

Contrast-Associated Acute Kidney Injury (CA-AKI) in Children: Special Considerations

Martin Windpessl, M.D.¹
Andreas Kronbichler, M.D., Ph.D.²

Department of Internal Medicine IV (Nephrology Section)¹, Klinikum Wels-Grieskirchen, Grieskirchner Straße 42, 4600 Wels, Austria, Department of Internal Medicine IV (Nephrology and Hypertension)², Medical University Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria

Corresponding author:

Martin Windpessl, M.D.

Department of Internal Medicine IV (Nephrology Section), Klinikum Wels-Grieskirchen, Grieskirchner Straße 42, 4600 Wels, Austria

Tel: 0043-724-241-592194

E-mail: martin.windpessl@klinikum-wegr.at

Andreas Kronbichler, M.D. Ph.D.

Department of Internal Medicine IV (Nephrology and Hypertension), Anichstraße 35, 6020 Innsbruck, Austria

Tel: 0043-512-504-81338

E-mail: andreas.kronbichler@i-med.ac.at

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Contrast-associated acute kidney injury (CA-AKI) is a major concern when iodinated contrast material is administered, especially in patients at risk. Efforts have been undertaken to understand the detrimental effects of contrast media (CM). With the use of low-osmolar or iso-osmolar CM the incidence of CA-AKI has steadily decreased within the past decade; however, especially in the pediatric population information is scarce. Incidence rates have been reported to range between 0% to 18.75%, particularly depending on indication, selection of population (i.e. pre-existing co-morbidities), and definition of AKI. Different biomarkers have been proposed, but confirmatory studies are either lacking or have contributed to their lack of diagnostic power. Proteomic approaches have been employed and may pave the way to such discovery. Prevention strategies have been tested and proposed, but the recently published AMACING and PRESERVE trials have shown that commonly used strategies (such as systematic hydration or administration of N-acetylcysteine) have no role in the prevention of CA-AKI. We propose that thoughtful assessment of one's fluid state is the most appropriate approach and depending on the hydration status diuretics or fluid administration should be provided to achieve an euvolemic state ahead of contrast exposure.

Key words: Contrast Media, Acute Kidney Injury, Renal Insufficiency

Introduction

The incidence of acute kidney injury (AKI) in childhood is rising and its epidemiology has changed significantly over the past decades. Concurrent with technologic improvements in pediatric intensive care, a shift from primary renal causes, sepsis, and burns to renal ischemia (predominantly in the setting of cardiac surgery) and nephrotoxin exposure has been noted. Therefore, hospitalized children increasingly develop AKI not from primary kidney disease but concomitant with other systemic illness or related to treatment¹.

Over the past decades, formidable advances in radiology have greatly improved the practice of medicine, and the frequency of diagnostic and interventional imaging remains on the rise². The use of contrast media (CM) is either indispensable in this context (e.g. coronary angiography) or greatly improves the diagnostic accuracy of the examination. Therefore, apart from radiation exposure, allergic reactions and renal toxicity remain limitations of radiological interventions.

Contrast-associated acute kidney injury (CA-AKI) refers to the sudden

deterioration in renal function following contrast exposure in the absence of other causes. The underlying pathophysiology is incompletely understood. Etiologic factors that have been incriminated include vasoconstriction and direct tubular toxicity. CA-AKI has repeatedly been linked with adverse outcomes, such as length of hospital stay, in-hospital mortality and risk of chronic kidney disease (CKD) in later life.

Notably, causality cannot be inferred from this sequence and few studies in the field had a suitable control group to permit separation of genuine contrast-induced nephropathy from CA-AKI. Although the administration of iodinated CM is considered a major risk factor for the development of AKI, numerous recent publications have questioned the danger of modern radio-agents, and there is emerging consensus, that the risk of CA-AKI has been vastly overemphasized. Furthermore, compared with individuals with multifactorial AKI, patients with CA-AKI appear to be more likely to experience only mild decrements in kidney function that recover completely³.

Contrast nephrotoxicity is practically non-existent in isolation and usually develops in association with concomitant insults such as hypotension, dehydration, administration of other nephrotoxins (e.g. antibiotics), and underlying comorbidities^{4,5}. The co-existence of several such triggers is not uncommon, particularly in the intensive care unit (ICU). Naturally, ascribing AKI to one specific cause frequently remains elusive.

Pre-existing renal disease is the greatest independent risk factor for CA-AKI; furthermore, diabetes and advanced age predispose adult patients to CA-AKI. Type and volume of CM are independent and potentially modifiable predictors for the development of CA-AKI. In the pediatric population, such predisposing factors are less well defined. Ostensibly, children might carry a lower background risk; however, they exhibit their own unique risk factors, such as prematurity and congenital organ anomalies, as discussed below.

