Acute kidney injury with iodinated contrast

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Diagnostic and interventional radiographic procedures in critically ill patients commonly depend on iodinated contrast media and consequently pose the risk of contrast-induced acute kidney injury. This is an important complication that accounts for a significant number of cases of hospital-acquired renal failure, with adverse effects on prognosis and healthcare costs. The epidemiology and pathogenesis of contrast-induced acute kidney injury, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies will be discussed in this article. An algorithm is suggested for the risk stratification and management of contrast-induced acute kidney injury as it relates to patients undergoing iodinated contrast exposure during critical illness. Contrast-induced acute kidney injury is likely to remain a significant challenge for intensivists in the future because the patient population is aging and chronic kidney disease and diabetes are becoming more common. (Crit Care Med 2008; 36[Suppl.]:S204–S211)

KEY WORDS: acute kidney injury; iodinated contrast media; prognosis; healthcare costs

Contrast-induced nephropathy acute kidney injury (AKI) is an important complication in the use of iodinated contrast media that accounts for a significant number of cases of hospital-acquired AKI (1–3). This iatrogenic complication has been a subject of concern to intensivists, radiologists, and cardiologists in recent years because of its adverse effect on prognosis and addition to healthcare costs. Several factors contribute to the increasing importance of this condition to intensivists (Fig. 1). There is growing use of imaging and interventional procedures in intensive care patients, specifically the increasing use of multidetector computed tomographic (CT) scanning in trauma patients, which inevitably means more patients will be exposed to intravascular iodinated contrast media. At the same time, many patients in intensive and critical care units have compromised renal function (4, 5), which is the most important risk factor for contrast-induced AKI. The aging of the population has resulted in more elderly patients being admitted to intensive care units (ICUs), and these patients are likely to have a high prevalence of chronic kidney disease (CKD).

Very few studies of contrast-induced AKI have been undertaken in the ICU setting, but in the absence of specific data, it seems reasonable to extrapolate from experience in the general hospital population. One of the aims of this review is to draw the attention of intensivists to the work of the Contrast-Induced Nephropathy (CIN) Consensus Working Panel, an international multidisciplinary group convened to address the challenges of contrast-induced AKI. The group systematically reviewed the published evidence and, together with expert opinion drawn from clinical practice, compiled a series of consensus statements and a management algorithm.

Evaluating the Literature on Contrast-Induced AKI

The CIN Consensus Working Panel comprised two radiologists, a CT expert, two cardiologists, and two nephrologists practicing in Europe and the United States. At the first meeting in November 2004, the overall scope and strategy for the project were agreed, and at the second meeting in September 2005, the Working Panel reviewed and discussed all the evidence and developed a series of consensus statements. A systematic search of the literature was undertaken to identify all references relevant to the subject of contrast-induced AKI, as a result of which 865 potentially relevant articles were identified and reviewed. The results of the literature search were used to compile reviews covering the epidemiology and pathogenesis of AKI, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies (6–12). After reviewing all the evidence, a series of consensus statements were developed (Table 1) (13). The results were also integrated into a proposed algorithm for the management of patients at risk of contrast-induced AKI (Fig. 2) (13).

Epidemiology and Prognostic Implications of Contrast-Induced AKI

Incidence. The reported incidence of contrast-induced AKI varies widely across the literature, depending on the patient population and baseline risk factors. Moreover, as with any clinical event, the incidence also varies depending on the criteria by which it is defined. Contrast-induced AKI is typically defined in the recent literature as an increase in serum creatinine occurring within the first 24 hrs after contrast exposure and peaking up to 5 days afterward. In most instances, the rise in serum creatinine is expressed either in absolute terms (0.5–1.0 mg/dL; 44.2–88.4 μmol/L) or as a proportional rise in serum creatinine of 25% or 50% above the baseline value. The most commonly used definition in clinical trials is a rise in serum creatinine of 0.5 mg/dL (44.2 μmol/L), or a 25% increase from the baseline value, assessed at 48 hrs after the procedure. The European Society of Urogenital Radiology defines contrast-induced AKI as impairment in renal function (an increase

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in serum creatinine of >0.5 mg/dL [44.2 μmol/L] or by >25% within 3 days after intravascular administration of contrast medium) without an alternative pathogenesis (14). The Acute Kidney Injury Network definition includes a rise in serum creatinine of ≥0.3 mg/dL with oliguria, is compatible with previous definitions, and will be a new standard to follow for the critical care community.

The best indication of the effect on health care of contrast-induced AKI comes from large studies of hospitalized patients. The frequency of contrast-induced AKI has decreased during the past decade from a general incidence of ~15% to ~7% of patients receiving iodinated contrast (15), due to a greater awareness of the problem, better risk prevention measures, and less nephrotoxic contrast media. However, many cases of contrast-induced AKI continue to occur because of the ever-increasing numbers of procedures requiring contrast medium. Nash et al. (3) reported that radiographic contrast media were the third commonest cause of hospital-acquired renal failure (after decreased renal perfusion and nephrotoxic medications) and were responsible for 11% of cases. The mortality rate in cases of contrast-induced AKI was 14%. The proportion of cases of hospital-acquired AKI attributed to contrast media (11%) was almost identical to earlier studies (16–18). However, in the more recent study, there were more cases after cardiac procedures and fewer after noncardiac angiography.

