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ORIGINAL ARTICLE

Incidence of contrast-induced acute kidney injury in a pediatric setting: a cohort study

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Abstract
Background Contrast-induced acute kidney injury (CI-AKI) is a common pathology among adult patients, with an incidence ranging from 3–25 % depending on risk factors. Little information is available regarding CI-AKI incidence, risk factors, and prognostic impact in the pediatric population.
Methods We performed a retrospective study of pediatric patients who underwent computed tomography (CT) scan with iodinated contrast media injection between 2005 and 2014 in five pediatric units of a university hospital. CI-AKI was defined according to Kidney Disease/Improving Global Outcomes (KDIGO) criteria.
Results Of 346 identified patients, 233 had renal function follow-up and were included in our analyses. CI-AKI incidence was 10.3 % [95 % confidence interval (CI) 6.4–14.2 %]. CI-AKI was associated with 30-day unfavorable outcome before (45.8 % vs. 19.7 %, $P=0.007$) and after [odds ratio (OR) 3.6; 95 % CI 1.4–9.5] adjustment for confounders. No independent risk factors of CI-AKI were identified.
Conclusions CI-AKI incidence was as high as 10.3 % following intravenous contrast media administration in the pediatric setting. As reported among adults, CI-AKI was associated with unfavorable outcome after adjustment for confounders. Although additional studies are needed in the pediatric setting, our data suggest that physicians should maintain a high degree of suspicion toward this complication among pediatric patients.

Keywords Acute kidney injury · Contrast-associated nephropathy · Pediatrics · Incidence · Risk factors · Prognosis

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Introduction

Acute kidney injury (AKI) develops in up to 60 % of critically ill patients and is associated with high morbidity and mortality rates and an increased risk of subsequent chronic kidney disease (CKD) [1–3]. Despite improvements in dialysis technology and supportive care, AKI-associated morbidity and mortality rates have not changed for several decades [4]. Several recent studies suggest that AKI itself may influence patient outcomes independently of the nature and severity of the underlying disease and metabolic consequences of renal dysfunction [5–7].

Contrast medium use is a major risk factor for AKI, and the increasing application of contrast media for diagnostic and interventional procedures has made contrast-induced acute kidney injury (CI-AKI) the third most common cause of hospital-acquired AKI [8, 9]. CI-AKI is most commonly

defined as serum creatinine (S_{Cr}) elevation of 0.5 mg/dl (44 μmol/L) or of 25 % within 48 h after exposure to contrast medium [10]. However, the relevance of this definition is controversial following reports of delayed S_{Cr} elevation and differences between AKI definitions and the specific CI-AKI definition [11, 12]. Thus, the recent Kidney Disease/Improving Global Outcomes (KDIGO) guidelines suggested their definition be used to define AKI even in this specific context [13].

CI-AKI incidence varies widely among studies depending on definitions used, study population, and baseline risk factors. CI-AKI may affect as little as 3 % of low-risk patients [14] and as many as 25 % of patients with risk factors, such as pre-existing renal dysfunction, diabetes, advanced age, or concurrent nephrotoxic drug exposure [15]. Only limited data report CI-AKI incidences in specific patient populations, including in the pediatric setting. A recent study reported a CI-AKI incidence ranging from 5 to 10 % in a population of 128 pediatric patients [16].

The primary objective of this study was to assess CI-AKI incidence among pediatric patients in a university hospital. Secondary objectives were to assess the risk factors and prognostic impact of CI-AKI in this setting.

Methods

Patients

We performed an observational retrospective cohort study in the following five units of the Saint-Etienne University Hospital: Pediatrics, Pediatric Oncology, Pediatric Surgery, Pediatric Intensive Care Unit, and Pediatric Emergency Department. The study involved pediatric patients (age <16 years) admitted between January 2005 and September 2014 who underwent computed tomography (CT) scan with iodinated contrast media injection. Patients without renal function assessment either before or following contrast media injection were secondarily excluded from the main analysis. In case of multiple CT scans with contrast media infusion or multiple hospitalizations, only the first was considered.

