Gadolinium-Based Contrast Agents

(GBCA)

Tobias Gilk - Sept 27, 2022

Outline

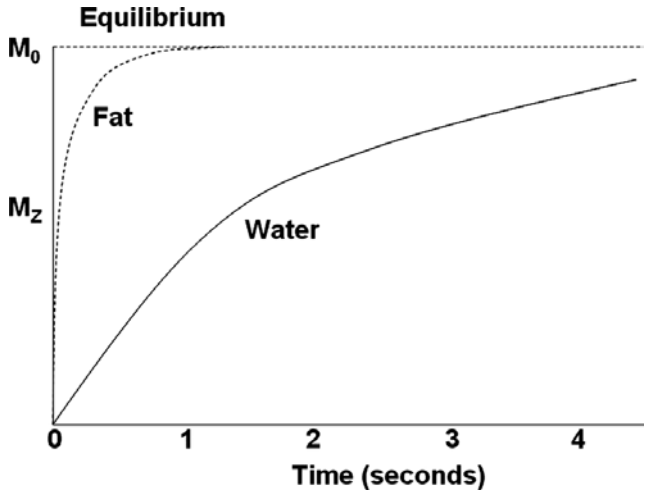
Gadolinium-Based Contrast Agents (GBCAs)

- Intro
- How GBCAs work
- Chelate Structures & Bonds
- NSF, Toxicity, Retention
- GBCAs in Pregnant / Pediatric Populations
- Q & A

How GBCAs Work

How GBCAs Work

- GBCAs change the relaxivity properties of water molecules near contrast molecules.
- Greater separation, over time, between water and other signal.



Chelate Structures & Bonds

Chelate Structures & Bonds

We Don’t Inject Gadolinium…

- Raw Gadolinium is a heavy metal & highly toxic
- We pair the Gd ion with another molecule to make it biologically inert
- Different chelates / ligands give the GBCA different attributes
  - Relaxivity
  - Stability

