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Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

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EDITORIAL

Prophylactic Hemodialysis for Protection Against Gadolinium-Induced Nephrogenic Systemic Fibrosis: *A Doll's House*

No doubt you, like I, have been informed by your radiologist that your advanced CKD or ESRD patient "must undergo hemodialysis" to prevent gadolinium-based contrast agent (GBCA)-induced nephrogenic systemic fibrosis (NSF) following a magnetic resonance imaging (MRI) study. Few disorders in nephrology have generated more excitement and fear than this devastating dermatologic disorder, first described in 2001 as a case series of 13 patients originally discovered in 1997 at the Sharp Clinic.[1] This disfiguring and disabling skin-scarring disorder, formerly labeled as nephrogenic fibrosing dermopathy, is attributed to the deposition of gadolinium chelates in the skin and other organs, hence, the "systemic" term. Fibrosing and sometimes calcified plaques have involved not just the skin but multiple internal organs including the bone, liver, spleen, skeletal muscle, heart, lungs, kidneys, and brain.[2-4] But why term it "nephrogenic," particularly when one of the pathogenic participants is a circulating fibrocyte, originated from bone marrow?[2,4] Essentially, all afflicted individuals were nephrology patients with low glomerular filtration rates, ie, CKD stages 4 or 5, or acute kidney injury who underwent MRI studies with GBCA enhancement. Fibrosis may be detected within weeks to years of GBCA administration.[5,6] The threshold dose for induction of human disease is unknown. The greater retention of gadolinium in renally impaired persons vs those without kidney disease who can excrete greater than 90% of a gadolinium load in 24 hours was considered the fundamental and pathogenic etiology. Less gadolinium in the body per unit time after gadolinium injection would prevent NSF, so we thought, and the majority of nephrologists still believe. Any remaining gadolinium may require years to excrete, entrenched in insoluble phosphorus tissue complexes. Furthermore, tissue retention is potentially promoted by putative transmetalation, the exchange of gadolinium ion from its organometallic compound with another cation, such as zinc.[7]

Your typical response was likely to have conducted a hemodialysis procedure within 4 hours of the receipt of a gadolinium contrast load. If the patient was CKD Stage 5D, it is even more probable that you hemodialyzed the patient soon after the completion of an MRI. You did so out of a true concern for your patient and to prevent the onset of a devastating disorder. Also, you may have been concerned that the American College of Radiology had convinced every card-carrying radiologist that they must enforce their non-evidence-based societal guidelines,[8] and it was too late in the night for you to argue with one. In fact, you may have "guaranteed" the promptness of the procedure to said radiologist, following a subtle coercive reference to the Radiology Society of North America's guidelines.[9] If you worked at a busy hospital, it is likely that this scenario of gadolinium load, dialysis, and the specter of looming NSF had produced a self-serving sigh of relief once dialysis had been completed urgently and then twice more on consecutive days.

In an informal survey that I conducted of nephrologists posed with the query of whether one's institution followed eGFR-based guidelines for prophylactic hemodialysis to prevent GBCA-induced NSF, the responses varied from hemodialysis commencing after procedural completion to dialysis within several hours to no dialysis at all or dialysis on the next scheduled procedure date. A few institutions had either a Web site with specified protocolization and/or multipage guidelines. Current guidelines from the Food and Drug Administration state that GBCA administration with a glomerular filtration rate of $\leq$30 mL/min/1.73 m^2 is contraindicated.[10] However, no cases of NSF are cited as the reason for this recommendation. Some experts suggest a more vigorous approach for CKD Stage 4 patients. These individuals should undergo 2 procedures: hemodialysis catheterization with its attendant harm and then prompt serial dialysis. I know not of a single instance where the patient agreed to this offer, instead declining an MRI procedure that may have been informative and beneficial to him/her. In this

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circumstance, the gadolinium policy certainly protected the patient from NSF, yet may have facilitated an undisclosed disease process. Even worse are cases where the radiologist on-call or even the radiology technician has unilaterally determined that no MRI should proceed—a form of malpractice. This is the opposite of the situation where a cardiologist requests nephrology consultation to dialyze a patient in advance of a percutaneous coronary intervention to avoid being penalized for attribution of the induction of iodinated contrast-induced acute kidney injury by the procedure. When confronted with the question of whether to conduct an MRI in a patient with compromised kidney function, do nephrologists actually make recommendations opposite to their internal advice, thereby avoiding any potential liability that is obtained from contravening current radiology recommendations?