Definitions

In accordance with the KDIGO classification system, AKI was defined as a S_{Cr} increase of ≥26.4 μmol/L within 48 h or of ≥150 % from baseline presumed to have occurred within the prior 7 days or as urine output of <0.5 ml/kg/h for ≥6 h (i.e., oliguria) [13, 17]. Baseline renal function was based on the baseline Cr and estimated glomerular filtration rate (eGFR; determined using the revised 2009 version of Schwartz's formula [18]) at the time of contrast media injection; any degree of AKI within 48 h was considered contrast-associated nephropathy. Urine output was defined as shift urine output observed or estimated according to weight of diapers in infants. Foley catheter was uncommonly used in the studied patients, except in intensive care unit (ICU) patients. Iodinated contrast media received during the previous 72 h either in another hospital or in prior ambulatory care was recorded. The American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions were used to evaluate sepsis, severe sepsis, or septic shock [19]. Hemorrhage was defined as any active hemorrhage requiring red blood cell transfusion. Hypovolemia at admission was diagnosed based on clinical judgment at the time of CT scan. An unfavorable outcome was defined as a need for hospital readmission within 30 days, need for ICU admission within 30 days, or 30-day mortality.

Protocol

Pediatric patients who underwent CT scan with contrast media injection were identified from the electronic hospital registry. The characteristics reported in Table 1 were extracted from the charts of these patients. We also recorded the reason for the scan, type and volume of contrast media used, unit of hospitalization, and outcome variables.

Statistical analysis

Results are reported as median and interquartile range (IQR) or as numbers and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the nonparametric Wilcoxon test. To identify variables significantly associated with CI-AKI and with unfavorable outcome, we performed conditional forward logistic regression analyses. The model included clinically relevant variables and variables yielding a P value of ≤0.20 in bivariate analysis, the latter being maintained in the final model. Variables are reported as estimated odds ratios (ORs) with their 95 % confidence intervals (95 % CIs). Co-linearity and interactions were tested. The Hosmer-Lemeshow test was used to check goodness of fit of the logistic regression. All tests were two sided, and P <0.05 was considered to indicate statistical significance. Statistical tests were performed using the SPSS 13 software package (IBM, Armonk, NY, USA).

Results

Study population

We identified 346 pediatric patients who underwent CT scan with contrast media injection (Fig. 1). Of these patients, 233 were followed for renal function and were therefore included in this study. Median patient age was of 5.9 years (IQR 1.9–

Table 1 Patient characteristics: number (%) or median [interquartile range (IQR)]

