Nephrogenic Systemic Fibrosis in Liver Disease: A Systematic Review

Sameer M. Mazhar, M.D.1, Masoud Shiehmorteza, M.D.2, Chad A. Kohl, M.D.2, Michael S. Middleton, M.D.2, and Claude B. Sirlin, M.D.2

1 Liver Imaging Group, Department of Medicine, Division of Gastroenterology, University of California, San Diego, San Diego, California, United States

2 Liver Imaging Group, Department of Radiology, University of California, San Diego, San Diego, California, United States

Abstract

Nephrogenic systemic fibrosis may develop in patients with liver disease, a fact highlighted by recent FDA announcements cautioning against the use of gadolinium-based contrast agents (GBCAs) in select liver disease patients. The purpose of this systematic literature review is to characterize the risk of NSF in patients with liver disease. All published articles on NSF from September 2000, through August 2008, were identified via Pubmed searches and examination of articles’ reference lists. Two reviewers independently read each article and identified unique patients with biopsy-proven or suspected NSF. Data on demographics, liver status, renal status, and GBCA exposure were collected. A total of 324 articles were reviewed, with 108 articles containing case descriptions on 335 unique NSF patients. After excluding the 95/335 (28%) patients in whom the presence or absence of liver disease was uncertain, liver disease was confirmed present in 41/239 (17%) patients. Renal insufficiency could be assessed in 35 of the liver disease patients; severe renal insufficiency, defined as a glomerular filtration rate (GFR) or estimated GFR (eGFR) < 30 mL/min/1.73m² or dialysis requirement, was present in 34/35 (97%) patients. The lone patient who developed NSF with mild-moderate renal insufficiency was atypical and received a total gadodiamide load of 0.76 mmol/kg over a 10-week period peri-liver transplantation. The published medical literature demonstrates that patients with liver disease who develop NSF also have severe renal insufficiency, suggesting that liver disease does not confer a risk for NSF beyond that of the underlying renal insufficiency.

Keywords

Nephrogenic systemic fibrosis; NSF; Nephrogenic fibrosing dermopathy; Dialysis-associated systemic fibrosis; Liver disease

INTRODUCTION

Initially recognized in 1997 and later published as a case series of 15 patients in 2000, Cowper et al. described a novel scleromyxedema-like dermatologic condition in patients with severe renal insufficiency that eventually came to be known as nephrogenic fibrosing dermopathy (1). Subsequent autopsy studies demonstrated more widespread fibrosis, involving the diaphragm, renal tubules, rete testes, psoas muscle, myocardium, and dura.
mater, ultimately yielding the more inclusive diagnostic term nephrogenic systemic fibrosis (NSF) (2–3). The principle manifestation, however, remains cutaneous, marked by plaque-like induration, thickening, and hyperpigmentation of the skin of the extremities and trunk, with facial sparing and lack of paraproteinemia. Progressive disease may result in joint contractures, limited range-of-motion, severe disability, and death.

Similar to its clinical description, the understanding of NSF causation has also become increasingly refined. In 2006, two retrospective case series detailing 18 combined patients suggested a robust association between the administration of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) or angiography (MRA) and the development of NSF in patients with renal disease (4–5). Since then, “the vast majority of published case reports have found a consistent association of NSF with GBCA exposure (6).”

Due to mounting evidence, the United States Food and Drug Administration (FDA) released a public health advisory cautioning against the use of GBCAs in patients with kidney failure (defined as either requiring dialysis or having a glomerular filtration rate [GFR] < 15 mL/min/1.73m\(^2\)) in June 2006 (7). Subsequently, in May 2007, the FDA ordered a “black box warning” added to the labeling of GBCAs, expanding the prior advisory to include those patients with “acute or chronic severe renal insufficiency (GFR < 30 mL/min/1.73m\(^2\)), or acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period (8).”

This expanded warning has two major implications: 1) liver disease confers a risk of NSF beyond that associated with renal insufficiency alone, and 2) liver patients with only mild or moderate renal insufficiency (non-dialysis patients with GFR ≥ 31 mL/min/1.73m\(^2\)) are also at risk for NSF. Taken together, these assertions greatly increase the number of patients considered at risk for developing NSF and introduce a new set of patients – those with liver disease – to closer scrutiny. In clinical practice, GBCA-enhanced MR plays a crucial role in monitoring for hepatocellular carcinoma in the pre-transplantation period, mapping of the vasculature prior to transplantation, and diagnosing post-operative transplantation complications. Limiting its use, therefore, may have deleterious consequences to the care of these tenuous patients. Despite the implications of this expanded warning, the risk of NSF in patients with liver disease is not well known beyond anecdotal descriptions in some case reports and case series.

