gadobenate dimeglumine (MultiHance, Bracco Diagnostics)
- Gadobutrol (Gadavist, Bayer HealthCare Pharmaceuticals; Gadovist in many countries)
- Gadoteric acid (Dotarem, Guerbet; Clariscan, GE Healthcare)
- Gadoteridol (ProHance, Bracco Diagnostics)

Group III: Agents for which data remain limited regarding NSF risk, but for which few, if any, unconfounded cases of NSF have been reported
- Gadoxetate disodium (Eovist, Bayer HealthCare Pharmaceuticals; Primovist in many countries)

Abbreviations: ACR, American College of Radiology; GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.Reproduced from the *ACR Manual on Contrast Media*[70] with permission of the copyright holder, the American College of Radiology.

JAMA Internal Medicine | Original Investigation

Risk of Nephrogenic Systemic Fibrosis in Patients With Stage 4 or 5 Chronic Kidney Disease Receiving a Group II Gadolinium-Based Contrast Agent
A Systematic Review and Meta-analysis

Sean A. Woolen, MD, MS; Prasad R. Shankar, MD; Joel J. Gagnier, ND, MSc, PhD; Mark P. MacEachern, MLIS; Lisa Singer, MD, PhD; Matthew S. Davenport, MD

Figure 1. Study Flow Diagram

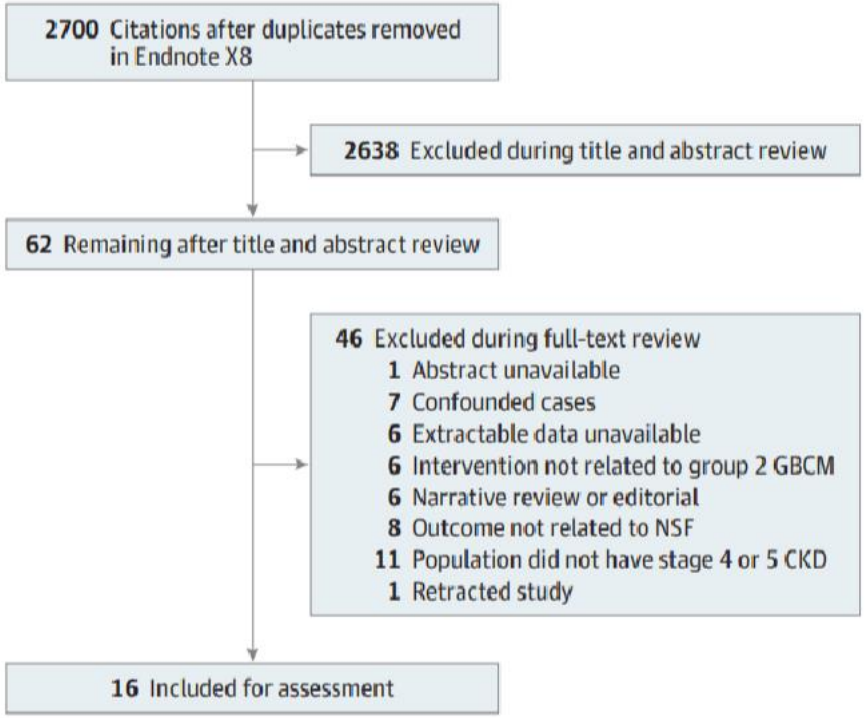
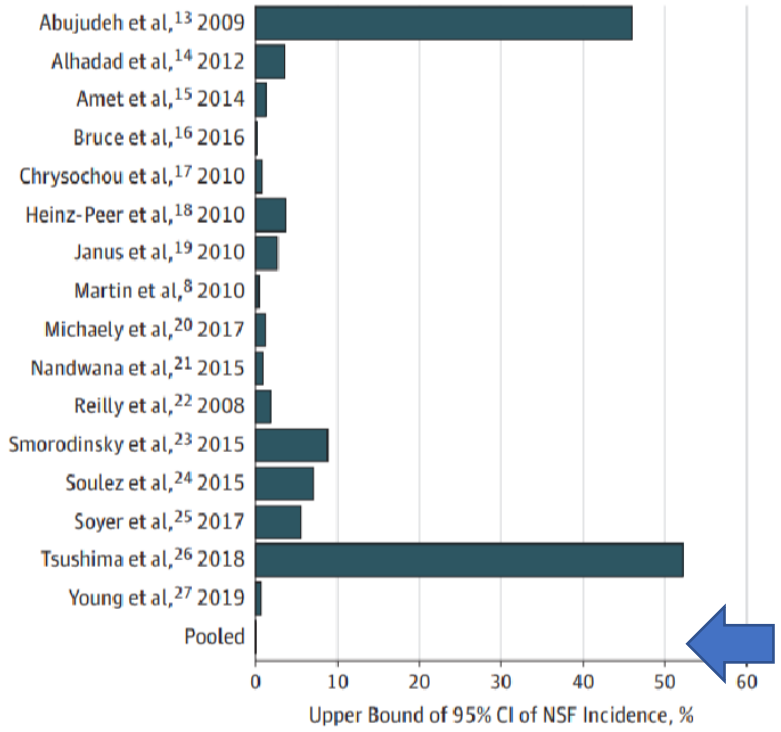


