Radiographic Contrast Media and the Kidney

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Abstract
AKI is a potential complication of intravascular iodinated contrast exposure. Contrast-associated AKI, which typically manifests as small and transient decrements in kidney function that develop within several days of contrast administration, is associated with serious adverse outcomes, including progressive kidney dysfunction and death. However, a causal link between the small increases in serum creatinine that characteristically occur with contrast-associated AKI and serious adverse outcomes remains unproved. This is important given mounting evidence that clinically indicated, potentially lifesaving radiographic procedures are underutilized in patients with CKD. This has been hypothesized to be related to provider concern about precipitating contrast-associated AKI. Intravascular gadolinium-based contrast, an alternative to iodinated contrast that is administered with magnetic resonance imaging, has also been linked with potential serious adverse events, notably the development of nephrogenic systemic fibrosis in patients with severe impairment in kidney function. Patients hospitalized in the intensive care unit frequently have clinical indications for diagnostic and therapeutic procedures that involve the intravascular administration of contrast media. Accordingly, critical care providers and others treating critically ill patients should possess a sound understanding of the risk factors for and incidence of such outcomes, the ability to perform evidence-based risk-benefit assessments regarding intravascular contrast administration, and knowledge of empirical data on the prevention of these iatrogenic complications.

Introduction
The nephrotoxic effects of intravascular iodinated contrast implicated in the pathophysiology of contrast-associated AKI (CA-AKI) include oxygen supply/demand mismatch from hemodynamic perturbations in the medulla of the kidney, a vascular territory particularly prone to hypoxia; direct toxicity to tubular epithelial cells (hypothesized to be related to DNA damage, mitochondrial dysfunction, and apoptosis); altered endothelial cell function; and generation of reactive oxygen species that contribute to oxidative stress and enhance tubular damage (1,2) (Figure 1). Postcontrast AKI has been referred to as contrast-induced AKI, although this term has fallen out of favor with the recognition that factors other than contrast likely contribute to postprocedure kidney injury. The incidence of CA-AKI varies on the basis of the burden of comorbid illness, type of procedure performed, and the threshold increase in serum creatinine used to define AKI. In patients with stage 3 or 4 CKD, Weisbord et al. (3) documented that the incident rates of CA-AKI, defined by increases in serum creatinine of ≥25%, were 13%, 9%, and 7% following nonemergent noncoronary angiography, coronary angiography, and contrast-enhanced computed tomography (CT), respectively. Among patients in the surgical intensive care unit (ICU), Valette et al. (4) reported that up to 19% of patients developed CA-AKI, with 10% of patients requiring kidney replacement therapy (KRT). In a review of various studies of patients in the ICU by Case et al. (5), the incidence of CA-AKI ranged from 12% to 19%.

Pathophysiology and Incidence of AKI Associated with Iodinated Contrast
Notwithstanding these seemingly alarming rates of CA-AKI, interpreting the true incidence of kidney injury attributable to iodinated contrast requires recognition that elevations in serum creatinine may occur coincidentally and independently of contrast exposure. In a cohort of 11,588 patients, many of whom had intact to near-intact kidney function and therefore low a priori risk for kidney injury from contrast, Bruce et al. (6) reported that the frequency of AKI following noncontrast CT (9%) was similar to that following CT enhanced with iso-osmolar ioxaglate (10%) or low-osmolar iohexol (10%). However, because many patients were at low risk for AKI, comparisons of CA-AKI rates across groups are less informative. Multiple additional observational studies compared the incidence of AKI following CT imaging with and without intravascular contrast using propensity score analyses (7–12). A meta-analysis by McDonald et al. (8) of more than a dozen such studies found a similar risk of AKI with contrast-enhanced compared with noncontrast procedures (relative risk, 0.79; 95% confidence interval [95% CI], 0.62 to 1.02). Several studies of patients in the ICU have observed similar findings (10,13–15). In a cohort of patients with sepsis and AKI, Goto et al. (14) compared rates of kidney injury and mortality between those who did and did not receive intravascular contrast in a propensity score-matched analysis. The rates of kidney injury and death were comparable between the groups, leading the authors to conclude that one-time contrast exposures were not
associated with worsening kidney function or mortality in this critically ill patient population.

