

Contrast Media Controversies in 2015: Imaging Patients With Renal Impairment or Risk of Contrast Reaction

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OBJECTIVE. The incidence and significance of complications related to intravascular contrast material administration have become increasingly controversial. This review will highlight current thinking regarding the imaging of patients with renal impairment and those at risk for an allergiclike contrast reaction.

CONCLUSION. The risk of contrast-induced acute kidney injury remains uncertain for patients with an estimated glomerular filtration rate (GFR) less than 45 mL/min/1.73m², but if there is a risk, it is greatest in those with estimated GFR less than 30 mL/min/1.73m². In this population, low-risk gadolinium-based contrast agents appear to have a large safety margin. Corticosteroid prophylaxis remains the standard of care in the United States for patients identified to be at high risk of a contrast reaction, but it has an incomplete mitigating effect on contrast reaction rates and the number needed to treat is large.

There is a widening gap between radiologists and other clinicians regarding the perceived nephrotoxic risk of intravascular iodinated contrast material [1–17]. Many in the nephrology [2], cardiology [15], and general medical [1, 16, 17] communities continue to consider all intravascular iodinated contrast material—regardless of whether it is administered intraarterially or IV—to be dangerous in patients with moderate or severe renal dysfunction (i.e., those with acute kidney injury [AKI] or stage III–V chronic kidney disease), whereas many in the radiology community are becoming increasingly convinced that the AKI risk from iodinated contrast media is overstated [3–14].

Contrast-Induced Acute Kidney Injury

AKI temporally related to contrast material administration, a common occurrence in hospitalized patients [1, 7], is often blamed on contrast material administration and not on one of potentially many other coexistent factors [1, 2, 4–6]. Ideally, postcontrast AKI, a correlative diagnosis of AKI that occurs for any of a variety of coincidental reasons after contrast material administration, should be differentiated from contrast-induced AKI—that is, AKI that occurs soon after contrast material administration and is directly caused by contrast material administration. Howev-

er, in routine practice, the differentiation of postcontrast AKI from contrast-induced AKI is often impossible in an individual patient because of the large number of patients who develop AKI unrelated to contrast material that can mimic contrast-induced AKI (i.e., there is a large false-positive fraction) [8–14]. Almost all prospective and retrospective studies investigating the nephrotoxic potential of iodinated contrast media have failed to disentangle contrast-induced AKI from postcontrast AKI, leading to confusing and sometimes uninterpretable results.

Fortunately, a series of recent large-scale (> 10,000 patients each) propensity-adjusted studies have assessed the risk of contrast-induced AKI in a quantitative fashion [8–10, 13, 14]; although their conclusions differ somewhat, they have much in common and give clarity to the true low nephrotoxic potential of IV low-osmolar contrast media (LOCM) and IV isosmolar contrast media (IOCM). Each of these studies shows with excellent power that the per-patient risk of contrast-induced AKI after IV LOCM or IV IOCM administration is either rare or nonexistent for patients with a stable estimated glomerular filtration rate (GFR) of 45 mL/min/1.73 m² or greater (i.e., normal kidney function or stage I–IIA chronic kidney disease). However, the studies reached different conclusions for patients with an estimated

GFR of less than 45 mL/min/1.73 m² (i.e., stage IIIB–V chronic kidney disease). Specifically, those with an estimated GFR of 30–44 mL/min/1.73 m² were determined to be at either borderline increased risk (odds ratio [OR], 1.40; 95% CI, 0.997–1.97) [13] or no risk [9], and those with an estimated GFR of less than 30 mL/min/1.73 m² were determined to be at either substantially increased risk (OR, 2.96; 95% CI, 1.22–7.17) [13] or no risk [9]. Therefore, in patients with severe renal impairment, the nephrotoxic potential of LOCM and IOCM remains uncertain. Assuming the worst-case point estimates among these studies, the number needed to harm would compute to 39 LOCM administrations for one case of contrast-induced AKI in patients with an estimated GFR of 30–44 mL/min/1.73 m² and to six LOCM administrations for one case of contrast-induced AKI in patients with an estimated GFR of less than 30 mL/min/1.73 m².

