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EDITORIAL

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# Radiocontrast-induced acute kidney injury in the ICU: worse than presumed?

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Contrast agents are administered to millions of patients annually worldwide [1]. Contrast-induced acute kidney injury (CI-AKI) is one of the most common complications of the use of iodinated contrast media. It accounts for up to 11% of hospital-acquired renal failures [2]. Reported incidences range from well below 2% in unselected collectives of patients [3] up to nearly 7% in patients with chronic kidney disease (CKD) and an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 $m^2$ [4, 5].

CI-AKI is associated with increased morbidity and mortality and does have significant implications for health care costs due to extended length of stay (LOS) in hospital and additional treatment requirements [5]. Pathophysiological features of this condition consist of transitory renal vasoconstriction and renal ischemia, especially in the renal outer medulla where oxygen levels are at a critical level, combined with direct tubular epithelial toxicity. CI-AKI has been defined in different ways, but an increase in serum creatinine ≥0.5 mg/dl or ≥25% within 48–72 h after contrast application is the most widely used criterion [5, 6].

CI-AKI rarely develops in patients with normal renal function, but several risk factors have been described. Decreased baseline renal function, heart failure, diabetes, dehydration, hypotension, older age, and the type and amount of contrast volume applied have been shown to have the greatest impact [5, 7]. The type of investigation may also influence the risk of developing CI-AKI with noncoronary angiography and coronary angiography/percutaneous coronary intervention possibly carrying the greatest risk [8]. The use of low-osmolar and iso-osmolar contrast agents and limiting the amount of administered contrast media as well as mild volume expansion with isotonic crystalloids are well established procedures for prevention [5, 9, 10]. All this knowledge, however, is mainly derived from non-critically ill patients undergoing CT scans, cardiac catheterization, or cardiovascular surgery. Very little is known about the risk factors and long-term outcome of CI-AKI in critically ill patients.

The study by Hoste et al. [11] published in the current issue of *Intensive Care Medicine* investigates a large cohort of 787 critically ill, primarily surgical (76.2%) patients receiving intravenous or intraarterial contrast media for CT scans or noncoronary angiography. Only iodinated nonionic, low-osmolar or iso-osmolar contrast media were applied. Using "conventional" criteria [6], CI-AKI was observed in 128 patients (16.3%), of whom about one-quarter progressed to AKI stage 3, and 14 patients (11%) required renal replacement therapy (RRT). CI-AKI also resulted in significantly increased LOS as well as both ICU and 1-year mortality. Applying the more sensitive KDIGO criteria, 175 patients (22%) were classified as CI-AKI with comparable to worse outcome in terms of RRT requirement or mortality. Multiple logistic regression analysis revealed increased serum creatinine as a reflection of reduced GFR, diuretic therapy, use of

vasopressors, and hypotension as independent risk factors for developing CI-AKI. No influence of the type of investigation, CT scan versus angiography, could be demonstrated.

This study, currently the largest one investigating CI-AKI in critically ill patients, makes a highly valuable and timely contribution to our knowledge of an iatrogenic complication of the routine diagnostic procedure of contrast agent administration. Despite its retrospective design, the study sheds light on several important aspects of CI-AKI. First of all, the incidence of CI-AKI in the range of 16–22% appeared to be much higher in critically ill patients than that described in other patient groups [5]. In conjunction with this, the requirement of RRT and a 1-year mortality of roughly 56% in patients suffering from CI-AKI were much higher than expected from previous trials in non-critically ill patients [12, 13]. When considering only the critically ill, mortality rates appeared roughly three times higher in patients developing CI-AKI in the study by Hoste et al. [11], which demonstrates the possibility that CI-AKI worsens severe and life-threatening conditions in critically ill patients.

The predominant risk factors for this specific group of patients were represented mainly by impaired baseline renal function and reduced renal perfusion. Diuretics turned out to be a further independent hazard for developing CI-AKI. Although use of diuretics might be interpreted simply as a therapeutic consequence of heart failure, previous prospective trials demonstrated that (loop) diuretics significantly enhance the incidence of AKI if given at the time of contrast application [14, 15]. Female sex, however—previously reported as risk factor for CI-AKI [16, 17]—was not found to be associated with a higher rate of AKI in the present study [11].

