

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

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In 2006, the first reported association between an antecedent exposure to gadolinium-based contrast media (GBCM) and the development of nephrogenic systemic fibrosis (NSF) ignited a debate on the safety of these agents in patients with kidney disease, with ensuing severe and appropriate-use restrictions put in place. In this issue of *Kidney360*, this debate is revived 15 years later, but with the tide reversing as their use is being reconsidered in these same patients. This debilitating, and often fatal, disease has fortunately receded into memory for many nephrologists. Its practical disappearance can be credited to both the implementation of protocols limiting GBCM use in patients with impaired kidney function or those on maintenance dialysis and the contraindication in those with CKD stages 4–5D or AKI (by the Food and Drug Administration [FDA] and the European Medicines Agency [EMA]) of the three most offending group I or high-risk GBCM, as per the American College of Radiology classification (Table 1) (1). Restrictions on the use of the other available GBCM in patients with kidney disease remain in place today at many centers around the world. In fact, the FDA black-box warning for group II, or low-risk, agents still carry a cautionary note on their use in patients with kidney disease. Recent data have emerged highlighting the safety of these agents in both patients with CKD stages 4–5 and those with ESKD, thus prompting a re-evaluation of practice and policies. The recent calls to revisit the restrictions in place take into consideration their unintended consequences, such as the acquisition of suboptimal diagnostic studies, a concern no longer overshadowed by the risk for NSF.

Although the majority of initial NSF reports were in patients with ESKD, 8% of patients reported at the peak of cases of NSF had CKD stages 4–5 and had received high-risk agents, especially gadodiamide (2). The interaction between GFR and GBCM type is clearly strongest for high-risk GBCM, but may not exist for low-risk ones. Of note, the intravenous use of high-risk GBCM in any patient was suspended by EMA in 2017, mostly over concern of gadolinium brain deposition, and these agents are no longer marketed in the United States.

As such, it is important for nephrologists to be aware of GBCM types because their chemical structures

appear to underlie their classification according to NSF risk by the ACR, EMA, and European Society of Urogenital Radiology (ESUR). As shown in Table 1, the main difference between ACR and EMA/ESUR is the inclusion of gadobenate dimeglumine among group II agents by ACR, but this agent is included in the intermediate- or medium-risk group by EMA/ESUR, along with limiting its use to hepatobiliary imaging. Nonetheless, its associated risk was quite low in two recent studies that included 154 patients with CKD stages 4–5 (3,4). These findings are seconded in the recent subanalysis of a large meta-analysis dataset with no patients with NSF identified among 2687 patients with CKD stages 4–5 who were exposed to group II GBCM (5,6).

Because I have already declared a position in favor of lifting restrictions on the use of group II GBCM in those with CKD (7), it is important to start this discussion by first heeding the expressed concerns raised by Pun and Crowley (8) in their con paper. The authors raise a number of important points, relying on data from a project of the US Veteran Affairs Evidence Synthesis Program (9). In 19 cohort studies and one nonrandomized trial with exclusive use of group II GBCM (except for one group III GBCM), no cases of NSF were identified in 83,291 patients. As noted, the CKD stages 3–5D subgroup represented <5% of the total, raising concern for representation and inclusiveness, especially that restrictive policies have likely excluded patients with CKD from getting GBCM. Nonetheless, there were no patients who developed NSF, including in patients with ESKD who were historically considered the most at risk with group I GBCM. In the recent, aforementioned subanalysis, there were 2666 patients with CKD stages 4–5 who were receiving either gadobenate or gadoterate, among whom 27% had CKD stage 5 and 32% received gadoterate. No patients with NSF were reported, with a recalculated risk of one in 694 exposed for this subgroup. Despite a smaller than desired number of collated patients with CKD stages 4–5 in cohort studies, the absence of NSF is reassuring. On the basis of NSF cases occurring in 40 patients with CKD stages 4–5, a modeled risk was calculated at one in 908 exposed to high-risk GBCM, and there was a predicted nil risk for low-risk GBCM