	No CI-AKI $n = 209$	CI-AKI $n = 24$	*P* value
Age (years)	6.1 (2.1–14.3)	8.3 (1.2–13.2)	0.77
Male gender	123 (58.9)	19 (79.1)	0.07
Comorbidities :			
Prematurity	12 (5.7)	1 (4.2)	0.99
Chronic heart failure	3 (1.4)	1 (4.2)	0.35
Chronic kidney Disease	6 (2.9)	2 (8.3)	0.19
History of glomerulopathy	1 (0.5)	1 (4.2)	0.20
Baseline renal function :			
Baseline eGFR (ml/mn/1.73 m^2)	102 (86–129)	131 (80–159)	0.08
Baseline creatinine (μmol/L)	39 (29–56)	34 (23–47)	0.23
Baseline creatinine (mg/dl)	0.44 (0.33–0.64)	0.39 (0.26–0.54)	
Exposure to nephrotoxic agents:			
NSAID	32 (15.5)	4 (16.7)	0.77
Aminoglycosides	24 (11.5)	4 (16.7)	0.50
Starches	9 (4.3)	3 (12.5)	0.11
Iodinated contrast media within 72 h	21 (10.1)	3 (12.5)	0.72
Cumulative number of nephrotoxic agents			0.32
None	*137 (65.6)*	*13 (54.2)*	
1	*55 (26.3)*	*7 (29.2)*	
2 or more	*17 (8.1)*	*4 (16.7)*	
Unit of hospitalization :			
Medical Ward	74 (35.4)	6 (25.0)	0.37
Surgical Ward	38 (18.2)	4 (16.7)	1
Intensive care unit	86 (41.1)	13 (54.2)	0.27
Emergency department	11 (5.3)	1 (4.2)	1
CT scan indication:			
Surgical assessment	107 (51.2)	11 (45.8)	0.67
Including preoperative CT scan	*41 (19.6)*	*4 (16.7)*	*0.99*
immediate postoperative CT scan	*28 (13.4)*	*3 (12.5)*	
other indication in surgical patients	*38 (18.2)*	*4 (16.7)*	
Cancer	24 (11.5)	2 (8.3)	0.99
Malformation	14 (6.7)	2 (8.3)	0.67
Epilepsy	22 (10.5)	2 (8.3)	0.99
Thromboembolism	11 (5.3)	3 (12.5)	0.16
Hemodynamic status at time of contrast media infusion and need for organ support:			
Nonsevere sepsis	77 (36.8)	8 (33.3)	0.82
Severe sepsis/Septic shock	27 (13.3)	5 (20.8)	0.34
Hemorrhage	11 (5.3)	2 (8.3)	0.63
Miscellaneous hypovolemia	15 (7.2)	3 (12.5)	0.41
Need for mechanical ventilation	43 (20.6)	9 (37.5)	0.07
Vasopressors	12 (5.7)	2 (8.3)	0.64
Outcome :			
Unfavorable outcome at day 30	41 (19.7)	11 (45.8)	0.007
Rehospitalization within 30 days	18 (8.6)	6 (25.0)	0.02
ICU admission within 30 days	9 (4.3)	3 (12.5)	0.11
Day 30 mortality	14 (6.7)	4 (16.7)	0.09

Italic informations include variables inclded in previous lines (number of toxic agents or reason for CT scan)

CI-AKI contrast-induced acute kidney injury, *eGFR* estimated glomerular filtration rate, *NSAID* nonsteroidal anti-inflammatory drugs, *ICU* intensive care unit

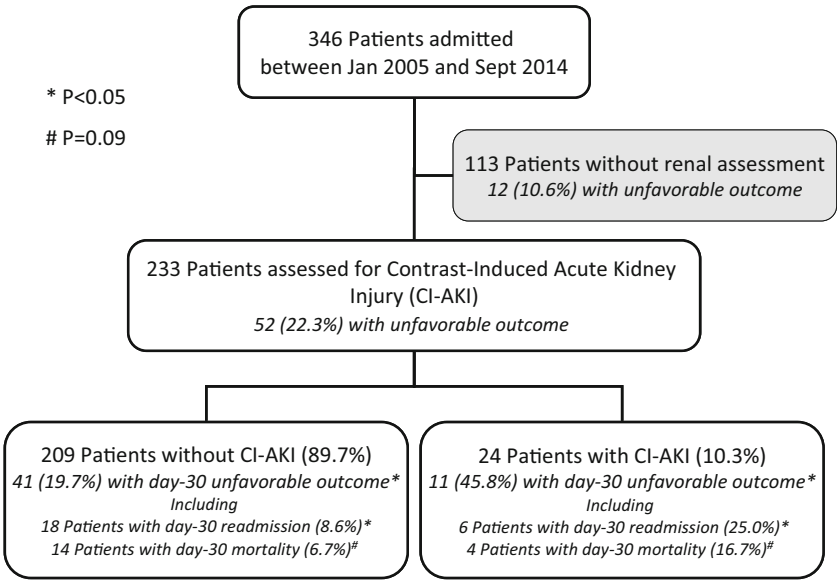

Fig. 1 Study flowchart. *CI-AKI* contrast-induced acute kidney injury

13.7 years), and 142 patients (60.9 %) were boys. Table 1 presents the main characteristics of the included patients.