As already noted, there are very few studies in the ICU population and there are no consistent data on prevalence. Polena et al. (19) observed an incidence of contrast-induced AKI (defined as an increase of >25% in serum creatinine from baseline) in 18% of ICU patients without preexisting renal disease receiving iodinated contrast medium, whereas in surgical ICU patients receiving intravenous contrast, the incidence of contrast-induced AKI (defined as an increase in serum creatinine of >0.5 mg/dL [44 μmol/L] within 48 hrs) was 1.4%, with a further 3.5% requiring renal dialysis (20).

It has been recognized for some time that the risk of death is increased in patients developing contrast-induced AKI. In a large retrospective study of >16,000 hospital inpatients undergoing procedures requiring contrast medium, a total of 183 subjects developed contrast-induced AKI (defined as a 25% increase in serum creatinine) (21). The risk of death during hospitalization was 34% in subjects who developed contrast-induced AKI compared with 7% in matched con-

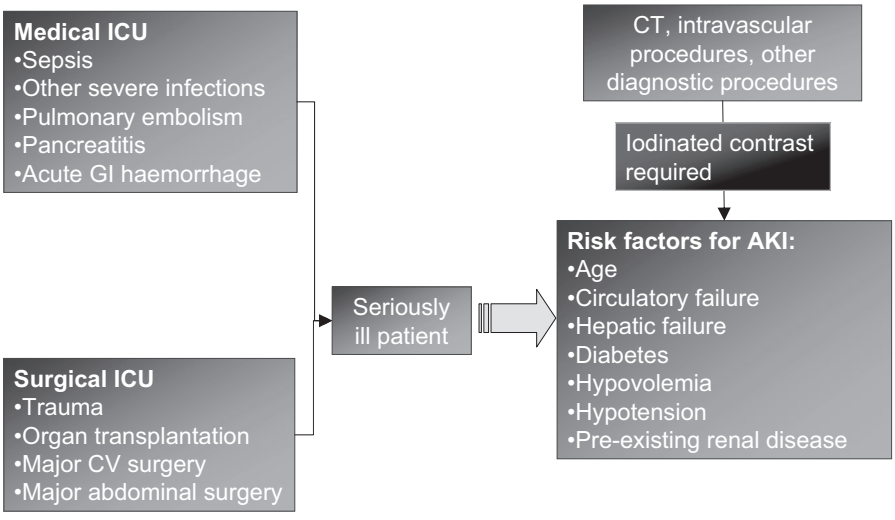
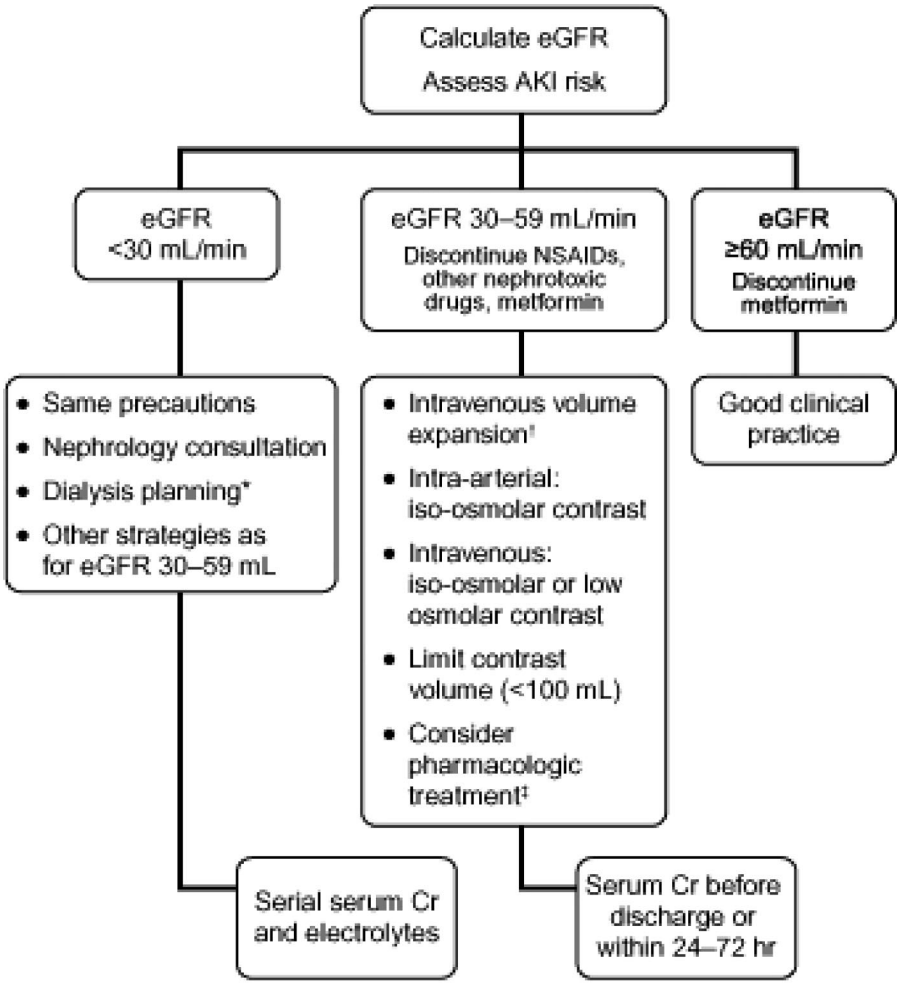


Figure 1. Interaction of risk factors for acute kidney injury (*AKI*) in the intensive care unit (*ICU*) patient. *GI*, gastrointestinal; *CV*, cardiovascular; *CT*, computed tomography.

