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Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: PRO

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Primum non nocere; few things speak louder in medicine. It seems so simple. But it is also too easy to hide behind these three powerful words. The truth is, we put patients at risk every day, but we try to do so with close attention to risk versus benefit. The benefit of gadolinium is obvious, but the risk has changed as gadolinium has changed over the last 20 years. In the following, I will argue that risk is minimal, and that gadolinium-based contrast media can be used safely for imaging in patients with stage 4/5 CKD. But first, let's review some background.

Gadolinium-based contrast media (GBCM) for magnetic resonance imaging (MRI) have been available since the late 1980s. Radiographic studies with MRI and GBCM provided improved imaging for many conditions compared with studies that used iodine-based contrast media (IBCM). Because the combination of MRI with GBCM was considered to be safe and, specifically, did not have the concerns of anaphylaxis and AKI that may be seen with IBCM, GBCM imaging became extremely popular, with millions of uneventful studies being performed every year. Thus, it is rather surprising that it took almost a decade for reports to emerge of a debilitating, chronic, fibrosing, skin condition in patients with ESKD. By 2000, it was realized that the disease was not limited to skin and this entity was entitled nephrogenic systemic fibrosis (NSF), describing its systemic involvement and its association with kidney failure. It still took six more years before this potentially fatal condition was linked to exposure to gadolinium, almost 20 years after GBCM MRI studies became available (1).

Once the association of NSF with GBCM was made, in 2007, the Food and Drug Administration (FDA) issued a "black-box warning" for patients with "severe kidney insufficiency" (2). Although reports of NSF were predominantly limited to patients with ESKD, there was not enough information to know exactly what level of kidney disease qualified for GBCM avoidance. Thus, many nephrologists, hospitals, and radiologists took the conservative position to simply avoid GBCM in anyone with CKD stage 4/5. This policy persists today for the majority of clinicians involved in the decision to use GBCM. The purpose of this paper is to convince the reader that this is a flawed position and that, when chosen properly, GBCM can be used safely for imaging in patients with stage 4/5 CKD.

Gadolinium is a lanthanide element with paramagnetic properties that make it an excellent contrast media for MRI by significantly improving diagnostic efficacy. However, "free" gadolinium that exists as a salt, *e.g.*, gadolinium chloride, is extremely toxic because it can interact with calcium-dependent biologic processes, resulting in various cytotoxic effects. To avoid these potential toxicities, gadolinium is chelated to organic ligands. These gadolinium chelates maintain their paramagnetic properties, while essentially trapping the gadolinium and preventing it from roaming free to wreak havoc on the skin and visceral organs (NSF). Most GBCM remain in the extracellular fluid and, because the majority are not bound to protein, they are rapidly excreted by the kidneys. Delayed excretion occurs in CKD and, although GBCM are significantly removed with hemodialysis (HD), there is no evidence that strategies using HD after GBCM prevents NSF (3).

There are nine GBCM chelates that differ in the structure of the organic chelating ligand (linear or macrocytic) and net charge (ionic or nonionic) (Table 1) (4). Although there is no hard-and-fast rule relating the thermodynamic stability (ability to prevent free circulating gadolinium) to these properties, the macrocytic GBCM are better at preventing dissociation of gadolinium from its chelate than linear GBCM. When NSF was first reported, the GBCM most commonly used were the linear group I agents gadodiamide, gadoversetamide, and gadopentetate. Indeed, almost all cases of NSF have been related to group I GBCM agents (often in repeated or higher-than-recommended doses), and these agents are no longer marketed or available in the United States (5,6).

By 2012 there were >1500 cases of NSF reported to the FDA, but this dropped dramatically after 2008 to single digits. The reason for this decrease is likely a combination of decreased administration in CKD, related to the FDA warning, and a decreased usage of group I GBCM (5,7). One problem is the difficulty in confidently relating NSF to a specific GBCM. Many patients with NSF did not have adequate documentation of the specific GBCM used because many of these patients presented months to years after the purported MRI study. In addition, other patients received more than one MRI study with different GBCM agents. Therefore, cause and effect needs to be limited to

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Table 1. American College of Radiology GBCM group designations

Generic Name	Structure	ACR Group
Gadodiamide	Linear nonionic	I
Gadoversetamide	Linear nonionic	I
Gadopentetate dimeglumine	Linear ionic	I
Gadobenate dimeglumine	Linear ionic	II
Gadoteridol	Macrocyclic nonionic	II
Gadobutrol	Macrocyclic nonionic	II
Gadoterate meglumine	Macrocyclic ionic	II
Gadoxetate disodium	Linear ionic	III

GBCM, gadolinium-based contrast media; ACR, American College of Radiology.