Accordingly, in this paper, we systematically review the English medical literature of all published cases of NSF in an attempt to characterize the risk of NSF in patients with liver disease.

**REVIEW OF THE LITERATURE**

We performed a review of the English medical literature to identify all published case reports, case series, and original research articles on NSF from September 2000, through August 2008. Evaluation of these articles yielded descriptive data detailing NSF risk specifically in patients with liver disease.

**Data collection**

Articles were identified via PubMed searches of the terms “nephrogenic systemic fibrosis,” “nephrogenic fibrosing dermopathy,” and “dialysis-associated systemic fibrosis.” Articles not identified through PubMed but referenced in searched articles were also reviewed. Two readers (SMM, MS) independently reviewed each article in full. Discrepancies were arbitrated by a third review of the article and subsequent mutual agreement between the
readers. If articles contained ambiguous or incomplete information, the readers emailed the corresponding authors for clarification.

Unique patients, both adult and pediatric, with biopsy-proven or suspected NSF were identified. Duplicate cases were tallied only once; however, if the same patient was discussed in more than one article, complementary information from the different articles was compiled. If multiple cases were described in different articles from the same institution or city, the readers e-mailed the corresponding authors to confirm the uniqueness of the cases. Any remaining uncertainties in unique case ascertainment were recorded.

The two readers extracted the following data for each unique patient, regardless of the presence of liver disease: (A) demographics, (B) liver status (presence of liver disease, presence of cirrhosis, etiology of liver disease, history of hepatorenal syndrome, history of liver transplantation, timing of liver transplantation relative to NSF development), (C) renal status (presence of renal disease, severity of renal disease, etiology of renal disease, GFR, dialysis requirement, history of renal transplantation), and (D) GBCA exposure (type of agent, number of exposures, dose, timing of dose relative to NSF development).

To ensure that data relevant to liver disease was not missed in the initial reading, articles were electronically searched using the following terms – “liver,” “cirrhosis,” “hepatitis,” and “hepatic” – via the embedded search engines of Adobe Acrobat (Adobe Systems Incorporated, San Jose, CA) or Mozilla Firefox (Mozilla Corporation, Mountain View, CA). If the GFR was not explicitly stated, the estimated GFR (eGFR) was approximated from creatinine values using the Modification of Diet in Renal Disease (MDRD) equation. Severe renal insufficiency was defined as either a GFR (or eGFR) < 30 mL/min/1.73m$^2$ or the necessity of hemodialysis or peritoneal dialysis. Patients were characterized as having acute kidney injury (AKI) or chronic kidney disease (CKD) if their renal dysfunction was unequivocably described as “acute” or “chronic” in the article. For those patients without such explicit description, AKI and CKD categorization was surmised based on whether the renal dysfunction was due to an acute (e.g., hepatorenal syndrome) or chronic (e.g., diabetes mellitus or polycystic kidney disease) etiology, respectively.

Data for select variables was categorized as either “yes,” “no,” or “uncertain.” A “yes” categorization was made if the article contained an explicit statement (e.g., “patient has a history of hepatitis C”) or implication (e.g., “positive hepatitis C antibodies on serum study”) that permitted positive ascertainment for a particular variable (e.g., liver disease is present). A “no” categorization was made if the article contained an explicit statement (e.g., “patient has no history of liver disease”) or implication (e.g., detailed medical history or laboratories without indication of liver disease) that permitted negative ascertainment for a particular variable (e.g., liver disease is absent). An “uncertain” categorization was made if the article did not provide sufficient information to make a positive or negative ascertainment, and the corresponding author did not respond to email inquiries.

**Data Analysis**

Patients were divided into two groups, those with liver disease and those without liver disease (patients in whom the presence of liver disease was uncertain were excluded). In each group, the proportions of patients with severe renal insufficiency and the proportion with mild-moderate renal insufficiency were calculated (patients in whom the severity of renal insufficiency was uncertain were not included in the calculation). Clinical features regarding liver-disease patients, including those with and without severe renal insufficiency, were summarized descriptively.
Articles Reviewed

A total of 324 articles were reviewed (303 articles via PubMed search and 21 articles not found in PubMed but cross-referenced in other NSF articles), with 108 (108/324, 33%) articles detailing patient cases (2–5,9–112).