Careful inspection of these studies reveals key methodologic limitations, most importantly the fact that many patients were not at higher risk for AKI. Moreover, those who did not receive intravascular contrast consistently demonstrated a higher level of comorbidity and greater baseline level of risk for AKI. Despite efforts to adjust for differences in baseline risk factors, including with the use of propensity score matching for known confounders, the relative risks/odds ratios (ORs) for several studies revealed strong trends toward lower rates of AKI among patients who did not receive contrast consistently. As iodinated contrast media are not nephroprotective, this observation likely reflects residual confounding and almost certainly underscores the higher baseline risk for kidney injury among those who did not receive contrast. These studies emphasize that baseline serum creatinine fluctuations and causal factors distinct from iodinated contrast administration must be considered when assessing the risk for and incidence of CA-AKI, particularly when this condition is defined by nominal changes in serum creatinine.

**Figure 1. Proposed pathophysiologic mechanisms of kidney injury with iodinated contrast.** Pathophysiology of contrast-induced AKI involves medullary hypoxia, direct tubular toxicity, and generation of reactive oxygen species.

**Risk Factors for Contrast-Associated AKI**

Risk factors for CA-AKI can be categorized as patient related or procedure related (Table 1). Preexisting CKD is the chief patient-specific risk factor with a graded and direct relationship between CKD severity and AKI risk (17). Diabetes enhances the risk in those with CKD but does not appear to increase risk in the absence of underlying impairment in kidney function (18). Absolute or effective depletion in intravascular volume may amplify the effects of contrast-induced renal vasoconstriction and increase CA-AKI risk (19,20). Similarly, nonsteroidal anti-inflammatory drugs, which inhibit vasodilatory prostaglandin synthesis, may elevate risk (21). Use of large volumes of contrast augments risk, although the precise amount of contrast above which risk rises significantly has not been definitively determined (22–25). Repeated administrations of intravascular contrast within short time frames also elevate risk. Low-osmolal contrast is less nephrotoxic than high-osmolal contrast, although there do not appear to be meaningful differences in risk between iso- and low-osmolal contrast (26). Finally, risk appears greater following intra-arterial compared with intravenous (IV) contrast exposure; however, this may reflect differences between patient populations undergoing different procedures. Additionally, cholesterol emboli are a risk factor for AKI that is unique to angiographic procedures.

**Association of Contrast-Associated AKI with Adverse Outcomes and Implications for Clinical Care**

Multiple studies have documented the association of CA-AKI with heightened short- and long-term mortality (Table 2) (23,27–29). McCullough et al. (23) reported that, among patients undergoing percutaneous coronary intervention, those with CA-AKI were more likely to experience nosocomial death than those without CA-AKI (7% versus 1%, P<0.001) (23). Solomon et al. (30) demonstrated an approximately three-fold greater risk of death, stroke, myocardial infarction, and/or kidney failure at 1 year among patients with postangiography CA-AKI compared with those without CA-AKI. CA-AKI also associates with greater health care utilization as evidenced by a study by Adolph et al. (31), which found that patients with CA-AKI were hospitalized an average of 2 days longer than those without CA-AKI. Additionally, a decision analysis by Subramanian et al. (32) documented that CA-AKI was associated with higher hospital expenses of approximately $10,000. CA-AKI is also linked with more rapid progression of underlying CKD (33–36). Goldenberg et al. (33) demonstrated that patients with transient CA-AKI experienced greater eGFR loss 2 years following angiography than patients without postangiography CA-AKI (ΔeGFR of −20±11 versus −6±16 ml/min per 1.73 m², P=0.02).