Chelate Structures & Bonds

Bonds

- Ionic
- Non-Ionic

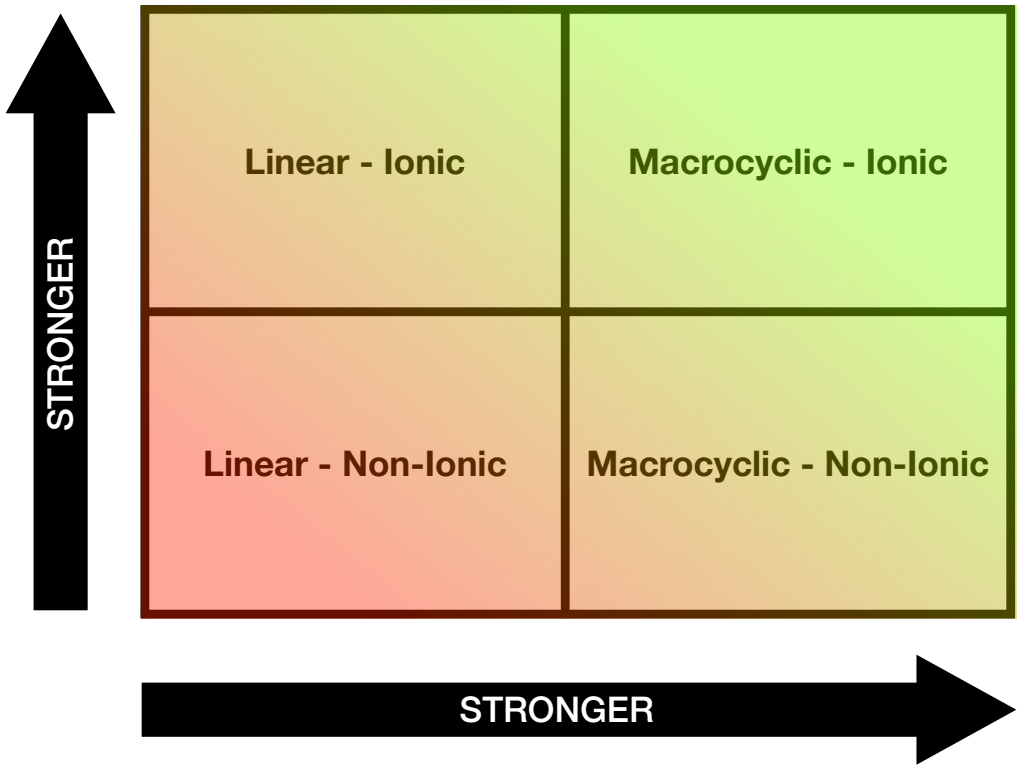
Chelate Structures & Bonds

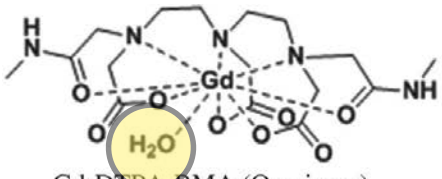
Structure

- Linear
- Macrocyclic

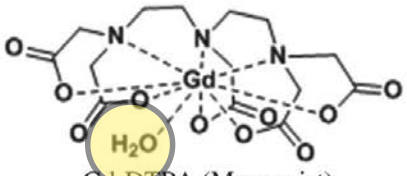
Chelate Structures & Bonds

Stability

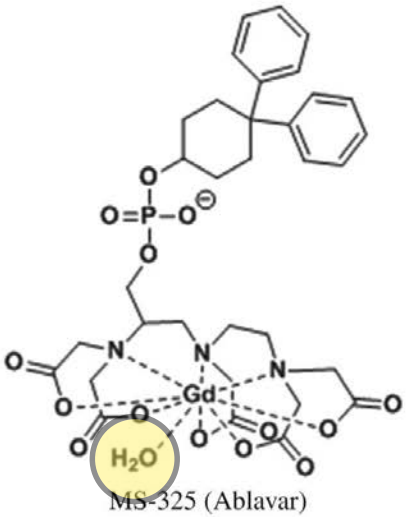




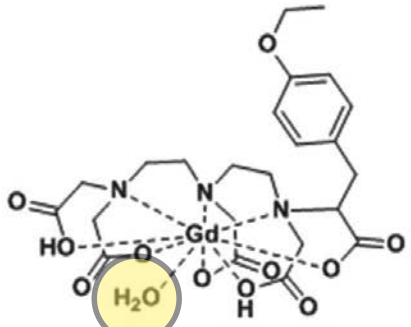
Gd-DTPA-BMA (Omniscan)
Gadodiamide
linear, charge-neutral



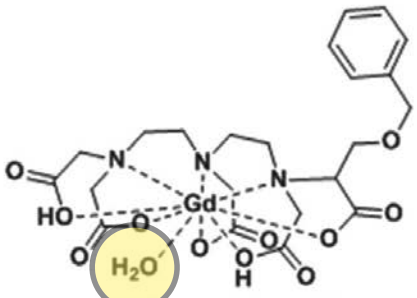
Gd-DTPA (Magnevist)
Gadopentetate dimeglumine
linear, charged



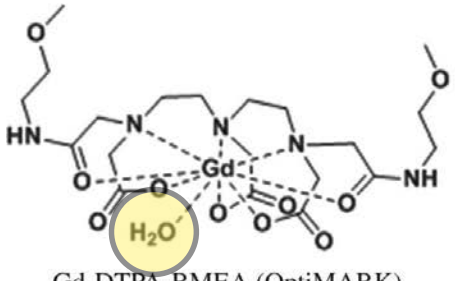
MS-325 (Ablavar)
Gadofosveset
linear, charged



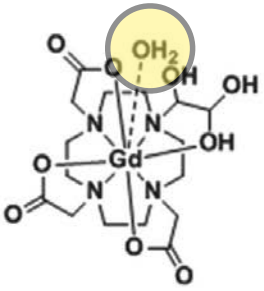
Gd-EOB-DTPA (Eovist)
Gadoxetic acid
linear, charged



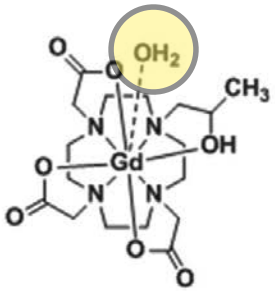
Gd-EOB-DTPA (Eovist)
Gadoxetic acid
linear, charged



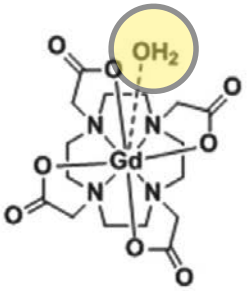
Gd-DTPA-BMEA (OptiMARK)
Gadoversetamide
linear, charge-neutral