In truth, most of the GBCA-enhanced MRIs done at night that require prompt hemodialysis will not be done promptly because it is impossible to do so on a practical basis. I can attest to this from my 1-day experience as a hemodialysis technician wheeling around a Fresenius K8 hemodialysis machine, its attendant reverse osmosis and carbon filter apparatuses, and chemicals, migrating with all this from patient-to-patient around a large, city hospital. So, who is correct: Are those who dialyze promptly right or those who believe that dialytic prophylaxis is of no benefit?

Since 2006, nephrologists have continued to conduct hemodialysis to prophylactically avoid NSF. In that year, the Federal Drug Administration issued a "black box" warning for all GBCAs.[10,11] Radiologists and their respective societies subsequently developed recommendations—stolid guidelines for prophylactic hemodialysis against NSF. Consequently, nephrologists, in a blind measure of collaborativity, complied and conducted numerous dialytic procedures to prevent the appearance of a disease most nephrologists have never seen. Cowper[12] maintained a registry of cases of NSF, but there have been no additional registrants in several years (personal communication, SC). Yet, we continue to hemodialyze patients that receive GBCAs for a disorder that has become or is becoming extinct, and possibly because nephrologists and/or radiologists are simply avoiding GBCAs in individuals with low kidney function. Unfortunately, there are no hard statistics to support or refute this surmise. Therefore, I submit that nephrologists who continue the practice of prophylactic dialysis for gadolinium are like Nora Helmer trapped in *A Doll's House*. Mrs Helmer is the principal character of Henrik Ibsen's iconic play, *Et dukkehjem*. She, dutifully and without fail, always stands by her husband and family in perfect alignment with Norwegian societal norms but at great personal cost. I fear that the bulk of nephrologists have in parallel slavishly acknowledged and participated in the nugatory practice of anti-NSF hemodialysis, becoming victims of the tyranny of an unseen majority. The great personal costs have not only been those of nephrologists. Significant costs have been borne by nurses, dialysis technicians, and most importantly, the patients who have endured nighttime procedures and been subjected to perhaps a bit of "false news." That is, the perception that hemodialysis would preclude the possibility of NSF absolutely. Alternatively, and worse, the patient may now harbor years of concern for the development of NSF.

Nephrologists must stop believing that they are benefiting patients by performing prophylactic hemodialysis in patients in receipt of gadolinium, be it of linear or macrocyclic nature.[13] The latter compounds have replaced the older linear complexes in many institutions because of their putatively enhanced chelating ability of gadolinium, ie, gadolinium escapes its avidly binding molecular cage much more slowly, thereby preventing tissue distribution and subsequent fibrogenesis (Table 1).

The studies by Wagner and colleagues are eye-opening in this regard.[2,3] First, in their cultured fibroblast model of NSF, cells exposed to the macrocyclic agent, gadoteridol, would be expected to be protected from gadolinium toxicity, attributable to gadoteridol's thermodynamic stability constant (K_{therm}) of 22.[13] Yet gadoteridol-exposed fibroblasts demonstrated greater secretion of the fibrogenic cytokine, transforming growth factor-β, and the extracellular matrix protein, fibronectin, than the theoretically less safe, linear product, gadodiamide which has a lower K_{therm} than gadoteridol. The majority of NSF cases have been attributed to gadodiamide, (Table 1). Correspondingly, the injection of rats with these 2 non-ionic agents showed greater transforming growth factor-β induction by gadoteridol. This observation reveals a flaw in the theory that macrocyclic gadolinium contrast agents are safer than linear ones and that the pathobiology of the disorder has not been clearly delineated. Second, taking the premise that gadolinium causes NSF and that gadolinium has been detected in NSF lesions, the K_{therm} of gadodiamide predicts a release of just 1 gadolinium ion for every 10 quintillion molecules (10^{18}). To put this into perspective, using average loads of gadoversetamide of approximately 270 mL or 135 mmol per MRI test, about 12 gadolinium molecules would be ultimately liberated. This means that the disease presents a nearly zero risk of occurring, if one ascribes the onset of disease to the release of gadolinium from its molecular cage. Third, and most importantly, Wagner and his collaborators delineate rapid distribution of gadolinium to tissues. The plasma distribution time of GBCAs is on the order of 10 minutes, with disappearance half-times that are 10 times greater. Mathematically, this means for the average dose of GBCA discussed previously, after