Importantly, the causal nature of the associations of CA-AKI, defined by small upticks in serum creatinine, with such serious adverse outcomes remains unproven. It is plausible that transient CA-AKI represents a marker of patients more vulnerable to adverse events because of greater underlying comorbidity, more severe acute illness, and/or less kidney reserve rather than a mediator of such outcomes (37). Recognition of this is critical as past research strongly suggests that providers may overestimate the risk for CA-AKI and associated adverse outcomes, leading to an underutilization of clinically indicated and potentially lifesaving contrast-enhanced procedures in those with kidney disease. Nearly two decades ago, Chertow et al. (38) compared the use of invasive coronary care, including coronary angiography with percutaneous intervention, for the treatment of acute myocardial infarction in 15,093 patients with CKD and 42,191 without CKD. Patients with CKD were >50% less likely to undergo coronary angiography than those without CKD after adjusting for the appropriateness of such care (OR, 0.47; 95% CI, 0.40 to 0.52). Among those who underwent angiography, revascularization was
performed less frequently in patients with CKD than those without CKD (55% versus 62%, P<0.001). Numerous other studies have documented that patients with CKD who are hospitalized with acute coronary syndrome, including ST segment elevation myocardial infarction, are considerably less likely to undergo invasive coronary care than those without CKD (Table 3) (38–54). Although less well studied than in the setting of atherosclerotic cardiac disease, utilization of contrast-enhanced procedures has also been studied in patients with peripheral vascular disease and CKD. In a cohort of 6227 patients with advanced lower limb ischemia, O’Hare et al. (55) found that those with eGFR values of 30–59 ml/min per 1.73 m² were significantly less likely to undergo revascularization than patients with eGFR values >60 ml/min per 1.73 m² (adjusted OR, 0.84; 95% CI, 0.72 to 0.96). More severe reductions in eGFR were associated with even less frequent revascularization.

This practice, which has been termed “renalism,” is of significant clinical relevance given evidence demonstrating reductions in short- and long-term mortality with the use of invasive coronary care compared with conservative treatment among patients with CKD (33,42,46,56). This finding was highlighted in a meta-analysis by Shaw et al. (57) that included ten clinical trials and observational studies comprising 147,908 patients with non-ST elevation acute coronary syndrome and CKD. Compared with conservative treatment, early invasive care was associated with a nearly 50% lower mortality (relative risk, 0.53; 95% CI, 0.45 to 0.62).

Data demonstrating reduced mortality following contrast-enhanced cardiac procedures in patients with CKD must be interpreted in the context of our current understanding of the relationship between CA-AKI and serious adverse outcomes, specifically that the small elevations in serum creatinine that define CA-AKI have not been confirmed to be causally linked with mortality. Accordingly, clinically indicated contrast-enhanced procedures should typically be performed in patients at heightened risk of kidney injury with the implementation of evidence-based prevention if there are no equally diagnostic/therapeutic imaging options that do not require contrast.

### Prevention of Contrast-Associated AKI

Once determined that a procedure with intravascular iodinated contrast is indicated, implementing evidence-based preventive care is important. A multitude of past clinical trials provide evidence on the efficacy of various interventions, although many were limited by small sample sizes and inadequate power to detect differences in less common but more serious patient-centered outcomes. Nonetheless, prior research has focused on four principal strategies to mitigate risk: (1) KRT to remove contrast from the circulation, (2) use of less nephrotoxic contrast media formulations, (3) prescribing medications that mechanistically counteract the nephrotoxic effects of contrast, and (4) administering IV crystalloid to mitigate the adverse hemodynamic effects and direct tubular toxicity of contrast. Prophylactic pericontrast hemodialysis has been shown to be potentially harmful and is not recommended (58). Data regarding continuous KRT are conflicting, with insufficient evidence to support this prophylactic strategy (59,60). Over several decades, the chemical formulation of iodinated contrast has evolved. Previous generation “high-osmolal” agents were associated with significantly elevated rates of CA-AKI compared with “low-osmolal” contrast (18).