Gd-DO3A-butrol (Gadovist)
Gadobutrol
cyclic, charge-neutral



Gd-HPDO3A (ProHance)
Gadoteridol
cyclic, charge-neutral



Gd-DOTA (Dotarem)
Gadoterate meglumine
cyclic, charged

Chelate Structures & Bonds

New US FDA-Approved Agents September, 2022

Guerbet gets FDA approval for Elucirem lower-dose MRI contrast

By Brian Casey, AuntMinnie.com staff writer

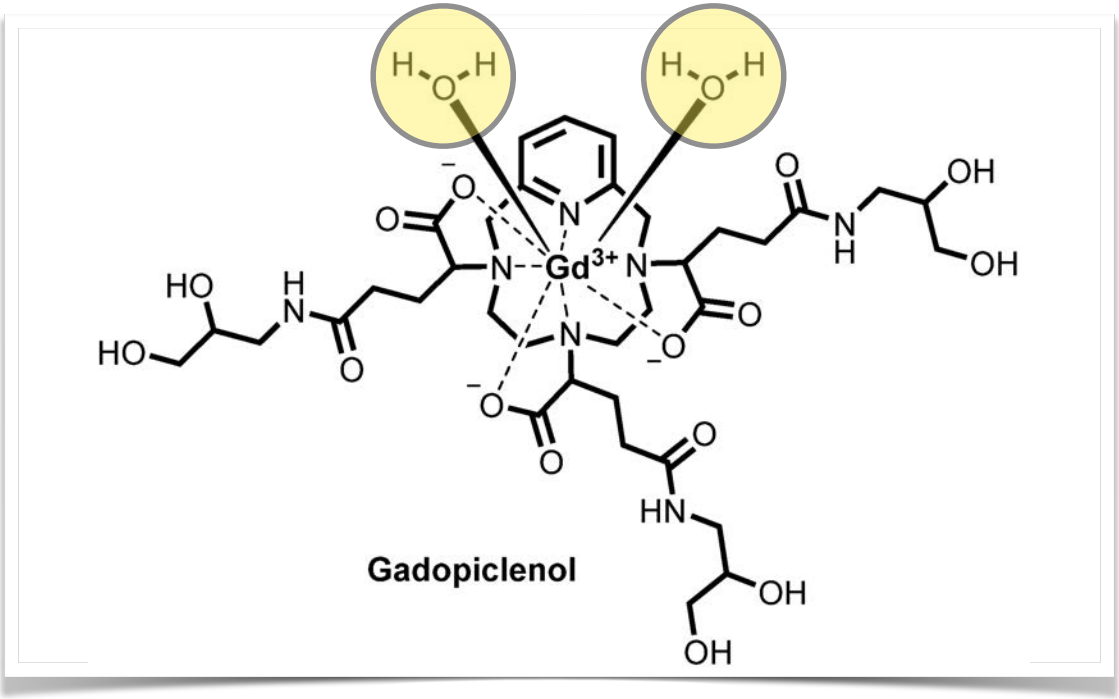
September 22, 2022 -- Contrast agent developer Guerbet has received approval from the U.S. Food and Drug Administration (FDA) for Elucirem (gadopiclenol), a new MRI contrast agent the company is developing in collaboration with Bracco.

Elucirem is a high-relaxivity macrocyclic gadolinium-based contrast agent (GBCA) that was developed with the goal of allowing radiology practices to use half the gadolinium dose of existing GBCAs. The product is designed to address ongoing concerns about gadolinium exposure in patients and has been designed with two sites for water molecule exchange to increase relaxivity and contrast, according to Guerbet.

Indications for the agent include detection and visualization of lesions with abnormal vascularity in

Chelate Structures & Bonds

New US FDA-Approved Agents September, 2022



Chelate Structures & Bonds

What Do GBCAs Do?

It increases visual contrast.

… computers can detect contrast at lower levels than the human eye, so does our future suggest AI-enhanced contrast displays with markedly lower doses?

NSF, Toxicity, Retention

NSF, Toxicity, Retention

Nephrogenic Systemic Fibrosis

In 2005 - 2006 we ‘discovered’ Nephrogenic Systemic Fibrosis.

A syndrome of symptoms linked to patients who had received GBCAs.

Symptoms included painful hardening of skin and organs.

Was originally believed to only occur in patients with very poor renal function. Though we have a small number of NSF cases without clear evidence of poor renal function.

