



# Is it time to relax nephrogenic systemic fibrosis guidelines and safely offer magnetic resonance imaging to more patients?

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Nephrogenic systemic fibrosis (NSF) is a potentially fatal fibrosing disorder that involves the skin and other internal organs. It is almost always associated with an advanced degree of chronic kidney disease (CKD) or acute kidney injury (AKI). Advances in medical knowledge underpinned some understanding of the pathophysiology and aetiology of this condition which then led to the emergence of strict guidelines for the use of gadolinium (Gd) enhanced MRI scans (Gd-MRI). In a recent issue of *Radiology*, Attari *et al.* present a systematic review of 639 biopsy confirmed cases of NSF derived from a thorough literature search which included 173 published articles (1). They present valuable information about the predisposing level of kidney disease and the type of scan of patients who developed NSF. Notably, almost all of these cases were administered primarily non-ionic linear Gd-based contrast agents (GBCA), and at high doses (>0.1 mmol/kg).

To fully understand this disorder and the current guidelines that have been developed to prevent it, a brief history of NSF is essential. In 1997, several reports were published about a skin disorder that resembled scleromyxedema. It was first named nephrogenic fibrosing dermopathy which then changed to NSF after a series of clinical observations indicated that disease features extended beyond the skin into internal organs. The cause of NSF remained unknown for almost a decade. A strong link was subsequently found with GBCA enhanced MRI (GBCA-MRI) scans after a landmark study from Denmark identified this relationship in 13 confirmed cases of NSF (2). All

of these patients had been exposed to GBCA between 2–75 days before showing signs and symptoms of the disease. Seven out of 13 patients were chronic haemodialysis patients, one received peritoneal dialysis and 5 had CKD stage 5. Subsequently, a surge of cases was published, all linking Gd-MRI to NSF, the majority of these cases having received non-ionic linear GBCA administered at high doses (3–5).

Of the 639 cases included in Attari *et al.*'s systematic review sufficient data about the degree of kidney impairment was found only in 322 patients. Of these, 278 (86.3%) were receiving dialysis. Only 3 patients had an estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73 m<sup>2</sup> but all of these patients had AKI thereby making the eGFR estimation inaccurate (1).

The exact pathogenesis of GBCA related NSF remains unclear. In patients with advanced kidney disease, the clearance of GBCA is significantly slower when compared to normal subjects as they are predominantly excreted by the kidneys. A study showed that people receiving dialysis may take up to 40-fold longer to clear GBCA when compared to volunteers with normal kidney function (6). The pathogenetic theory concentrates on the possibility that during this extended period of bioavailability, transmetallation (transfer of ligands from one metal to another) with endogenous ions has a greater opportunity to occur. Also of relevance here is the acidic environment in patients with advanced kidney disease, as this could allow easier dissociation of Gd ions (7–9).

All available Gd contrast agents are chelates that contain

the Gd ion (Gd<sup>3+</sup>). GBCA can be categorized according to structure into cyclical and linear agents; the former has superior characteristics of binding to Gd<sup>3+</sup> to allow more efficient clearance but also limited release of free Gd. Another classification considers the charge of the GBCA, with a greater likelihood of transmetallation with non-ionic molecules compared to ionic molecules (10).

Recent investigations have suggested that the responsible cell in the pathogenesis of NSF is a cell involved in wound healing and tissue remodeling, the circulating fibroblast (CF) (11), which is distinct from other dermal fibroblasts. It has a CD34/ $\alpha$ 1(I) procollagen dual-positive profile and is blood borne, which provides an explanation for the systemic features of NSF (12). These cells can target areas of cell injury where they can differentiate and cause scarring along with activation of local cellular immunity (13). Wermuth *et al.* showed that GBCA has a direct effect on inducing activation of monocytes resulting in gene activation and release of cytokines and other chemical compounds. These, in turn, can activate fibroblasts to induce tissue changes in NSF (14).

Attari *et al.* found that there were 525 cases of GBCA-related NSF. Only one of these NSF cases was associated with the use of a cyclical Gd preparation used alone. The patient was a 59-year-old male with an eGFR of 34 mL/min/1.73 m<sup>2</sup> (calculated by MDRD) who had an MRI in 2008 and subsequent biopsy proven NSF (15). Unfortunately, no documentation of the patient's weight is available in the published article, and it is possible that the MDRD eGFR may have been inaccurate.