Table 1. Consensus statements

Consensus statement 1: Contrast-induced acute kidney injury (AKI) is a common and potentially serious complication after the administration of contrast media in patients at risk for acute renal injury.
Consensus statement 2: The risk of contrast-induced AKI is elevated and of clinical importance in patients with chronic kidney disease (particularly when diabetes is also present), recognized by an estimated glomerular filtration rate of <60 mL·min^{-1}·1.73 m^{-2}.
Consensus statement 3: When serum creatinine or estimated glomerular filtration rate is unavailable, then a survey may be used to identify patients at higher risk for contrast-induced AKI than the general population.
Consensus statement 4: In the setting of emergency procedures, in which the benefit of very early imaging outweighs the risk of waiting, the procedure can be performed without knowledge of serum creatinine or estimated glomerular filtration rate.
Consensus statement 5: The presence of multiple contrast-induced AKI risk factors in the same patient or high-risk clinical scenarios can create a very high risk for contrast-induced AKI (~50%) and acute renal failure (~15%) requiring dialysis after contrast exposure.
Consensus statement 6: In patients at increased risk for contrast-induced AKI undergoing intra-arterial administration of contrast, ionic high-osmolality agents pose a greater risk for contrast-induced AKI than low-osmolality agents. Current evidence suggests that for intra-arterial administration in high-risk patients with chronic kidney disease, particularly those with diabetes mellitus, nonionic, iso-osmolar contrast is associated with the lowest risk of contrast-induced AKI.
Consensus statement 7: Higher contrast volumes (>100 mL) are associated with higher rates of contrast-induced AKI in patients at risk. However, even small (~30 mL) volumes of iodinated contrast in very high-risk patients can cause contrast-induced AKI and acute renal failure requiring dialysis, suggesting the absence of a threshold effect.
Consensus statement 8: Intra-arterial administration of iodinated contrast seems to pose a greater risk of contrast-induced AKI above that with intravenous administration.
Consensus statement 9: Adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL·kg^{-1}·hr^{-1}) for 3–12 hrs before the procedure and continued for 6–24 hrs afterward can lessen the probability of contrast-induced AKI in patients at risk. The data on oral as opposed to intravenous volume expansion as a contrast-induced AKI prevention measure are insufficient.
Consensus statement 10: No adjunctive medical or mechanical treatment has been proven to be efficacious in reducing the risk of AKI after exposure to iodinated contrast. Prophylactic hemodialysis or hemofiltration has not been validated as an effective strategy.

Adapted from McCullough et al (13).



* Plans should be made in case CIN occurs and dialysis is required.

† Intravenous volume expansion consisting of intravenous isotonic crystalloid 1–1.5 mL/kg/h for 3–12 hr before and 6–24 hr after the procedure.

‡ Consider potentially beneficial agents, such as theophylline, 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins), ascorbic acid (vitamin C), and prostaglandin E_1 (not approved for this indication).

Cr = creatinine; eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

Figure 2. Algorithm for management of patients receiving iodinated contrast media. *eGFR*, estimated glomerular filtration rate; *AKI*, acute kidney injury; *NSAID*, nonsteroidal anti-inflammatory drug; *Cr*, creatinine; Adapted from McCullough et al (13).

trols who had received contrast medium but did not develop contrast-induced AKI. Even after adjusting for comorbid disease, patients with contrast-induced AKI had a 5.5-fold increased risk of death (21). The high risk of in-hospital death associated with contrast-induced AKI was also documented in a retrospective analysis of 7,586 patients, of whom 3.3% developed contrast-induced AKI. Among the patients who developed contrast-induced AKI, the in-hospital death rate was 22% (22). The mortality rates of those who survived and were discharged at 1 yr after development of contrast-induced AKI (12.1%) and at 5 yrs (44.6%) indicated that the increased risk of death persisted in the long term. A further study confirmed the high mortality in patients who develop contrast-induced AKI, especially in those who require dialysis. The hospital mortality was 7.1% in contrast-induced AKI patients and 35.7% in patients who required dialysis. By 2 yrs, the mortality rate in patients who required dialysis was 81.2% (17). Contrast-induced AKI (defined as an increase of ≥25% in serum creatinine) occurred in 37% of 439 patients with renal impairment (baseline serum creatinine of ≥1.8 mg/dL) undergoing percutaneous coronary intervention (PCI) (23). In this group, the hospital mortality rate was 14.9%, compared with 4.9% in patients without contrast-induced AKI ($p = .001$). The cumulative 1-yr mortality rates were 37.7% and 19.4%, respectively. The 1-yr mortality was 45.2% for patients with contrast-induced AKI requiring dialysis and 35.4% for those with contrast-induced AKI not requiring dialysis (23). In patients undergoing primary PCI for acute myocardial infarction, short- and long-term mortality rates were also significantly higher in those who developed contrast-induced AKI (24, 25). Furthermore, in this group, it has been shown that contrast-induced AKI is an independent predictor of mortality (26).