Evaluation of kidney function in children and definition of pediatric CA-AKI

There is no gold standard for estimating the glomerular

filtration rate (GFR) in children, and the limitations of serum creatinine in this context, its rate of production being proportional to muscle mass, are obvious. Although various formulas for estimating GFR exist, the Bedside Schwartz equation (estimated $GFR = [0.413 \times \text{height}] / \text{serum creatinine}$), valid in children from 1 to 16 years, remains the most practicable method in pediatrics. In 2004, the Acute Dialysis Quality Initiative (ADQI) termed the RIFLE criteria (risk, injury, failure, loss of function, end-stage renal disease). Three years later, a pediatric modified RIFLE (pRIFLE) AKI definition was developed in critically ill children⁶.

There is ongoing debate about the ideal definition of AKI in children. A new creatinine-based criterion for pediatric AKI (termed pROCK) defines AKI as a creatinine increase of both $\geq 20 \mu\text{mol/l}$ and $\geq 30\%$ over the initial value within 7 days. This was tested in 102,817 Chinese children and compared to the KDIGO and pRIFLE criteria. The authors identified AKI in 5432 (5.3%), 10,446 (10.2%) and 15,647 (15.2%) of participants when using the pROCK, KDIGO and the pRIFLE definitions⁷. Differences in the occurrence of AKI have also been reported among children with hospitalization. In line, the pRIFLE criterion found the highest rate of AKI (51.1%) as compared to 40.3% and 37.3% with the KDIGO and AKIN criteria, respectively⁸.

However, serum creatinine is an imperfect marker for the diagnosis of AKI in general and of CA-AKI in particular. Numerous novel biomarkers are being scrutinized, and candidates include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18) and liver-type fatty acid-binding protein (L-FABP)^{9,10}. For instance, Hirsch and co-workers observed substantial upregulation of urine and plasma NGAL 2 hours after CM in a patient population undergoing cardiac catheterization, which predicted occurrence of contrast nephropathy. 91 children were included prospectively and NGAL was measured at baseline and after 2 and 6 hours. A significant increase in urinary and plasma NGAL was observed as early as 2 hours after contrast administration in those with CA-AKI, which was defined as a 50% or greater increase in serum creatinine (11 subjects). Using a cut-off value of 100 ng/mL yielded in an excellent sensitivity, specificity and area under the receiver-operating characteristic (AUC) for the 2-hour urine NGAL (73%, 100%, and

0.92) and 2-hour plasma NGAL (73%, 100%, and 0.91, respectively). Measurement of NGAL was found to be the most powerful predictor of childhood CA-AKI in this investigation¹¹. In contrast, another study recruiting 50 children undergoing cardiac catheterization found CA-AKI in 16 subjects within a period of 24 hours and reported a comparable increase in serum NGAL within the first 6 hours in both, the AKI and the non-AKI group¹².

No CA-AKI event was observed in a small study from Korea including 26 children undergoing cardiac catheterization. In line, urinary NGAL remained stable over 48 hours of follow-up, while the authors observed a steady increase of urine KIM-1, and a transient increase of L-FABP. The former increase became irrelevant when adjusted for urinary creatinine excretion. In the absence of meaningful creatinine changes, the authors concluded that L-FABP may be a useful biomarker to detect subclinical AKI⁹.

A study of 123 children and adolescents with a prospective follow-up included one group (n=58) receiving angiography with iopromide and one group (n=65) undergoing magnetic resonance (MR) angiography/urography with gadolinium (Gd)-based CM. CA-AKI occurred in two patients in the iopromide group (3.9%), while 9.7% (6 patients) in the second group developed AKI. In the prediction of AKI normalized urinary KIM-1 showed the most convincing results with a AUC at 24 hours of 0.76 (sensitivity 83.3% and specificity of 54.2%). Other markers, such as NGAL and urinary NGAL could not predict CA-AKI accurately¹³.

Ideally a biomarker predicts the risk of CA-AKI at baseline. A proteomic approach was chosen to identify such markers and ten children developed AKI within 24 hours of cardiac catheterization compared to seven without. The absence of the 41 amino acid-variant of human beta-defensin-1 yielded an AUC of 0.89–0.99 and the presence of a 4631 Da large marker had an AUC of 0.84¹⁴. Together, both markers may provide an accurate forecast identifying children at risk to develop AKI following contrast exposure.

A prospective study of children undergoing cardiac surgery without preoperative AKI examined the differences between a creatinine-defined versus a cystatin C-defined AKI incidence. The authors found a substantially lower incidence of AKI when cystatin C was used to define AKI and in those with AKI interleukin-18 and KIM-1 as putative biomarkers more closely correlated with this definition¹⁵.