Overview of NSF Patients

The 112 articles described 434 conceivably unique cases, but due to ambiguity in some reports and lack of success in contacting the corresponding authors, the readers could not confirm the uniqueness of 99 of the 434 cases. As shown in Table 1, none of these 99 potentially duplicate cases had liver disease or mild-moderate renal insufficiency; these subjects were excluded from further analysis. The remaining 335 unique patients with NSF had a mean age of 49.6 years (range 8–87 years). Among these 335 patients, NSF was histologically-proven in 328 (328/335, 98%) patients and clinically-inferred (without histologic analysis) in 4 (4/335, 1%) patients – the performance of histologic analysis was uncertain to have been conducted in 3 (3/335, 1%) patients.

As summarized in Figure 1, the presence or absence of liver disease was uncertain in 95 (95/335, 28%) patients. All of these patients had either severe (89/95, 94%) or uncertain (6/95, 6%) renal insufficiency; these subjects were excluded from further analysis. Of the remaining 239 patients, 41 (41/239, 17%) had liver disease and 198 (198/239, 83%) did not have liver disease. The presence or absence of renal insufficiency was uncertain in 6 (6/41, 15%) and 19 (19/198, 10%) of the patients with and without liver disease, respectively.

In the 35 patients with liver disease in whom renal disease could be assessed, 34 (34/35, 97%) had severe renal insufficiency (CKD stage IV or V; GFR < 30 mL/min/1.73m² or dialysis requirement), and one (1/35, 3%) had mild-moderate renal insufficiency (CKD stage II or III; GFR ≥ 30 and < 90 mL/min/1.73m²), as described further below. Similarly, in the 179 patients without liver disease in whom renal disease could be assessed, 177 (177/179, 99%) had severe renal insufficiency and two (2/179, 1%) had mild-moderate renal insufficiency. No patient had normal renal function.

NSF Patients with Liver Disease

Etiology and Severity of Liver Disease—Among the 41 patients with confirmed liver disease (mean age 53.0 years, range 32–77 years), the etiology of liver disease was reported for 27 (27/41, 66%) patients and not reported for 14 (14/41, 34%) patients. Hepatitis C viral infection (10/27, 37%) was the most common reported etiology, followed by hepatitis B viral infection (4/27, 15%) and combined hepatitis C and alcoholic liver disease (3/27, 11%) (Figure 2A). As noted in Table 2, 29 (29/41, 71%) of the 41 patients with liver disease had cirrhosis. The other 12 (12/41, 29%) patients had non-cirrhotic liver disease characterized by acute liver injury with hepatic recovery or mild chronic disease.

Liver Transplantation—Twenty-seven (27/41, 66%) of the 41 liver disease patients underwent liver transplantation (Table 2) – 26 (26/27, 96%) of these patients had severe renal insufficiency; the remaining patient (1/27, 4%) had mild-moderate renal insufficiency. In 18 (18/27, 67%) of the 27 liver transplant patients, the temporal relation of NSF development to transplantation could be assessed: the median time interval between liver transplantation and NSF development was 1.75 months (range 6–120 months); 15 (15/18, 83%) of the 18 patients developed NSF within 6 months of liver transplantation and 3 (3/18, 17%) developed NSF more than 6 months after liver transplantation.

GBCA Exposure—Table 3 summarizes the reported GBCA exposure in NSF patients with liver disease. GBCA exposure was confirmed in 16 (16/41, 39%) liver disease patients,

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15 of whom received gadodiamide (Omniscan; GE Healthcare Medical Diagnostics, Little Chalfont, Buckinghamshire, UK) alone and one who received gadodiamide and gadobenate dimeglumine (Multihance; Bracco Diagnostics Incorporated, Princeton, NJ) in succession. GBCA exposure was not mentioned in 24 (24/41, 59%) patients. In one patient, GBCA exposure was specifically denied in the published report (22).