Few patients had important comorbidities, including eight patients with pre-existing CKD, four with chronic heart dysfunction, three with history of hypertension, and two with history of glomerular disease without renal dysfunction. No patient was diagnosed with diabetes. The most common reason for performing a CT scan was a surgical condition (118 patients; 50.6 %). According to the usual indications of CT scan in our institution, every scan was done within 48 h following admission. The median S_{Cr} level at the time of CT scan was 38 μmol/L (IQR 28–55 μmol/L) and median baseline eGFR 107 ml/min/1.73 m^2 (IQR 89–132 ml/min/1.73 m^2). All CT scans were performed using iso- or hypo-osmolar contrast media. Median contrast media volume was 1.9 ml/kg (IQR 1.6–2.1 ml/kg). At the time of CT scan, 57 patients (16.6 %) had received nephrotoxic drugs within the previous 72 h. No patient developed an anaphylactic reaction or required renal replacement therapy (RRT) at time of inclusion or of contrast media infusion.

Contrast-induced acute kidney injury

Among the included patients, 24 (10.3 %; 95 % CI 6.4–14.2 %) developed CI-AKI, of whom nine (38 %) had no previous history of CKD and no other identified risk factors of AKI (concomitant nephrotoxic agents or hypovolemia). Volume of infused contrast media was similar in patients without [1.9 ml/kg (IQR) 1.6-2.1] and with CI-AKI (1.9 ml/kg [IQR 1.7-2.1]; $P=0.67$). Of these patients, 15 (63 %) showed elevated S_{Cr}. The remaining nine were classified as having AKI based on oliguria and two patients having both criteria. Maximum AKI severity was stage 1 in seven patients (29 %), stage 2 in six (25 %), and stage 3 in 11 (46 %). A single patient with CI-AKI required RRT. Logistic regression analysis found no factors independently associated with CI-AKI (Table 2). Factors retained in the final model, as well as OR trends, were unchanged in subgroup analyses evaluating patients reaching AKI criteria separately according to oliguria or S_{Cr} elevation.

Outcome

Unfavorable outcome was reported for 41 patients without (19.7 %) and 11 patients with (45.8 %; $P=0.007$) CI-AKI. The rate of hospital readmission within 30 days was 25 % among patients with vs. 8.6 % among patients without CI-AKI ($P=0.02$). Hospital mortality rate was 16.7 % among patients with vs. 6.7 % among those without CI-AKI ($P=0.09$) (Fig. 2). After adjustment for confounders, unfavorable outcome was independently associated with severe sepsis or septic shock at the time of CT scan (OR 3.5; 95 % CI 1.5–7.8), younger age (OR per year 0.89; 95 % CI 0.84–0.95), and contrast-associated nephropathy (OR 3.6; 95 % CI 1.4–9.5). Lastly, unfavorable outcome in patients with CI-AKI according to S_{Cr} and urine output criteria are reported in supplementary appendix (Figure S1).

Discussion

To the best of our knowledge, this is the largest study to assess CI-AKI incidence in a pediatric setting. Using the KDIGO definition, which was recently validated in children [17], we found a CI-AKI rate similar to previously reported rates in adult patients [14, 15]. Also in line with previous studies, our findings suggest that CI-AKI is associated with poorer outcome, including a higher rehospitalization rate and a trend

Table 2 Logistic regression of factors associated with contrast-induced acute kidney injury (CI-AKI)

	OR	95 % CI	*P* value
Hypovolemia or shock at contrast-media infusion	1.98	0.78–5.05	0.15
Underlying chronic kidney disease	3.16	0.53–18.6	0.20
Cumulative number of nephrotoxic agents			
None	Ref	–	–
1	0.93	0.32–2.68	0.89
≥2	3.63	0.86–15.40	0.08

Variables identified by forward conditional logistic regression

Hosmer-Lemeshow $\kappa^2 = 1.29$; df = 3; $P = 0.73$

When forced in the final model, sepsis, surgical condition, type of unit (ICU vs. other), and need for mechanical ventilation were not retained, nor did they change the final model

CI confidence interval, *OR* odds ratio

toward a higher 30-day mortality rate. Our analyses identified no independent risk factors for AKI in the pediatric setting.