Taken together, the predictive value of proposed markers of CA-AKI is controversial and more research in this direction with a larger sample size is needed. In line, uniform definition of AKI in this context is also necessary to directly compare different studies with each other. Whether a cystatin C-based definition of AKI is more informative and more closely associates with biomarkers needs to be tested in future trials.

AKI in children

AKI is a frequent comorbidity experienced by hospitalized children and exposure to nephrotoxic agents¹⁶. Next to antibiotics such as aminoglycosides and vancomycin, CM ranks among the most common potential culprits prescribed to exposed individuals¹⁷. In the ICU setting, various factors such as sepsis, cardiac dysfunction, dehydration or volume overload, may compromise renal blood flow.

It is estimated that drugs, including contrast agents, contribute to approximately 15% of all AKI cases in adults but children are usually less prone to nephrotoxicity¹⁸.

The Nephrotoxic Injury Negated by Just-in-time Action (NINJA) recently reported a high prevalence of nephrotoxin use following congenital heart disease (CHD) surgery¹⁸. Nephrotoxins were defined according to pre-specified criteria, and this list included CM. Although no association between high nephrotoxin exposure and AKI was observed, this was ascribed to the multitude of competitive renal insults. The authors conclude that nephrotoxin exposure may represent a modifiable risk factor for AKI in high risk individuals.

In an Israeli single center study performed on a neonatal ICU the authors demonstrated underreporting of AKI, with episodes of kidney injury often not recorded in patients' medical files¹⁹. This is of particular concern, because over the past decade the long-term consequences of AKI have garnered increased attention and several cohort studies demonstrate that pediatric AKI is a gateway for proteinuria, hypertension, and CKD in later life. This association seems to be dose-dependent, i.e. individuals with more severe forms of AKI show a higher risk for progression to CKD.

Specific pediatric risk factors

In recent times, the impact of prematurity on future kidney health has attracted attention, and it is now established that children born at low birth weight show an increased risk for CKD in adulthood²⁰. With 50,000 infants born each year at less than 28 weeks of gestation in the United States alone, the prospective impact of this trend cannot be overestimated. Reduced global nephron mass and incomplete nephrogenesis are underlying mechanisms. Subsequent postnatal events, such as infections, may further impair the development of intact tubular structures, and render individuals prone to tubular damage, when exposed to nephrotoxic agents²⁰.

CHD constitutes the most common congenital disorder in neonates. Critical CHD, defined as need for surgery or catheter-based intervention in the first year of life, occurs in approximately one quarter of such individuals²¹. Congenital anomalies of kidneys and urinary tract (CAKUT) represent another sizeable proportion of anomalies identified prenatally and are a major cause of end-stage renal disease (ESRD) in children²². For obvious reasons, both entities are associated with an increased long-term need for radiologic procedures. A vast array of other forms of congenital kidney diseases, such as idiopathic nephrotic syndrome and hereditary tubulopathies, though rare individually, amount to a substantial number of children with CKD in specialist centers. Lastly, pediatric transplant recipients are another vulnerable cohort posing unique challenges²³.

Incidence of pediatric CA-AKI

Few studies have specifically examined CA-AKI in pediatric populations. In the trial by Hwang et al., no increase in serum creatinine levels was observed in a cohort with normal kidney function, corroborating the safety of CM in patients without CKD⁹. Along similar lines, a study from a trauma center, evaluating the incidence of CA-AKI in severely injured pediatric patients (n=211), showed no difference in the incidence of contrast nephropathy between a non-contrast group and a group exposed to CM (8.5% vs. 7.3%, *P* value=0.76)²⁴. Two recent trials reported incidences of pediatric CA-AKI between 4-10%, but, as is frequently

the case in this context, the lack of controls does not permit to draw causal inference from these results²⁵. A study by Bedoya et al.²⁶, involving 140 neonates (age 0–30 days), with 59 receiving intravenous iodinated CM, found no evidence of contrast nephrotoxicity when compared to propensity-matched control groups, not exposed to CM. Recently, McDonald et al. were able to replicate this finding in the largest cohort reported to date. Among 2,201 pediatric patients (mean age 15 years), outcomes were compared between individuals who received contrast-based computed tomography (CT)-imaging (n=1,773) versus patients who received non-contrast scans (n=428). Demographics were not balanced among the two groups, with more ICU admissions in the group receiving CM, while pre-disposing comorbidities were more frequent in the non-contrast scan group (i.e. CKD and calcineurin inhibitor use). AKI and dialysis occurred in 3.3% and 0.1%, respectively, with no significant difference between the two groups. Of note, all patients with post-CT stage 3 AKI also had contrast-independent causes of AKI, such as hypovolemia, hypotension, and nephrotoxic medications. However, only a minority of patients (n=145) had an estimated GFR <60 ml/min/1.73 m², limiting the generalizability of these data²⁷ (see Table 1 for further details).