NSF, Toxicity, Retention

Nephrogenic Systemic Fibrosis

In 2007 the US FDA started grouping agents based on NSF association

Group 1		Group 2		Group 3	
~~Magnevist~~	~~(L-I)~~	Gadovist	(M-NI)	Ablavar	(L-I)
~~Omniscan~~	~~(L-NI)~~	Multihance	(L-I)	Eovist / Primavist	(L-I)
~~Optimark~~	~~(L-NI)~~	Prohance	(M-NI)		
		Dotarem / Clarisan	(M-I)		
		Elucerim / Vueway	(M-NI)		

NSF, Toxicity, Retention

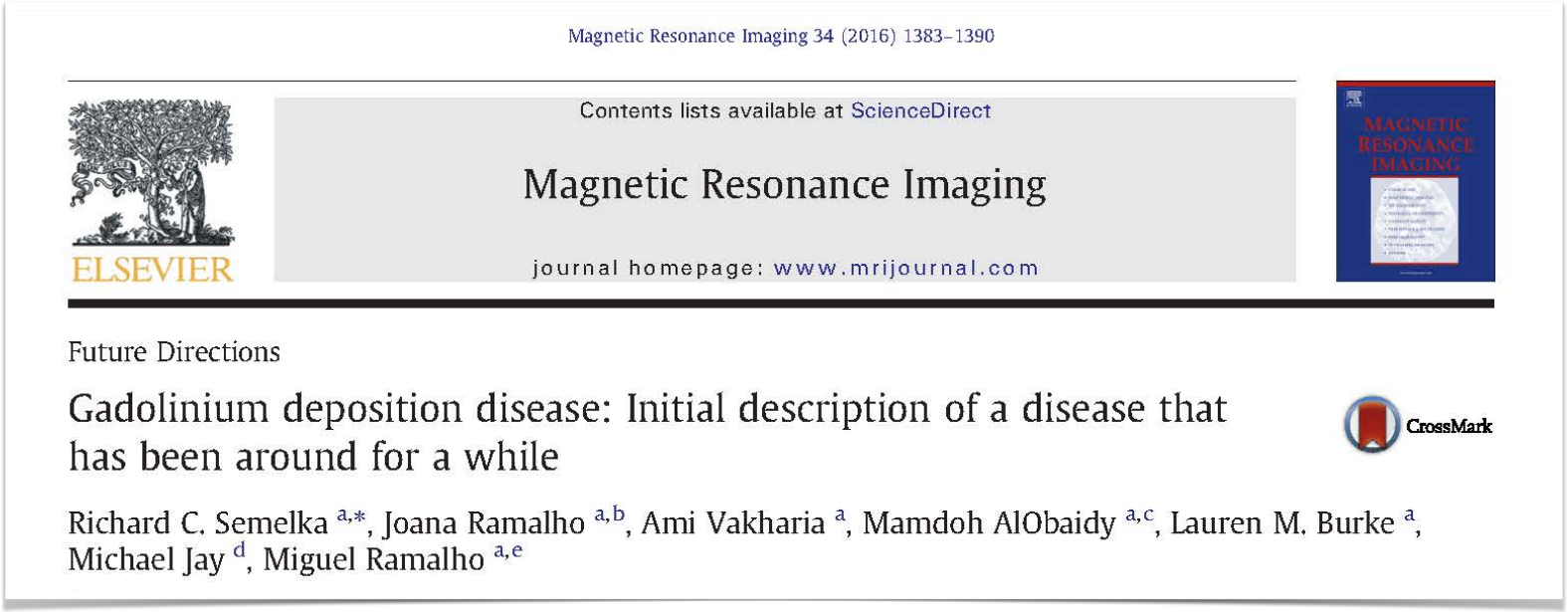
Sub-NSF Toxicity

> "Lead is a potent neurotoxin, affecting the way our kids learn and behave. There is no safe level of lead for children."
>
> — Dr. Sean Palfrey, Medical Director, Boston Lead Poisoning Prevention Clinic

NSF, Toxicity, Retention

Sub-NSF Toxicity

- In 2016 Semelka et al describe ‘Gadolinium Deposition Disease’



Magnetic Resonance Imaging 34 (2016) 1383–1390

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

Future Directions

Gadolinium deposition disease: Initial description of a disease that has been around for a while