In 2008, and after the surge of NSF reported cases, new guidelines emerged around the safety of GBCA use in MRI scans, and some of these have subsequently been modified. UK guidelines from the Royal College of Radiologists (RCR) are stricter than the American counterpart. Current RCR guidelines advise administering GBCA for people with moderate CKD (eGFR 30–59 mL/min) only when it is “necessary”. For patients with advanced CKD (eGFR <30 mL/min), it recommends using low-risk cyclical GBCA agents (gadobutrol, gadoterate meglumine or gadoteridol) (16). However, the American College of Radiologists guidelines recommend no precautions for people with an eGFR above 30 mL/min/1.73 m<sup>2</sup>. In addition, the administration of low-risk GBCA (e.g., cyclical GBCA agents, referred to as group II) does not require informed consent regardless of kidney function and the state of dialysis as “the risk is very low if any” (17).

The very low/negligible risk of NSF in CKD patients

without end-stage kidney disease, and with use of cyclical GBCA agents, was supported by our findings reported in 2009 (18). A total of 2,053 patients underwent 2,278 GBCA-MRI scans in two large renal centres in the United Kingdom (Salford Royal and Hammersmith hospitals); 491 (23.9%) patients had stage 4 and 117 (5.7%) had pre-dialysis stage 5 CKD. No cases of NSF were identified during an average follow-up period of 28.6 (18.2) months. This study was undertaken after our critical review of the available literature in 2009 which combined data from the multicentre Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study in which 347 patients underwent GBCA-MRI, 32% of these had CKD stages 4/5 (19). By extrapolation, 1/1,735 patients screened for the ASTRAL trial developed NSF, giving a crude incidence rate of 0.06%. We identified that there was a positive reporting bias in the literature and recommended that patients with CKD stage 4 could safely undergo GBCA-MRA, albeit using a minimal dose of a macrocyclic agent and avoiding repeat doses.

The crucial finding of Attari *et al.*'s systematic review is that since 2008 there was a dramatic decline in NSF cases which in large part has undoubtedly been due to adherence to the strict guidelines adopted by major radiology societies around the world. In fact, only eight reported cases of NSF were identified since 2008. The details of these cases are shown in *Table 1*. Six of these subjects were receiving dialysis during the time of exposure to GBCA. One patient had bilateral nephrectomies with no dialysis information (but must have been treated with dialysis) and another had an unspecified degree of CKD. Attari *et al.* also presented follow up data for 341 of the NSF patients in the review; 12 patients were cured of the condition and 72 patients partially improved including one during pregnancy. Interestingly, among these 84 patients reported as cured or improved NSF, this only occurred after renal function restoration in 41% of the patients.

In summary, the guidelines implemented in 2008 have radically reduced the worldwide incidence of NSF. The rate of NSF per million exposures to GBCA was 2.07 (95% CI: 1.90–2.26) up until 2008 whereas this figure is estimated to be 0.028 per million exposures (95% CI: 0.012–0.060) since 2008 (P<0.001), a >70-fold reduction. The question now raised is whether the limitations imposed by the guidelines are too strict, likely denying many people a crucial diagnostic investigation. Attari *et al.*'s systematic review provides confidence that people who are not in AKI or have concomitant illness, and have a stable eGFR above 15 mL/min/1.73 m<sup>2</sup>, can safely have an MRI with GBCA.

**Table 1** Biopsy-proven NSF cases after 2008

Study authors (reference)	CKD degree	Primary renal disease	Gad used (group)	Age (years)	Sex
Chuang <i>et al.</i> (20)	Dialysis (not specified)	Membranous nephropathy	Gadoversetamide (group I)	61	Male
Fuah <i>et al.</i> (21)	Peritoneal dialysis	Glomerulonephritis	Omniscan (group I)	23	Female
Lohani <i>et al.</i> (22)	eGFR 23 mL/min/1.73 m <sup>2</sup>	Data not available	Unknown gad	57	Female
Kreuter <i>et al.</i> (23)	Hemodialysis	Data not available	Unknown gad	50	Male
	Dialysis (not specified)	Data not available	Unknown gad	54	Female
	Bilateral nephrectomies (must be on dialysis)	Data not available	Unknown gad	28	Female
Thomson <i>et al.</i> (24)	Haemodialysis	Data not available	Multiple exposures with at least one dose of gadodiamide (group I)	67	Male
Mitkov <i>et al.</i> (25)	CKD (not specified)	Data not available	Unknown gad	66	Male

NSF, nephrogenic systemic fibrosis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Gad, gadolinium.

People with eGFR less than 15 mL/min/1.73 m<sup>2</sup> or those receiving dialysis should only have group 2 (low risk) GBCA to avoid the small but well-accepted risk of NSF.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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