Preventive hydration procedures including volume expansion with normal saline and sodium bicarbonate as well as N-acetyl-cysteine (NAC) were carried out in patients with reduced baseline renal function in a non-standardized way, which may be considered a major limitation of the study by Hoste et al. [11]. Despite implementation of such procedures a large number of patients developed CI-AKI and a few progressed to more severe stages of the disease. This, however, does not necessarily mean that conventional preventive measures are useless: in this study, they were probably implemented in patients who were identified as carrying a higher risk for developing AKI. However, the measures appeared to be inadequate. It is possible that in this study of critically ill patients, use of conventional criteria for both patient selection and type and/or intensity of preventive interventions may have led to missing other important risk factors whose identification might have helped to optimize implementation of more effective measures to prevent CI-AKI.

What are the consequences of this study for our daily clinical practices? First of all, it becomes obvious that the critically ill are a group of patients who are clearly at high risk for developing CI-AKI. Even more, CI-AKI poses a significant hazard to this population in terms of increased requirements for RRT as well as increased LOS and higher mortality rates.

Secondly, in addition to the well known risk factors for CI-AKI such as chronic renal disease, diabetes, and heart failure, reduced renal perfusion characterized by decreased mean arterial pressure as well as use of vasopressors to treat hypotension in the ICU setting likely represents a predominant risk factor. Third, as already shown previously, periprocedural application of (loop) diuretics increases the risk for CI-AKI and should be avoided. Obviously discontinuation of any other nephrotoxic drug (e.g., aminoglycosides, NSAIDS) is highly warranted [10].

This leads us to the important issue of prevention. Although no clear benefit of any preventive measure could be demonstrated in this study by Hoste et al. [11], it may be concluded from the data presented that renal perfusion must be optimized before administering radiocontrast agents. According to currently available data this should preferably be achieved by periprocedural volume expansion using either normal saline or isotonic sodium bicarbonate [10]. Fast prehydration protocols with isotonic bicarbonate have been shown to be beneficial for emergent procedures in some studies [18–20]. Which crystalloid to use and how to ideally perform volume expansion in critically ill patients, however, are questions that can only be reliably answered by a large prospective randomized trial.

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# Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis

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**Abstract** *Purpose:* Intensive care unit (ICU) patients frequently undergo contrast-enhanced radiographic examinations, which carries a risk for development of contrast-associated acute kidney injury (CA-AKI). Data on this in ICU patients are scarce. The aim of this study was therefore to evaluate the epidemiology and short- and long-term outcomes of CA-AKI in ICU patients. *Methods:* A retrospective single-centre cohort study covering the period 1 March 2004 to 31 December 2008 on ICU patients who underwent a radiography examination with parenteral administration of iodinated radio contrast media was conducted. Data analysis included univariate and multivariate analyses of patients with and without CA-AKI. *Results:* A total of 787 ICU patients were included in the study. CA-AKI occurred in 128 (16.3%) and was associated with higher need for RRT [30 (4.6%) vs. 21 (16.4%), $p < 0.001$], worse kidney function at discharge, longer length of ICU and hospital stay, and higher 28-day and 1-year mortality [28-day: 86 (13.1%) vs. 46 (35.9%), $p < 0.001$, and 1-year: 158 (24.0%) vs. 71 (55.5%), $p < 0.001$]. Higher serum creatinine, lower mean arterial pressure, and administration of diuretics and vasoactive therapy were associated with development of CA-AKI in multivariate analysis.After correction for confounders we found that CA-AKI was associated with 28-day mortality in this cohort of ICU patients (odds ratio = 2.742, 95% confidence interval 1.374–5.471). *Conclusions:* CA-AKI occurred in one out of six ICU patients who underwent a contrast-enhanced radiography examination and was associated with both short-and long-term worse outcomes such as need for RRT, worse kidney function at discharge, increased length of stay in the ICU and hospital, and mortality.

**Keywords** Acute kidney injury/acute renal failure · Hemodialysis · Contrast-induced acute kidney injury/contrast nephropathy/contrast-associated acute kidney injury · Intensive care unit · Outcomes · Retrospective cohort study

## Introduction

Parenteral administration of iodine-containing radio contrast media in intensive care unit (ICU) patients may be associated with development of contrast-associated acute kidney injury (CA-AKI) [1–3]. We prefer to use the term "associated" instead of "contrast-induced" AKI because in the specific ICU setting development of AKI is most probably heterogeneous in origin [4]. Besides nephrotoxicity caused by contrast media, factors such as sepsis, hypotension, hypovolemia, and nephrotoxicity by, e.g., antibiotics may also play a role in the pathogenesis of AKI. When CA-AKI occurs it may have an important impact because it is associated with worse outcomes such as increase in length of hospital stay, complications, cost, and mortality. Levy et al. [5] assessed in their hallmark study the association of occurrence of CA-AKI and mortality. Even after correction for covariates they found an association of CA-AKI and death (odds ratio 5.5). This has since been reproduced by others in various settings [6–13].