On the whole, the true incidence of contrast nephrotoxicity in pediatrics appears to be very low and in patients with normal kidney function, the risk of CA-AKI seems negligible.

Prevention

There are no evidence-based guidelines for CA-AKI prevention in children. In the adult population, a large number of intervention studies has been performed in this field; such studies are scarce in children. Therefore, preventive strategies in pediatrics frequently extrapolate data from the adult literature, and it can often only be assumed that such measures also provide some degree of protection for children (and do no harm). Moreover, high-quality trials with adequate follow-up and clinically meaningful endpoints beyond “delta creatinine at day 7” have only recently started to emerge in the adult literature and frequently challenge purported standards of care. For instance, the

benefit of preventive approaches in adults has been seriously questioned by two recent high-profile trials, namely AMACING and PRESERVE^{28,29}; as an aside, overall AKI risk was remarkably low in both studies, despite their purported high-risk cohorts.

1. Type of contrast

The past four decades have seen a continuous decrease of osmolality of contrast agents, reaching physiologic levels with iso-osmolar agents (IOCM) such as iodixanol. Following a meta-analysis by Barrett and Carlisle, published in 1993, the use of hyperosmolar CM (HOCM) has largely been abandoned³⁰. In a large Italian cohort undergoing percutaneous coronary intervention, there were no differences in the adjusted risk of CA-AKI across 4 low-osmolar CM (LOCM), compared with iodixanol, suggesting that overall risk is low with all modern contrast agents^{31,32}. In line, Zo'o and colleagues performed a trial comparing the LOCM iobitrol with iodixanol. 128 children (age 8.7±4.7 years) undergoing CT were randomized and no significant difference of AKI was found in this low risk cohort²⁵.

2. Volume of contrast

The amount of CM used is frequently cited as an independent predictor for the development of contrast nephropathy. However, according to the recent manual of the American College of Radiology (ACR), there is a lack of robust data to support a dose-toxicity relationship for intravenous (IV) iodinated CM, with only intra-arterial CM showing a directly proportional relationship³³. Very small volumes of contrast agents, typically 1.5–2ml/kg, are usu-

ally administered in neonates and infants³⁴, and, as stated in a previous review, the “volume of contrast should be determined by the size of the child, the imaging study being performed, and the estimated GFR³⁵”. Nevertheless, it seems prudent to limit contrast volume in at-risk individuals, provided that the quality of diagnostic imaging is not jeopardized. An ALARA (as low as reasonably achievable) concept is usually recommended.

3. Route of administration

The majority of data in the field of contrast nephropathy stems from cardiology studies. Unlike IV contrast administration, in coronary angiography the injection is intra-arterial and supra-renal. Cholesterol emboli, dislodged by the catheter, are possible competitor strikes, and the kidneys are exposed to a more abrupt and concentrated CM dose. Consequently, a higher overall incidence of CA-AKI is usually found in studies of cardiac angiography than in studies involving IV contrast administration. However, McDonald et al. recently reported a similar risk of AKI after intra-arterial and IV administration of CM (9.9% versus 11%) in a large cohort of patients that received both routes of administration³⁶. Despite this, patients undergoing such intra-arterial procedures should be monitored with particular attention, because intra-arterial angiography is associated with a higher risk of post-contrast AKI, regardless of etiology.

4. Hydration

Fluid administration increases urine flow rate, reduces CM concentration in the tubule and expedites CM elimi-

Table 1. Studies of Contrast-associated Acute Kidney Injury in Children. Studies Showed a Wide Range of Incidence Rates, which is in Analogue with Adult Data. Among other Factors this Range is Clearly Influenced by Diverse Criteria used to Define Acute Kidney Injury

Author	Year of publication	N (iodinated CM)	Type of study	Control group propensity	Age (years)	Intervention	AKI definition	Incidence
Ajami ⁴⁸	2010	80	prospective	no	<18	CA	RIFLE	18.75%
Zo'o ²⁴	2011	145	prospective	iodixanol vs. iobitridol	≤16	CT	CrCl changes; CA-AKI (<25% reduction in CrCl)	4.8% (iobitridol), 10.6% (iodixanol)
Hwang ⁸	2014	26	prospective	no	7.1	CA	-	0%
Cantais ⁴⁹	2016	346	retrospective, cohort	no	<16	CT	KDIGO	10.3%
McDonald ²⁶	2018	2,201 (1,391)	retrospective, cohort	yes	<18	CT	KDIGO	3.5% (contrast), 7.8% (no contrast)
Paul ²³	2019	211	retrospective	Contrast versus no CT contrast	<15	CT	AKIN	7.3% (contrast), 8.5% (no contrast)