### Table 1. Contrast-associated AKI risk factors

<table>
<thead>
<tr>
<th>Patient Associated</th>
<th>Procedure Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced GFR, acute or chronic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High-osmolal contrast</td>
</tr>
<tr>
<td>Diabetes mellitus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Large volume of contrast</td>
</tr>
<tr>
<td>Reduced intravascular volume</td>
<td>Serial contrast procedures</td>
</tr>
<tr>
<td>Concomitant nephrotoxic medications</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Defined as eGFR <45 ml/min per 1.73 m² with other risk factors or <30 ml/min per 1.73 m².
<sup>b</sup>Augments risk in patients with underlying kidney function impairment.

### Table 2. Contrast-associated AKI and mortality risk

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>No. of Patients</th>
<th>Contrast-Associated AKI Definition</th>
<th>Adjusted Odds Ratio/ Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy et al. (92)</td>
<td>357</td>
<td>↑ Cr≥25% to ≥2.0 mg/dl</td>
<td>5.5</td>
<td>2.9 to 13.2</td>
</tr>
<tr>
<td>Gruberg et al. (93)</td>
<td>439</td>
<td>↑ SCR&gt;25%</td>
<td>3.9</td>
<td>2.0 to 7.6</td>
</tr>
<tr>
<td>Shema et al. (94)</td>
<td>1111</td>
<td>↑ Cr≥50% or ↑ eGFR≥25%</td>
<td>3.9</td>
<td>1.2 to 12.0</td>
</tr>
<tr>
<td>McCullough et al. (23)</td>
<td>1826</td>
<td>↑ Cr&gt;25%</td>
<td>6.6</td>
<td>3.3 to 12.9</td>
</tr>
<tr>
<td>From et al. (28)</td>
<td>3236</td>
<td>↑ Cr&gt;25% or ≥0.5 mg/dl</td>
<td>3.4</td>
<td>2.6 to 4.4</td>
</tr>
<tr>
<td>Rihal et al. (95)</td>
<td>7586</td>
<td>↑ Cr&gt;0.5 mg/dl</td>
<td>10.8</td>
<td>6.9 to 17.0</td>
</tr>
<tr>
<td>Bartholomew et al. (27)</td>
<td>20,479</td>
<td>↑ Cr≥1.0 mg/dl</td>
<td>22</td>
<td>16 to 31</td>
</tr>
<tr>
<td>Weisbord et al. (3,29,67)</td>
<td>27,608</td>
<td>↑ Cr=0.25–0.5 mg/dl</td>
<td>1.8</td>
<td>1.4 to 2.5</td>
</tr>
<tr>
<td><strong>Longer-term mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldenberg et al. (33)</td>
<td>78</td>
<td>↑ Cr≥0.5 mg/dl or ≥25%</td>
<td>2.7</td>
<td>1.7 to 4.5</td>
</tr>
<tr>
<td>Solomon et al. (30)</td>
<td>294</td>
<td>↑ Cr≥0.3 mg/dl</td>
<td>3.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1 to 8.7</td>
</tr>
<tr>
<td>Harjai et al. (96)</td>
<td>985</td>
<td>↑ Cr≥0.5 mg/dl</td>
<td>2.6</td>
<td>1.5 to 4.4</td>
</tr>
<tr>
<td>Roghi et al. (97)</td>
<td>2860</td>
<td>↑ Cr≥0.5 mg/dl</td>
<td>1.8</td>
<td>1.0 to 3.4</td>
</tr>
<tr>
<td>Brown et al. (98)</td>
<td>7856</td>
<td>↑ Cr≥0.5 mg/dl</td>
<td>3.1</td>
<td>2.4 to 4.0</td>
</tr>
</tbody>
</table>

Cr, creatinine; SCR, serum creatinine.
<sup>a</sup>Denotes the incident rate ratio of the composite outcome of death, cerebrovascular accident, myocardial infarction, or kidney failure.
However, trials and meta-analyses comparing low- or iso-osmolal formulations have been conflicting (61). The American College of Cardiology/American Heart Association and the European Society of Urogenital Radiology clinical practice guidelines recommend using either low- or iso-osmolal contrast in at-risk patients (62,63).