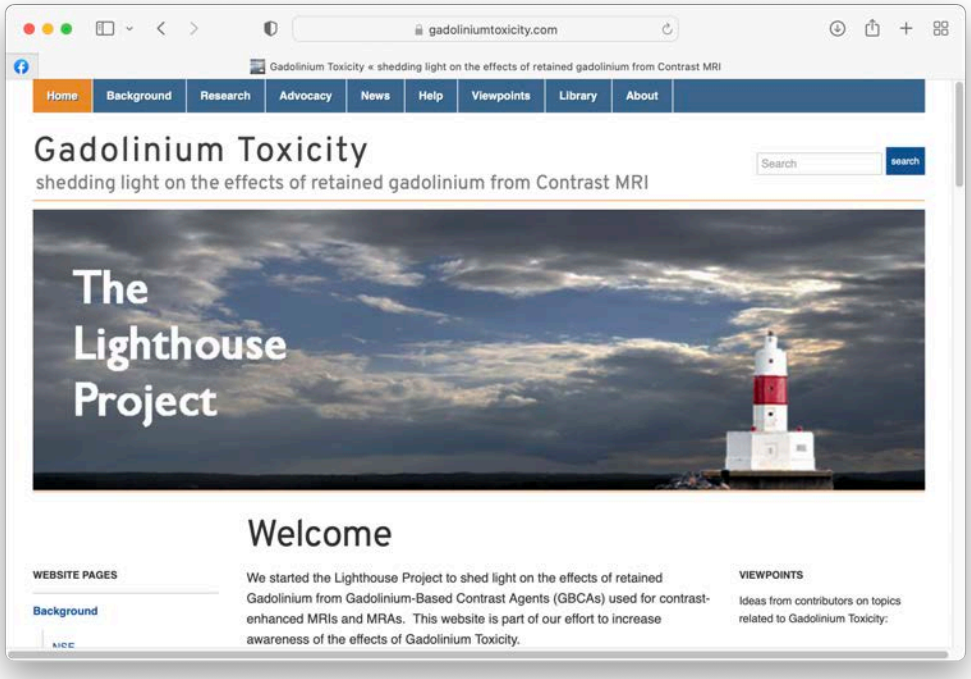
Richard C. Semelka [a,*], Joana Ramalho [a,b], Ami Vakharia [a], Mamdoh AlObaidy [a,c], Lauren M. Burke [a], Michael Jay [d], Miguel Ramalho [a,e]

https://mriquestions.com/uploads/3/4/5/7/34572113/gd_emelka_jrmi.pdf

NSF, Toxicity, Retention

Sub-NSF Toxicity

- GDD / Gadolinium Toxicity is not formally recognized as a disease.



NSF, Toxicity, Retention

Benign GBCA Retention

We used to think *all* GBCA was excreted.

It's not.

Some GBCA from every agent may be retained, indefinitely…

producing enhancement in regions where it collects.

NSF, Toxicity, Retention

Benign GBCA Retention

Recently, residual gadolinium has been found within the brain tissue of patients who received multiple doses of GBCAs over their lifetimes. For reasons that remain unclear, gadolinium deposition appears to occur preferentially in certain specific areas of the brain, even in the absence of clinically evident disease and in the setting of an intact blood brain barrier. Such deposition is not expected, and led the FDA to publish a Safety Alert in July of 2015 indicating that they were actively investigating the risk and clinical significance of these gadolinium deposits. To date, no adverse health effects have been uncovered, but the radiology community has initiated a rigorous investigation.

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

NSF, Toxicity, Retention

Benign GBCA Retention

Since small quantities of GBCA will remain / reside in patients, stability of the the agent is of significant importance.

Nonionic Linear GBCAs:

Optimark [21 (19–22) %, 0.44 (0.40–0.51) %/d) and Omniscan [20 (17–20) %, 0.16 (0.15–0.17) %/d].

Ionic Linear GBCAs:

Magnevist [1.9 (1.2–2.0) %, 0.16 (0.12–0.36) %/d], Multihance [1.9 (1.3–2.1) %, 0.18 (0.13–0.38) %/d], Vasovist [1.8 (1.4–1.9) %, 0.12 (0.11–0.18) %/d], and Primovist [1.1 (0.76–1.2) %, 0.07 (0.05–0.08) %/d].

Macrocyclic GBCAs:

Gadovist, Prohance, and Dotarem (all < limit of quantification of 0.1%, <0.007%/d).

