To: Department of Radiology, University of Wisconsin, Madison, WI
From: Laura B. Eisenmenger MD; Scott B. Reeder, MD, PhD; Ali Pirasteh MD; Howard A. Rowley, MD; Elizabeth A. Sadowski, MD, on behalf of the University of Wisconsin MRI Safety Committee
Re: Updated NSF Screening Procedure at the University of Wisconsin
Date: 01/13/2021, new guidelines effective 08/25/2021

Purpose: This document describes modified screening procedures for mitigating the risk of nephrogenic systemic fibrosis (NSF) in patients with renal failure undergoing gadolinium-enhanced MRI.

Background: In 2006-2007, it was recognized that patients with renal failure who were exposed to gadolinium-based contrast agents (GBCAs) were at increased risk of developing a potentially fatal disorder known as nephrogenic systemic fibrosis (NSF). As a result, the FDA issued a black box warning on the use of all GBCAs in patients with renal failure. Through intense international effort it has been determined that some GBCAs are strongly associated with NSF, while others are not. The three agents most associated with NSF include gadodiamide (Omniscan), gadopentetate dimeglumine (Magnevist), and gadoversetamide (Optimark). We note that of these agents, only gadodiamide remains commercially available.

At the University of Wisconsin, Sadowski et al (Radiology 2007) reported 13 cases of NSF. All of these patients were inpatients with renal failure, a pro-inflammatory condition, and exposure to gadodiamide. In patients with this risk profile (inpatients, renal failure, pro-inflammatory condition), it was determined that there was an approximate risk of 3-5% of developing NSF after exposure to gadodiamide. More recently, Starekova et al (Radiology 2020) reported a total of 18 patients with NSF at UW, 17 of whom had been exposed to gadodiamide with 1 patient exposed to an undocumented agent at an outside institution in 2006.

Initially, screening procedures to identify inpatients with renal failure and pro-inflammatory conditions were developed. Dedicated screening of all inpatients using the “yellow NSF form” was required. Inpatients with renal failure and a pro-inflammatory condition were flagged as high risk. In these patients, ad hoc review for the need to use gadolinium was necessary. If deemed necessary, a discussion with the referring physician and documentation of this communication in the radiology report was required. In many cases this led to significant delays, and a GBCA was ultimately administered to most patients.

Since that time, gadodiamide, the only agent used at UW-Madison known to be related to NSF, has been dropped from UW formulary. Further, there are no unconfounded cases of NSF associated with gadobenate dimeglumine (Multihance®) reported anywhere in the world, despite tens of millions of doses. Recently, a publication by Bruce et al (Invest Radiol 2016), reported the absence of NSF in over 1400 high-risk inpatients at UW-Madison injected with gadobenate dimeglumine. Nandwana et al (Emory group, Radiology 2015) also found no cases of NSF in a group of 401 patients with renal impairment (303 dialysis-dependent) who received gadobenate dimeglumine. Based on changes in practice and the avoidance of specific GBCAs, there are no reported cases of NSF with any agent anywhere in the world since 2008, and the use of the “yellow NSF form” at UW was discontinued.

In addition, although less is known about the safety of group 3 GBCAs in comparison to group 2 agents, UW also has completed extensive research into the potential risk of the group 3 GBCA gadoxetic acid (Eovist®). As an institution, we have performed 7,820 gadoxetic acid-enhanced MRI exams in 5,351 patients, and no cases of NSF were detected. In a subanalysis focused on patients with impaired renal function, 482 MRI exams were performed in 383 patients with eGFR <45/min/1.73m^2, including 299 exams (242 patients) with eGFR =30-44 mL/min/1.73m^2, 109 exams (94 patients) with eGFR =15-29 mL/min/1.73m2, 40 exams (39 patients) with eGFR <15 mL/min/1.73m^2, and 34 exams (27 patients) on hemodialysis.

The following GBCAs are available on the UW formulary: gadobenate dimeglumine (MultiHance®), gadoterate meglumine (Dotarem®), and gadoxetic acid (Eovist®). None of these agents have been associated with NSF when administered as the sole agent. Despite the excellent safety profile of these GBCAs and the extremely low theoretical risk of NSF even in the setting of renal failure, the FDA black box warning remains for all agents. The American College of Radiology (ACR) has stated that renal screening is optional when using group 2 agents. Mindful of the FDA warning, the safety profile of the GCBAs on the UW formulary, and

also the need to obtain important diagnostic imaging information for our patients, the MRI Safety Committee has modified the UW NSF screening procedure, as follows.

Modified Procedures for Administering Gadolinium in Patients :

1. The following procedures only apply to the three agents currently on the formulary: gadobenate dimeglumine, gadoterate meglumine, and gadoxetic acid. Should other agents be introduced on an *ad hoc* basis, please review with the Chair of the MRI Safety Committee or Chief of MRI prior to use in patients with renal failure. Should new GBCAs be added to the formulary in the future, this document will be modified / amended.
2. We continue to recommend caution when considering administration of GBCAs to patients with risk factors for NSF. As with all MRI exams, the protocolling radiologist who prescribes the GBCA is verifying that contrast agent administration is indicated given a risk-benefit analysis, considering patient-specific circumstances and clinical indications.
3. Effective 04/07/2021, a modified process of screening patients will be instituted as follows:
   a. No renal function screening is required for *outpatients* when administering either the UW formulary group 2 or group 3 contrast agents: gadobenate dimeglumine (MultiHance®), gadoterate meglumine (Dotarem®), and gadoxetic acid (Eovist®). This is consistent with previous procedures.
   b. No renal function screening is required for *inpatients* when administering either of the group 2 agents on formulary: gadobenate dimeglumine (MultiHance®) and gadoterate meglumine (Dotarem®). The theoretical risk of NSF with group 2 contrast agents, even in the setting of renal failure, is extremely low.
   c. Given that no cases of NSF were observed in patients with or without renal failure after administration of gadoxetic acid (Eovist®), we now approach gadoxetic acid as we do group 2 GBCAs and no longer require renal function screening in either the *outpatient or inpatient* setting.
   d. For patients who are at an elevated risk due to hemodialysis, good-faith attempts will be made to coordinate MRI with hemodialysis. Ideally, hemodialysis should be performed the same day, following gadolinium enhanced MRI. However, coordination of MRI with dialysis should not delay an MRI exam if the delay leads to negative clinical impact. It is important to note that although GBCAs are removed by hemodialysis, there are no data that demonstrate the benefit of dialysis for reduced risk of NSF. It is not necessary to document that the MRI was coordinated with dialysis.
   e. The principles outlined here will also apply to research subjects undergoing MRI at UW-Madison.
4. No specific documentation of eGFR or otherwise pertaining to renal function is required.

It is our goal that the above modified screening procedures will ensure standardization, improve consistency, avoid dosing errors and create a streamlined and efficient approach that will avoid confusion and delay of important care to our patients.

Questions: Please contact: Laura Eisenmenger (Pager 41708), Scott Reeder (Pager 6713), Ali Pirasteh (Pager 41570); Howard Rowley (Pager 2518), or Elizabeth Sadowski (Pager 9036).