The incidence of CA-AKI ranges between 0 and 50% depending on the case mix and the definition for CA-AKI that is used [1, 3, 4, 14, 15]. The most commonly used definition is an increase of serum creatinine $\geq$0.5 mg/dL or $\geq$25% from baseline, assessed 48–72 h after the procedure [16]. Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) group defined a modified version of the definition for AKI that was previously developed by the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN) (http://www.KDIGO.org) [17, 18]. This consensus defines AKI as an increase of creatinine $\geq$0.3 mg/dL within a 48-h period, or $\geq$50% compared to baseline within a 7-day period, or an episode of oliguria lasting $\geq$6 h.

In a hospital-wide study, 11% of all episodes of AKI were contrast-associated, and contrast administration was the third most important cause of AKI [19]. The incidence in intensive care unit (ICU) patients with different risk profiles for CA-AKI is reported to be between 1.4 and 61% [20, 21].

Despite being a well-known complication, data on CA-AKI in ICU patients are scarce, come from relative small datasets, and only report on short-term outcomes [20–25]. Therefore, the aim of this study was to assess the epidemiology and short- and long-term outcomes of CA-AKI in a large general ICU cohort.

## Materials and methods

### Setting and design

This is a retrospective single-centre study in a 56-bed teaching hospital ICU. The ICU consists of a 22-bed adult surgical ICU, a 14-bed medical ICU, an 8-bed cardiac surgery ICU, a 6-bed pediatric ICU, and a 6-bed burn unit.

### Data collection

Data were retrieved from the electronic database of the Department of Radiology, the electronic ICU patient database management system (PDMS), the electronic patient file of the hospital, and the electronic hospital International Classification of Diseases version 9 (ICD-9) diagnosis database. The PDMS was introduced in the surgical ICU in 2003, the cardiac surgery ICU in 2005, the medical ICU in 2006, the burn unit in 2007, and the pediatric ICU in 2008.

### Study population

We included all ICU patients who underwent a diagnostic or therapeutic computed tomography (CT) scan or non-coronary angiography with intravenous or intra-arterial administration of iodinated contrast media during the period 1 March 2004 through 31 December 2008 and who had data recorded in the ICU PDMS. Only the first contrast administration was considered for this analysis. We excluded patients who had another intravenous or intra-arterial iodinated contrast administration within a 3-day period after the index procedure. Also excluded were patients who were treated with renal replacement therapy (RRT) at time of contrast administration, and patients who had no serum creatinine concentrations recorded immediately before contrast administration.

### Processes of care

Serum creatinine is measured routinely on a daily basis, and up to four times a day on clinical indication. Preventive measures for CA-AKI are recommended in patients at risk for CA-AKI (eGFR <60 mL/min or creatinine >1.2 mg/dL) and consist of volume loading with isotonic saline or isotonic sodium bicarbonate according to the protocol of Merten et al. and/or administration of *N*-acetylcysteine [26, 27].

Contrast media used during the study period were all nonionic, and iso-osmolar or low-osmolar. Angiography examinations were exclusively performed with a nonionic and iso-osmolar contrast agent (iodixanol).

Severity of illness at time of ICU admission was assessed by the APACHE II score [28]. Kidney function was assessed by serum creatinine concentration at time of ICU admission and at time of contrast administration. In addition, we estimated the glomerular filtration rate

(eGFR) on the basis of the short re-expressed MDRD equation [29, 30].

At the time of contrast administration, we recorded concomitant administration of drugs that may increase the risk for development of CA-AKI. These included diuretic agents, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), amphotericin B (also included were the liposomal or lipid-coated forms), aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAID), and acetylsalicylic acid.

Patients who were treated with norepinephrine, epinephrine, dopamine (in doses >4 μg/kg/min), dobutamine, milrinone, or vasopressin were categorized as treated with vasoactive therapy.