Stability of Gadolinium-Based Magnetic Resonance Imaging Contrast Agents in Human Serum at 37°C

Frenzel et al

https://journals.lww.com/investigativeradiology/Abstract/2008/12000/Stability_of_Gadolinium_Based_Magnetic_Resonance.1.aspx

NSF, Toxicity, Retention

Renal Function Testing

Assessment of Risk (See Table 1 for the classification of GBCAs)

Group II agents

Based on the most recent scientific and clinical evidence [32-39] the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration. As in all instances, group II GBCAs should only be administered if they are deemed necessary by the supervising radiologist, and the lowest dose needed for diagnosis should be used as deemed necessary by the supervising radiologist.[1]

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

NSF, Toxicity, Retention

Renal Function Testing

Assessment of Risk (See Table 1 for the classification of GBCAs)

Group II agents

Based on the most recent scientific and clinical evidence [32-39] the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration. As in all instances, group II GBCAs should only be administered if they are deemed necessary by the supervising radiologist, and the lowest dose needed for diagnosis should be used as deemed necessary by the supervising radiologist.[1]

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

NSF, T
Renal Fu

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 ml/min/1.73m2), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

https://www.guerbet.com/en-us/products-solutions/contrast-agents/dotarem-gadoterate-meglumine-injection

GBCAs In Pregnant / Pediatric Populations

GBCAs In Pregnant / Pediatric Populations

Pregnant Patients

- Gadolinium Based Contrast Agents cross the placenta
- Once fetal kidneys are functional, GBCA will deposit in amniotic fluid

GBCAs In Pregnant / Pediatric Populations

Pregnant Patients

RESULTS Of 1 424 105 deliveries (48% girls; mean gestational age, 39 weeks), the overall rate of MRI was 3.97 per 1000 pregnancies. Comparing first-trimester MRI (n = 1737) to no MRI (n = 1 418 451), there were 19 stillbirths or deaths vs 9844 in the unexposed cohort (adjusted relative risk [RR], 1.68; 95% CI, 0.97 to 2.90) for an adjusted risk difference of 4.7 per 1000 person-years (95% CI, −1.6 to 11.0). The risk was also not significantly higher for congenital anomalies, neoplasm, or vision or hearing loss. Comparing gadolinium MRI (n = 397) with no MRI (n = 1 418 451), the hazard ratio for NSF-like outcomes was not statistically significant. The broader outcome of any rheumatological, inflammatory, or infiltrative skin condition occurred in 123 vs 384 180 births (adjusted HR, 1.36; 95% CI, 1.09 to 1.69) for an adjusted risk difference of 45.3 per 1000 person-years (95% CI, 11.3 to 86.8). Stillbirths and neonatal deaths occurred among 7 MRI-exposed vs 9844 unexposed pregnancies (adjusted RR, 3.70; 95% CI, 1.55 to 8.85) for an adjusted risk difference of 47.5 per 1000 pregnancies (95% CI, 9.7 to 138.2).

Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes
Ray et al
https://jamanetwork.com/journals/jama/article-abstract/2547756

GBCAs In Pregnant / Pediatric Populations

Pregnant Patients

CONCLUSIONS AND RELEVANCE Exposure to MRI during the first trimester of pregnancy compared with nonexposure was not associated with increased risk of harm to the fetus or in early childhood. Gadolinium MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and for stillbirth or neonatal death. The study may not have been able to detect rare adverse outcomes.

Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes
Ray et al
https://jamanetwork.com/journals/jama/article-abstract/2547756

GBCAs In Pregnant / Pediatric Populations

Pregnant Patients

Gadolinium Pregnancy Screening Statement

It has been shown that some gadolinium-based contrast agents (GBCAs) pass the placental barrier into the fetal circulation of nonhuman primates [1]. While multiple small sample size studies have not shown convincing evidence of adverse effects from fetal exposure to GBCAs [2,3], a 2016 retrospective study cited an increased risk of stillbirth/neonatal death as well as increased risk of rheumatologic, inflammatory, or infiltrative skin conditions in the offspring after GBCA exposure during pregnancy [4]. While, questions have been raised regarding study methodology, and these results have not been independently confirmed, both uncertainty and an abundance of caution in general about the effect of GBCA exposure and retention on the developing fetus has led to statements in the ACR Manual on Contrast Media [5] and the ACR Manual on MR Safety [6] recommending avoidance of routine administration of GBCAs to pregnant patients. A decision to administer GBCAs to a pregnant woman should only be made when there is the potential for significant clinical benefit that outweighs the unknown risk of fetal exposure and should be the product of discussion that involves the referring provider and patient.