NSF Patients with Liver Disease and Concomitant Severe Renal Insufficiency
Among the 35 patients with liver disease and known renal status, 34 had severe renal insufficiency. Thirty-three (33/34, 97%) of the 34 patients with liver disease and severe renal insufficiency had a history of dialysis; 30 (30/34, 88%) with hemodialysis and 3 (3/34, 9%) with peritoneal dialysis (Table 2). Eight (8/34, 24%) underwent renal transplantation, with 6 (6/8, 75%) of the patients requiring dialysis after transplantation due to graft failure or rejection. The etiology of renal disease was reported in 25 of the 34 (25/34, 74%) severe renal insufficiency patients and not reported in 9 (9/34, 26%) patients. Hepatorenal syndrome (7/25, 28%) and glomerular disease (7/25, 28%) were the most common etiologies, followed by cyclosporine toxicity (4/25, 16%) (Figure 2B). In 29 (29/34, 85%) patients, the renal disease could be categorized as either acute (12/29, 41%) or chronic (17/29, 59%) (Table 1).

NSF Patients with Liver Disease but without Severe Renal Insufficiency
All patients with liver disease developed NSF in the setting of severe renal insufficiency except for one (Patient #5 from Sadowski, et al.), who contracted NSF in the setting of mild-moderate renal insufficiency (89). The etiology of the renal failure was attributed to acute hepatorenal syndrome. He had a liver transplant with severe post-operative complications of hepatic artery thrombosis leading to graft failure, bile leak with peritonitis, and internal bleeding. His renal function progressively worsened from an initial eGFR of 69.6 mL/min/1.73m² to 34.6 mL/min/1.73m². During this time, he received four double-dose infusions of gadodiamide (total dose of 0.76 mmol/kg) for abdominal MR angiography over a ten-week period, within 10 to 75 days of NSF development.

DISCUSSION
In this study, we summarize empirical data from the medical literature reporting of NSF in patients with liver disease from September 2000, through August 2008, identifying 41 such individuals out of a total of at least 355 unique cases. The most common etiology of liver disease was hepatitis C viral infection, mirroring its status as the most frequent cause of chronic liver disease in the West in general. Hepatorenal syndrome was a leading cause of renal insufficiency, an expected finding in this sample consisting of a majority of cirrhotic patients who eventually progressed to liver transplantation. Renal therapy was also pervasive and representative of NSF patients in general, with most patients in our sample receiving hemodialysis and some requiring renal transplantation.

Severe renal insufficiency was present in similar proportions of NSF patients with and without liver disease (greater than 97% in both groups), suggesting that liver disease does not confer increased risk for NSF development. With one exception, every NSF patient with liver disease also had severe renal insufficiency. Therefore, while the FDA “black box warning” cautioning against the use of GBCAs in patients with severe renal insufficiency is supported by the data from our review as well as the work of others, the extension of this warning to liver patients with renal insufficiency of any severity is not substantiated by our analysis.
The lone patient in the medical literature (Patient #5 from Sadowski, et al.) who fulfills the FDA’s extended warning of having liver disease but not severe renal insufficiency is a highly atypical one (89). He had a liver transplant with several severe post-operative complications, and he received an unusually large cumulative gadodiamide dose of 0.76 mmol/kg during a relatively short time period. His renal function progressively deteriorated from an initial eGFR of 69.6 mL/min/1.73m² to 34.6 mL/min/1.73m², close to the demarcation for severe renal insufficiency. Thus, several factors may have contributed to the development of NSF in this complex patient and, as this is the only patient in the published literature with liver disease to develop NSF without documented severe renal insufficiency, it is not clear that liver disease per se was a pivotal factor.

Similarly, while the occurrence of NSF in the peri-operative liver transplant period is stressed by the FDA warning and others (13,16,18), our review demonstrates that, even in the subset of patients with NSF and a history of liver transplantation, NSF onset did not exclusively occur within the six month peri-transplantation period. This suggests that, unlike renal insufficiency, liver transplantation may not be a pivotal risk factor for NSF development.

GBCA administration was confirmed in 16 (16/41, 39%) NSF patients with liver disease, denied in one (1/41, 2%) patient, and not reported in 24 (24/41, 59%) patients. In the 15 patients with GBCA exposure, 14 received gadodiamide and one received gadiodiamide and gadobenate dimeglumine – this predominance of gadodiamide exposure in NSF development in liver patients corroborates prior observations that gadodiamide is the most commonly associated agent in NSF patients regardless of concomitant liver disease (6).