Indications for renal replacement therapy (RRT) as well as the modality chosen [i.e., intermittent (duration 2–4 h per treatment session) or continuous hemodialysis (IHD/CHD), continuous veno-venous hemofiltration (CVVH), or slow extended daily dialysis (SLEDD) (duration 6–12 h per treatment session)] were determined in consensus between the attending intensivist and nephrologist [31]. Criteria for initiation of RRT for AKI included volume overload and oliguria, acidosis, hyperkalemia, uremic symptoms, or uremia [32].

### Outcomes

The primary outcome, CA-AKI, was defined as an increase of serum creatinine of 25% or 0.5 mg/dL or greater within 3 days after contrast administration [16]. Secondary outcomes included the KDIGO definition for AKI (a modification of the RIFLE and AKIN definition for AKI), defined as an increase of serum creatinine of 0.3 mg/dL or greater within a 48-h period or 50% or greater increase from baseline within 7 days [17, 18]. Baseline creatinine was the lowest of serum creatinine on ICU admission and at time of contrast administration. This alternative definition was also measured during the 3-day observation period. In addition, we recorded treatment with RRT, initiated during a 10-day period following contrast administration, length of ICU and hospital stay, and mortality at day 28, day 60, day 90, 1 year, and at time of ICU and hospital discharge.

### Statistical analysis

Data are reported as count (percentage) and median (25% quartile, 75% quartile). Univariate analysis for continuous variables was with the Mann-Whitney *U*-test, and for categorical variables with the $\chi^2$ test. Survival analysis was performed with the Kaplan-Meier statistic and log rank test. Double-sided $p < 0.05$ was considered as statistically significant.

Multivariate logistic regression analysis (enter method) was used for assessment of covariates that were associated with occurrence of CA-AKI and for covariates associated with 28-day mortality. Variables initially included in this analysis had a clinical plausible association and a $p$ value of <0.25 in univariate analysis. Correlation tables were used to assess co-linearity between variables. Interaction between variables was also evaluated. Final models were obtained by stepwise backward and forward selection of the variables (Wald method). For the mortality model, we also used a propensity score to correct for the risk of developing CA-AKI. This propensity score was developed with the model for development of CA-AKI. The models were evaluated with a goodness of fit test (Hosmer-Lemeshow), and the area under the curve (AUC) for the receiver operating characteristic (ROC) curve.

All statistical analyses were performed with the statistical software package SPSS, version 15.0 for Windows (SPSS, Chicago, IL, USA).

### Ethics approval

The study was approved by the Ethics Committee of the Ghent University Hospital and conducted in accordance with the declaration of Helsinki. Informed consent was waived for this study.

## Results

During the study period 18,866 patients were admitted to the ICU. Of these, 1,419 patients met the inclusion criteria for the study [Fig. 1 of the electronic supplementary material (ESM)]. After exclusion of 632 patients for various reasons, the final study cohort consisted of 787 patients. Median age of the patients was 59 years (46.5, 70.2), 490 were male (62.3%), and the majority were admitted to the surgical ICU [surgical ICU 600 patients (76.2%), medical ICU 159 (20.2%), cardiac surgery ICU 23 (2.9%), and pediatric ICU 5 (0.6%)]. The median length of stay between ICU admission and contrast administration was 2.6 days (1.4, 6.4). Contrast was administered for a contrast-enhanced CT scan in 619 patients (78.7%); in 168 patients (21.3%) the indication was angiography.

CA-AKI occurred in 128 patients (16.3%). Severity of AKI in the majority of patients was limited to AKI stage 1; 31 patients (24.2% of AKI patients) had severe AKI defined as AKI stage 3, of these, 14 patients (45.2%) were treated with RRT. In one-quarter of patients, duration of AKI was 2 days or less (transient azotemia). When defined by the KDIGO definition for AKI, AKI was

present in 175 patients (22.2%). Compared to the definition used for the primary outcome, the KDIGO system was unable to detect 27 patients. On the other hand, KDIGO classified 74 patients as CA-AKI who remained undetected by the standard definition. Compared to the standard definition, KDIGO had a sensitivity of 78.9%, specificity of 88.8%, positive predictive value of 57.7%, and negative predictive value of 95.6%. Outcomes of patients who had CA-AKI as defined by KDIGO were comparable or even worse for relevant outcomes such as need for RRT and mortality (see Table 1 in the ESM).