Effect of Contrast-Induced AKI on Clinical Course and Outcome. In addition to an increased risk of death, contrast-induced AKI is also associated with other adverse outcomes, including late cardiovascular events after PCI. In one registry series of 5,967 PCI patients, the development of contrast-induced AKI was associated with an increased incidence of myocardial infarction and target vessel revascularization at 1 yr (26). Another large PCI study documented the link between contrast-induced AKI, postprocedural increases in creatinine kinase MB subfraction, and the risk of late cardiovascular events (27). In a group of 5,397 patients, a postprocedural rise in serum creatinine was a more powerful predictor of late mortality than creatinine kinase–MB elevation. Creatinine increases were associated with a 16% rate of death or myocardial infarction at 1 yr, rising to 26.3% when creatinine kinase–MB levels were also elevated (27).

More in-hospital events, such as bypass surgery, bleeding requiring transfusion, and vascular complications, were observed in patients who developed contrast-induced AKI, both in those with previous renal dysfunction and those with previously normal renal function. At 1 yr, the cumulative rate of major adverse cardiac events was significantly higher in patients who had developed contrast-induced AKI ($p < .0001$ for patients with and without CKD) (28). However, others have observed no difference in the rates of myocardial infarction and target vessel revascularization in patients with contrast-induced AKI (23).

The development of contrast-induced AKI has also been associated with an increased hospital stay. In one series, the

postprocedure hospital stay was longer in patients who developed contrast-induced AKI, regardless of baseline renal function (28). In a series of 200 patients undergoing PCI for acute myocardial infarction, patients who developed contrast-induced AKI had a longer hospital stay, a more complicated clinical course, and a significantly increased risk of death compared with those without contrast-induced AKI (25).

Economic Impact. A recent economic analysis of the direct costs associated with contrast-induced AKI from a U.S. perspective showed that the average additional cost of a case was $10,345 for the initial hospital stay and $11,812 to 1 yr (29). The incidence and outcome data were determined from studies identified through a systematic literature search and combined with unit costs from the literature in a decision analytic model. The major driver of the increased costs associated with contrast-induced AKI was the cost of the prolonged initial hospital stay.

Risk of Contrast-Induced AKI Requiring Dialysis. Although most cases of contrast-induced AKI reflect mild transient impairment of renal function, dialysis is needed in a small proportion of patients. The need for dialysis after contrast-induced AKI varies according to patients' underlying risks at the time of contrast administration but is generally <1% (17, 30, 31), although it was considerably higher in some older studies with early use of high-osmolar contrast media (32, 33). In contemporary studies, contrast-induced AKI requiring dialysis developed in almost 4% of patients with underlying renal impairment (34) and 3% of patients undergoing primary PCI for myocardial infarction (25). Although contrast-induced AKI requiring dialysis is relatively rare, the effect on patient prognosis is considerable, with high hospital and 1-yr mortality rates as summarized above (17, 23).

Pathophysiology of Contrast-Induced AKI

The pathophysiology of contrast-induced AKI starts with a patient who is in most cases already critically ill with trauma, severe medical illness (sepsis, pulmonary embolism, pancreatitis, etc.), or after major surgery (cardiopulmonary bypass, major vascular, or major abdominal) and includes renal vasoconstriction, impaired vasodilation, medullary hypoxia leading to oxidative stress, and direct tubular injury. Because iodinated contrast is water soluble, it collects and dwells in the urinary space of the glomerulus and the renal tubules, where it causes direct cytotoxicity to renal tubular cells. A detailed review of pathophysiology is outside the scope of this article, and the reader is referred to the review of McCullough et al. (9) for further information.

Role of Baseline Renal Function Screening

Virtually every report describing risk factors for contrast-induced AKI lists abnormal baseline serum creatinine, low estimated glomerular filtration rate (eGFR), or CKD as independent risk factors for contrast-induced AKI (1, 15, 22, 30, 34, 35). The risk of contrast-induced AKI is increased in patients with an eGFR of <60 mL/min (equivalent to serum creatinine of ≥1.3 mg/dL [≥114.9 μmol/L] and ≥1.0 mg/dL [≥88.4 μmol/L] in elderly men and women, respectively). These statements apply to stable renal function. In ICU patients, renal function may be dynamic and compromised (due to sepsis, heart failure, dehydration, rhabdomyolysis, drug-induced injury, etc.), making the risk state greater, and thus, clinical judgment must be applied to the assessment of baseline renal function.

Measurement of Baseline Renal Function. It is important to assess renal function before administration of contrast medium to ensure that appropriate steps are taken to reduce the risk. Because serum creatinine alone does not provide a reliable measure of renal function, the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) recommends that clinicians should use an eGFR calculated from the serum creatinine, age, sex, and race (36) in stable patients.

Use of Surveys and Questionnaires. It is highly desirable to have an eGFR value (calculated from a recent serum creatinine measurement) available to assess the risk of contrast-induced AKI, but this may be impractical in some circumstances (e.g., outpatient radiology suites). When renal function data are unavailable, a simple survey or questionnaire may be used to identify outpatients at higher risk for AKI (37–39). For patients being admitted to or originating from the ICU, the serum creatinine should be available before contrast is given.

Emergency Situations. In the setting of emergency procedures, in which the benefit of very early imaging outweighs the risk of waiting for the results of a blood test, it may be necessary to proceed without serum creatinine assessment or eGFR calculation (8). This is particularly relevant in the case of emergency admissions to the ICU, for which the patient history is unlikely to be immediately available.

Risk Markers for AKI After Iodinated Contrast

The term *risk marker* is preferred to *risk factor* because many of these indicators are nonmodifiable patient characteristics that are not necessarily directly causative (6). The most important element of risk stratification is baseline renal filtration, which is a surrogate for reduced nephron mass and renal parenchymal function. As already noted above, baseline renal impairment is an independent risk predictor for contrast-induced AKI (9). The risk of contrast-induced AKI is increased in patients with an eGFR of <60 mL/min going into the procedure, and special precautions should be taken in these patients.

