

EDITORIAL



Contrast-associated acute kidney injury is a myth: Yes

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Introduction

Contrast medium (CM) administration is widely cited as a leading cause of hospital-acquired acute kidney injury (AKI) [1]. Concern over precipitation of AKI by CM is pervasive, and has influenced clinical decision-making related to diagnostic imaging and therapeutic interventions for more than half a century. So-called contrast-induced AKI (CI-AKI) is defined as an acute impairment in renal function occurring within 3 days of CM administration *that is not attributable to any other etiology* [1, 2]. Yet, nearly all studies establishing CI-AKI as a clinical entity were performed in the absence of control populations not exposed to CM. These studies assumed causality from association, and considered all cases of AKI in CM-exposed patients as CI-AKI, even when alternative explanations were obvious (Fig. 1) [3–5]. A growing body of evidence, derived from studies that include adequate control populations and discussed in more detail below, now suggests that risk for AKI attributable to CM administration is modest at most. Yet, outsized fear of CI-AKI persists.

Clinical importance

The distinction between a causal and associative relationship between CM and AKI is not purely academic. The prevailing belief that CM plays a central role in AKI has had major impacts over several decades, including promotion of potentially suboptimal clinical care at the patient level and subversion of a research agenda at the scientific level. Withholding CM on the basis of overestimated risk deprives individual patients of diagnostic studies and therapeutic interventions, many of which

convey substantial proven benefit [6, 7]. There are scenarios in which CM administration is unavoidable, however, and the perceived risk of CM administration associated with such scenarios has driven intense interest in preventive measures for CI-AKI. Indeed, an entire field of investigation aimed at their identification and evaluation has been established. An enormous amount of funding has been allocated to this line of research and a very large number of patients have been exposed to experimental interventions including *N*-acetylcysteine, sodium bicarbonate, fluid loading, statins, vitamin C, vasoactive medications, theophylline, preconditioning ischemia, and renal replacement therapy—none of which are devoid of side effects [8]. The preponderance of negative trials testing similar preventive strategies for CI-AKI is in itself a strong argument against a causative relationship between CM and AKI, and even raises potential ethical concerns for enrollment of patients in such studies. Interestingly, all three authors of this editorial, as initial believers in CI-AKI, planned or initiated interventional trials aimed at its prevention in their respective fields of emergency medicine, critical care, and cardiology. In doing so, each abandoned their efforts after independently concluding, in the light of the available literature, that the role of CM in AKI has been vastly overestimated.

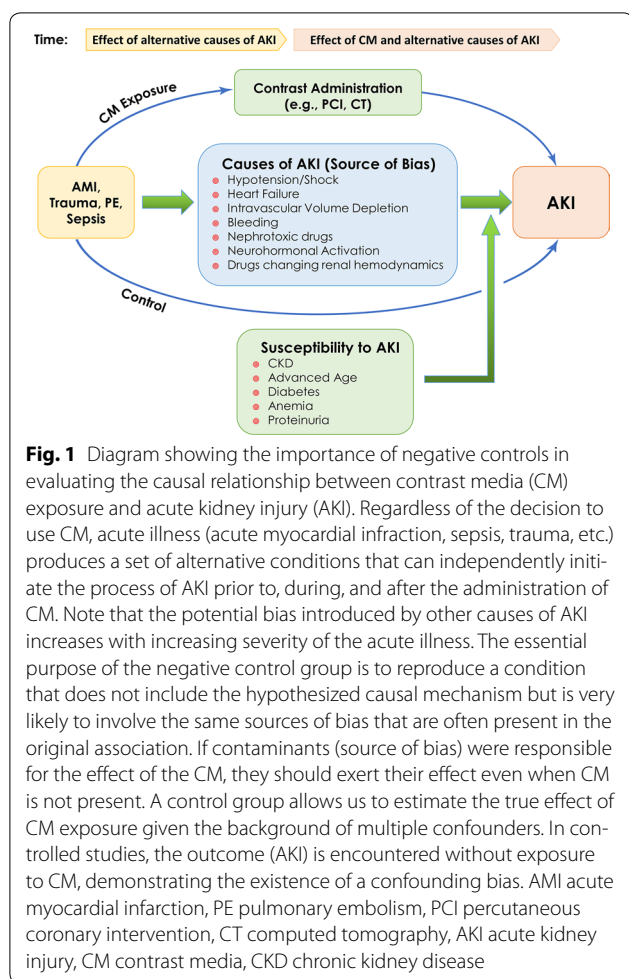
Intravenous contrast media and acute kidney injury in the general population

