Canadian Journal of Emergency Medicine (2021) 23:432–436
https://doi.org/10.1007/s43678-021-00126-7

CJEM DEBATE SERIES

CJEM Debate Series: contrast-enhanced imaging should not be withheld for emergency department patients as contrast-induced acute kidney injury is very uncommon

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Received: 23 February 2021 / Accepted: 25 March 2021 / Published online: 3 April 2021
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Keywords Contrast-induced nephropathy · Contrast-induced acute kidney injury · Computed tomography · Chronic kidney disease

Introduction: Paul Atkinson (@PaulAtkinsonEM)

This series of editorials provides CJEM readers with the opportunity to hear differing perspectives on topics pertinent to the practice of Emergency Medicine.The debaters have been allocated opposing arguments on topics where there is some controversy or perhaps scientific equipoise.

We continue with the topic of Contrast-enhanced imaging in the emergency department. "What is the creatinine?" asks the radiologist when an emergency contrast-enhanced computed tomography (CT) is requested for a patient with suspected ischemic bowel. Is this a reasonable concern that should be raised to prevent permanent kidney injury or an out-of-date mantra, that fails to balance the risk for injury against the risk of delay in a critical case? Is the creatinine even relevant or should standard precautions be taken to minimize risk, but ensure timely investigation?

The Rosenberg, Hiremath and Yadav team argues that contrast-induced acute kidney injury is uncommon and that the risk is largely overstated, whereas their opponents in this debate, Neilipovitz, Savage, Ohle and Alaref argue that caution is required as in some circumstances there is still a role for delaying a contrast-enhanced imaging.

Readers can follow the debate on Twitter and vote for either perspective, by going to @CJEMonline or by searching #CJEMdebate.

For: Hans Rosenberg (@hrosenberg33), Swapnil Hiremath (@hswapnil), Krishan Yadav (@KrishanYadavMD)

"Contrast associated acute kidney injury should not be a concern for emergency physicians"

Contrast-enhanced computed tomography (CT) is commonly used in the emergency department (ED) setting to aid clinicians in making important and often critical diagnoses. The focus of this debate concerns the use of intravenous contrast (e.g., CT imaging) and does not cover intra-arterial delivery of contrast (e.g., coronary angiography). Historically, clinicians have used the term *contrast-induced nephropathy* (CIN), and now *contrast-induced acute kidney injury* (CI-AKI) to describe acute kidney injury (AKI) occurring within 48–72 h of intravenous contrast administration, after the exclusion of other nephrotoxic causes [1]. This nomenclature is problematic, as it

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implies causation—as opposed to association—with AKI. This has in part led to the overestimation of the role of contrast media in AKI [2]. Therefore, the terms *contrast-associated AKI* (CA-AKI) and *post-contrast AKI* (PC-AKI) should be used instead, which are more accurate in not implying any causation [3]. CA-AKI is defined as AKI (based on Kidney Disease Improving Global Outcomes [KDIGO] criteria [4] occurring within 48 h of contrast administration. Importantly, CA-AKI implies correlation, not causation. CI-AKI is a subset of CA-AKI where the administration of contrast directly causes AKI. The latest consensus is that the risk of CI-AKI has been largely overstated, the extent of which is specifically relevant to the ED setting [3].

CI-AKI is uncommon and its risk is overstated

CI-AKI is uncommon and in our opinion, the risk is largely overstated. Much of the purported risk of CI-AKI was driven by early studies that do not mirror current practice in the ED setting. First, initial studies examining the incidence and risk of CI-AKI involved patients receiving high osmolar contrast media (HOCM). A meta-analysis by Barrett et al. found that use of low osmolar contrast media (LOCM) resulted in a decreased likelihood of nephrotoxicity in patients with pre-existing kidney failure [5]. Today, HOCM has been replaced by LOCM or iso-osmolar contrast media. In a propensity-matched study of patients receiving intravenous LOCM, there was no association with nephrotoxicity in patients with a baseline estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 or greater [6]. Second, early research involved patients receiving intra-arterial contrast. Delivery of contrast via the intra-arterial route may lead to higher renal artery concentrations of contrast, and truly higher risk of CI-AKI compared to intravenous contrast. Intra-arterial contrast also carries the risk of cholesterol embolization causing AKI, reflected by a higher risk of AKI with femoral versus radial catheterization, and not a relevant factor for intravenous contrast [7]. While observational data are conflicting, a recent randomized trial of patients with suspected coronary artery disease found a lower rate of AKI in patients receiving intravenous contrast for CT angiography versus coronary angiography using the intra-arterial route [8]. Third, early studies commonly lacked a control group of patients who did not receive contrast and were confounded by a number of definitions for CI-AKI [1, 2]. Even with intravenous contrast, patients undergoing contrast imaging often have other pathophysiologic processes for AKI, such as acute tubular necrosis from sepsis or shock, and acute interstitial nephritis from drugs, as an example, with accurate attribution to contrast being almost impossible.