Abbreviations: CM (contrast media), CA (coronary angiography), CT (computed tomography), RIFLE (risk, injury, failure, loss, ESRD), CrCl (creatinine clearance), CA-AKI (contrast-associated acute kidney injury), KDIGO (Kidney Disease Improving Global Outcomes), AKIN (Acute Kidney Injury Network).

nation, thereby limiting exposure time of tubular cells to the deleterious effects of CM. Consequently, intravenous hydration is considered standard of care for patients at risk for CA-AKI, with 0.9% normal saline (NS) being the most common utilized fluid. However, in the AMACING trial²⁸, involving 660 adult patients with CKD stage 3, preventive hydration with NS not only failed to show benefit in terms of AKI risk but reported 13 episodes (4%) of symptomatic heart failure in the treatment group versus none in the control group. Along similar lines, Liu et al. observed an increased risk of CA-AKI and death in patients with CKD with “excessively high hydration”, as calculated by hydration volume to weight³⁷. It seems obvious that children at increased risk for contrast nephropathy, such as patients with CHD, are also particularly prone to volume overload, so a cautionary approach regarding hydration is mandatory.

Limiting exposure of the kidney to radiocontrast by generating high urine flow without causing hypovolemia (“forced diuresis”) remains an accepted tool in preventing CA-AKI; this concept is also cited in the pediatric literature³⁵. In adults, the P.R.I.N.C.E. study³⁸, published in 1999, provided evidence that “good urine output” (urine flow rates above 150 ml/h) following contrast exposure is associated with a reduced risk of AKI. The study involved 98 patients with CKD stage 3–4 (median estimated creatinine clearance of 32 ml/min) undergoing elective coronary angiography. In hindsight, assessment of volume status in this study appears unduly invasive, with right heart catheterization performed in all participants, and Swan-Ganz catheterization in individuals randomized to the experimental arm; moreover, all patients had urinary catheters placed. Therefore, the practicality of this frequently cited paper seems questionable. The RenalGuard® system, a device delivering replacement solution in real-time and in an amount matched to urinary output, thereby maintaining euvolemia, is a relatively new strategy for CA-AKI prevention. It also involves placement of a urinary catheter; price issues and lack of data in children remain limitations³⁹.

For all hydration strategies, the optimal type, quantity, timing, and duration of fluid administration remain largely unresolved issues and well-defined protocols are lacking, especially for children.

Pharmacologic strategies

1. No approved drugs exist for the prevention of CA-AKI.

N-Acetylcysteine (NAC), a free radical scavenger antioxidant, arguably represents the best-known agent in the field of CA-AKI prevention. The landmark paper by Tepel et al.⁴⁰ sparked a flurry of studies, which have been subject to a number of meta-analyses. Due to the heterogeneity of study designs, it was difficult to draw clear conclusions. Following the publication of the ACT trial and the PRESERVE study^{29,41}, both reporting no benefit of NAC in adult patients with CKD, this compound has lost much of its appeal. There are no publications pertaining to its use in the field of pediatric CA-AKI. Some experts continue to use this agent in conjunction with hydration in children deemed at high risk for contrast nephropathy, although they acknowledge that this approach is not backed by the available literature, and its routine for AKI prophylaxis is not recommended. Notably, NAC should not be seen as a substitute for appropriate pre-procedural patient screening and other measures, as outlined below.

Acetazolamide, a carbonic anhydrase inhibitor, has been proposed to be beneficial in the prevention of CA-AKI. One study involving 96 pediatric patients with CKD (aged 3 to 19 years, mean creatinine clearance 52 ml/min/1.73 m²), who underwent coronary angiograms, CT, or renal angiograms, found that urinary alkalinization with acetazolamide resulted in a lower incidence of postcontrast AKI than intravenous sodium bicarbonate (0.0 versus 8.7%; $P=0.049$)⁴². However, the difference in mean serum creatinine (1.32±0.13 mg/dL versus 1.39±0.14 mg/dL) 48 hours after contrast exposure, although statistically significant, is of doubtful clinical relevance. No corroborating evidence in pediatric cohorts has emerged since publication of this trial.