Other risk factors include diabetes mellitus (26, 28), heart failure, volume depletion (40), nephrotoxic drugs, hemodynamic instability (27, 41), and other comorbidities. Importantly, diabetes is neither necessary nor sufficient as a determinant for contrast-induced AKI. However, diabetes seems to act as a risk multiplier, meaning that in a patient with CKD, it amplifies the risk of contrast-induced AKI. Several large series of PCI patients have shown an association between contrast-induced AKI and indicators of hemodynamic instability, such as periprocedural hypotension and use of an intra-aortic balloon pump (26, 28). It is not surprising that hypotension increases the risk of contrast-induced AKI because it increases the likelihood of renal ischemia and is a significant risk factor for AKI in acutely ill patients. Anemia has also been reported as a predictor of contrast-induced AKI (42).

The effect of risk factors is additive, and the likelihood of contrast-induced AKI rises sharply as the number of risk factors increases (17, 41). A similar pattern of additive risk has been documented for AKI requiring dialysis (30).

The additive nature of risk has allowed the development of prognostic scoring schemes (15, 41), but because none of the published schemes has been adequately studied or prospectively validated in different populations, it is not appropriate

to recommend routine use of any particular risk scoring in the ICU. However, the concept is that in a patient with CKD, diabetes mellitus, and other comorbidities, predicted risks of contrast-induced AKI and dialysis can approach ~50% and ~15%, respectively.

High-Risk Situation and Procedures

Many clinical situations may arise in the ICU in which the risk of contrast-induced AKI is increased (6). However the evidence is very limited for many situations, and in all cases, the decision to administer contrast medium is a matter for clinical judgment based on the clinical status of the patient and the expected benefits of the investigation or procedure. For example, patients with cirrhosis undergoing transarterial chemoembolization or interventional contrast procedures are thought to be at increased risk. As already noted, in PCI patients, periprocedural hemodynamic instability may be associated with an increased risk of contrast-induced AKI, but no published evidence was identified on the significance of shock or hypotension in other situations. The published literature on the risk of contrast-induced AKI in renal and heart transplant recipients is inconsistent (6). In view of the lack of published data, the CIN Consensus Panel did not make specific recommendations for the management of ICU patients, but it is reasonable to ensure that specific precautions are taken to reduce the risk of contrast-induced AKI if there is a probability that the patient's renal function is impaired.

Contrast Medium Use

Choice of Contrast Medium. In general, the higher the osmolality of contrast media, the higher the nephrotoxicity. A meta-analysis published in 1992 evaluated the relative nephrotoxicity of high-osmolar contrast media and low-osmolar contrast media (LOCM). The pooled odds ratio for the prevalence of contrast-induced AKI events (rise in serum creatinine of >44.2 μmol/L [>0.5 mg/dL]) in 25 trials was 0.61 (95% confidence interval, 0.48–0.77), indicating a significant reduction in risk with LOCM (43). Studies published since this meta-analysis generally support these findings (44).

Most studies comparing different LOCM have been small trials that have not shown clinically relevant variation between the renal effects of different LOCM, and there is insufficient evidence to draw definitive conclusions about possible differences (7).