Multiple pharmacologic agents have been evaluated for CA-AKI prevention. Some were found to be ineffective and even potentially deleterious (64) (Table 4). Discordant findings of trials and meta-analyses that investigated N-acetylcysteine (NAC) resulted in lingering uncertainty on its potential benefits (65,66). The Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, which enrolled 4993 patients undergoing nonemergent angiography, demonstrated that compared with placebo, oral NAC was not associated with a reduction in 90-day death, need for dialysis, persistent impairment in kidney function (OR, 1.02; 95% CI, 0.78 to 1.33), or CA-AKI (9% in NAC and 9% for placebo; OR, 1.06; 95% CI, 0.87 to 1.28) (67). Hence, there is currently no role for NAC or other oral agents in CA-AKI prevention.

The cornerstone of prevention of CA-AKI is the provision of isotonic IV crystalloid. Several past studies support the use of IV volume expansion (68,69). Recent research has focused on IV fluid composition, specifically the comparison of isotonic sodium bicarbonate with isotonic sodium chloride. An initial trial by Merten et al. (70) that enrolled 119 patients found a lower incidence of CA-AKI with IV isotonic bicarbonate than IV isotonic saline (2% versus 14%, P=0.02). This striking effect of bicarbonate spawned a proliferation of clinical trials and meta-analyses that reported conflicting results (36,71–77). To resolve the persistent clinical uncertainty, the aforementioned PRESERVE trial also randomized high-risk patients to receive IV isotonic sodium bicarbonate (n=2511) or IV isotonic sodium chloride (n=2482) prior to, during, and following angiography (67). Compared with IV sodium chloride, sodium bicarbonate was not associated with lower rates of 90-day death, need for dialysis, persistent decrement in kidney function (OR, 0.93; 95% CI, 0.72 to 1.22), or incident CA-AKI (10% for sodium bicarbonate and 8% for sodium chloride; OR, 1.16; 95% CI, 0.96 to 1.41) (64). Thus, on the basis of current evidence, IV sodium-based isotonic crystalloid with either bicarbonate or chloride as the component anion should be considered the standard of care to mitigate CA-AKI risk. However, sodium chloride is generally preferred given its lower cost, availability, and avoidance of the risk for errors in administration. A series of trials of patients undergoing angiography has investigated the RenalGuard device, which matches IV fluid with furosemide-induced urinary flow, for the

### Table 3. Studies documenting the differential use of invasive treatment for acute coronary syndrome in patients with and without CKD

