Risk Factors for NSF: a Meta-analysis

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Introduction: To better understand who can safely undergo Gd injection with minimal risk of NSF, this article compiles risk factor data from 260 NSF patients described in detailed case reports from January, 2003 up until October, 2008.

Methods: Pubmed was searched for '***Nephrogenic Systemic Fibrosis***'. Articles where patients were repeated from previous studies were excluded to avoid double-counting of cases. For each NSF patient, age, gender, race, type of Gd enhanced imaging, other imaging studies, Gd type and dose immediately preceding diagnosis, lifetime Gd dose, interval between Gd and NSF symptom onset, glomerular filtration rate (GFR), dialysis, interval between Gd and dialysis, acuteness of renal failure, kidney transplant, co-morbidity, serum phosphorus, acidosis, epoetin, pro-inflammatory events and NSF symptoms, were recorded on an excel spreadsheet. This excel spreadsheet was then sent to each corresponding author for corroboration and to fill in as much missing data as possible.

Results: Fifty-nine articles detailing information on 260 patients supplemented by author correspondence in 12 articles were included.
Demographic features: The gender distribution was approximately equally weighted in 225 cases with gender available (M:F = 118:107). For 240 patients with age reported, the mean was 51.7 years (9 to 87 years). Figure 1 shows the age distribution of NSF (blue) compared to routine age distribution (pink) for Gd MR exams suggesting that very young <10 years and older, > 60 years are protected. In 107 patients with race indicated, the majority were Caucasians and the number of Asian patients was low compared to worldwide population likely reflecting use of lower Gd doses in Asia.
Renal Function: All NSF patients had renal dysfunction with highest prevalence for GFR < 15 mL/min. 225 NSF patients were on dialysis around the time of developing NSF (HD = 26, PD = 21, CVVH = 3, unspecified = 146). Three patients with GFR ≥ 30 mL/min were all in acute renal failure (ARF) so that the true renal function was over estimated from the serum creatinine.
Acute vs. Chronic Renal Failure: For those with adequate information, 42% (36/87) had ARF. ARF was reported as an NSF risk factor with odds ratio of 13.4. One paper showed that NSF risk can be substantially reduced in ARF patients by either dialyzing after Gd injection or by delaying the MRI until the renal failure begins to resolve.
Timely Dialysis: For the 23 patients in whom the interval between Gd administration and dialysis could be determined, dialysis was performed the same day in 3 patients, a day later in 2 patients, 2 days later in 1 patient and ≥ 3 days later in 17 patients. This suggests that most patients reported to be on dialysis, actually had a substantial delay between receiving Gd and receiving dialysis. This is consistent with the widely held belief that prompt effective dialysis protects against NSF. One paper reports 0.4% incidence of NSF in dialysis patients and zero percent incidence if the dialysis is performed within 24 hours of high dose Gd administration but an 8.8% incidence of NSF in patients with GFR < 15 mL/minute who are not on dialysis at the time of high dose Gd. All these data support the hypothesis that prompt dialysis within 24 hours of Gd administration reduces NSF risk on the order of 20-fold.

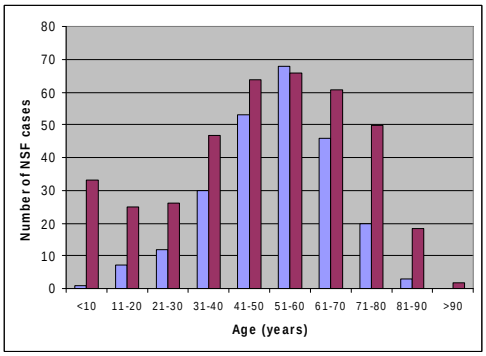

Figure 1. Incidence of NSF by Age. For 240 NSF cases, the number of patients in each decade are shown in blue. The age distribution for 39,166 MRI examinations at local hospital is shown in pink. Note that the peak incidence is in the 40-60 range with virtually no cases in the first decade of life and a dwindling incidence for age > 60 years.

Gd type: Many reports do not indicate the type of Gd utilized and several authors admitted reporting errors. Gadodiamide (n = 134), magnevist (n = 28) or multiple agents including multihance have been injected within a short period prior to the onset of NSF symptoms.
Gd Dose: Several dose reporting errors were corrected in the correspondence with authors. In the 143 cases with dose data available, 13 patients received a standard dose (0.1 mMol/kg) prior to developing NSF and 130 patients received greater than a standard dose. The mean dose is estimated to be 31.9 mL assuming 0.1 mMol/kg = 15 mL. Given that ~90% of Gd:MRIs use standard dose, high dose is an important risk factor. One paper reported zero cases of NSF in 63,597 single dose gadodiamide administrations (without screening for renal function) but 15 cases of NSF following 8997 high dose Gd administrations. Similarly Broome describes 12 cases of NSF in 210 dialysis patients receiving high dose gadodiamide but zero cases of NSF in 94 dialysis patients receiving standard dose gadodiamide. This yielded an odds ratio of 12:1 for high dose gadodiamide causing NSF indicating that risk of NSF can be reduced 12-fold simply by using a standard dose, 0.1 mMol/kg. Additional data on the increased NSF risk with higher doses of GBCA is listed in Table 1.
Other risk factors include pro-inflammatory events (45 of 50 patients with major surgery, infection, thrombosis, etc), Epoetin usage (35 of 50 patients with data), acidosis (in 31 patients) and hyperphosphatemia (mean = 7.4 mg/dL in 31 patients with data).

Table 1. Effect of GBCA dose on risk of NSF in case control studies.

Author	# of controls	# with NSF	Gd dose Controls	Gd dose NSF	P value
Kallen	14	13	20 mL	80 mL	.01
Markmann	19	19	.34 mmol/kg	.44 mmol/kg	.05
Coolidge	408	13	30 mL	45 mL	.008

Conclusion: This meta-analysis of 260 reported cases suggests that order of magnitude reductions in risk can be attained with each of the following: 1) avoiding high dose, 2) avoiding nonionic linear chelates, 3) dialyzing within 24 hours of Gd administration for patients already on dialysis, 4) avoiding injecting acute renal failure patients while serum creatinine is rising. In addition, it appears that very young (< 10 years old) and older patients (> 60 years old) have lower risk of NSF. Understanding these risk factors can refine practice patterns to allow safe Gd enhanced MR in most patients.