The term “harm” in this context means the development of AKI as a result of contrast material administration (i.e., contrast-induced AKI). Morbidity and mortality data for contrast-induced AKI have suffered from methodologic limitations similar to those of the diagnosis itself; postcontrast AKI after coronary angiography has been strongly correlated with increased morbidity and mortality [18–22], but these data are not available for contrast-induced AKI (i.e., AKI caused by contrast material and not just temporally related to it). The same research group that found no evidence of contrast-induced AKI from IV LOCM or IOCM exposure regardless of renal function [9, 10] also found no evidence of permanent renal damage or mortality resulting from IV contrast medium administration in their population [8].

None of the recent large-scale propensity-adjusted studies [8–10, 13, 14] have been prospective trials of patients randomized to receive or not receive contrast material. Each of these studies is making adjustments on a retrospective population. Therefore, these data provide no reassurance about the risk of contrast-induced AKI in the absence of standard-of-care prophylactic measures conventionally administered to patients deemed to be at risk for AKI using older risk-threshold paradigms. Even in the studies with negative findings, it is not possible to conclude that contrast-induced AKI does not exist (i.e., postcontrast AKI only) because many patients in these populations were preselected and may have been given prophylaxis in an effort to prevent the disease under study.

In spite of their limitations, these studies and their predecessors have had an immediate effect on contrast medium administration practices in the United States and Europe [23, 24]. Many fewer patients are now considered to be “at risk” of contrast-induced AKI from IV contrast media by radiologists [23–26]. Only 2.1% (603/28,390) of inpatients [26] and 0.2% (6/2689) of outpatients [25] presenting for CT have an estimated GFR of less than 30 mL/min/1.73 m². Compared with an old risk-threshold model using an estimated GFR cutoff of less than 60 mL/min/1.73 m² [25], between 12.4% more inpatients (3525/28,390 if assuming a new threshold of estimated GFR of < 45 mL/min/1.73 m²) and 19.0% more inpatients (5390/28,390 if assuming a new threshold of estimated GFR of < 30 mL/min/1.73 m²) are no longer considered to be at risk [26]. If future data support the notion that contrast-induced AKI is nonexistent after IV administration irrespective of renal function [8, 9], a total of 21.1% more inpatients (5993/28,390) would no longer be considered at risk [26].

Because there remains scientific uncertainty about the true incidence and significance of contrast-induced AKI, the American College of Radiology (ACR) [23] suggests that we proceed as if it is a real phenomenon, albeit one that occurs in a limited and infrequently encountered patient population. Prospective trials investigating the role of contrast material in the development of postcontrast AKI are still needed.

Contrast-Induced Acute Kidney Injury: Intracardiac Versus IV Contrast Material

There is an ongoing controversy regarding the possibility of differential nephrotoxicity between IV and intraarterial (specifically, intracoronary and suprarenal) iodinated contrast material administration [24, 27, 28]. This difference has been posited to help explain the disparity in postcontrast AKI rates in the post-CT and postangiography populations. However, a fundamental difference between coronary angiography and CT is that one of these studies places a catheter into the aorta above the kidneys capable of producing atheroembolic showers to the renal arteries and kidneys (a known cause of postcontrast AKI [29–31]) and the other does not. Additionally, to our knowledge no study of contrast-induced AKI after coronary angiography has provided a control group (e.g., a group of patients who received sham injections through their insert-

ed catheters) to determine whether the contrast material was truly the causative factor in the development of postcontrast AKI rather than some other cause. Finally, the patient populations imaged with CT and coronary angiography are not the same; their diseases, presentation, and perhaps illness severity likely differ. It is still unknown to what degree contrast material explains the incidence of postcontrast AKI after coronary angiography. Therefore, comparing the incidences of postcontrast AKI between groups of patients who receive intraarterial injections and groups of patients who receive IV injections of contrast material is not a feasible way to determine differences in contrast-induced AKI incidence in these populations.