Recent studies including ED patients have shown the risk of CI-AKI is low in this population

ED patients often require contrast-enhanced imaging to allow clinicians to make critically important diagnoses, such as pulmonary embolism or ischemic colitis. However, the potential for kidney injury with contrast-enhanced CT imaging is an issue faced by emergency physicians and radiologists daily. A recent meta-analysis involving 107,335 patients in the ED, intensive care unit and inpatient settings found that when compared to non-contrast CT imaging, contrast-enhanced CT was not significantly associated with AKI, need for renal replacement therapy, or all-cause mortality [9]. The authors correctly concluded that other factors (i.e., related to the acute illness or patient factors) likely play a more important role in the development of AKI. An ED-based cohort study comparing patients receiving contrast-enhanced CT versus non-contrast CT imaging found no increased risk of AKI following intravenous contrast administration, with an odds ratio of 0.96 (95% CI 0.85–1.08) [10]. Importantly, patients with a serum creatinine $\geq$ 354 µmol/L, kidney transplant recipients or those on hemodialysis were excluded. A recent systematic review disproves the fear of contrast having an effect on residual kidney function in dialysis patients [11]. A number of studies have shown no evidence of CI-AKI regardless of chronic kidney disease (CKD) stage. However, these studies are observational and are underpowered to establish risk in severe CKD (eGFR < 30 mL/min/1.73 m^2) [3].

Who is at risk for CA-AKI?

Although the majority of ED patients can safely receive intravenous contrast material, there are some populations where caution should be exercised to minimize the risk of CA-AKI. The most important risk factor is pre-existing severe CKD with a baseline eGFR < 30 mL/min/1.73 m^2 [3]. Other potential factors associated with CA-AKI are states that cause reduced kidney perfusion [12] (e.g., sepsis, hypotension, congestive heart failure). These risk factors are not absolute contraindications to contrast-enhanced imaging in the ED, especially when the indication for the test is to rule out life-threatening pathology.

Most interventions to prevent CA-AKI are ineffective and should be abandoned. However, it is reasonable to consider intravenous hydration for patients at high risk of CA-AKI

Small trials which reported changes in serum creatinine as an outcome led to the rapid uptake of interventions such as n-acetylcysteine and bicarbonate volume expansion. Larger and definitive trials performed since, with clinical

outcome reporting, prove that these have no advantage over 0.9% saline alone [13] for prevention of CA-AKI. Current consensus supports the use of prophylactic intravenous volume expansion with isotonic fluids (0.9% normal saline or Ringer's lactate) for the prevention of CA-AKI in patients who have AKI or those with an eGFR < 30 mL/min/1.73 m^2 [3]. Caution should be exercised in those patients who cannot tolerate volume expansion (e.g., those with advanced congestive heart failure). Volume expansion is not indicated in patients with a stable eGFR ≥ 30 mL/min/1.73 m^2. A large randomized clinical trial investigating prophylactic intravenous fluid hydration versus no prophylaxis found the latter was non-inferior in the prevention of CI-AKI [14].

Contrast media should not be withheld for ED patients where contrast-enhanced imaging is necessary

Anytime physicians make a decision to order contrast-enhanced CT imaging, a risk versus benefit analysis should be undertaken to justify the test. The main risks to consider are a severely reduced eGFR < 30 mL/min/1.73 m^2 or the presence of AKI. In these patients, isotonic volume expansion should be administered when safe and feasible to do so. Ultimately, if the diagnosis in question is critical or life-threatening (e.g., aortic dissection), the clinician should never withhold intravenous contrast. If there is ever a concern in high-risk patients where a less critical diagnosis is in question, a dialogue should occur between the emergency physician and the radiologist about alternative imaging strategies (e.g., ultrasonography or unenhanced CT) for the best course of action. The reality when reviewing the modern literature, is that with the exception of very few ED patients, intravenous contrast material can be safely administered with minimal concern for CI-AKI. With the latest evidence, it is time all clinicians to get onto the same page: contrast-enhanced imaging should not be withheld for the vast majority of ED patients as CI-AKI is very uncommon.