Figure 2. Incidence and Upper Bound of 95% CI of Nephrogenic Systemic Fibrosis (NSF) in Patients With Stage 4 or 5 Chronic Kidney Disease by Study



The pooled incidence of NSF was 0 of 4931 (0%; upper bound of 95% CI, 0.07%)

Conclusions from this meta-analysis

- The risk of NSF from group II GBCA administration in patients with stage 4 or 5 CKD is likely less than 0.07%.
- The harms of withholding group II GBCA for indicated examinations may outweigh the risk of NSF in this population.

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Nephrogenic Systemic Fibrosis Risk After Liver Magnetic Resonance Imaging With Gadoxetate Disodium in Patients With Moderate to Severe Renal Impairment

Results of a Prospective, Open-Label, Multicenter Study

TABLE 3. History of Renal Disease by Degree of Renal Impairment (FAS)

			Moderate					
	Mild		Extended Moderate		Moderate		Severe + Dialysis		Overall	
Renal Impairment	**n = 47**		**n = 32**		**n = 193**		**n = 85**		**n = 357**	
Years since renal diagnosis										
N*	27		19		85		19		150	
Mean	0.54 ± 1.76		0.93 ± 1.64		1.53 ± 2.74		5.46 ± 7.79		1.78 ± 3.82	
Cause of renal disease, n (%)										
Diabetes	8	(17.0)	7	(21.9)	72	(37.3)	33	(38.8)	120	(33.6)
Glomerulonephritis	0		2	(6.3)	5	(2.6)	16	(18.8)	23	(6.4)
Collagen disease	1	(2.1)	0		1	(0.5)	0		2	(0.6)
Hypertension	16	(34.0)	12	(37.5)	85	(44.0)	42	(49.4)	155	(43.4)
Polycystic kidney disease	1	(2.1)	0		5	(2.6)	8	(9.4)	14	(3.9)
Other	25	(53.2)	17	(53.1)	105	(54.4)	30	(35.3)	177	(49.6)
Receiving dialysis, n (%)										
Any	0		0		0		39	(45.9)	39	(10.9)
Peritoneal dialysis	0		0		0		1	(1.2)	1	(0.3)
Hemodialysis	0		0		0		38	(44.7)	38	(10.6)

Lauenstein T et al. Invest Radiol 2015;50: 416–422

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Nephrogenic Systemic Fibrosis Risk After Liver Magnetic Resonance Imaging With Gadoxetate Disodium in Patients With Moderate to Severe Renal Impairment

Results of a Prospective, Open-Label, Multicenter Study

- Eighty five patients with CKD stage 4 and 5 were followed up for 2 years after performing MRI using gadoxetate disodium (group III)
- **No patient developed symptoms conclusive of NSF** within the 2-year follow-up.

Lauenstein T et al. Invest Radiol 2015;50: 416–422

Dose relationship to NSF risk

Radiology

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Incidence of Nephrogenic Systemic Fibrosis at Two Large Medical Centers[1]

Purpose: To determine the incidence and associated risk factors of nephrogenic systemic fibrosis (NSF) in patients who undergo gadolinium-based contrast agent (GBCA)-enhanced magnetic resonance (MR) imaging.

Materials and Methods: Institutional review board approval was obtained for retrospective review of the medical records from two hospitals to identify all cases of biopsy-confirmed NSF and all patients administered a GBCA from January 1, 1997, to June 30, 2007. Informed patient consent was not required. The incidence of NSF was calculated for patients who received