Upon deposition in various tissues, GBCAs are thought to play a central role in NSF development by providing a target for fibrocyte recruitment and activation of the fibrotic process (113). Accordingly, cutaneous gadolinium deposition has been confirmed by advanced microscopic and spectroscopic techniques in patients with NSF (14,114). GBCAs are primary renally excreted (though the clearance of some GBCAs is augmented by the liver); in fact, the half-life of GBCAs has been demonstrated to be longer in patients with end-stage renal disease or on dialysis compared to healthy volunteers (115). Gadolinium ions are thought to be deposited in tissue through the process of transmetallation, in which they are exchanged with endogenous ions and released from their chelate (116). Many of these endogenous ions, including calcium, phosphates, hydrogen, zinc, and copper, are elevated in patients with renal insufficiency, making transmetallation presumably more likely to occur in this population (117).

While these factors clearly provide a plausible mechanism for GBCA involvement in the pathogenesis of NSF in patients with advanced renal disease, the incorporation of liver disease within this model is less clear. First, unlike the kidneys, the liver does not play a primary role in the clearance of GBCAs. Second, independent of its relationship with renal disease, liver disease is not associated with elevations in the endogenous ions thought to be instrumental in transmetallation. Hence, there appears to be no plausible biological reason to expect that liver disease would increase the risk of NSF development independent of underlying renal disease.

Renal dysfunction is common in patients with end-stage liver disease, particularly those in the peri-operative and post-operative liver transplantation period. Multiple insults to the kidneys are possible, including the inappropriate vasoconstriction of the renovasculature leading to hepatorenal syndrome, acute tubular necrosis related to volume shifts and peri-operative hypotension, intravenous contrast nephropathy, and medication nephrotoxicity from antibiotics, antifungal agents, and calcineurin inhibitors. As such, patients with liver
disease may be at risk for NSF, but only to the extent that they are physiologically prone to severe renal insufficiency.

eGFR is recognized to be a suboptimal measure of renal function in patients with liver disease. It is calculated from a formula that takes into account creatinine and three demographic features (age, gender, and race) that are surrogates of lean muscle mass. Patients with liver disease have atrophy of lean muscle mass unaccounted for by this formula; therefore, eGFR underestimates severity of renal insufficiency in patients with liver disease. Nevertheless, no patient in the medical literature with liver disease and an eGFR ≥ 30 mL/min/1.73m$^2$ developed NSF except for the one atypical patient described above, suggesting that an eGFR ≥ 30 mL/min/1.73m$^2$ conveys an acceptably low risk of developing NSF in patients with liver disease. Therefore, contrary to the extended “black box” warning, the existing peer-reviewed medical literature does not support a conclusion that patients with liver disease and renal disease of any severity are at increased risk for developing NSF.

Our retrospective review of the reported literature has inherent limitations. Most importantly, we were restricted by the summary nature of some reports. Though we attempted to collect data for a variety of variables, most articles did not provide sufficient detail to make this consistently possible for all variables of interest. In particular, articles prior to Grobner’s seminal work in 2006 failed to mention exposure to GBCAs (4), which is to be expected as the association between NSF and GBCAs was not known at the time. Similarly, many articles did not provide sufficient detail to confidently discern the nature of each patient’s liver and kidney disease. Recognizing this, we removed cases with insufficient information from our analysis, including only those patients who were satisfactorily described; excluding the 95 patients in whom liver disease was uncertain did not significantly impact our results given that all of these patients had severe renal insufficiency. The lack of uniform reporting also limited our statistical analysis, confining us to a descriptive analysis rather than more refined testing. Going beyond the medical literature, we attempted to contact the corresponding authors of articles in question to gather more information. However, it is possible that the authors of other review articles have been more successful in gleaning additional information from such correspondences. Additionally, the identification of unique cases proved difficult. Thus, although 335 cases are included in our analysis, there may be up to 99 additional cases that we were unable to substantiate as being unique. Not including these potentially duplicate cases was a conservative decision that increased the apparent proportion of mild-moderate renal insufficiency among patients with liver disease because all such individuals had severe renal insufficiency.

In conclusion, our review of the reported NSF literature provides insight into a subpopulation of NSF patients who are impacted by the recent “black box warning” extension regarding GBCA use – those with liver disease. While it is clear that patients with liver disease also have severe renal insufficiency, the published literature provides no compelling evidence to suggest that liver disease confers a risk for NSF beyond that of the underlying renal insufficiency itself.