The alpha-2-receptor agonist dexmedetomidine is approved for sedation in adult ICU patients, but is increasingly used off-label in the pediatric setting for various indications⁴³. Its low risk of respiratory depression makes it a comparatively safe agent. In a murine model, alpha-2-receptor agonists exhibited renal protective effects following iohexol injection⁴⁴. Attenuation of contrast-mediated renal blood reduction after radiocontrast injection is a postulated mechanism⁴⁴. The use of dexmedetomidine for the pre-

vention of AKI of diverse etiologies, including CA-AKI, has been championed by a Turkish group. Bayram et al.⁴⁵⁾ analyzed the effect of dexmedetomidine in a randomized, controlled trial (RCT) involving 60 children with CHD, scheduled for coronary angiography. The authors observed CA-AKI (pRIFLE criteria) in 3 patients (10%) in the intervention arm and in 11 (36.7%) in the control arm. Moreover, renin and NGAL levels at 24 hours after angiography were significantly lower in the dexmedetomidine group. Although bradycardia was noted in 7 patients in the active arm as compared to 3 in the control group, this did not reach statistical significance. A recent meta-analysis of pharmacological interventions for AKI prevention after pediatric cardiac surgery reported a lower incidence of AKI in the dexmedetomidine groups (OR 0.65)⁴⁶⁾. Future trials should clarify the effectiveness of this agent for the prevention of CA-AKI and it remains to be seen, whether this drug will stand the test of time.

Numerous other agents have been evaluated, without showing benefit beyond single center trials³⁵⁾.

Given that multiple lines of evidence suggest that no single intervention strategy may successfully prevent CA-AKI, a multimodal approach for renoprotection has been advocated⁴⁷⁾. We propose that currently physicians should identify at-risk groups, hold potentially nephrotoxic drugs prior to contrast administration, approach the interventionalist preemptively with a view to minimizing contrast volume, and target euvolemia.

Once CA-AKI has occurred, management follows general recommendations for AKI; in this context, it is important to avoid “second hits” i.e. repeat CM administration⁴⁸⁾.

CA-AKI: Much ado about little?

CA-AKI is widely cited as a leading cause of in-hospital AKI and its validity remains a clinical dogma. Newhouse et al.⁴⁹⁾ were the first to observe that patients who were not exposed to iodinated contrast showed rates of AKI similar to patients with contrast nephropathy after CT. These authors showed that controlling for potentially confounding clinical conditions that may trigger AKI is difficult and that a “post hoc, ergo propter hoc” reasoning has been in

place for too long. Several recent publications^{50,51)}, using propensity score-matching, have further challenged the doctrine of CA-AKI as a stand-alone entity. Moreover, in hospitalized individuals, random changes in serum creatinine (‘background noise’) may result in AKI misclassification, irrespective of CM being present. Patients who receive contrast often have numerous other independent risk factors for AKI, either from their primary pathology or comorbidities, independent of contrast administration. As stated by Ehrmann et al.⁵²⁾, this distinction between a causal and an associative relationship between CM and AKI is of great importance, because suboptimal care may result from excessive caution (“renalism”). For fear of nephrotoxicity, patients may undergo unenhanced imaging which is less accurate than contrast-enhanced imaging, resulting in negative impact on clinical decisions related to treatment. Lastly, the bulk of negative trials in the field of CA-AKI prevention could be regarded as another piece in the chain of evidence indicating that contrast nephropathy may be more fiction than fact.

Conclusion

In the absence of randomized controlled trials, widespread lack of meaningful endpoints, and with only a handful of good quality papers available, it is difficult to make firm recommendations. Likewise, in view of the growing body of literature, the search for a single panacea to prevent contrast nephropathy in general and in pediatrics in particular will likely remain futile. Children at risk for AKI should be treated with due diligence, regardless of whether CA-AKI is interpreted as contrast-induced AKI (i.e. a causative diagnosis) or post-contrast AKI (a correlative diagnosis). This should entail a multimodal approach aimed at AKI prevention, close cooperation between care providers, and early (preemptive) nephrology consultation.

Conflict of interest

Both authors declare no competing conflicts of interest related to the submitted work.