Dose relationship to NSF risk

NSF Incidence Based on GBCA Use and Renal Function

Characteristic*	All GBCAs	Gadodiamide	Gadopentetate Dimeglumine	Gadobenate Dimeglumine	Gadoteridol
All patients	15/83 121 (0.02)	14/71 441 (0.02)	0/8669	1/2785 (0.04)	0/226
Received standard dose	0/74 124	0/63 597	0/7702	0/2619	0/206
Received high dose	15/8997 (0.17)	14/7844 (0.18)	0/967	1/166 (0.6)	0/20
eGFR ≥ 15 but < 30 mL/min	2/387 (0.5)	2/311 (0.6)	0/73	0/3	0/9
eGFR < 15 mL/min†	10/114 (8.8)	10/100 (10)	0/14	0/0	
In chronic hemodialysis regimen‡	1/265 (0.4)	1/227 (0.4)	0/30	0/9	0/4
In chronic peritoneal dialysis regimen	0/19	0/15	0/4	0	0
eGFR < 30 mL/min, no acute renal failure	4/655 (0.6)	4/552 (0.7)	0/94	0/9	0
Acute renal failure	11/131 (8.4)	10/101 (10)	0/27	1/3 (33)	0
Acute renal failure, contrast agent administered during increasing Cr, delayed dialysis§	11/58 (19)	10/48 (21)	0/8	1/2 (50)	0

Dose relationship to NSF risk

NSF Incidence with Multiple Standard Doses versus with One High Dose of GBCA

Contrast Agent Dose Protocol	No. of Patients	No. of NSF Cases	Cumulative Dose (mL)	NSF Incidence (%)
Multiple standard doses	5725	0	31	0
Single high dose	5119	9	32	0.2*

* Incidence was significantly different ($P < .05$) from that with multiple standard (0.1 mmol/kg) doses.

Other risk factors for NSF

Continuous Variables as Univariate Predictors of NSF

Parameter*	With NSF: No. of Patients	With NSF: Value†	Without NSF: No. of Patients	Without NSF: Value†	*P* Value
Age (y)	15	50.5 ± 16.0‡	771	63.8 ± 15.0‡	<.001
Creatinine level (mg/dL)	14	6.5 (2.2–9.0)	488	3.8 (1.8–18)	.023
eGFR (mg/dL)	14	9 (5–27)	488	21 (3–29)	<.001
Albumin level (g/dL)	12	3.1 (2.0–4.4)	450	3.3 (1.2–5.0)	.29
Preinjection iron level (μg/dL)	4	58 (23–141)	69	32 (8–284)	.36
Postinjection iron level (μg/dL)	3	71 (60–155)	38	42.5 (10–175)	.14
Preinjection TIBC (μg/dL)	3	208 (153–241)	67	191 (23–365)	.98
Postinjection TIBC (μg/dL)	5	216 (84–239)	40	211.5 (8–317)	.97
Preinjection ferritin level (ng/mL)	5	966 (185–1300)	63	323 (27–3080)	.18
Postinjection ferritin level (ng/mL)	1	964	40	578 (49–6538)	N/A
Preinjection phosphorus level (mg/dL)	14	5.9 (3.6–10.8)	369	4.1 (1.3–10.1)	<.001
Postinjection phosphorus level (mg/dL)	11	6.1 (3.4–11.6)	352	4.2 (1.3–32.3)	<.001
Preinjection magnesium level (mg/dL)	14	2.0 (1.3–3.0)	381	1.9 (1.1–3.3)	.21
Postinjection magnesium level (mg/dL)	11	2.0 (1.3–3.8)	364	1.9 (0.9–3.6)	.37
pH	5	7.3 (7.3–7.5)	39	7.4 (7.2–7.5)	.05
Injection-dialysis interval (d)§	9	5 (1–12)	270	0 (1–8)	<.001
Creatinine level increase at injection (mg/dL)	11	4.0 (1.5–8.4)	49	1.8 (0.6–6.0)	.0003

* TIBC = total iron-binding capacity.

† All except age data are median values, with ranges in parentheses.

‡ Mean age ± standard deviation.

§ Time between GBCA administration and dialysis.