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

GBCAs In Pregnant / Pediatric Populations

Breastfeeding Patients

Less than 0.04% of the intravascular dose given to the mother is excreted into the breast milk in the first 24 hours [4-6]. Because less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [6,7], the expected systemic dose absorbed by the infant from the breast milk is less than 0.0004% of the intravascular dose given to the mother. This ingested amount is far less than the permissible dose for intravenous use in neonates. The likelihood of an adverse effect from such a minute fraction of gadolinium chelate absorbed from breast milk is remote [2]). However, the potential risks to the infant include direct toxicity (including toxicity from free gadolinium, because it is unknown how much, if any, of the gadolinium in breast milk is in the unchelated form) and allergic sensitization or reaction. These are theoretical concerns but none of these complications have been reported [5]. As in the case with iodinated contrast medium, the taste of the milk may be altered if it contains a gadolinium-based contrast medium [2].

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

GBCAs In Pregnant / Pediatric Populations

Breastfeeding Patients

Recommendation

Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent [6].

https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

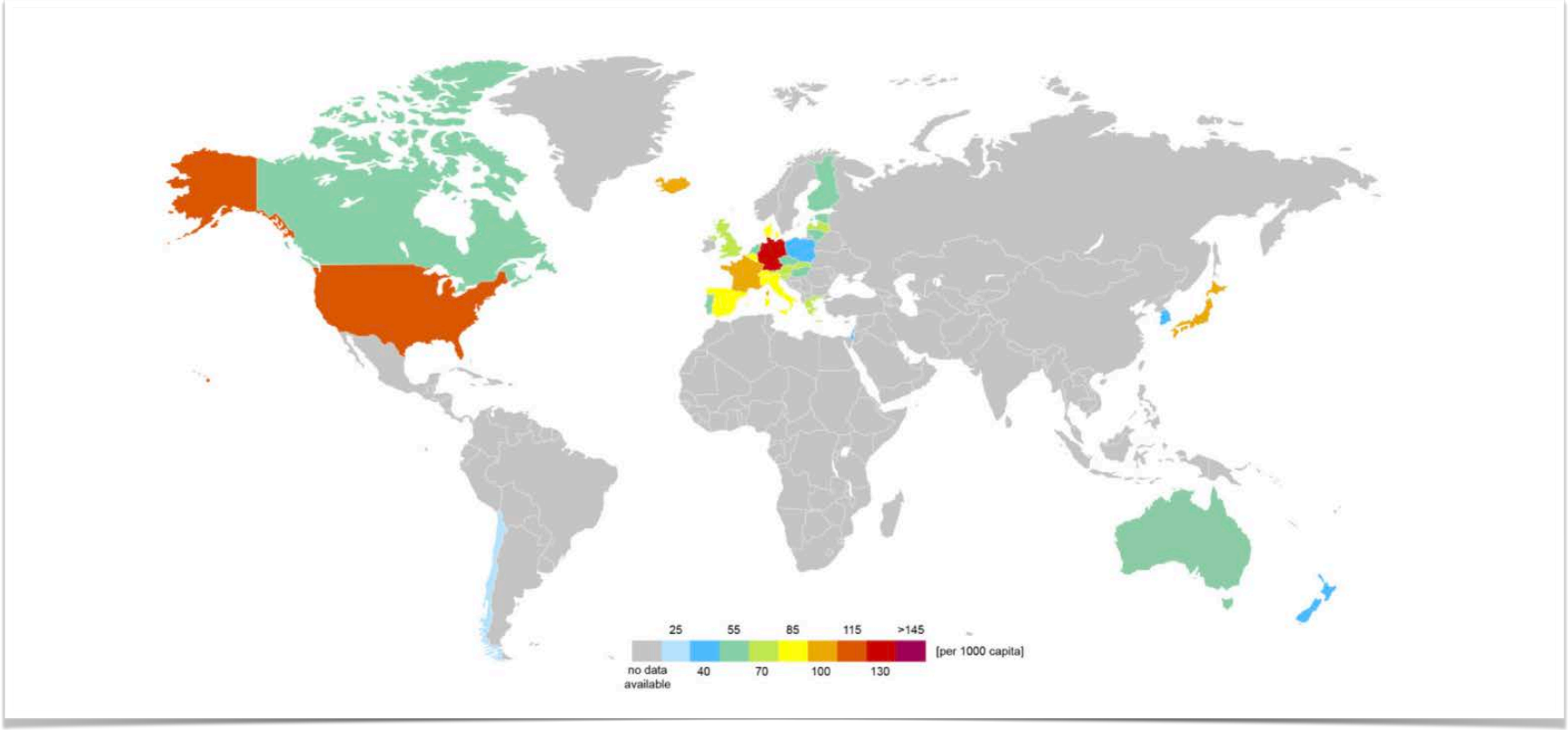
GBCAs In Pregnant / Pediatric Populations