ORCID

Andreas Kronbichler <https://orcid.org/0000-0002-2945-2946>

References

- Goldstein SL. Acute kidney injury in children and its potential consequences in adulthood. *Blood Purif* 2012;33:131-7.
- Katzberg RW, Haller C. Contrast-induced nephrotoxicity: clinical landscape. *Kidney Int Suppl* 2006;S3-7.
- Tandukar S, Rondon-Berrios H, Weisbord SD. Intravascular Iodinated Contrast Is an Independent Cause of Acute Kidney Injury Following Coronary Angiography. *South Med J* 2019;112:541-6.
- Windpessl M, Kronbichler A. Pro: Contrast-induced nephropathy-should we try to avoid contrast media in patients with chronic kidney disease? *Nephrol Dial Transplant* 2018;33:1317-9.
- Ewing MJ, Eidt JF. Con: Contrast-induced nephropathy-should we try to avoid contrast media in patients with chronic kidney disease? *Nephrol Dial Transplant* 2018;33:1320-2.
- Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007;71:1028-35.
- Xu X, Nie S, Zhang A, Jianhua M, Liu HP, Xia H, et al. A New Criterion for Pediatric AKI Based on the Reference Change Value of Serum Creatinine. *J Am Soc Nephrol* 2018;29:2432-42.
- Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol* 2015;10:554-61.
- Hwang YJ, Hyun MC, Choi BS, Chun SY, Cho MH. Acute kidney injury after using contrast during cardiac catheterization in children with heart disease. *J Korean Med Sci* 2014;29:1102-7.
- Yim HE. Neutrophil Gelatinase-Associated Lipocalin and Kidney Diseases. *Child Kidney Dis* 2015;19:79-88.
- Hirsch R, Dent C, Pfriend H, Allen J, Beekman RH, 3rd, Ma Q, et al. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. *Pediatr Nephrol* 2007;22:2089-95.
- Tkaczyk M, Tomczyk D, Jander A, Goreczny S, Moszura T, Dryzek P, et al. Glomerular filtration decrease after diagnostic cardiac catheterisation in children with congenital cardiac malformation - the role of serum creatinine, cystatin C, neutrophil gelatinase and urine output monitoring. *Postepy Kardiologii Interwencyjnej* 2018;14:67-74.
- Spasojevic-Dimitrijeva B, Kotur-Stevuljevic J, Dukic M, Paripovic D, Milosevski-Lomic G, Spasojevic-Kalimanovska V, et al. Serum Neutrophil Gelatinase-Associated Lipocalin and Urinary Kidney Injury Molecule-1 as Potential Biomarkers of Subclinical Nephrotoxicity After Gadolinium-Based and Iodinated-Based Contrast Media Exposure in Pediatric Patients with Normal Kidney Function. *Med Sci Monit* 2017;23:4299-305.
- Bennett MR, Ravipati N, Ross G, Nguyen MT, Hirsch R, Beekman RH, et al. Using proteomics to identify preprocedural risk factors for contrast induced nephropathy. *Proteomics Clin Appl* 2008;2:1058-64.
- Zappitelli M, Greenberg JH, Coca SG, Krawczeski CD, Li S, Thiessen-Philbrook HR, et al. Association of definition of acute kidney injury by cystatin C rise with biomarkers and clinical outcomes in children undergoing cardiac surgery. *JAMA Pediatr* 2015;169:583-91.
- Uber AM, Montez-Rath ME, Kwiatkowski DM, Krawczeski CD, Sutherland SM. Nephrotoxin exposure and acute kidney injury in critically ill children undergoing congenital cardiac surgery. *Pediatr Nephrol* 2018;33:2193-9.
- Goldstein SL, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. *Kidney Int* 2016;90:212-21.
- Uber AM, Sutherland SM. Acute kidney injury in hospitalized children: consequences and outcomes. *Pediatr Nephrol* 2018.
- Cleper R, Shavit I, Blumenthal D, Reisman L, Pomeranz G, Haham A, et al. Neonatal acute kidney injury: recording rate, course, and outcome: one center experience. *J Matern Fetal Neonatal Med* 2019;32:3379-85.
- Starr MC, Hingorani SR. Prematurity and future kidney health: the growing risk of chronic kidney disease. *Curr Opin Pediatr* 2018;30:228-35.
- Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics* 2013;131:e1502-8.
- Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 2003;18:796-804.
- Abbas FM, Julie BM, Sharma A, Halawa A. "Contrast nephropathy" in renal transplantation: Is it real? *World J Transplant* 2016;6:682-8.
- Paul KM, 2nd, Johnson J, Garwe T, Sarwar Z, Motghare P, Daly W, et al. Computed Tomography with Intravenous Contrast Is Not Associated with Development of Acute Kidney Injury in Severely Injured Pediatric Patients. *Am Surg* 2019;85:e1-e5.
- Zo'o M, Hoermann M, Balassy C, Brunelle F, Azoulay R, Pariente D, et al. Renal safety in pediatric imaging: randomized, double-blind phase IV clinical trial of iobitridol 300 versus iodixanol 270 in multidetector CT. *Pediatr Radiol* 2011;41:1393-400.
- Ciavatta DJ, Yang J, Preston GA, Badhwar AK, Xiao H, Hewins P, et al. Epigenetic basis for aberrant upregulation of autoantigen genes in humans with ANCA vasculitis. *J Clin Invest* 2010;120:3209-19.
- McDonald JS, McDonald RJ, Tran CL, Kolbe AB, Williamson EE, Kallmes DF. Postcontrast Acute Kidney Injury in Pediatric Patients: A Cohort Study. *Am J Kidney Dis* 2018;72:811-8.
- Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM,