Contrast-Induced Acute Kidney Injury: Risk Stratification by Estimated Glomerular Filtration Rate or Serum Creatinine Value

In comparison with the medical community, many in the radiology community have been somewhat slow to adopt conventionally accepted methods of renal function assessment (e.g., estimated GFR) that have existed for more than a decade [32, 33]. Estimated GFR is used to assign stages of chronic kidney disease [34]; predict hospitalization, cardiovascular events, and risk of death [33]; estimate the nephrotoxic risk for a variety of medications [2]; determine the need for renal replacement therapy [34]; and stratify the probability of nephrogenic systemic fibrosis (NSF) before gadolinium-based contrast medium administration [35]. Estimated GFR is superior to serum creatinine as a measure of stable renal function because it accounts for patient age, patient race, and patient sex—all factors known to influence a patient's renal function [33, 36]. Although estimated GFR is not perfect because it is based on serum creatinine and therefore is subject to similar limitations, it is widely used because of its relative ease of acquisition, low cost, repeatability, and prognostic power [37].

If contrast media are nephrotoxic, they should be treated like all other nephrotoxic drugs [2]: defined the same way (i.e., using the same thresholds of serum creatinine change for the definition of AKI) and risk-stratified the same way (i.e., risk assessment based on estimated GFR instead of serum creatinine value). This mantra has been argued not just for contrast-induced AKI but for all types of AKI [2]. A unified definition not only makes physiologic sense but also allows a comparison of AKI rates across the spectrum of potential nephro-

TABLE 1: Acute Kidney Injury Network (AKIN) Classification of Acute Kidney Injury^a

AKIN Stage of Acute Kidney Injury	Laboratory Criteria	Urine Output
Stage I	Increase in serum creatinine ≥ 0.3 mg/dL or increase in serum creatinine by 1.5- to 2.0-fold above baseline	< 0.5 mL/kg/h for > 6 h
Stage II	Increase in serum creatinine by > 2.0 - to 3.0 -fold above baseline	< 0.5 mL/kg/h for > 12 h
Stage III	Increase in serum creatinine by > 3.0 -fold above baseline or increase in serum creatinine ≥ 0.5 mg/dL to a level of ≥ 4.0 mg/dL	< 0.3 mL/kg/h for 24 h or anuria for 12 h

^aReprinted from [40] (Mehta RL, Kellum JA, Shah SV, et al.; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31) with permission of BioMed Central.

toxins. The heterogeneous definitions of AKI (once uniquely assigned by cause and type [e.g., contrast-induced AKI] [38]) have been joined under a series of consensus definitions: Risk Injury Failure Loss End-Stage (RIFLE) criteria [39] and more recently Acute Kidney Injury Network (AKIN) criteria [40] (Table 1). The ACR [23] has supported using these consensus definitions for the diagnosis of postcontrast AKI and specifically for the diagnosis of contrast-induced AKI when that term is applicable.

Although historical investigations of contrast-induced AKI focused on risk stratification using serum creatinine values, two of the recent large controlled propensity-adjusted studies have done so using estimated GFRs [9, 13]. Additionally, it has been shown that using estimated GFRs instead of serum creatinine values may more correctly identify patients who may be at risk of contrast-induced AKI compared with risk stratification using serum creatinine values [26]. Therefore, there are now reasonable contrast-induced AKI-specific data supporting the use of estimated GFR instead of serum creatinine values for estimating preprocedure contrast-induced AKI risk. It is important to remember that no laboratory-based estimate of renal function—including estimated GFR or serum creatinine—is accurate when the renal function is unstable [41]. Therefore, clinically used renal function thresholds and research methods incorporating laboratory-based estimates of renal function must consider the importance of antecedent AKI in their risk determinations.