Most studies have assessed CI-AKI incidence following cardiac catheterization, and thus CI-AKI incidence remains poorly evaluated in specific settings, such as among pediatric and ICU patients. Moreover, CI-AKI incidence varies widely across studies depending on definitions used, study population, and baseline risk factors. The recent KDIGO guidelines underline the need for further epidemiological studies in specific settings to improve available CI-AKI knowledge [12]. A recent study assessed the renal safety of two iso-osmolar contrast agents in 128 children and found CI-AKI incidences ranging from 5–10 % depending on the contrast media [11], similar to the results of our study. Interestingly, AKI risk in the pediatric population would be expected to be lower, since this patient group shows a relative lack of usual risk factors and always receives contrast media administration IV—two conditions that are usually associated with a lower CI-AKI rate [20, 21]. Interestingly, although pre-existing CKD trended to be associated with higher rate of CI-AKI, patients developing CI-AKI trended also to have higher baseline eGFR and lower baseline creatinine. This finding may reflect an augmented renal clearance previously described in sepsis and trauma patients, especially if critically ill [22, 23]. Additional studies are needed to further explore whether augmented renal clearance is a surrogate for patient severity and whether it may help identify patients at high risk of CI-AKI.

Also in accordance with previous findings, we found that CI-AKI was associated with a poorer 30-day outcome, including an increased rehospitalization rate and a trend toward higher mortality. Several studies have indicated an independent association between AKI and morbidity, hospital mortality, and long-term outcome in adult [1, 6, 24] and pediatric [25–29] settings. Similarly, CI-AKI was reportedly related to rates of higher morbidity, mortality, and long-term risk of adverse events [30–32]. Although the 30-day risk of death was not significantly higher in the CI-AKI group in our study, the heterogeneous population evaluated, the low mortality rate (7.7 %), and the wide CI (OR 2.8; 95 % CI 0.6–10.0) suggest a potential lack of statistical power to detect such an effect.

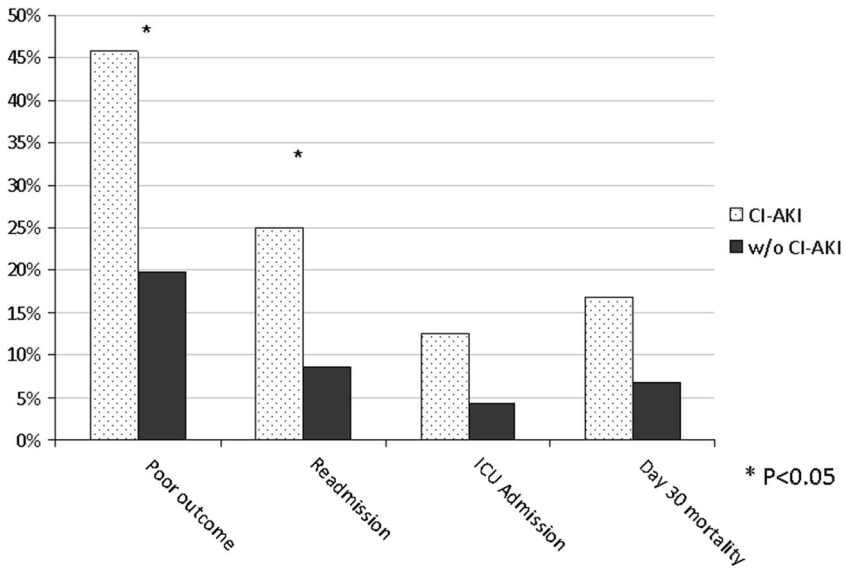

Fig. 2 Contrast-induced acute kidney injury (CI-AKI) and unfavorable outcome at day 30. *ICU* intensive care unit, *w/o* without

Several limitations of our study should be addressed. First, the population was heterogeneous, which may have limited the precision of our results and our ability to detect risk factors. Wide variations among evaluated patients should be expected with regard to CI-AKI risk and incidence and the potential consequences of this complication. However, this pilot study was performed with the aim of assessing global CI-AKI incidence within a pediatric population. Although our results remain to be confirmed, they clearly show an important risk of CI-AKI in the pediatric setting despite the lack of usual risk factors and the IV route of contrast media administration in this population.