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References


Fig. 1. Characterization of NSF in the medical literature relative to concomitant liver disease and renal insufficiency
Mild/Mod = mild/moderate renal insufficiency
Fig. 2.
Fig. 2A. Etiologies of liver disease in the 41 NSF patients with concomitant liver disease. HBV = hepatitis B viral infection, HCV = hepatitis C viral infection, EtOH = alcoholic liver disease. * α1-antitrypsin deficiency, hemochromatosis, amiodarone hepatotoxicity, primary biliary cirrhosis, “biliary disease,” and HELLP syndrome.
Fig. 2B. Etiologies of renal disease in the 41 NSF patients with concomitant liver disease. HRS = hepatorenal syndrome, Glomerular Dz = glomerular disease, CSA toxicity = cyclosporine toxicity, HTN = hypertension, DM = diabetes mellitus.
† Interstitial nephritis, polycystic kidney disease, and post-partum eclampsia.
Table 1
Clinical characteristics of the 99 potentially duplicate NSF patients.

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<th>Renal Insufficiency</th>
<th>Liver Disease</th>
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<tr>
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<tr>
<td>Severe*</td>
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</tr>
<tr>
<td>No, mild, or moderate</td>
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<tr>
<td>Uncertain</td>
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</tr>
<tr>
<td>Total</td>
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* Severe = Dialysis requirement or (e)GFR < 30 mL/min/1.73m2
## Table 2
Clinical characteristics of the 41 NSF patients with concomitant liver disease.

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<tr>
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<th>No</th>
<th>Uncertain</th>
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<tbody>
<tr>
<td><strong>Liver Status</strong></td>
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<td></td>
<td></td>
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<td>0</td>
</tr>
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<td>Liver Transplantation</td>
<td>27</td>
<td>14</td>
<td>0</td>
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<tr>
<td>NSF Peri-Liver Transplantation(†)</td>
<td>15</td>
<td>3</td>
<td>9</td>
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<td><strong>Renal Status</strong></td>
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<td></td>
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<td>History of Dialysis</td>
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<td><strong>GBCA Exposure</strong></td>
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<td>1</td>
<td>24</td>
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\(†\) Peri-Liver Transplantation = within 6 months of transplantation
Table 3

Demographic and clinical characteristics of the 41 published (Sep 2000–Aug 2008) NSF patients with concomitant liver disease.