Screening based on estimated GFR is advocated by the ACR [23] because it is supported by the nephrology community [2, 34], is a superior method of predicting renal function and potentially contrast-induced AKI risk compared with serum creatinine [2, 26, 34], is more practical than true measures of GFR [41], and aligns institutional guidelines for NSF and contrast-induced AKI (i.e., a provider-to-provider conversation is triggered when a patient is in active AKI or has an estimated GFR of < 30 mL/min/1.73 m²) [35].

Contrast-Induced Acute Kidney Injury: Prophylactic Strategies

The most effective prophylactic maneuver to mitigate any potential risk of contrast-induced AKI is to avoid the administration of intravascular iodinated contrast material. However, in many patient care situations, the use of iodinated contrast material is perceived to be beneficial. A few published examples of applications in which contrast material dose can be reduced without sacrificing diagnostic accuracy include pulmonary CT angiography using dual-energy CT [42], CT angiography with a reduced tube voltage [43], and dynamic multiphase hepatic CT using a reduced tube voltage and a hybrid iterative reconstruction technique [44].

Although it is obvious that avoiding iodinated contrast material entirely would completely eliminate any potential contrast-induced AKI risk, the precise threshold at which a dose reduction translates into a clinically significant risk reduction in any patient is unknown. The dose-response curve for iodinated contrast material and contrast-induced AKI is not well understood, may depend on patient baseline risk [45, 46], or may be a spurious phenomenon related to collinearity with procedure duration (i.e., previously described dose-response relationships for coronary angiography and contrast media hypothetically may be due to a correlation with longer procedure times and therefore a greater exposure to atheroembolic showers or an indirect measure of the severity of underlying disease).

Many of the various strategies that have been proposed over the years to reduce the risk of contrast-induced AKI have failed to show consistent benefit. Additionally, because it is unknown how much postcontrast AKI is actually caused by contrast material, it is also unknown how much any given putative prophylactic regimen may be protective against true contrast-induced AKI versus protective against renal damage from other causes. For example, a typical often-cited intraarterial contrast-induced AKI study

[47] included patients who suffered complications such as myocardial infarction, multiple organ failure, pulmonary edema, and hypotension and did not exclude them from contrast-induced AKI analysis even though contrast-induced AKI is classically defined as AKI that develops after the parenteral administration of contrast media “in the absence of other causes” [16, 23, 24, 48]. Although there are now data from large controlled studies that have attempted to separate the incidence of contrast-induced AKI from postcontrast AKI [8–10, 13, 14], those studies were not designed to assess the effect of prophylactic maneuvers on contrast-induced AKI risk reduction.

IV volume expansion is the standard against which other attempts to reduce contrast-induced AKI risk are generally measured. Most studies have compared one volume expansion regimen against another, and few have tried to answer the basic question of whether volume expansion works at all (when compared with a control group of patients who have not received any volume expansion). Trivedi et al. [49] compared IV normal saline against unrestricted oral fluids in cardiac catheterization patients and found that 24 hours of IV normal saline reduced the postcontrast AKI rate compared with unrestricted oral fluids, although the absolute increase in serum creatinine was not significantly different after 48 hours. There was no sham group (i.e., a group not receiving contrast material) in this study to test whether volume expansion simply diluted serum creatinine and depressed the apparent AKI rate without acting to preserve renal function [50, 51].

Regardless of how effective volume expansion may actually be, it is relatively inexpensive and low risk, and it is considered the minimum standard of care for patients at high risk for developing postcontrast AKI [23, 24]. The minimum and the optimum effective regimen are not known and may vary by patient [52, 53]. Normal saline is widely accepted as an appropriate fluid [54]. Studies comparing sodium bicarbonate solution

with saline have shown mixed results, and meta-analyses [55, 56] have given contradictory results. Even positive meta-analyses for the use of sodium bicarbonate [56] have not shown a substantial difference between solution types in long-term clinical results. As a result of this insufficient evidence of efficacy, IV sodium bicarbonate is not recommended for contrast-induced AKI risk reduction [23].

