



Contrast-associated acute kidney injury

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Iodinated contrast media (ICM) is widely used in clinical practice for diagnostic imaging. Although patients benefit tremendously from such diagnostic tests, ICM is also associated with acute kidney injury (AKI) (1,2). Traditionally, AKI following contrast exposure has been called contrast-induced nephropathy (CIN); however, it has recently been recommended that the correct terminology for this specific type of injury should be contrast-associated AKI (CA-AKI) (1). Evidence for CA-AKI has come from both from animal and human studies (3), and it is typically associated with oliguric kidney failure with creatinine elevation within 24 to 48 hours (peaking at 2 to 3 days) after exposure to an ICM (2,4). Although CA-AKI is reversible (returning to baseline creatine in 1 to 3 weeks), it is also associated with a higher risk of both short- and long-term mortality (2,4).

The incidence of CIN varies (ranging from 0 % to 21%) across studies and depends on patient comorbidities, procedure type, route of ICM administration [intra-arterial (IA) versus intravenous (IV)], ICM type, AKI definition, timing of postcontrast serum creatinine (SCr) measurement, and prophylactic strategy (2,3). Several risk factors, including older age (>75 years), use of nephrotoxic medications, hypovolemia, higher contrast volume, chronic kidney disease (CKD), sepsis, and IA administration are associated with an increased risk of CA-AKI. Although

several risk models have been reported, none have exclusively addressed patients receiving contrast media by IV (4). Recently, a systemic review of 16 risk models and a meta-analysis of 74 risk models concluded that additional research is needed before the utility of such models in routine clinical care (heterogeneity was significant and predictive values were moderate at best) (5,6).

Over the last several decades, multiple therapeutic agents (including statins, ascorbic acid, sodium bicarbonate, fenoldopam, dopamine, L-arginine, endothelin antagonists, trimetazidine, and N-acetylcysteine) and strategies (such as ischemic preconditioning and prophylactic hemodialysis) have been investigated, showing no success (7). Currently, the only effective strategy for CIN prevention is IV hydration with normal saline. Recently, a novel strategy employing closed-loop fluid management using the RenalGuard system (RenalGuard Solutions, Inc Milford MA, UA) seemed to show effectiveness against CA-AKI in patients with CKD (7). Although RenalGuard is approved for sale in Europe and specific countries around the world, additional, larger clinical trials on larger patient populations are needed before its routine use in clinical practice worldwide.

Despite the critical clinical problems and the need for solutions, conflicting and confusing opinions (in both the literature and clinical practice) about the definition, investigation, and management of CA-AKI remain. Therefore,

the American College of Radiology and the National Kidney Foundation have recently released a joint consensus statement to standardize the definition and management of CA-AKI (8). Highlights from this consensus statement are:

- ❖ The traditional definition of CIN, “AKI occurring within 48 hours of exposure of ICM after excluding other nephrotoxic agents,” has been problematic. In older, poorly conducted studies, it has not always been possible to exclude other potential causes of nephropathy. Thus, labeling every case of AKI following exposure to ICM as CIN has been misleading and has overestimated the risk of contrast induced (CI)-AKI (9).
- ❖ More recently, several well-conducted studies have suggested that a majority of AKI cases following exposure to ICM cannot be directly attributed to the contrast media (10).
- ❖ Routine use of the CI-AKI for every case of AKI following exposure to ICM in clinical practice can be misleading because the majority of those cases could be due to exposure to other nephrotoxic agents or insults around the time of exposure to ICM (8,10).
- ❖ The correct terminology for the definition of AKI was proposed as “CA-AKI” or “postcontrast AKI (PC-AKI)” that occurs within 48 hours of exposure to ICM. Both terminologies suggest association but not causation (8). On the other hand, if the AKI can be causally linked to ICM exposure, the term CI-AKI which is subtype of CA-AKI, should then be used (8).
- ❖ This consensus statement endorses the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI: an “increase in SCr (serum creatinine) by ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) within 48 hours or increase in SCr to ≥ 1.5 times baseline (which is known or presumed to have occurred within the prior 7 days) or urine volume < 0.5 mL/kg/h for 6 hours.” (1).
- ❖ The risk of CA-AKI is directly correlated to the stage of CKD and is 5%, 10%, 15%, and 30% when the estimated glomerular filtration rate (eGFR) values are ≥ 60 , 45–59, 30–44, and < 30 mL/min/1.73 m^2 , respectively (8,10). On the other hand, the exact risk of CI-AKI in patients with CKD is less certain, but seems to be significantly lower than CA-AKI. There are no good randomized trials evaluating the risk of CI-AKI at different stages of CKD. Based on observational studies, the risk of CI-AKI seems to be 0%, 0–2%, and 0–17% when the eGFR values are ≥ 45 , 30–44, and < 30 mL/min/1.73 m^2 , respectively (8,10).
- ❖ Several patient-related conditions, such as diabetes, exposure to nephrotoxic agents, hypovolemia, albuminemia, and congestion heart failure (CHF), are associated with CA-AKI (1,5). On the other hand, no well-conducted studies have linked patient-related factors to CI-AKI beyond the eGFR alone (3,10).
- ❖ The best current evidence seems to suggest that there is no clinically relevant difference in the risks of CA-AKI between low- and iso-osmolarity contrast media [low-osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM), respectively] for procedures requiring IV administration (11). Similarly, based on clinical trials, there seems to be no clinically significant difference in the risks of CI-AKI between LOCM and IOCM (11).
- ❖ No studies have exclusively evaluated the role of prophylaxis in the prevention of CI-AKI. However, based on studies evaluating the risk of CA-AKI, in patients with AKI or CKD (not on dialysis) and values for eGFR at ≤ 30 mL/min/1.73 m^2 , prophylaxis is indicated (2,8). Clinicians could also consider prophylaxis with IV saline for patients with multiple risk factors for CA-AKI and values for eGFR between 30 and 44 mL/min/1.73 m^2 .
- ❖ Prophylactic IV saline can lead to CHF; thus, prophylaxis is not recommended when eGFR is stable at > 30 mL/min/1.73 m^2 in patients at high risk for CHF or those on chronic dialysis (8,12).
- ❖ Diabetes by itself should not be an indication for prophylaxis because it does not seem to be an independent risk factor for CI-AKI beyond eGFR values (8).
- ❖ The preferred fluid for prophylaxis is normal saline (1–3 cc/kg/h) starting 1 hour before ICM administration and continuing 3–12 hours postprocedure (8). Though saline infusion for more than 12 hours could be more effective, it is not practical in most outpatient cases (2,8). Alternatively, a fixed dose volume protocol of 500 mL normal saline both before and after the procedure can be used.
- ❖ Ideally, IV hydration should start pre-procedure; however, in emergencies, when there is no time for pre-procedure prophylaxis, postprocedural IV hydration with normal saline can be considered (8).
- ❖ There are no well-conducted studies evaluating the efficacy of oral hydration for the prevention of CA-AKI when eGFR ≤ 30 mL/min/1.73 m^2 or in patients with AKI (8).
- ❖ N-acetylcysteine and bicarbonate are not