<table>
<thead>
<tr>
<th>Case</th>
<th>Article</th>
<th>Patient ID in Article</th>
<th>Age/Sex</th>
<th>Liver Disease Etiology and Severity</th>
<th>Liver Transplant (LT-NSF onset interval)</th>
<th>Renal Disease Etiology</th>
<th>Renal Status</th>
<th>GBCA Comments on Dosing and Timing Relative to NSF (if available)</th>
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<td>HRS</td>
<td>HD</td>
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<td>2</td>
<td>42/M</td>
<td>HCV, Cirrhosis</td>
<td>Y (120 m)</td>
<td>HTN/CSA toxicity</td>
<td>HD</td>
<td>?</td>
</tr>
<tr>
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<td>50/M</td>
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<td>61/M</td>
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<td>DM/HTN</td>
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<td>HTN</td>
<td>HD, RT</td>
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<td>HTN</td>
<td>PD</td>
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<td>Swartz, 2003</td>
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<td>43/?</td>
<td>HCV, Cirrhosis</td>
<td>Y (?)</td>
<td>Polycystic kidneydisease</td>
<td>HD, RT</td>
<td>?</td>
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<td>Swartz, 2003</td>
<td>9</td>
<td>51/?</td>
<td>?, Cirrhosis</td>
<td>N</td>
<td>Chronic GN</td>
<td>RT, PD</td>
<td>?</td>
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<td>HELLP</td>
<td>N</td>
<td>ARF secondary to?</td>
<td>HD</td>
<td>?</td>
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<td>Swartz, 2003</td>
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<td>N</td>
<td>HRS</td>
<td>HD, RT</td>
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<td>12</td>
<td>56/?</td>
<td>HCV/EtOH, Cirrhosis</td>
<td>Y (?)</td>
<td>CSA toxicity</td>
<td>HD</td>
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<td>13</td>
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<td>53/?</td>
<td>“Biliary disease”, Cirrhosis</td>
<td>Y (?)</td>
<td>CSA toxicity</td>
<td>HD</td>
<td>?</td>
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<tr>
<td>14</td>
<td>Chiu, 2004</td>
<td>1</td>
<td>56/F</td>
<td>A1AT deficiency, Cirrhosis</td>
<td>Y (?)</td>
<td>Idiopathic membranous nephropathy</td>
<td>HD</td>
<td>?</td>
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<tr>
<td>15</td>
<td>Evenepoel, 2004</td>
<td>2</td>
<td>57/M</td>
<td>Hemochromatosis, Cirrhosis</td>
<td>Y (2 m)</td>
<td>Idiopathic MPGN</td>
<td>HD</td>
<td>?</td>
</tr>
<tr>
<td>16</td>
<td>Hauser, 2004</td>
<td>1</td>
<td>53/M</td>
<td>HBV</td>
<td>N</td>
<td>Interstitial nephritis</td>
<td>HD, RT</td>
<td>?</td>
</tr>
<tr>
<td>17</td>
<td>Dundova, 2005</td>
<td>1</td>
<td>50/M</td>
<td>“Hepatitis”</td>
<td>N</td>
<td>Chronic GN</td>
<td>HD, RT</td>
<td>?</td>
</tr>
<tr>
<td>18</td>
<td>Ruiz-Genao, 2005</td>
<td>1</td>
<td>44/M</td>
<td>HBV</td>
<td>N</td>
<td>FSGS</td>
<td>RT, HD</td>
<td>?</td>
</tr>
<tr>
<td>19</td>
<td>Maloo, 2006</td>
<td>1</td>
<td>60/M</td>
<td>HBV/HCV, Cirrhosis</td>
<td>Y × 2 (5 m after 2nd LT)</td>
<td>?</td>
<td>HD</td>
<td>≥ 1 Gadodiamide exposure; 2–6 weeks prior</td>
</tr>
<tr>
<td>20</td>
<td>Maloo, 2006</td>
<td>2</td>
<td>51/M</td>
<td>HCV, Cirrhosis</td>
<td>Y (1 m)</td>
<td>HRS</td>
<td>HD</td>
<td>≥ 1 Gadodiamide exposure; 2–6 weeks prior</td>
</tr>
<tr>
<td>21</td>
<td>Maloo, 2006</td>
<td>3</td>
<td>76/M</td>
<td>EtOH, Cirrhosis</td>
<td>Y (2 m)</td>
<td>“Acute-on-chronic” RF</td>
<td>HD</td>
<td>≥ 1 Gadodiamide exposure; 2–6 weeks prior</td>
</tr>
<tr>
<td>22</td>
<td>Boyd, 2007</td>
<td>1</td>
<td>68/F</td>
<td>HCV, Cirrhosis</td>
<td>Y (132 m)</td>
<td>CSA toxicity</td>
<td>HD</td>
<td>Gadodiamide × 1</td>
</tr>
<tr>
<td>Case</td>
<td>Article</td>
<td>Patient ID in Article</td>
<td>Age/Sex</td>
<td>Liver Disease Etiology and Severity</td>
<td>Liver Transplant (LT-NSF onset interval)</td>