IV volume expansion has been traditionally considered more effective than oral hydration for contrast-induced AKI risk reduction [49, 57], but a 2013 meta-analysis has suggested the equivalence of the two methods [58]. A careful review of this meta-analysis shows that the total patient population was only 513 patients in the six studies investigated, there was substantial study heterogeneity, the 95% CI for the ORs was wide (95% CI for ORs, 0.46–3.10), and the exclusion of two studies individually resulted in significant changes in the results in opposite directions [58]. As a result, there is insufficient evidence to support the use of oral hydration over IV volume expansion. Because of the practical benefits of oral hydration (in lieu of IV volume expansion), clinical trials are needed to determine whether it would be an adequate substitute.

The replacement of HOCM by LOCM for intravascular iodinated contrast material administration was driven by both reduced acute adverse reactions and a lower rate of postcontrast AKI [59]. Given that one possible cause for the lower rate of postcontrast AKI was the lower osmolality of LOCM [60], it was reasonable to explore IOCM as a way to further decrease postcontrast AKI risk. A large number of contradictory individual studies addressing this issue have led to a few meta-analyses, systematic reviews, and a large propensity-matched observational study. These studies have differed in their conclusions [47, 60–66]. Additionally, most studies comparing LOCM and IOCM have been coronary angiography studies that do not directly inform IV use [47, 60–66]. To date, there is insufficient evidence to recommend IV or intraarterial IOCM in place of LOCM for contrast-induced AKI risk reduction.

A wide number of pharmacologic interventions have been proposed as possible ways to reduce contrast-induced AKI risk [50], but few have gained widespread acceptance. Statins have recently had encouraging results, with several trials indicating that statin administration around the time

of coronary angiography is effective in reducing the postcontrast AKI rate [67, 68]. One review [67] of statin trials and meta-analyses concluded that statins may reduce contrast-induced AKI risk in low-risk patients with normal or mildly abnormal renal function, but not in patients with moderate to severe renal dysfunction. If true, this will have little application to IV use because it is very unlikely that contrast-induced AKI occurs in patients with normal or mildly abnormal renal function [8–10, 13, 14]. There are no trials supporting the use of statin therapy for contrast-induced AKI prevention in patients receiving IV LOCM or IV IOCM. It is interesting to consider what type of postcontrast AKI statin therapy is actually preventing (e.g., contrast-induced AKI, sequela of atheroembolic showers, other?) when administered to patients undergoing coronary angiography.

The most widely used prophylactic pharmaceutical agent has been *N*-acetylcysteine (NAC), which has been the subject of numerous contradictory individual trials. The first meta-analyses were published in 2003 [69, 70], and additional meta-analyses continue to be published [71]. These meta-analyses have been split as to whether NAC is effective; there have even been analyses of the meta-analyses [72–75]. Both a large multicenter randomized trial [76] and a large propensity-matched observational study [77] showed no efficacy from oral NAC. Some researchers have now moved on to use IV NAC and have produced multiple small inconclusive studies followed by meta-analyses [71] with the net result of no clear clinical direction. To date, there is insufficient evidence to recommend NAC for contrast-induced AKI risk reduction.

To summarize, for prophylaxis against contrast-enhanced AKI, volume expansion with isotonic IV fluid remains the standard method to reduce postcontrast AKI risk, although no single protocol can claim superiority or uniform acceptance. Use of the lowest effective dose of iodinated contrast material is reasonable, but there is no conclusive evidence supporting a dose-toxicity relationship for contrast-induced AKI within the range of clinically used doses. The use of specific contrast agents or pharmaceuticals to reduce contrast-induced AKI risk for IV studies has little evidence to recommend it, although it is likely that statins provide some protection against postcontrast AKI after coronary angiography (with postcontrast AKI perhaps

resulting from the contrast material or potentially some other patient-specific or procedure-related cause). The list of pharmacologic interventions that have been touted but remain unproven is long [50].