Studies performed in unselected populations with controls do not support a meaningful role for intravenous CM in causing AKI. Meta-analysis of 13 studies in which incidence of AKI was directly compared between patients who were and were not exposed to CM failed to demonstrate any increased risk of AKI, dialysis, or death associated with CM [9]. This is supported by a recent nationwide analysis of administrative data for almost 6 million patients in the USA, where rates of AKI were

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For contrasting viewpoints, please go to <https://doi.org/10.1007/s00134-017-4970-2> and <https://doi.org/10.1007/s00134-017-5015-6>.



nearly identical in patients who did and did not receive CM [10]. Direct comparison of populations, as performed in these studies, is confounded by selection bias associated with the decision to administer or withhold CM. Several subsequent studies have utilized propensity matching analysis to minimize this bias. None of these studies identified an independent association between intravenous CM administration and risk for AKI, dialysis, or death in the general population [11–13]. While one group did report increased risk of AKI associated with CM administration in the less than 5% of patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m², two others did not [11–13].

Contrast media and acute kidney injury in the critically ill

Critically ill patients have long been considered a population at particularly elevated risk of CI-AKI [14]. A recent systematic review revealed that this belief has been driven by a large body of uncontrolled data [15]. Meta-analysis of three propensity-matched controlled studies showed a

lack of significant difference in AKI incidence among 560 critically ill patients who were exposed or unexposed to CM [15]. Those data were reinforced by a large monocentric database analysis showing a lack of significant association between CM and AKI, renal replacement therapy, and mortality among 6877 propensity-matched intensive care unit patients [16]. These findings have important clinical implications, as the utility of CM for diagnosis and treatment of immediately life-threatening conditions may be even greater among critically ill patients than in the general population.

Contrast media and acute kidney injury in patients undergoing percutaneous intervention

The reported incidence of CI-AKI following percutaneous intervention (PCI) ranges from 1–2% in patients undergoing elective PCI to 10–20% in patients undergoing PCI for ST-elevation myocardial infarction (STEMI) [1, 3, 4, 7]. While attributed to CM exposure, the marked increase in AKI rates in these patients more likely results from associated conditions including hypotension, hemodynamic instability/cardiogenic shock, acute heart failure, hemorrhage, and initiation of medications that alter renal hemodynamics (Fig. 1). Indeed, multiple retrospective controlled studies in patients undergoing PCI were unable to show a meaningful adverse effect of CM exposure [6, 7, 10]. Further, a study performed in a large inpatient sample that controlled for comorbidity and acuity of illness found that patients with acute coronary syndromes ($n = 1,251,812$) who received CM experienced an unexpectedly lower rate of AKI as compared to patients who were not exposed to contrast (6.4% versus 17.4%) [10]. Finally, a propensity-matched cohort study of patients with non-STEMI reported one additional episode of AKI for every 62 participants treated with an early invasive approach instead of a conservative approach, with similar risks of dialysis or long-term risk of end-stage renal disease, but better long-term survival with the invasive approach [6] and in a propensity-matched cohort study of patients with STEMI, the risk of AKI was similar with and without CM exposure [7].

Conclusion

Mythology and science share a common purpose: to provide meaning to and understanding of phenomena that are readily observed but not easily explained. The two disciplines diverge dramatically in process, however, with the prior relying on imagination and conjecture and the latter on a rigorous method that includes observation followed by hypothesis formulation, testing through structured experimentation, and finally rejection or acceptance. In keeping with this, and the data discussed above, we support the clause under debate:

contrast-induced acute kidney injury is a myth. The concept of CI-AKI arose from observation and assumed causality, and despite a lack of rigorous hypothesis testing, has driven clinical practice for more than five decades. While a randomized controlled trial has not been conducted, there is now substantial evidence suggesting that CM contributes minimally, if at all, to the development of AKI [6, 7, 9, 11, 13, 15–17]. Despite the existence of such evidence, a pervasive preoccupation with what should be referred to as contrast-associated AKI (CA-AKI) persists in clinical practice, medical texts, and even among clinical researchers. There are many well-established risk factors for AKI (Fig. 1), many of which have clear causal relationships with AKI and are readily modifiable, yet are often ignored as episodes of AKI are attributed to CM. Disproportionate focus on CM also results in misappropriation of critical human and monetary capital that could be more effectively harnessed to reduce AKI-associated harms.

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Compliance with ethical standards

Conflicts of interest

None of the authors has a conflict of interest related to the present manuscript.

Received: 19 September 2017 Accepted: 23 September 2017

Published online: 14 December 2017

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