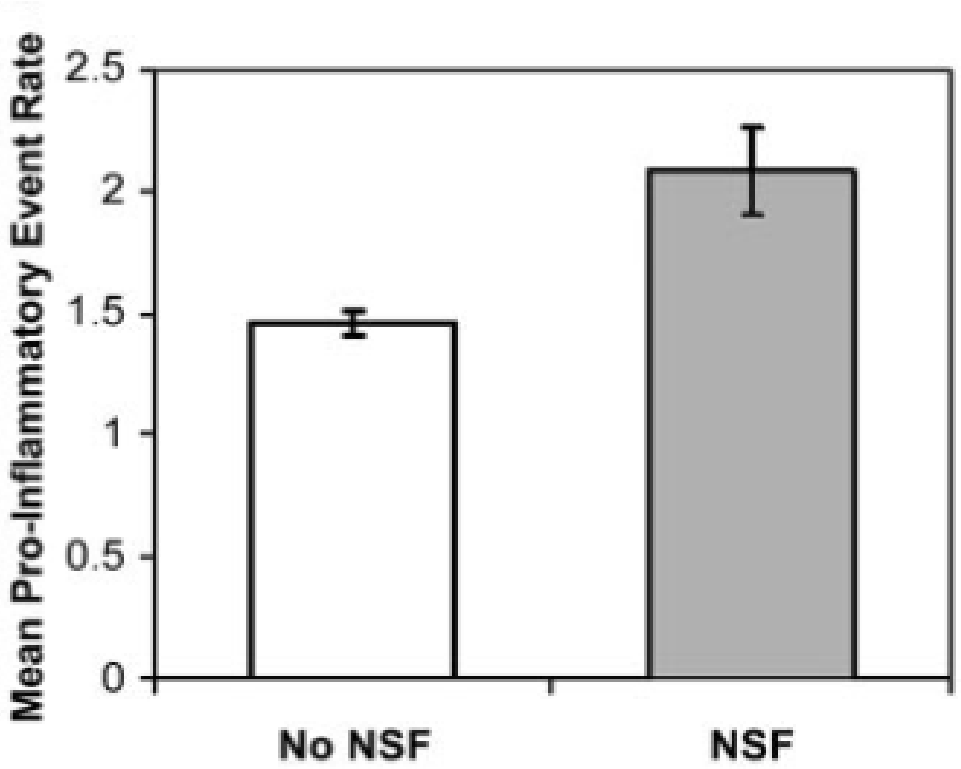
Pro-inflammatory events as risk factors for NSF

Proinflammatory events include all processes in which the body has **sustained major tissue injury** such as

- Vascular surgery, transplantation surgery, or other major surgery.
- Sepsis, pneumonia, osteomyelitis, or other major infection.
- Arterial or venous thrombosis causing ischemia and organ or limb damage.

In all these states, the body is attempting **an intense healing response** following activated **major inflammatory pathways.** This can explain onset of NSF.

Pro-inflammatory events as risk factors for NSF



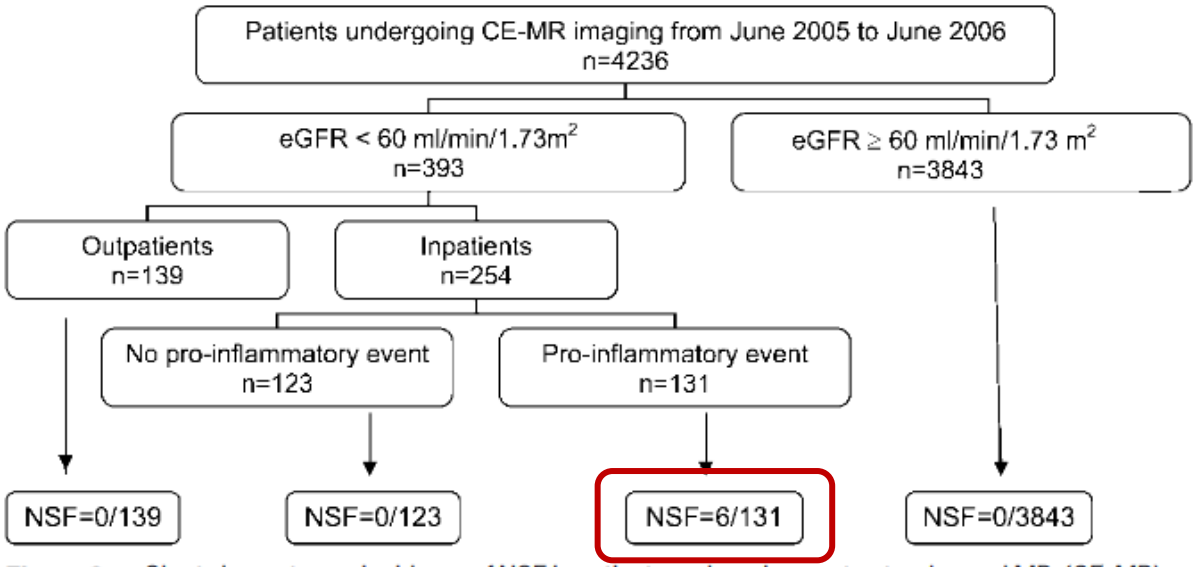
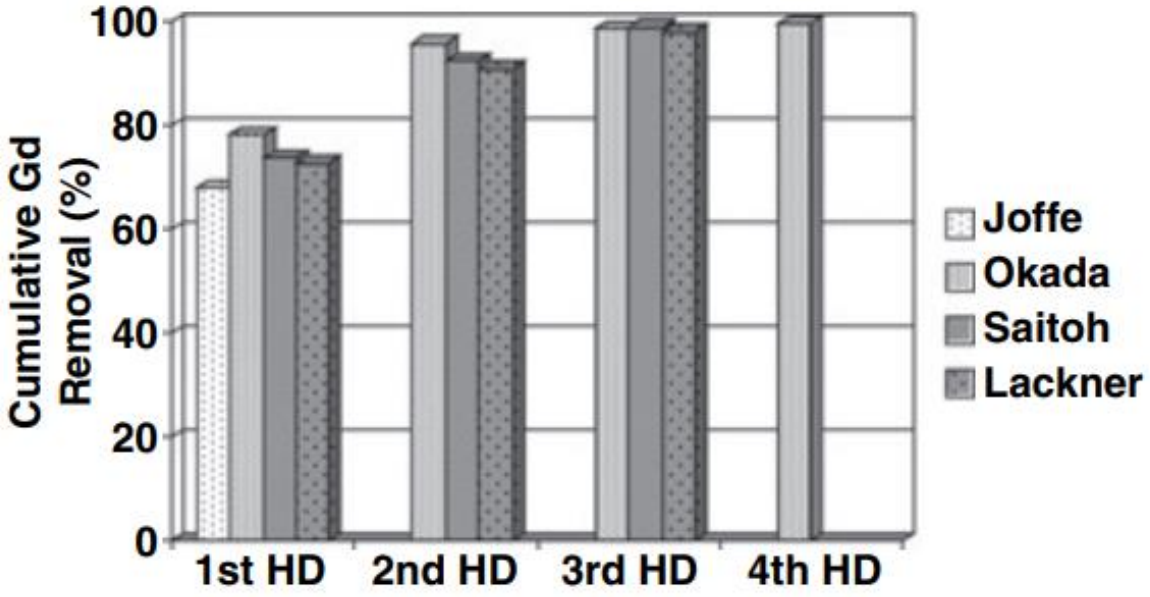