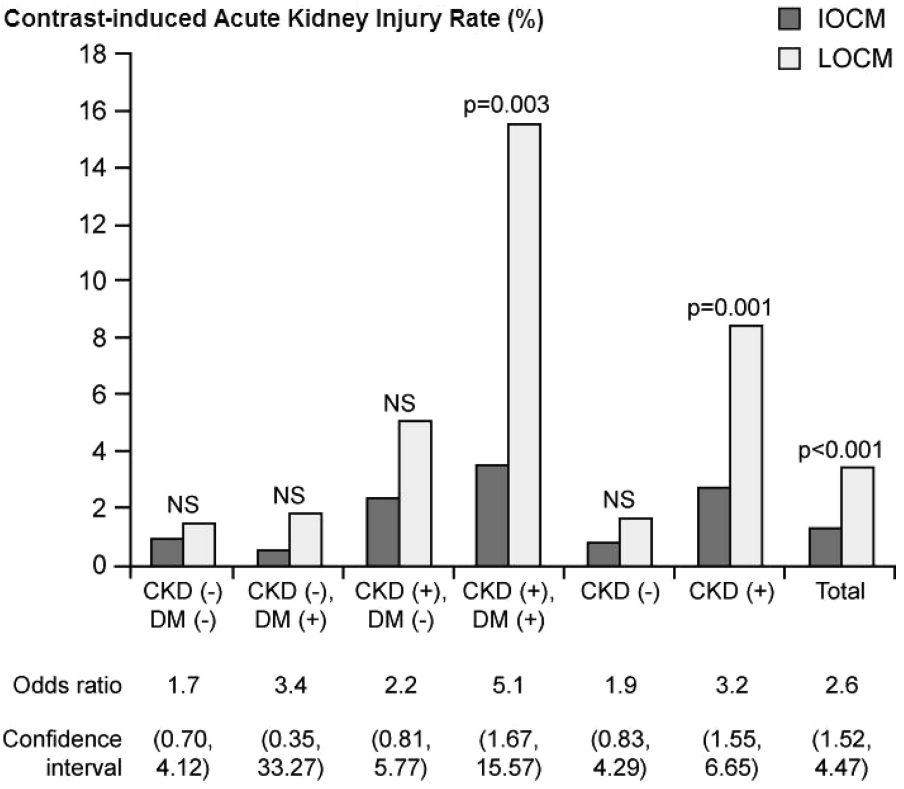


Figure 3. Rates of contrast-induced acute kidney injury (increase in serum creatinine of >0.5 mg/dL) in a meta-analysis of 16 head-to-head trials comparing isosmolar (*IOCM*) iodixanol with low-osmolar contrast media (*LOCM*). Odds ratios for harm are given for low-osmolar contrast agents. *NS*, not significant; *CKD*, baseline chronic kidney disease defined as an estimated creatinine clearance of <60 mL/min; *DM*, diabetes mellitus.

Evidence to date suggests isosmolar contrast medium (IOCM) is the least nephrotoxic (45–47). In a pooled analysis of 16 trials (2,727 patients) of intraarterial contrast medium, the incidence of contrast-induced AKI was significantly lower with iodixanol than with the comparator LOCM (Fig. 3) (47). Another systematic review was also consistent with a low rate of contrast nephropathy with iodixanol (IOCM) (48). A total of 17 prospective clinical trials (1,365 patients) were included, but only two of these trials were randomized comparisons of LOCM and IOCM, and the other data came from the placebo arms of 13 trials of preventive strategies for contrast-induced AKI and the LOCM arms of two trials comparing LOCM and high-osmolar contrast media. Finally, a meta-analysis of the renal tolerability of another IOCM, iotrolan 280, provides further evidence that IOCM are associated with a lower risk of postprocedure renal impairment (49). In an analysis of 14 double-blind studies, it was found that iotrolan had less effect on renal function than the LOCM with which it was compared (iopamidol, iohexol, iopromide).

On the basis of these results, in critically ill patients with background CKD and diabetes mellitus undergoing angiographic procedures, nonionic IOCM (iodixanol) is a reasonable choice for intravascular procedures (Fig. 2).

Several more clinical trials have been published since the release of the CIN Consensus Working Panel findings. The RECOVER trial showed a significantly lower rate of contrast-induced AKI with iodixanol compared with ioxaglate in high-risk patients undergoing coronary angiography (50). However, in trials in lower-risk patients, the rates of contrast-induced AKI were similar with iodixanol and iopamidol (LOCM) after intravenous administration for CT (IMPACT trial) (51) or intracoronary administration (CARE trial) (52). One group of researchers recently concluded from a small series that short- and long-term renal function is better preserved after IOCM in elderly patients with severe CKD who underwent

cardiac catheterization, compared with historical controls (53).

Volume of Contrast. Numerous studies have shown that the volume of contrast medium is a risk factor for contrast-induced AKI and that the mean contrast volume is higher in patients with contrast-induced AKI, and most multivariate analyses have shown that contrast volume is an independent predictor of contrast-induced AKI (17, 26, 30, 41). However, even small volumes (~30 mL) of contrast medium can have adverse effects on renal function in patients at particularly high risk (54). As a general rule, the volume of contrast received should not exceed twice the baseline level of eGFR in milliliters.

Intra-arterial vs. Intravenous Administration. A number of studies have provided circumstantial evidence that the risk of contrast-induced AKI may be higher after intra-arterial administration than after intravenous injection (55, 56). However, none of these studies provides an insight into the significance of the route of administration for contrast-induced AKI risk in contemporary practice, especially with regard to CT studies, for which a comparatively large volume of contrast medium may be given as a compact intravenous bolus rather than an infusion. The limited evidence that is available suggests that there is a significant risk of contrast-induced AKI in these circumstances (57).

Other Strategies for Reducing Risk

Volume Expansion. Volume expansion and treatment of dehydration has a well-established role in prevention of contrast-induced AKI, although few studies address this theme directly. There are limited data on the most appropriate choice of intravenous fluid, but the evidence indicates that isotonic crystalloid (saline or bicarbonate solution) is probably more effective than half-normal saline (58). Additional confirmatory trials with sodium bicarbonate (59) are needed because the largest trial to date showed no benefit of sodium bicarbonate over normal saline (60).

There is also no clear evidence to guide the choice of the optimal rate and duration of infusion. However, good urine output (>150 mL/hr) in the 6 hrs after the procedure has been associated with reduced rates of AKI in one study (61). Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion (62).

Dialysis and Hemofiltration. Contrast medium is removed by dialysis, but there is no clinical evidence that prophylactic dialysis reduces the risk of AKI, even when carried out within 1 hr or simultaneously with contrast administration. Hemofiltration performed before and after contrast deserves further investigation given reports of reduced mortality and need for hemodialysis (63), but the high cost and need for prolonged ICU care will also limit the utility of this prophylactic approach.

Pharmacologic Strategies. There are no currently approved pharmacologic agents for the prevention of AKI. With iodinated contrast, the pharmacologic agents tested in small trials that deserve further evaluation include theophylline, statins, ascorbic acid, and prostaglandin E_1 (10). Only one uncontrolled study has been published of pharmacologic treatment in ICU patients, and this showed that the incidence AKI after contrast exposure was very low (2%) in patients who received prophylactic intravenous theophylline before the administration of contrast medium (64).