To allow adequate assessment and comparability of our results, we used the KDIGO definition, which is validated both in the pediatric setting [17, 27, 28, 33] and for assessing renal consequences of contrast media administration [31]. However, this definition is highly sensitive, which may partly explain the high incidence of CI-AKI in our study [34]. Nevertheless, the higher rate of poor outcome in the group with CI-AKI suggests that this definition was adequate for estimating the risk of subsequent complications following renal insult. Additionally, the use of this definition even in a specific context, such as CI-AKI, is recommended by KDIGO guidelines [13].

Additionally, this study was not designed to assess accountability of contrast media on the observed CI-AKI. Previous studies suggest the specific toxic effect of nonionic, low-osmolar iodinated contrast medium to be minimal, especially in patients with multiple causes of renal insult [35]. These findings are to be tempered by the known pathophysiological effects of contrast media in experimental models [36]. In those models, contrast media are associated with renal hypoperfusion, direct tubular damage, and formation of reactive oxygen species that may cause further tissue damage [36]. Future studies in specific settings are required to more clearly assess the specific influence of contrast media in initiating or expanding subclinical renal insult.

The retrospective design of our study precluded adequate assessment of adherence to preventive measures or of the influence of these measures in preventing CI-AKI in this population. Hence, in the participating units, no dedicated protocol was available regarding prevention of CI-AKI. It must be noted, however, that this lack of protocol dedicated to prevention of CI-AKI was a result of the lack of information regarding the incidence of this complication in the pediatric setting. Also, our results may prompt implementation of preventive measures in this specific population. Moreover, urine output was infrequently assessed using a Foley catheter. Hence, both shift estimate in urine output and estimation of diaper weight maybe inaccurate, which might have led to erroneous estimation of urinary output [37, 38], and some patients may have been misclassified as a consequence. Additionally, we were unable to assess AKI duration in this setting, as several patients had unrecognized AKI and were discharged before renal dysfunction recovery. The retrospective design was also associated with a high dropout rate related to the absence of renal assessment following contrast media injection. One third of children exposed to contrast media had no renal function assessment or follow-up. It is not known how these excluded patients might have influenced the CI-AKI incidence in the studied population. However, this excluded population showed a 10 % rate of 30-day complications, compared with rates of 20 % in the patients without and 46 % in patients with CI-AKI (P <0.0001). This suggests that CI-AKI incidence may have been lower among the excluded patients and therefore in the exposed population. However, in the worst-case scenario, and assuming that none of these patients developed CI-AKI, this translates into a 6.4 % incidence of CI-AKI (95 % CI 4.3-9.6), which remains higher than expected in a population of patients usually considered at low risk of CI-AKI.

Despite its limitations, our study results suggest a 10.3 % incidence of CI-AKI according to the KDIGO definition (95 % CI 6.4–14.2 %) and suggests that CI-AKI is independently associated with poor short-term outcome. Thus, despite the limited prevalence of risk factors in this population and the IV administration of contrast media, pediatric patients remain exposed to CI-AKI. Additional studies are needed to confirm our results, assess risk factors, and investigate the preventive measures provided in this specific population. However, our findings suggest that physicians should maintain a high degree of suspicion toward this complication among pediatric patients. Additionally, our results may help in the design of future studies in this field by providing an estimation of CI-AKI incidence in this specific population.

Compliance with ethical standards This study was approved by the institutional review board of the French Society for Intensive Care Medicine (SRLF-CE-14-24). The need for informed consent was waived in accordance with French law. However, patients and family members were informed via a family leaflet and the hospital website's family information pages that retrospective studies might be performed using patients' charts.

Conflicts of interest None.

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