Against:Jonathan Neilipovitz, David W. Savage(@DavidSavageEM), Robert Ohle(@robertohle), Amer Alaref

"Contrast associated acute kidney injury is a concern for some patients and should guide imaging decisions"

Often in medicine when the needle shifts, it moves past the point of reason, swinging wildly, one theory or approach is often replaced by another until finally settling on the "best evidence". However, the truth is rarely so clear. There is a growing body of low-quality evidence that suggests contrast-induced nephropathy in the ED patient population is rare. This has led to the ever increasing cries of emergency physicians that we no longer need a creatinine prior to any contrast study. "Its so rare!", "Increased creatinine is not a patient oriented outcome!", "The radiologists are just out to get us!".

However, when we dig deeper into these studies, we find that there is in fact a subset of patients who are at increased risk of kidney injury following the administration of contrast. Although these studies are often not adequately powered to find a more patient-oriented outcome such as mortality, we know that AKI, no matter what the cause, is associated with worse patient outcomes. We need to redefine our view of CIN but we need to do this in a balanced manner informed by the evidence and not the cries of the mob.

Contrast-induced acute kidney injury is likely rare but more common in those with baseline-impaired renal function

Since it was first described in the literature in 1954, the prevalence of CA-AKI in the general public was thought to be less than 2%, with an estimated prevalence of 40% in high risk populations [15]. Since 2007, studies have questioned these estimates of prevalence and attempted to reduce bias and confounding variables in estimating the true prevalence of CA-AKI [15]. Previous studies have documented that significant morbidity and mortality is associated with CA-AKI [16]. A 2018 systematic review by De Simone et al. found the rate of CA-AKI was largely negligible in patients with normal renal function [17]. However, they were concerned that the rate of CI-AKI could be as high as 25% in patients with reduced renal function and comorbidities such as diabetes, vascular disease, advanced age (70 + years), and those patients taking nephrotoxic medications. These studies often did not include confounding factors, contained non-standardized definitions of the disease and have failed to account for certain biases. Therefore, they are only useful for hypothesis generation.

A randomized trial that would account for the multitude of confounding factors is extremely unlikely. However, there is an alternative study design for investigating this problem, specifically propensity matching. This is where patients are matched 1–1 based on all known confounding factors. A study by Davenport et al. found that a population with a creatinine > 141 umol/L had a higher incidence of AKI than matched controls. This effect was not seen in those with creatinine levels < 132 umol/L., lending credence that CIN does exist but more likely in those with a baseline-impaired renal function [2].

The evidence is prone to selection bias

A meta-analysis published in 2018 by Aycock et al. included a large number of studies that demonstrated there was no association with contrast and mortality or renal replacement therapy [9]. However, like all meta-analyses, the conclusions are only as good as the studies used to generate them. There are two issues with the included studies. One, the study is biased towards finding no effect of contrast administration as the patients included largely had a normal creatinine. We agree that those with normal renal function are likely at low risk of CI-AKI. In these studies, greater than two thirds of patients had a normal creatinine. They are largely underpowered to find a significant difference in outcomes in those with underlying renal impairment. Issue number two is the vast majority of studies are at risk of selection bias with a higher rate of patients with baseline renal impairment being allocated to the non-contrast population. This selection bias is illustrated by Oleinik et al. which was included in the meta-analysis [18]. The non-contrast group had a baseline renal impairment of 22% and the contrast group only 6%.

CI-AKI can be reasonably expected to increase in rate as populations age and rise in specific comorbidities

The current incidence of CIN seems to be rare. As stated, this may be a related to the fact that the number of patients with baseline renal impairment is also low. Numerous studies including De Simone et al. caution that CA-AKI must be considered during imaging studies for patients with decreased renal function and specific comorbidities [16, 18]. With an aging population and the rate of diabetes increasing [19], these two factors alone may be significant risk factors for an increase in the prevalence of CI-AKI. Statistics Canada shows a 25% rise in diabetes over the past five years from approximately 2 million patients in 2015, to almost 2.5 million in 2019 [19]. In addition, the proportion of seniors in Canada is rising and the population over age 65 is approximately 18% of Canada's population in 2019, up from 15.6% in 2014 and expected to rise to 23% by 2030 [20]. As more patients are at risk for CA-AKI, its logical that the rate of incidence may increase as well.

