Is Chronic Liver Disease an Independent Risk Factor for Nephrogenic Systemic Fibrosis? A Comprehensive Literature Review

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INTRODUCTION: Nephrogenic systemic fibrosis (NSF) is a rare but emerging disorder of widespread tissue fibrosis in patients with renal insufficiency.[1] It has also been reported in patients with liver disease and concomitant renal insufficiency in the perioperative liver transplantation period.[2] The pathogenesis of this entity has not been elucidated, though reports indicate an association between NSF and the administration of gadolinium-based contrast agents (GBCAs).[3] In May 2007, the FDA issued a black box warning, cautioning against the use of GBCAs in patients with "acute or chronic severe renal insufficiency (glomerular filtration rate [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."[4] This warning implies that chronic liver disease is an independent risk factor for NSF and that NSF may occur in liver patients with only mild or moderate renal insufficiency (GFR > 31 mL/min/1.73m^2). In clinical practice, GBCA-enhanced MR imaging plays a central role in monitoring for hepatocellular carcinoma in the pre-transplant period and diagnosing post-operative transplant complications. Limiting its use, therefore, may have deleterious consequences to the care of these tenuous patients. Accordingly, our aim is to systematically review the literature in an attempt to better characterize NSF risk in liver disease patients.

METHODS: We reviewed the English medical literature to identify all case reports and original research articles on NSF between September 2000 and August 2007. Articles were found by Pubmed searches that included, but were not limited to, the terms "nephrogenic systemic fibrosis", "nephrogenic fibrosing dermopathy", and "dialysis-associated systemic fibrosis". The following data were collected for each unique patient: (A) demographics, (B) GBCA exposure, (D) renal status (creatinine, GFR, dialysis requirement), and (E) liver status (etiology of liver disease, presence of cirrhosis, history of hepatorenal syndome, history of orthotopic liver transplantation). In accordance with nephrology societies, severe renal insufficiency was defined as either a GFR < 30 mL/min/1.73m^2 or the necessity for dialysis. As with prior studies, if the GFR was not explicitly stated in the article, it was approximated from creatinine values using the Modification of Diet in Renal Disease equation. If there was insufficient information in the article to make a confident determination about a particular data category, then that item was marked as "uncertain". Two investigators independently evaluated each article. Discrepancies were arbitrated by a third review of the article and subsequent mutual agreement between the investigators.

RESULTS: A total of 291 unique patients diagnosed with NSF have been described in the English medical literature (mean age 49.8 years, range 8-81). Of these, liver disease was clearly absent in 118 patients (40.1%) and uncertain in 139 patients (47.8%) (Figure 1). In the 118 patients in whom liver disease was absent, severe renal insufficiency was present in 107 patients (99.1%), absent in 1 patient (0.93%), and uncertain in 10 patients (not included in mathematical analysis). Of the 139 patients in whom liver disease was uncertain, severe renal insufficiency was present in 123 patients (100%) and uncertain in 16 patients (not included in mathematical analysis). Thirty-four patients (11.7%) were confidently assessed as having liver disease, with hepatitis C being the most common etiology. Thirty-three (97.1%) of these patients had concurrent severe renal insufficiency. The proportion of patients with severe renal insufficiency was similar in the 3 groups (> 97.0%).

Among the patients with liver disease and severe renal insufficiency, 21 (63.7%) proceeded to liver transplantation. The lone liver patient without severe renal insufficiency who developed NSF had a GFR of 69.6 mL/min/1.73m^2 prior to the first of four double-dose GBCA infusions (totaling 0.76 mmol/kg) for abdominal MR angiographies in the setting of failed liver transplant. His renal function subsequently worsened, with a nadir GFR of 34.6 mL/min/1.73m^2, and his post-operative course was further complicated by hepatic artery thrombosis, bile leak with peritonitis, and gastrointestinal bleed.

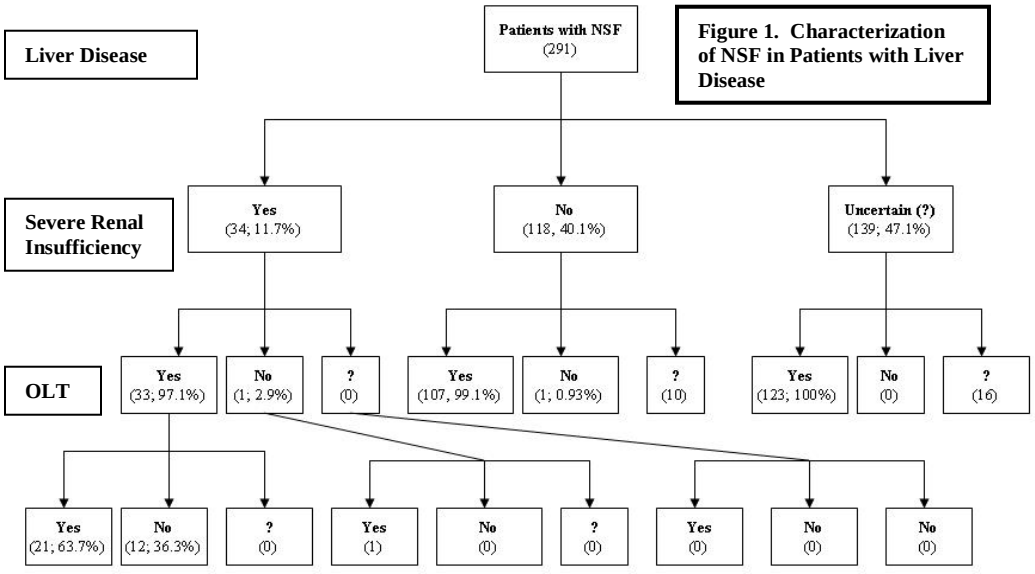

Figure 1. Characterization of NSF in Patients with Liver Disease

DISCUSSION: To our knowledge, this is the most exhaustive and systematic literature review of NSF conducted, including more patients and variables than in prior reviews and drawing from articles in radiology, pathology, nephrology, dermatology, and rheumatology journals. Severe renal insufficiency was present in similar proportions of NSF patients with and without liver disease. This points away from liver disease as an independent risk factor for NSF. Patients with liver disease may be at risk for NSF, but only to the extent that they are physiologically prone to severe renal insufficiency. While the FDA warning regarding the use of GBCAs in patients with severe renal insufficiency is well-substantiated, we believe the extension of the warning to liver patients with renal insufficiency of *any severity* may be premature. In the published literature, the only NSF patient with liver disease and without severe renal insufficiency was a severely ill patient with a large GBCA exposure and complicated post-operative course. Because renal insufficiency may develop rapidly and unpredictably in patients with liver disease, it may be prudent to measure GFR contemporaneously to the time of GBCA-exposure. However, if the GFR > 31 mL/min/1.73m^2, the risk of NSF appears to be negligible.

CONCLUSION: With the limitations inherent to retrospective review, liver disease is not an independent risk factor for the development of NSF. A prospective, multicenter evaluation of NSF incidence in liver patients receiving gadolinium would be beneficial.

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