Table 1. Chemical and structural characteristics of gadolinium-based contrast agents available in the US for clinical use.

Chemical Name	Structure
Gadobenate (MultiHance)	Linear, ionic
Gadofosveset (Ablavar)	Linear, ionic
Gadopentetate (Magnevist)	Linear, ionic
Gadoxetate (Eovist, Primovist)	Linear, ionic
Gadodiamide (Omniscan)	Linear, nonionic
Gadoversetamide (Optimark)	Linear, nonionic
Gadoterate (Dotarem)	Macrocyclic, ionic
Gadobutrol (Gadavist)	Macrocyclic, nonionic
Gadoteridol (ProHance)	Macrocyclic, nonionic

500 minutes of "perfect" hemodialysis, more than 300 quadrillion molecules of GBCA would be circulating. Therefore, tissue distribution is more rapid than the best extracorporeal membrane can remove—we have done this in vitro—even if concurrent dialysis is carried out. In general, any disorder that is generated by rapid tissue distribution of a toxin via first-pass kinetics, such as iodinated contrast medium, cannot be aborted by any form of extracorporeal removal. Collectively, the experimental data steer us away from "known knowns" and to "known unknown" factors that participate in the pathogenesis of NSF, which requires more investigation. Some of these factors may include differences among the microenvironmental characteristics of individual patients, eg, dermal tension as a function of extracellular matrix and inherent influences of susceptibility to fibrogenesis, in general, eg, phenotypic characteristics of fibroblasts and fibroblastic reactivity.[14]

I conclude that the only patients who should undergo hemodialysis following receipt of GBCAs are those who have ESRD and already undergoing kidney replacement therapy as hemodialysis. They should only undergo hemodialysis as regularly scheduled. This proposal defies current radiological recommendations and may establish me as an "enemy of the people." However, unlike Dr Thomas Stockmann of Ibsen's play of the same name, I am not asking my townspeople to "do something" to remediate a problem but to "do nothing" in response to gadolinium exposure.

The current guidelines regarding the use of GBCAs in advanced CKD patients are based on biological plausibility and logical treatments derived therefrom. However, this "mechanism of disease" approach, which has been repetitively tested in practice, requires modification based on experimental findings and clinical outcomes. The biological evidence for GBCA incitement of an inflammatory and fibrogenic response is known as is the presence of gadolinium in fibrotic lesions. Nonetheless, the evidence that one can effectively minimize the potential for gadolinium release from its chelating agent is on the order of zero.

In the climax of *A Doll's House*, Nora's reputation is threatened for actions that she had undertaken to protect her husband. Her spouse repudiates her for those long-ago actions. Disavowed by her husband, Nora—as heroine—leaves him, her children, and her comfortable home life, slamming the door on her way out. Nephrologists should follow her.

END QUOTATION

> I'm in revolt against the lie that truth is always vested in the majority!
>
> —Dr Thomas Stockmann in *Enemy of the People* by Norwegian playwright, Henrik Ibsen (1882).

Jerry Yee, MD
Editor-in-Chief
Division of Nephrology and Hypertension
Department of Internal Medicine
Henry Ford Hospital
Detroit, MI

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