When considering contrast media, risk stratify the patient and optimize in a safe manner

The diagnostic value of performing a contrast-enhanced CT scan in patients with acute trauma or hemodynamic instability outweighs the risk of nephropathy. It would be clinically irresponsible to delay the investigations for patients presenting with symptoms indicative of a life threatening, time dependent emergency (i.e., ischemic limb, acute aortic syndrome, ruptured viscus). However, many of the patients assessed in the ED are not in extremis. If patients are at risk of renal impairment, they may benefit from delaying their imaging for a short time to assess their eGFR and ensure proper hydration.

Let us thoughtfully consider the deficits in the literature for and against CI-AKI. There is still a role for delaying a contrast-enhanced imaging study in those with risk factors for AKI.

Funding No funds were used to produce this manuscript.

Declarations

Conflict of interest The authors have no competing interests to declare.

References

1. Media AMOC. American College of Radiology. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Published 2020. (Accessed May 3, 2020).
2. Davenport MS, Cohan RH, Khalatbari S, Ellis JH. The challenges in assessing contrast-induced nephropathy: where are we now? AJR Am J Roentgenol. 2014;202(4):784–9.
3. Davenport MS, Perazella MA, Yee J, et al. Use of intravenous iodinated contrast media in patients with kidney disease: consensus statements from the American college of radiology and the national kidney foundation. Radiology. 2020;294(3):660–8.
4. James M, Bouchard J, Ho J, et al. Canadian society of nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5):673–85.
5. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology. 1993;188(1):171–8.
6. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology. 2013;268(3):719–28.
7. Andò G, Gragnano F, Calabrò P, Valgimigli M. Radial vs. femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: a systematic review and meta-analysis. Catheter CardiovascInterv. 2018;92(7):E518-e526.
8. Schönenberger E, Martus P, Bosserdt M, et al. Kidney injury after intravenous versus intra-arterial contrast agent in patients suspected of having coronary artery disease: a randomized trial. Radiology. 2019;292(3):664–72.
9. Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute kidney injury after computed tomography: a meta-analysis. Ann Emerg Med. 2018;71(1):44-53.e44.
10. Hinson JS, Ehmann MR, Fine DM, et al. Risk of acute kidney injury after intravenous contrast media administration. Ann Emerg Med. 2017;69(5):577-586.e574.
11. Oloko A, Talreja H, Davis A, et al. Does iodinated contrast affect residual renal function in dialysis patients? A Syst Rev Meta-AnalySIS Nephron. 2020;144(4):176–84.
12. Toprak O, Cirit M. Risk factors for contrast-induced nephropathy. Kidney Blood Press Res. 2006;29(2):84–93.
13. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603–14.

14. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017;389(10076):1312–22.
15. UlHaq MF, Yip CS, Arora P. The conundrum of contrast-induced acute kidney injury. J Thorac Dis. 2020;12(4):1721–7.
16. Rudnick M, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences? Clin J Am SocNephro. 2008;3(1):263–72.
17. De Simone B, Ansaloni L, Sartelli M, Gaiani F, Leandro G, Luigi Angelis G, Di Mario F, Coccolini F, Catena F. Is the risk of contrast-induced nephropathy a real contraindication to perform intravenous contrast enhanced computed tomography for non-traumatic acute abdomen in emergency surgery department? Acta Biomed. 2018;89:158–72.
18. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, Delgado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN. CT angiography for intracerebralhemorrhage does not increase risk of acute nephropathy. Stroke. 2009;40(7):2393–7.
19. Statistics Canada. Table 13-10-0096-07 diabetes, by age group. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=13100096 07&pickMembers%5B0%5D=1.1&pickMembers%5B1%5D=3.1&cubeTimeFrame.startYear=2015&cubeTimeFrame.endYear=2019&referencePeriods=20150101%2C20190101. Modified 2020. (Accessed Aug 29, 2020).
20. Government of Canada. Action for seniors report. https://www.canada.ca/en/employment-social-development/programs/seniors-action-report.html Published fall 2014. Modified March 2019. (Accessed 29, Aug 2020).