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>CKD, N</th>
<th>Clinical Presentation</th>
<th>Invasive Treatment, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keeley et al.</td>
<td>1654</td>
<td>ACS</td>
<td>CKD 16*; No CKD 22*</td>
</tr>
<tr>
<td>Freeman et al.</td>
<td>889</td>
<td>ACS</td>
<td>CKD 27*; No CKD 43*</td>
</tr>
<tr>
<td>Keough-Ryan et al.</td>
<td>5549</td>
<td>ACS</td>
<td>CKD 24*; No CKD 31*</td>
</tr>
<tr>
<td>Medei et al.</td>
<td>778</td>
<td>ACS</td>
<td>CKD 37*; No CKD 46*</td>
</tr>
<tr>
<td>Lau et al.</td>
<td>1227</td>
<td>ACS</td>
<td>CKD 33*; No CKD 57*</td>
</tr>
<tr>
<td>Han et al.</td>
<td>6560</td>
<td>NSTE-ACS</td>
<td>CKD 30*; No CKD 54*</td>
</tr>
<tr>
<td>Rhe et al.</td>
<td>1540</td>
<td>NSTE-ACS</td>
<td>CKD 32*; No CKD 42*</td>
</tr>
<tr>
<td>Goldenberg et al.</td>
<td>13,141</td>
<td>NSTE-ACS</td>
<td>CKD 50; No CKD 68</td>
</tr>
<tr>
<td>Chertow et al.</td>
<td>15,093</td>
<td>NSTE-MSTEMI</td>
<td>CKD 55; No CKD 62</td>
</tr>
<tr>
<td>Charytan et al.</td>
<td>1210</td>
<td>NSTE-MSTEMI</td>
<td>CKD 9*; No CKD 54*</td>
</tr>
<tr>
<td>Shlipak et al.</td>
<td>47,644</td>
<td>NSTE-MSTEMI</td>
<td>CKD 16*; No CKD 24*</td>
</tr>
<tr>
<td>Saad et al.</td>
<td>199</td>
<td>NSTE-MSTEMI</td>
<td>CKD 76; No CKD 94</td>
</tr>
<tr>
<td>Fox et al.</td>
<td>13,069</td>
<td>NSTEMI</td>
<td>CKD 45*; No CKD 72*</td>
</tr>
<tr>
<td>Fox et al.</td>
<td>5808</td>
<td>STEmi</td>
<td>CKD 66*; No CKD 73*</td>
</tr>
<tr>
<td>Szummer et al.</td>
<td>4839</td>
<td>NSTEMI</td>
<td>CKD 34*; No CKD 58*</td>
</tr>
<tr>
<td>Szummer et al.</td>
<td>2569</td>
<td>STEmi</td>
<td>CKD 70*; No CKD 77*</td>
</tr>
<tr>
<td>Szummer et al.</td>
<td>5689</td>
<td>NSTEMI</td>
<td>CKD 34*; No CKD 57*</td>
</tr>
<tr>
<td>Medi et al.</td>
<td>3450</td>
<td>STEmi</td>
<td>CKD 46*; No CKD 62*</td>
</tr>
<tr>
<td>Bhatt et al.</td>
<td>2475</td>
<td>NSTE-ACS</td>
<td>OR, 0.51; 95% CI, 0.46 to 0.58</td>
</tr>
<tr>
<td>Chew et al.</td>
<td>923</td>
<td>ACS</td>
<td>OR, 0.35; 95% CI, 0.21 to 0.60</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; NSTE-ACS, non-ST elevation acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; STEmi, ST elevation myocardial infarction; OR, odds ratio; 95% CI, 95% confidence interval.

*Calculated on the basis of raw data from the original manuscript.

**The same study from Fox et al. (42) with two separate analyses.

*The same study from Szummer et al. (53) with two separate analyses.

### Table 4. Pharmacologic agents evaluated for the prevention of contrast-associated AKI

<table>
<thead>
<tr>
<th>Ineffective</th>
<th>Indeterminate Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Theophylline/aminophylline</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Atorvastatin/rosuvastatin</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Prostaglandin analogs</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Alilopurinol</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td></td>
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</table>

*Potentially deleterious.
prevention of CA-AKI (78,79). Although these studies demonstrated lower risk for CA-AKI and associated adverse outcomes with this treatment system, they were limited by small sample sizes and/or the use of surrogate primary outcomes. Larger trials powered to definitively determine the effect of this intervention on serious, adverse, patient-centered outcomes are needed before recommendations can be made for its use.