Although popular, *N*-acetylcysteine has not been consistently shown to be effective. Nine published meta-analyses were identified in the review (10), all documenting the significant heterogeneity between studies and pooled odds ratios for *N*-acetylcysteine approaching unity. Importantly, only in those trials in which *N*-acetylcysteine reduced serum creatinine below baseline values because of decreased skeletal muscle production did renal injury rates seem to be reduced. Thus, *N*-acetylcysteine seems to falsely lower creatinine and not fundamentally protect the kidney against injury. However a recent study suggested that the use of volume supplementation with sodium bicarbonate together with *N*-acetylcysteine was more effective than *N*-acetylcysteine alone in reducing the risk of CIN (65). Fenoldopam, dopamine, calcium channel blockers, atrial natriuretic peptide, and L-arginine have not been shown to be effective in the prevention of contrast-induced AKI. Furosemide, mannitol, and an endothelin-receptor antagonist are potentially detrimental (10).

Future Approaches

Because contrast-induced AKI has a timed injury to the kidney, it is one of the most amenable forms of AKI for clinical trials. Future approaches include large planned studies of oral and intravenous antioxidants, forced hydration with marked elevations of urine output to reduce the transit time of iodinated contrast in the renal tubules, and novel, hopefully less toxic forms of radio-opaque contrast agents.

CONCLUSION

The consensus statements summarized in this article can guide the management of patients receiving iodinated contrast medium in the ICU setting. More studies in the ICU setting are clearly needed. Intensivists should be aware of the current state of knowledge developed on iodinated contrast and AKI outside of the ICU and consider its relevance to their clinical practice.

REFERENCES

1. McCullough PA, Soman SS: Contrast-induced nephropathy. *Crit Care Clin* 2005; 21:261–280
2. Gleeson TG, Bulugahapitiya S: Contrast-induced nephropathy. *AJR Am J Roentgenol* 2004; 183:1673–1689
3. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; 39:930–936
4. Chew DP, Astley C, Molloy D, et al: Morbidity, mortality and economic burden of renal impairment in cardiac intensive care. *Intern Med J* 2006; 36:185–192
5. Bagshaw SM, Mortis G, Doig CJ, et al: One-year mortality in critically ill patients by severity of kidney dysfunction: A population-based assessment. *Am J Kidney Dis* 2006; 48:402–409
6. Becker CR, Davidson C, Lameire N, et al: High-risk situations and procedures. *Am J Cardiol* 2006; 98:37K–41K
7. Davidson C, Stacul F, McCullough PA, et al: Contrast medium use. *Am J Cardiol* 2006; 98:42K–58K
8. Lameire N, Adam A, Becker CR, et al: Baseline renal function screening. *Am J Cardiol* 2006; 98:21K–26K
9. McCullough PA, Adam A, Becker CR, et al: Risk prediction of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:27K–36K
10. Stacul F, Adam A, Becker CR, et al: Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:59K–77K
11. Tumlin J, Stacul F, Adam A, et al: Pathophysiology of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:14K–20K
12. McCullough PA, Adam A, Becker CR, et al: Epidemiology and prognostic implications of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:5K–13K