Figure 2: Chart shows 1-year incidence of NSF in patients undergoing contrast-enhanced MR *(CE-MR)* imaging.

Sadowski E et al. Radiology 2007; 243 (1):148-157

Dialytic Therapies to Prevent NSF Following Gadolinium Exposure in High-Risk Patients

- The gadolinium chelates have **MW** that range from 500 to 1000 Da. As they are **hydrophylic** and **do not bind to plasma proteins** therefore, they are excellent candidates for removal through hemodialysis.
- The gadolinium removal with peritoneal dialysis are much less effective than hemodialysis.



Rodby R. Seminars in Dialysis 2008; 21(2):145–9

Dialytic Therapies to Prevent NSF Following Gadolinium Exposure in High-Risk Patients

- Canadian Association of Radiologists (CAR) recommends that in patients Grade 5D, **HD should continue after receiving GBCA** and should be performed the same day as GBCA administration, **ideally within 2 to 3 hours of MRI.**
- There is insufficient evidence to support initiation of dialysis in grade 4 or 5, change from PD to HD, or altering dialysis prescription to reduce the risk of NSF.

Schieda N et al. Canadian Journal of Kidney Health and Disease 2018;5:1-17

It is safe to give GBCA to CKD 4,5

Recommendations for GBCA Use in CKD stage 4, 5

- **Correction of risk factors**; adequate hydration status, correction of acidosis, and the treatment of hyperphosphatemia should be undertaken.
- **Macrocyclic ionic compounds (group II)** is advised.
- **Standard dose** not higher dose is recommended.
- **Multiple doses with spacing at least one week** apart between 2 doses is advised.
- **In CKD stage 5D, HD session should be** performed the same day as GBCA administration, **ideally within 2 to 3 hours of MRI.**

Thank You

Table 1. ACR Classification of GBCM Relative to Associations with NSF

U.S. Trade Name	Generic Name	Structure	ACR Group
Omniscan	Gadodiamide	Linear nonionic	I
OptiMark	Gadoversetamide	Linear nonionic	I
Magnevist	Gadopentetate dimeglumine	Linear ionic	I
MultiHance	Gadobenate dimeglumine	Linear ionic	II
ProHance	Gadoteridol	Macrocyclic nonionic	II
Gadavist	Gadobutrol	Macrocyclic nonionic	II
Dotarem	Gadoterate meglumine	Macrocyclic ionic	II
Clariscan	Gadoterate meglumine	Macrocyclic ionic	II
Eovist	Gadoxetate disodium	Linear ionic	III

unsafe

Safe with evidence

Safe with no evidence