<td>Renal Disease Etiology</td>
<td>Renal Status</td>
<td>GBCA Comments on Dosing and Timing Relative to NSF (if available)</td>
</tr>
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<td>------</td>
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<td>------------------------</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>23</td>
<td>Broome, 2007</td>
<td>1</td>
<td>45/M</td>
<td>?, Cirrhosis</td>
<td>Y (0.6 m)</td>
<td>HRS</td>
<td>HD</td>
<td>Gadodiamide (0.2 mmol/kg × 40 mL) × 1</td>
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<tr>
<td>24</td>
<td>Broome, 2007</td>
<td>2</td>
<td>46/M</td>
<td>?, Cirrhosis</td>
<td>Y (1 m)</td>
<td>HRS</td>
<td>HD</td>
<td>Gadodiamide (0.2 mmol/kg × 40 mL) × 1</td>
</tr>
<tr>
<td>25</td>
<td>Broome, 2007</td>
<td>3</td>
<td>64/M</td>
<td>?, Cirrhosis</td>
<td>Y (0.6 m)</td>
<td>HRS</td>
<td>HD</td>
<td>Gadodiamide (0.2 mmol/kg × 40 mL) × 1</td>
</tr>
<tr>
<td>26</td>
<td>Broome, 2007</td>
<td>4</td>
<td>49/M</td>
<td>?, Cirrhosis</td>
<td>Y (0.6 m)</td>
<td>HRS</td>
<td>HD</td>
<td>Gadodiamide (0.2 mmol/kg × 32 mL) × 1</td>
</tr>
<tr>
<td>27</td>
<td>Collidge, 2007</td>
<td>4</td>
<td>54/F</td>
<td>HCV</td>
<td>N</td>
<td>GN</td>
<td>HD</td>
<td>No exposure</td>
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<tr>
<td>28</td>
<td>Hamilton-Persaud, 2007</td>
<td>4</td>
<td>?/F</td>
<td>“Hepatitis”</td>
<td>N</td>
<td>?</td>
<td>HD</td>
<td>1 GBCA exposure of ? type</td>
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<tr>
<td>29</td>
<td>Introcaso, 2007</td>
<td>5</td>
<td>48/F</td>
<td>HCV</td>
<td>N</td>
<td>Lupus Nephritis</td>
<td>PD</td>
<td>?</td>
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<tr>
<td>30</td>
<td>Pryor, 2007</td>
<td>4</td>
<td>65/F</td>
<td>Cirrhosis</td>
<td>Y (?)</td>
<td>DM</td>
<td>HD</td>
<td>Gadodiamide × 5; 7–20 months prior</td>
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<tr>
<td>31</td>
<td>Richmond, 2007</td>
<td>4</td>
<td>57/F</td>
<td>PBC, Cirrhosis</td>
<td>Y (2 m)</td>
<td>ARF post-LT</td>
<td>HD</td>
<td>Gadodiamide × 1; 8 weeks prior</td>
</tr>
<tr>
<td>32</td>
<td>Sadowski, 2007</td>
<td>4</td>
<td>7/F</td>
<td>?, Cirrhosis</td>
<td>Y (?)</td>
<td>?</td>
<td>eGFR = 21.6–23.9</td>
<td>Gadodiamide (0.23 mmol/kg × 1) + Gadobenate dimeglumine (0.23 mmol/kg) × 1; 30 days prior</td>
</tr>
<tr>
<td>33</td>
<td>Sadowski, 2007*</td>
<td>5</td>
<td>?/M</td>
<td>?, Cirrhosis</td>
<td>Y (?)</td>
<td>?</td>
<td>eGFR = 34.6 → 69.6</td>
<td>Gadodiamide (0.19 mmol/kg) × 4; 10–75 days prior</td>
</tr>
<tr>
<td>34</td>
<td>Caccetta, 2008</td>
<td>1</td>
<td>47/M</td>
<td>HCV/ EtOH, Cirrhosis</td>
<td>Y × 2 (1.5 m after 2nd LT)</td>
<td>ARF post-LT</td>
<td>HD</td>
<td>Gadodiamide (14 mL) × 2</td>
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<td>35</td>
<td>Kallen, 2008</td>
<td>?</td>
<td>?/F</td>
<td>HCV, Cirrhosis</td>
<td>Y (?)</td>
<td>?</td>
<td>HD</td>
<td>At least 1 GBCA exposure of ? type</td>
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<td>41</td>
<td>Shabana, 2008</td>
<td>?</td>
<td>?/F</td>
<td>?, Cirrhosis</td>
<td>Y (?)</td>
<td>?</td>
<td>?</td>
<td>?</td>
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</tbody>
</table>
The lone NSF patient in the medical literature with concomitant liver disease and mild-moderate renal insufficiency.

Liver disease etiology: EtOH = Alcoholic liver disease; HBV = Hepatitis B viral infection; HCV = Hepatitis C viral infection, PBC= Primary biliary cirrhosis.

Renal disease etiology: ARF= Acute renal failure; CSA toxicity = Cyclosporine toxicity; DM = diabetes mellitus; FSGS= Focal segmental glomerulosclerosis; GN= Glomerulonephritis; HRS = Hepatorenal syndrome; HTN = Hypertension; MPGN= Membranoproliferative glomerulonephritis; RF= Renal failure.

LT= Liver transplant; HD= Hemodialysis; PD= Peritoneal dialysis; RT= Renal transplant; ?= Uncertain.