"unconfounded" cases in which it is certain that there was only one specific GBCM administered before the development of NSF. In fact, the GBCM group I–III designation (Table 1) was created by the American College of Radiology (ACR) on the basis of the risk of NSF using unconfounded cases, with NSF having been essentially limited to the use of one of the group I GBCM agents. Because these agents are no longer available in the United States for this reason, the issue at hand is the use of group II and III GBCM in patients with CKD stage 4/5.

To answer this, we must scrutinize the data regarding safety of the GBCM groups II and III in CKD stage 4/5. There are essentially no unconfounded cases of NSF associated with group II GBCM. It is noteworthy that all three of the GBCM group I chelates that have been linked to NSF are linear. Group II GBCM consist of four macrocytic and one linear GBCM. So, it may come as a surprise that a linear GBCM, gadobenate, is included in group II. However, the ACR designated it as such because there is extensive data showing that there is minimal to no risk of NSF with its usage. Clearly, there is more to the development of NSF than just molecular structure. Gadobenate does have some hepatobiliary excretion that may play a role in its safety, despite it being a linear gadolinium chelate (8–10).

There are two ways to assess the risk of group II GBCM and NSF. One can look at patients with NSF and determine what GBCM was administered; alternatively, one can assess the development of NSF in patients with CKD stage 4/5 that received a group II agent. In a series of 405 patients that developed NSF, there were 23 that were related to group II exposure, however, only two of these were unconfounded (5,8,11). In a meta-analysis of 4931 group II GBCM administrations in patients with CKD stage 4/5, there were no patients with NSF, conferring a risk of 0% (10). Because the risk may be greater in CKD stage 5 than in stage 4, a subanalysis separating these groups was performed and the upper limit of the 95% CI of risk was found to be 0.2% (1/500) for CKD stage 5D (ESKD on dialysis), on the basis of zero patients with NSF in 1849 exposed individuals with ESKD, and 0.5% (1/200) for CKD stage 5 (not receiving dialysis), also on the basis of zero patients with NSF in 732 exposed individuals. For the CKD stage 5 group as a whole, the 95% CI upper limit was 0.1% (1/1000), again on the basis of zero patients with NSF. Although these exposure numbers may be small relative to the potential risk, there is not even a signal that using group II GBCM in patients with CKD stage 4/5 puts them at any significant risk of NSF. I would reiterate, zero patients with NSF in 4931 group II exposures in patients with CKD stage 4/5.

When NSF was first recognized, group I GBCM had the majority market share in the United States. Realizing this could bias the risk assessment, a balanced market-share analysis was performed and determined that group I GBCM had a 190-fold increased rate of NSF compared with group II GBCM (1.52 versus 0.008 per million average risk exposures; $P<0.001$) (5).

There is also a dose relationship to NSF risk when group I agents were used that is relevant to this discussion. It was not uncommon to administer a "double" or greater dose of GBCM. In one review of patients that developed NSF, only 10% had received a standard, single dose (12). In another retrospective study of 74,124 patients (all levels of renal function) that received the standard, single 0.1 mmol/kg of GBCM, there were no patients that developed NSF, whereas 15 of 8997 (0.17%; $P<0.001$) patients who received 0.2–0.4 mmol/kg developed NSF (13). Additionally, all cases of NSF were related to group I GBCM. Because double doses of group II GBCM are not typically performed, this may play an independent role in their safety in patients with CKD.

The only group III GBCM in Table 1 is gadoxetate, a linear ionic gadolinium chelate. It has 50% biliary excretion, which may be protective in the setting of CKD. No unconfounded cases of NSF have been reported using gadoxetate, but the data on its use in CKD are limited. The largest series included 85 patients with CKD stage 4/5, and there were no reported patients who developed NSF (14). Because of the limited experience using this GBCM in advanced CKD, an opinion regarding its use in advanced CKD will not be offered in this discussion.

To conclude, although NSF seemed epidemic at one point, new cases appear to have been eliminated by avoiding the high-risk, group I, linear GBCM chelates. Lower dosing may also be playing a role. Regardless, the data do not support the avoidance of group II GBCM in patients with CKD stage 4/5, who would benefit from GBCM over standard imaging using IBCM. There is also no role for increased or accelerated HD after GBCM administration.

Primum non nocere is a basic tenet of medicine, but it must be based on facts and not irrational fear.

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Author Contributions

R.A. Rodby wrote the original draft.

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See related debate, "Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: CON," and commentary, "Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: COMMENTARY," on pages 13–15 and 16–19, respectively.