A Practical Evidence-Based Approach to Risk Mitigation of Contrast-Associated AKI in the Intensive Care Unit Setting

Patients in the ICU in need of iodinated contrast imaging procedures who are at heightened risk for CA-AKI should undergo such procedures if there are no comparably accurate imaging options that do not use iodinated contrast, albeit with the implementation of preventive therapy when clinically feasible. Enhanced risk is typically defined on the basis of the level of kidney function. An eGFR of <60 ml/min per 1.73 m² is an appropriate threshold below which preventive care should be implemented, if feasible, in those in need of intra-arterial procedures. As patients undergoing contrasted CT are generally believed to be at lower risk for CA-AKI, a lower eGFR threshold is reasonable for the implementation of preventive care, although equipoise exists on whether an eGFR of <30 or <45 ml/min per 1.73 m² is most appropriate (80). In patients with underlying diabetes or other risk factors, an eGFR<45 ml/min per 1.73 m² is an appropriate threshold to define risk in those receiving IV contrast. A important caveat is that these recommendations assume a steady-state serum creatinine, which is necessary for the accurate calculation of eGFR (81). Clearly, a disproportionate number of patients in the ICU have fluctuating serum creatinine and/or frank AKI. Such patients should be considered at heightened risk and receive appropriate preventive care when feasible.

The following are evidence-based steps that are appropriate in high-risk patients undergoing contrast-enhanced procedures (Figure 2). Nonsteroidal anti-inflammatories should be discontinued prior to contrast exposure. The minimum required volume of low- or iso-osmolar contrast should be administered. If feasible, isotonic IV crystalloid should be administered prior to and following nonemergent contrast-enhanced procedures, whereas postprocedure IV isotonic crystalloid should be administered following emergent procedures even if proprocedure administration is not feasible. Short durations of IV fluid (e.g., 3 ml/kg per hour for 1 hour prior to contrast and 1.5 ml/kg per hour for 4–6 hours postcontrast) have not been shown to be inferior to more sustained volume expansion and may be more practical in the ICU setting. The Prevention of Contrast Renal Injury with Different Hydration Strategies trial showed that providing targeted IV fluid volumes to patients with elevated left ventricular end diastolic pressure undergoing coronary angiography is both safe and effective (82). Accordingly, cautious IV fluid administration should be implemented, when feasible, in patients with nondecompensated heart failure. Kidney function should be followed in the days after contrast administration to identify evidence of early kidney injury.

Gadolinium-Based Contrast and Nephrogenic Systemic Fibrosis

Until the mid-2000s, gadolinium-enhanced magnetic resonance imaging (MRI) was a preferred imaging modality in patients with advanced kidney disease. Although there is some evidence for direct gadolinium nephrotoxicity, current evidence suggests that gadolinium, when used at typical clinical doses, imparts minimal risk for significant AKI (83). However, studies have linked gadolinium-based contrast agents (GBCAs) with the development of nephrogenic systemic fibrosis (NSF), an often debilitating fibrosing disorder of skin, connective tissue, and, in certain cases, internal organs in patients with significantly impaired kidney function (84–86). Skin is the primary site of fibrosis, can result in organ dysfunction.

The initial clinical manifestations of NSF typically present within weeks to several months following GBCA exposure, and definitive diagnosis requires skin/soft tissue biopsy and clinical/histologic correlation (87). Although improvement in symptoms may accompany AKI recovery or transplantation, there is currently no well-established effective therapeutic intervention, and the development of this condition commonly leads to significant morbidity and mortality.
Because of its toxicity in vivo, free gadolinium is complexed to a chelate/ligand (86). GBCAs are classified on the basis of the strength of their association with NSF (88). Group 1 agents are complexed to a linear ligand and have been associated with nearly all cases of NSF reported in the literature. Conversely, group 2 GBCAs, all but one of which are complexed to a macrocyclic ligand, have been independently associated with few to no cases of NSF. The group 3 agent gadoxetate disodium has not been associated with cases of NSF, although it is characterized by less frequent use than group 1 and 2 agents. Understanding the molecular differences and epidemiologic evidence regarding the differential incidence of NSF among these three chemical groups is essential for NSF prevention.