13. McCullough PA, Stacul F, Davidson C, et al: Overview. *Am J Cardiol* 2006; 98:2K–4K.
14. Thomsen HS: Guidelines for contrast media from the European Society of Urogenital Radiology. *AJR Am J Roentgenol* 2003; 181: 1463–1471
15. Bartholomew BA, Harjai KJ, Dukkipati S, et al: Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 2004; 93: 1515–1519
16. Hou SH, Bushinsky DA, Wish JB, et al: Hospital-acquired renal insufficiency: A prospective study. *Am J Med* 1983; 74:243–248
17. McCullough PA, Wolyn R, Rocher LL, et al: Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. *Am J Med* 1997; 103:368–375
18. Iakovou I, Dangas G, Mehran R, et al: Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. *J Invasive Cardiol* 2003; 15:18–22
19. Polena S, Yang S, Alam R, et al: Nephropathy in critically Ill patients without preexisting renal disease. *Proc West Pharmacol Soc* 2005; 48:134–135
20. Haveman JW, Gansevoort RT, Bongaerts AH, et al: Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: A retrospective analysis. *Intensive Care Med* 2006; 32:1199–1205
21. Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality: A cohort analysis. *JAMA* 1996; 275:1489–1494
22. Rihal CS, Textor SC, Grill DE, et al: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; 105:2259–2264
23. Gruberg L, Mintz GS, Mehran R, et al: The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 2000; 36:1542–1548
24. Sadeghi HM, Stone GW, Grines CL, et al: Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation* 2003; 108: 2769–2775
25. Marenzi G, Lauri G, Assanelli E, et al: Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 2004; 44: 1780–1785
26. Lindsay J, Apple S, Pinnow EE, et al: Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. *Catheter Cardiovasc Interv* 2003; 59:338–343
27. Lindsay J, Canos DA, Apple S, et al: Causes of acute renal dysfunction after percutaneous coronary intervention and comparison of late mortality rates with postprocedure rise of creatine kinase-MB versus rise of serum creatinine. *Am J Cardiol* 2004; 94:786–789
28. Dangas G, Iakovou I, Nikolsky E, et al: Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol* 2005; 95:13–19
29. Subramanian S, Tumlin J, Bapat B, et al: Economic burden of contrast-induced nephropathy: Implications for prevention strategies. *J Med Econ* 2007; 10:119–134
30. Freeman RV, O'Donnell M, Share D, et al: Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol* 2002; 90:1068–1073
31. Birck R, Krzossok S, Markowetz F, et al: Acetylcysteine for prevention of contrast nephropathy: Meta-analysis. *Lancet* 2003; 362: 598–603
32. Martin-Paredero V, Dixon SM, Baker JD, et al: Risk of renal failure after major angiography. *Arch Surg* 1983; 118:1417–1420
33. Gomes AS, Baker JD, Martin-Paredero V, et al: Acute renal dysfunction after major arteriography. *AJR Am J Roentgenol* 1985; 145: 1249–1253
34. Nikolsky E, Mehran R, Turcot DB, et al: Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol* 2004; 94:300–305
35. Davidson CJ, Hlatky M, Morris KG, et al: Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization: A prospective trial. *Ann Intern Med* 1989; 110:119–124
36. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 1):S1–266
37. Tippins RB, Torres WE, Baumgartner BR, et al: Are screening serum creatinine levels necessary prior to outpatient CT examinations? *Radiology* 2000; 216:481–484
38. Choyke PL, Cady J, DePollar SL, et al: Determination of serum creatinine prior to iodinated contrast media: Is it necessary in all patients? *Tech Urol* 1998; 4:65–69
39. Olsen JC, Salomon B: Utility of the creatinine prior to intravenous contrast studies in the emergency department. *J Emerg Med* 1996; 14:543–546
40. Krumlovsky FA, Simon N, Santhanam S, et al: Acute renal failure: Association with administration of radiographic contrast material. *JAMA* 1978; 239:125–127
41. Mehran R, Aymong ED, Nikolsky E, et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol* 2004; 44: 1393–1399
42. Nikolsky E, Mehran R, Lasic Z, et al: Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int* 2005; 6:706–713
43. Barrett BJ, Carlisle EJ: Metaanalysis of the relative nephrotoxicity of high- and low- osmolality iodinated contrast media. *Radiology* 1993; 188:171–178
44. Rudnick MR, Goldfarb S, Wexler L, et al: Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: The Iohexol Cooperative Study. *Kidney Int* 1995; 47:254–261
45. Aspelin P, Aubry P, Fransson SG, et al: Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003; 348: 491–499
46. Chalmers N, Jackson RW: Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol* 1999; 72:701–703
47. McCullough PA, Bertrand ME, Brinker JA, et al: A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol* 2006; 48: 692–699
48. Solomon R: The role of osmolality in the incidence of contrast-induced nephropathy: A systematic review of angiographic contrast media in high risk patients. *Kidney Int* 2005; 68:2256–2263
49. Clauss W, Dinger J, Meissner C: Renal tolerance of iotrolan 280: A meta analysis of 14 double-blind studies. *Eur Radiol* 1995; 5:S79–S84
50. Jo SH, Youn TJ, Koo BK, et al: Renal toxicity evaluation and comparison between Visipaque (iodixanol) and Hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: The RECOVER study. A randomized controlled trial. *J Am Coll Cardiol* 2006; 48:924–930
51. Barrett BJ, Katzberg RW, Thomsen HS, et al: Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: A double-blind comparison of iodixanol and iopamidol. *Invest Radiol* 2006; 41:815–821
52. Solomon RJ, Natarajan MK, Doucet S, et al: Cardiac Angiography in Renally Impaired Patients (CARE) study: A randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 2007; 115:3189–3196
53. Hsieh YC, Liu TJ, Liang KW, et al: Isoosmolar contrast medium better preserves short- and long-term renal function after cardiovascular catheterizations in patients with severe baseline renal insufficiency. *Int J Cardiol* 2006; 111:182–184
54. Manske CL, Sprafka JM, Strony JT, et al: Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 1990; 89:615–620
55. Campbell DR, Flemming BK, Mason WF, et al: A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography. *Can Assoc Radiol J* 1990; 41:133–137
56. Moore RD, Steinberg EP, Powe NR, et al: Nephrotoxicity of high-osmolality versus low-osmolality contrast media: Randomized clinical trial. *Radiology* 1992; 182:649–655
57. Tepel M, van der Giet M, Schwarzfeld C, et al: Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000; 343:180–184

58. Mueller C, Buerkle G, Buettner HJ, et al: Prevention of contrast media-associated nephropathy: Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; 162:329–336
59. Merten GJ, Burgess WP, Gray LV, et al: Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. *JAMA* 2004; 291:2328–2334
60. Brar S: A randomized controlled trial for the prevention of contrast induced nephropathy with sodium bicarbonate vs. sodium chloride in persons undergoing coronary angiography (the MEENA trial): Abstract 209-9. Presented at the 56th Annual Scientific Session of the American College of Cardiology, New Orleans, LA, March 24–27, 2007
61. Stevens MA, McCullough PA, Tobin KJ, et al: A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: Results of the P.R.I.N.C.E. study. *J Am Coll Cardiol* 1999; 33:403–411
62. Taylor AJ, Hotchkiss D, Morse RW, et al: PREPARED: Preparation for Angiography in Renal Dysfunction. A randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest* 1998; 114:1570–1574
63. Marenzi G, Marana I, Lauri G, et al: The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; 349:1333–1340
64. Huber W, Jeschke B, Page M, et al: Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: A prospective comparison to series of patients at similar risk. *Intensive Care Med* 2001; 27:1200–1209
65. Briguori C, Airoldi F, D'Andrea D, et al: Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): A randomized comparison of 3 preventive strategies. *Circulation* 2007; 115:1211–1217