Iodinated Versus Gadolinium-Based Contrast Media in the Renally Impaired: Contrast-Induced Acute Kidney Injury Versus Nephrogenic Systemic Fibrosis

It is controversial whether low-risk iodinated contrast media (LOCM, IOCM) or low-risk gadolinium-based contrast media (macrocytic agents, certain linear ionic agents) [23, 35, 78] are more dangerous in patients with severe renal impairment (i.e., AKI or stage IV or V chronic kidney disease [estimated GFR < 30 mL/min/1.73 m²]). No study has compared these two groups of contrast agents directly (contrast-induced AKI vs NSF); therefore, data must be derived from disparate sources to reach a conclusion. If one assumes that both types of examinations (i.e., contrast-enhanced CT, contrast-enhanced MRI) would provide identical information, one can isolate one's attention to the agents themselves. However, in some cases the information provided by the two tests may not be identical, and this difference may also have to be factored into the decision-making process.

Since the association between NSF and gadolinium administration was identified in 2006, dosing and usage restrictions for gadolinium-based contrast media have been successful at driving the incidence of this disease to near zero [79–81]. Certain agents (e.g., gadobenate dimeglumine [MultiHance, Bracco Imaging], gadoteridol [ProHance, Bracco Imaging], gadobutrol [Gadovist, Bayer HealthCare], gadoterate meglumine [Dotarem, Guerbet]) have been associated with zero or single-digit unconfounded cases of NSF. In some cases, this low incidence is despite millions of doses being administered both before and after NSF-related restrictions were put into place. In the studies in the literature that were performed after 2007 (i.e., after dose and agent restriction), the incidence of NSF in patients at highest risk who received gadolinium-based contrast medium has been reported to be 0% (0/784, gadobenate dimeglumine) [79], 0% (0/36, gadobenate dimeglumine) [80], 0% (0/147, gadobenate dimeglumine) [81], and 0% (0/402, gadobenate dimeglumine) [81].

This incidence compares favorably to the potential relative risk of contrast-induced AKI from LOCM and IOCM, for which the number needed to harm in this highest-risk subgroup (estimated GFR < 30 mL/min/1.73 m²) may be as low as 1 in 6 [13].

We and other investigators [82, 83] believe that a dose-conscious contrast-enhanced MRI examination performed using a low-risk agent [23, 35] has a clearer safety margin than contrast-enhanced CT using LOCM or IOCM when the likelihood of a diagnostic result is the same with both tests. Therefore, in patients with AKI or severe chronic kidney disease who require a contrast-enhanced study and the only options are contrast-enhanced CT or contrast-enhanced MRI and the likelihood of a diagnostic result is identical with both modalities, we suggest a gadolinium-enhanced MRI study be performed using a low-risk gadolinium-based contrast agent first.

Nephrogenic Systemic Fibrosis in 2015

The substantial reduction in NSF incidence since 2006 [79–81] is likely a result of two factors: first, preprocedure screening of patients who may be at risk and avoidance of gadolinium-based contrast medium in patients identified to be at risk; and, second, the use of lower-risk gadolinium-based contrast media (i.e., a gadolinium-based contrast medium associated with zero or single-digit unconfounded cases of NSF) in high-risk patients [84–87]. Preprocedure screening is directed to identify patients with AKI (determination of estimated GFR is unreliable) and those with stage IV or V chronic kidney disease (estimated GFR < 30 mL/min/1.73 m²); these thresholds work well and provide an excellent margin of safety. However, not all patients with poor renal function who receive gadolinium-based contrast medium develop NSF [88, 89], so there are likely other factors that contribute to increased or decreased risk in this setting. Some of these other factors are likely patient-related factors, and various possible factors have been proposed, but definitive associations have proved elusive. Nevertheless, it is clear that avoiding the use of the higher risk gadolinium-based contrast media in patients with severe renal dysfunction has brought the incidence of new cases of NSF to near zero.