Pediatric Patients

- The ACR & US FDA offer no specific guidance on GBCAs in pediatric populations.
- They defer to GBCA Manufacturer IFU

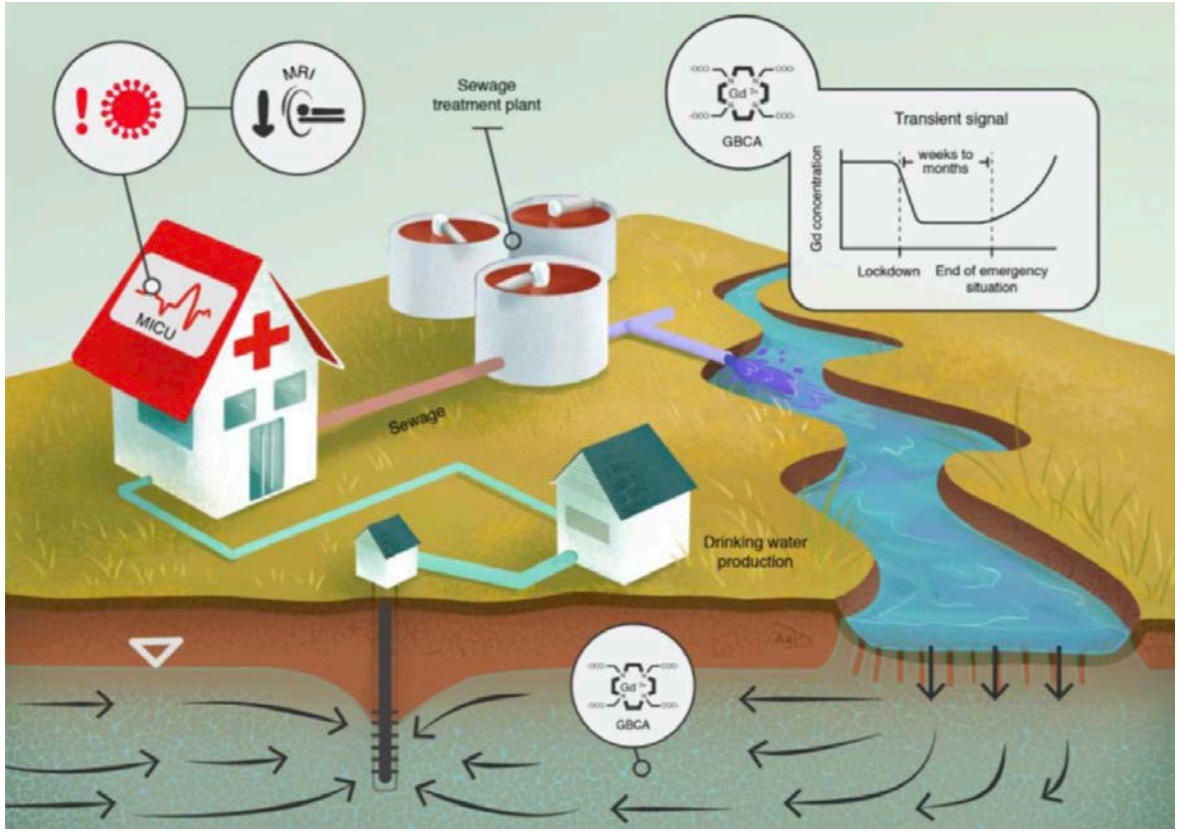
Anthropogenic Gadolinium Exposure

Anthropogenic Gadolinium Exposure



https://reader.elsevier.com/reader/sd/pii/S0043135420305030

Anthropogenic Gadolinium Exposure



https://reader.elsevier.com/reader/sd/pii/S0043135420305030

Q&A

Thank You

Tobias Gilk, MRSO, MRSE

TGilk@GilkRadiologyConsultants.com
@tobiasgilk
www.facebook.com/groups/MRIsafety