- Vermeeren MA, 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;389:1312-22.
29. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. *N Engl J Med* 2018;378:603-14.
30. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 1993;188:171-8.
31. Azzalini L, Vilca LM, Lombardo F, Poletti E, Laricchia A, Beneduce A, et al. Incidence of contrast-induced acute kidney injury in a large cohort of all-comers undergoing percutaneous coronary intervention: Comparison of five contrast media. *Int J Cardiol* 2018;273:69-73.
32. Kronbichler A, Shin JI, Windpessl M. What is left to prevent contrast-induced acute kidney injury? No difference between low and iso-osmolar contrast media. *Int J Cardiol* 2018;273:94-5.
33. Media ACoDaC. ACR Manual On Contrast Media. 2018.
34. Trout AT, Dillman JR, Ellis JH, Cohan RH, Strouse PJ. Patterns of intravenous contrast material use and corticosteroid premedication in children--a survey of Society of Chairs of Radiology in Children's Hospitals (SCORCH) member institutions. *Pediatr Radiol* 2011;41:1272-83.
35. Verghese PS. Contrast nephropathy in children. *J Pediatr Intensive Care* 2014;3:45-52.
36. McDonald JS, Leake CB, McDonald RJ, Gulati R, Katzberg RW, Williamson EE, et al. Acute Kidney Injury After Intravenous Versus Intra-Arterial Contrast Material Administration in a Paired Cohort. *Invest Radiol* 2016;51:804-9.
37. Liu Y, Li H, Chen S, Chen J, Tan N, Zhou Y, et al. Excessively High Hydration Volume May Not Be Associated With Decreased Risk of Contrast-Induced Acute Kidney Injury After Percutaneous Coronary Intervention in Patients With Renal Insufficiency. *J Am Heart Assoc* 2016;5.
38. Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, 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. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol* 1999; 33:403-11.
39. Mattathil S, Ghumman S, Weinerman J, Prasad A. Use of the RenalGuard system to prevent contrast-induced AKI: A meta-analysis. *J Interv Cardiol* 2017;30:480-7.
40. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;343:180-4.
41. Investigators ACT. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 2011; 124:1250-9.
42. Assadi F. Acetazolamide for prevention of contrast-induced nephropathy: a new use for an old drug. *Pediatr Cardiol* 2006;27: 238-42.
43. Phan H, Nahata MC. Clinical uses of dexmedetomidine in pediatric patients. *Paediatr Drugs* 2008;10:49-69.
44. Billings FTt, Chen SW, Kim M, Park SW, Song JH, Wang S, et al. alpha2-Adrenergic agonists protect against radiocontrast-induced nephropathy in mice. *Am J Physiol Renal Physiol* 2008; 295:F741-8.
45. Bayram A, Ulgey A, Baykan A, Narin N, Narin F, Esmoğlu A, et al. The effects of dexmedetomidine on early stage renal functions in pediatric patients undergoing cardiac angiography using non-ionic contrast media: a double-blind, randomized clinical trial. *Paediatr Anaesth* 2014;24:426-32.
46. Liu Y, Sheng B, Wang S, Lu F, Zhen J, Chen W. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2018; 18:7.
47. McCullough PA. Multimodality prevention of contrast-induced acute kidney injury. *Am J Kidney Dis* 2008;51:169-72.
48. Lakhali K, Ehrmann S, Robert-Edan V. Iodinated Contrast Medium Renal Toxicity: The Phantom Menace or Much Ado About Nothing? *Crit Care Med* 2017;45:e745-e6.
49. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *AJR Am J Roentgenol* 2008;191:376-82.
50. McDonald JS, McDonald RJ, Williamson EE, Kallmes DF, Kashani K. Post-contrast acute kidney injury in intensive care unit patients: a propensity score-adjusted study. *Intensive Care Med* 2017;43: 774-84.
51. McDonald JS, McDonald RJ, Williamson EE, Kallmes DF. Is Intravenous Administration of Iodixanol Associated with Increased Risk of Acute Kidney Injury, Dialysis, or Mortality? A Propensity Score-adjusted Study. *Radiology* 2017;285:414-24.
52. Ehrmann S, Aronson D, Hinson JS. Contrast-associated acute kidney injury is a myth: Yes. *Intensive Care Med* 2018;44:104-6.