Until more data are published confirming the suspected low or negligible risk of NSF for low-risk gadolinium-based contrast media, it is prudent to follow the U.S. Food and Drug Administration guidelines and avoid

administering gadolinium-based contrast media (all types) to patients with AKI and to those with an estimated GFR of less than 30 mL/min/1.73 m² when possible. In patients who require a gadolinium-based contrast medium but have severe renal impairment and no other reasonable options, it may be worthwhile to obtain informed consent and then perform the study using the lowest clinically diagnostic dose of low-risk gadolinium-based contrast medium.

Corticosteroid Prophylaxis

Corticosteroid prophylaxis—defined as the administration of corticosteroids with or without diphenhydramine for the prevention of allergiclike contrast reactions—is the standard of care in the United States for patients identified to be at increased risk of a contrast reaction [23, 90], but this use is more controversial in Europe [91]. The primary reason it is administered is to prevent severe, life-threatening contrast reactions in at-risk patients [23]. “At-risk” is defined as patients at “higher risk for an acute allergiclike reaction” [23], with the relative risk in this population ranging from 2 to 10 times that of the general population [92, 93]. It is worth noting that the allergiclike reaction rate in the general population is only 0.6% (545/84,928) [94]. The primary reason corticosteroid prophylaxis is controversial is twofold. First, there is no level I evidence supporting its use for the prevention of severe reactions to LOCM, IOCM, or gadolinium-based contrast media; level I evidence exists only for higher-risk iodinated high-osmolar contrast media (HOCM) [95, 96]. Second, severe breakthrough reactions occur despite premedication [97, 98].

The best evidence supporting the efficacy and safety of corticosteroid prophylaxis comes from two randomized controlled trials by Lasser et al. [95, 96]. In a randomized controlled trial of average-risk patients ($n = 6763$) receiving HOCM, Lasser et al. [95] reported in 1987 that two doses of 32-mg oral methylprednisolone (12 and 2 hours before contrast material administration) significantly reduced the occurrence of severe, mild, and aggregate contrast reactions compared with placebo. The number of patients needed to treat to prevent one so-called grade III (i.e., serious) reaction in an average-risk patient receiving HOCM was 205 (0.2% [5/2513] vs 0.7% [11/1603]). This study design was repeated in 1994 for LOCM [96], but the study was underpowered ($n = 1155$)

because of a lack of funding. Significant reductions were seen in grade I (i.e., mild) and in aggregate reactions but not in more severe grade II or grade III reactions. The number of patients needed to treat to prevent one reaction of any severity in an average-risk patient receiving LOCM was 32 (1.7% [10/580] vs 4.9% [28/575]). The number of patients needed to treat to prevent one severe reaction was unclear. Both of these studies [95, 96] combined allergiclike and physiologic reactions into the same groups, and both studied average-risk patients from the general population. Therefore, their relevance for predicting the effect of prophylaxis in preventing an allergiclike reaction in a patient at increased risk of having an allergiclike reaction to LOCM, IOCM, or gadolinium-based contrast media is limited.

Because of these limitations, recent work has attempted to quantify the number needed to treat to prevent one severe reaction to LOCM in high-risk patients [93]. This information can be used to estimate the benefit of giving steroids to a single patient. In a retrospective cohort study of 1051 patients receiving a 13-hour oral prophylaxis regimen (50 mg of prednisone 13 hours, 7 hours, and 1 hour before contrast administration and 50 mg of diphenhydramine 1 hour before contrast administration), Mervak et al. [93] found that prophylaxis reduced the aggregate reaction rate from a historical control rate of 3.5% (2998/84,928 [estimated]) to 2.1% (13/626) for patients with a prior contrast reaction; these results support the notion that corticosteroid prophylaxis likely has an incomplete mitigating effect on allergiclike reactions to LOCM in high-risk patients. Based on the data from Mervak et al., the number needed to treat to prevent one allergiclike reaction of any severity in high-risk patients receiving LOCM is 69 (95% CI, 39–304), and the number needed to treat to prevent one severe allergiclike reaction is 569 (95% CI, 389–1083).