Upon recognition of the association of gadolinium-based contrast with NSF, providers became wary of performing MRIs with IV GBCAs, particularly those agents most commonly associated with NSF, in patients with severely impaired kidney function. However, available evidence demonstrates that the risk for NSF with group 2 GBCAs is exceedingly low (although not zero, particularly for repeated episodes of contrast exposure or a single high-dose exposure). Such agents have become the standard in patients with impairment in kidney function who require MRI with contrast (89). This practice is supported by a recent meta-analysis by Woolen et al. (89) that included 16 studies comprising 4931 patients with stage 4 or 5 CKD, including those dependent on dialysis, who received a group 2 GBCA. None of the patients developed NSF, with an upper bound of the two-sided 95% CI of 0.07% (89).

Prevention of Nephrogenic Systemic Fibrosis

Among high-risk patients being considered for GBCA-enhanced imaging, evaluation of alternative radiographic modalities that do not utilize GBCA but provide comparable diagnostic information is important. However, much like the recommended approach with intravascular iodinated contrast, clinically indicated GBCA-enhanced MRIs should typically be performed in at-risk patients if comparably accurate noncontrasted imaging is not an option, albeit with evidence-based preventive care. Patients at risk for NSF in whom preventive care is critical include those with kidney failure on dialysis (hemodialysis or peritoneal dialysis), CKD with an eGFR <30 ml/min per 1.73 m², or AKI (90). The crux of preventive care in such patients involves the use of group 2 GBCAs in the lowest necessary dose. Group 1 and 3 GBCAs should not be administered to these individuals. There is no direct evidence that postexposure dialysis mitigates NSF risk. However, hemodialysis does efficiently remove gadolinium, which may attenuate NSF risk if the pathogenesis is not immediate following GBCA exposure (91). If feasible, patients with kidney failure or AKI who are already on hemodialysis should undergo the GBCA-enhanced procedure prior to a hemodialysis treatment. Data on the risk-benefit ratio of performing hemodialysis following GBCA exposure in patients on long-term peritoneal dialysis, with advanced nondialysis-dependent CKD, or with severe nondialysis-dependent AKI are lacking.

Considering the risks associated with dialysis catheter placement, dialyzing these patients is generally not recommended if a group 2 GBCA is administered.

Conclusions

Imaging or procedures that utilize intravascular contrast media, iodinated or gadolinium based, are commonly indicated for diagnostic and/or therapeutic purposes in patients in the ICU with acute kidney disease and/or CKD. Although these contrast agents are associated with certain adverse outcomes that should be considered prior to proceeding with their use, the risks for these outcomes, particularly when appropriate preventive interventions are implemented, should not be overestimated. Among at-risk patients with a clinical indication for a procedure that requires intravascular iodinated contrast in whom there are no equally diagnostic/therapeutic noncontrasted imaging options, the procedure should be performed, albeit after discussing the potential risks and benefits with the patient/surrogate and with the implementation of evidence-based prevention. Such prevention comprises the use of the lowest necessary volume of iso- or low-osmolar iodinated contrast, withdrawal of concomitant nephrotoxic agents when appropriate, and intravascular volume expansion with periprocedural IV crystalloid if feasible. Among those requiring an MRI with GBCA enhancement in whom alternative imaging options with equal accuracy are not available, the lowest necessary dose of a group 2 agent should be used. Adopting a practical and evidence-based approach to the use of contrast-enhanced imaging in patients in the ICU will help ensure that such procedures provide the critical information that commonly informs therapeutic interventions and optimizes patient outcomes.

Disclosures

W. Cashion reports many individual stocks but nothing in the health care or biotechnology sectors. S.D. Weisbord reports consultancy agreements with Takeda.

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Author Contributions

W. Cashion and S.D. Weisbord were responsible for data curation, wrote the original draft, and reviewed and edited the manuscript.

References


segment elevation acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. JAMA 292: 2096–2104, 2004


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