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Table 1. Classification of gadolinium-based media according to their risk for nephrogenic systemic fibrosis by three organizations

Classification per NSF risk			Chemical Name	Chelate Structure	Notes
ACR	EMA	ESUR			
Group I	High	Highest	Gadodiamide	Linear nonionic	Contraindicated in those with CKD stages 4–5D and AKI Intravenous use suspended by EMA No longer marketed in the United States
Group I	High	Highest	Gadopentetate dimeglumine	Linear ionic	
Group I	High	Highest	Gadoversetamide	Linear nonionic	
Group II	Low	Lowest	Gadoterate meglumine	Macrocyclic ionic	Contraindicated in those with CKD stages 4–5D and AKI Intravenous use suspended by EMA No longer marketed in the United States Withdrawn by marketing authorization holder in Europe in 2017 No longer marketed in the United States
Group II	Low	Lowest	Gadoteridol	Macrocyclic nonionic	
Group II	Low	Lowest	Gadobutrol	Macrocyclic nonionic	
Group II	Medium	Intermediate	Gadobenate dimeglumine	Linear ionic	
Group III	Medium	Intermediate	Gadoxetate disodium	Linear ionic	

Limited to hepatobiliary imaging by EMA
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(2). This can be seen as reassuring because risk was infinitesimally small in CKD stages 4–5, even with high-risk agents, and practically nil with low-risk II GBCM.

Inherent limitations to all of the included studies are raised by the authors, such as the lack of standardized assessment for NSF, despite published diagnostic criteria (10), and repeated administrations. Of note, an interesting point is made about patients with risk factors for CKD not being included, although NSF risk has been confined to presence of CKD *per se*. Informed consent is not recommended prior to GBCA group II injection, but deference is made to local practice preferences.

Rodby (11), on the pro side of this debate, presented an argument for unrestricting the use of group II GBCM in patients with CKD stages 4–5, supported by accumulating evidence for absence of NSF in the >3000 patients exposed to GBCM reported in recent papers. He made reference to the aforementioned recent stratified analysis by CKD stage at the request of the National Kidney Foundation in the United States (6). He cautioned against using more than the standard dose, a case in point made in a recently reported patient with CKD stage 3a who developed NSF after 185 days postexposure to 1.5 times the standard dose of the group II GBCM gadoterate (12). This was a major risk factor with group I GBCM and should be avoided with all GBCM. Important notes are made about the sole GBCM in group III being insufficiently studied in patients with CKD, and that direct GBCM nephrotoxicity is not a concern with standard intravenous dosing.

As the debate starts to move beyond the safety of low risk for NSF in group II GBCM in those with CKD stages 4–5, lingering concerns include the potential increase in patients developing NSF as the use of group II GBCM become more unrestricted (13) and the recently reported deposition of gadolinium in the brain, although to a lesser degree with group II GBCM in all patients (14). Other points worth mentioning are not initiating hemodialysis in patients with CKD stages 4–5 for the sole purpose of GBCM removal and, in contrast to patients with ESKD who are anuric, the risk of contrast-induced nephropathy with iodinated radiocontrast agents is germane to the discussion when assessing risk-benefit ratio in CKD stages 4–5, with the balance tipping in favor of using group II GBCM when needed. In this regard, it remains important to discuss with the radiologist all possible imaging options, including noncontrast magnetic resonance imaging, so as to limit the exposure to GBCM to that which is absolutely needed. This is especially true given that repeat administrations within a short period, or lifetime cumulative exposure, remain of concern.

In summary, the use of group II or low-risk GBCM will be expected to increase in the coming years in patients with CKD stages 4–5, allowing for better diagnostic information to be obtained, when necessary, in these patients. Although the preponderance of data from recent cohort studies support this approach, as with any matter still under debate, it is important to remain vigilant as clinicians, maintaining strict adherence to the set boundaries for safe use and promptly reporting any adverse events.

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Author Contribution

A. Abu-Alfa wrote the original draft and reviewed and edited the manuscript.

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See related debates, “Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: PRO,” and “Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: CON,” on pages 10–12 and 13–15, respectively.