Interestingly, breakthrough reaction severity is usually (80% [103/128]) the same as the index reaction [97]. Davenport et al. [97] found in a retrospective cohort study of high-risk patients premedicated before LOCM-enhanced examinations that the repeat breakthrough reaction rate in patients with a prior breakthrough reaction was only 12% (23/197), indicating that only approximately 1 in 10 premedicated patients with a prior breakthrough reaction will react again if given the opportunity.

The fundamental problem with using corticosteroids to prevent severe contrast reactions is that severe contrast reactions—even in “at-risk” patients—are rare. Therefore, a very large number of patients must be premedicated to achieve any effect (approximate number needed to treat before LOCM or IOCM administration = 569 [93]). This result means that, for many patients, premedication is not beneficial and merely contributes inconvenience and cost to the system. The evidence supporting corticosteroid prophylaxis for the prevention of severe contrast reactions to LOCM, IOCM, and gadolinium-based contrast medium is weak, and for the evidence that does exist, the magnitude of effect is small. This is balanced against the prevailing standard of care in the United States regarding contrast reaction prevention and the knowledge that severe reactions will occur regardless of whether corticosteroids are administered [97, 98].

With these issues in mind and until further study can clarify the cost-effectiveness of premedication, premedication is indicated in the United States for patients who have had a prior allergiclike reaction to the same class of contrast material [23]. For patients who cannot wait for premedication to be administered (minimum duration of oral premedication shown to be efficacious is 12 hours [95, 96]), some have suggested administering corticosteroids that can be given IV over a 5-hour period [99] and then performing the study as ordered. This accelerated protocol is unproven and supported by only a single small case series [99]. There are two categories of patients for whom the risk of a severe contrast reaction is high regardless of premedication: patients who have had a prior severe allergiclike reaction to the same class of contrast material and those who have had a prior moderate or severe allergiclike breakthrough reaction to the same class of contrast material [97].

Conclusion

The real and apparent safety margin of modern contrast agents continues to widen. Contrast-induced AKI is rarer than previously thought, but there remains controversy about its incidence for patients with an estimated GFR of less than 45 mL/min/1.73 m². If contrast-induced AKI exists after IV contrast administration, patients with an estimated GFR of less than 30 mL/min/1.73 m² are at highest risk. Until more definitive data are available, iodinated contrast material should be defined in the same manner as oth-

er potential nephrotoxins using standardized criteria. IV volume expansion remains the standard prophylactic measure for reducing the risk of contrast-induced AKI and post-contrast AKI, although many questions of timing and dose persist. In patients with severe renal dysfunction, a contrast-enhanced MRI examination with a low-risk gadolinium-based contrast medium may have a more favorable risk profile than a contrast-enhanced CT examination given the exceptionally low rate of NSF after low-risk gadolinium-based contrast medium administration. Premedication with corticosteroids to reduce the risk of acute allergiclike reaction to modern contrast agents is incompletely effective, and the number needed to treat to prevent a severe reaction is large.

Future research may be best directed at determining the following: first, the incidence and significance of contrast-induced AKI (abstracted from the incidence of post-contrast AKI) in patients undergoing coronary angiography and IV contrast-enhanced studies; second, the incidence of NSF in patients with severe renal impairment receiving a low-risk gadolinium-based contrast medium; and, third, the cost-effectiveness of corticosteroid prophylaxis stratified by allergiclike risk factors.

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