recommended for the prevention of CA-AKI (8,13).

- ❖ Non-essential nephrotoxic agents should be stopped (if possible) before the use of ICM in patients with high risks for CA-AKI (2).
- ❖ Patients should be screened for CI-AKI based on eGFR rather than SCr (14).
- ❖ When $\text{eGFR} \leq 30 \text{ mL/min/1.73 m}^2$ in CKD patients, the number needed to induce injury from ICM exposure varies from 6 to infinity (no harm) in observational studies (8,9). Thus, use of ICM in those patients is not an absolute contraindication for appropriate clinical indication (8). Therefore, referring clinicians and radiologists should discuss the risks, benefits, and alternatives to ICM with patients presenting values for $\text{eGFR} \leq 30 \text{ mL/min/1.73 m}^2$ and those with AKI or non-anuric patients on dialysis (8,9).
- ❖ Patients on dialysis who produce $>100 \text{ cc}$ urine are non-anuric; those patients are at risk of losing of residual renal function after exposure to ICM. Therefore, use of ICM is relatively contraindicated in those patients and must be discussed with those patients (1,9).
- ❖ A single normal functioning kidney is not an independent risk factor for CI-AKI (15).
- ❖ In patients at risk of CI-AKI, appropriate conventional diagnostic doses of ICM should be used (instead of lower doses) to avoid suboptimal or nondiagnostic studies (8).
- ❖ If possible, nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, certain antibiotics, and chemotherapy agents, should be withheld in patients at high risk of CI-AKI both 48 hours before and after ICM administration (8,16).
- ❖ There are conflicting data as to whether withholding renin-angiotensin-aldosterone system inhibitors (RAASis) before ICM exposure has neutral, beneficial, or even harmful effects (17). However, this consensus guideline recommends withholding RAASis 48 hours before the use of ICM in patients at high risk for CA-AKI (8). This is just cautionary advice to avoid potential hypotension and hyperkalemia (in case those patients develop CA-AKI).
- ❖ Metformin itself does not cause CA-AKI. However, the Food and Drug Administration recommends withholding metformin prior to ICM exposure when $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ to avoid lactic acidosis (in case the patient develops CA-AKI) (8).
- ❖ If a patient develops CA-AKI, then if clinically feasible, non-essential nephrotoxic agents should be

withheld until renal function recovers (8).

- ❖ Prophylactic hemodialysis or ultrafiltration should not be used to decrease the risk of CI-AKI.
- ❖ There are no suitable studies in pediatric patients regarding this clinical issue. Pediatric patient care has been based on extrapolating data from adult populations. Therefore, these guidelines should also be applicable to the pediatric patient (pending additional research specifically relevant to children and infants) (8).

Several points about these recommendations deserve attention. First, it is a well-known fact that the risk of AKI is higher in procedures requiring IA versus IV administration of ICM (18). Therefore, these recommendations apply to procedures including IV contrast use and are not applicable to those including IA administration (as with coronary and peripheral vascular angiographies). Second, these recommendations clarify the definition of AKI after exposure to ICM exposure, recommending the avoidance of the traditional but misleading term CIN, which is commonly used in the literature (11,12). The term CA-AKI is recommended because not all cases of AKI after exposure to a contrast agent were actually induced by the agent. Third, contrary to KDIGO 2012 guidelines, these recommendations clearly state “*not to use bicarbonate and N-acetylcysteine*” for the prevention of CI-AKI (1,8). Fourth, these guidelines suggesting that RAASis be withheld for at least 48 hours before the procedure when the patient is at high risk for CA-AKI. Finally, these guidelines suggest the actual risk of CI-AKI is very small, and the risk has been overstated in the literatures due to the inclusion of older, poorly conducted observational studies (8).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims.2020.03.20>). The authors have no conflicts of interest to declare.

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