## Comparison of patients with and without CA-AKI

Serum creatinine peaked at day 2 after contrast administration in CA-AKI patients (Fig. 1). In patients without CA-AKI (no CA-AKI) we recorded a decrease of serum creatinine after contrast administration. Patients who developed CA-AKI were older, had a worse baseline kidney function, were more severely ill on admission, and a greater proportion were admitted to the medical ICU (Table 1). Higher CKD stages were associated with a higher occurrence rate of CA-AKI. The incidence of CA-AKI was comparable among patients who underwent a contrast-enhanced CT scan and those who underwent angiography (respectively 16.3 and 16.1%, $p = 0.966$). CA-AKI patients had a more positive volume balance and a lower urine output. At time of contrast administration, CA-AKI patients had lower hemoglobin concentration, a lower blood pressure, and a greater proportion were treated with vasoactive therapy and mechanical ventilation. They more frequently had a urinary sodium concentration below 20 mmol/L, indicating prerenal azotemia and were more often treated with diuretic therapy. Finally, a greater proportion of CA-AKI patients were treated with drugs that may enhance the risk for CA-AKI.

After backward and forward stepwise selection of covariates in a multivariate logistic regression model, serum creatinine, administration of diuretics, lowest mean arterial blood pressure, and vasoactive therapy, all at day of contrast administration, were risk factors associated with occurrence of CA-AKI (Table 2).

## Preventive measures for CA-AKI

Preventive measures for CA-AKI with *N*-acetylcysteine or sodium bicarbonate were applied in 307 patients (39.0%) of the whole study cohort. They were more frequently applied in risk patients. In patients with an eGFR <60 mL/min at time of admission and in patients with serum creatinine >1.2 mg/dL at time of contrast administration, 130 (61.3%) and 136 patients (67.0%), respectively, received these therapies. There was a higher incidence of CA-AKI in patients who received preventive measures, especially in patients with CKD stages 1 or 2 (Table 2 of the ESM). There was no difference in occurrence rate of CA-AKI between patients with and

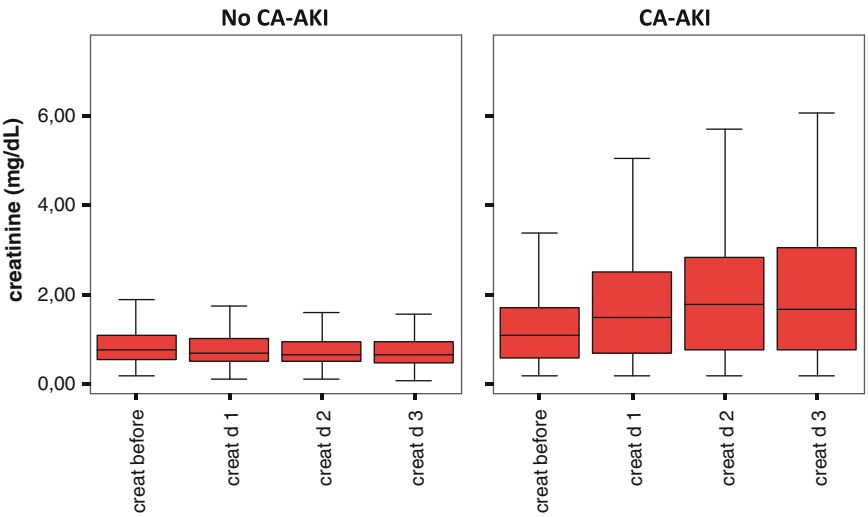


**Fig. 1** Evolution of serum creatinine in patients without and with contrast-associated acute kidney injury (CA-AKI). *creat* Serum creatinine (mg/dL), *d* day, *N* number of recordings, *25%/75%* 25th and 75th percentiles, respectively. *$P < 0.001$ compared to creatinine before (Wilcoxon signed ranks test)

| | No CA-AKI | | | | CA-AKI | | | |
|---|---|---|---|---|---|---|---|---|
| | Creat before | Creat d1* | Creat d2* | Creat d3* | Creat before | Creat d1* | Creat d2* | Creat d3* |
| N | 659 | 647 | 651 | 544 | 128 | 126 | 127 | 108 |
| Median | 0.77 | 0.68 | 0.65 | 0.64 | 1.11 | 1.50 | 1.77 | 1.69 |
| 25% | 0.55 | 0.51 | 0.49 | 0.48 | 0.58 | 0.70 | 0.75 | 0.76 |
| 75% | 1.09 | 1.01 | 0.94 | 0.94 | 1.73 | 2.52 | 2.86 | 3.07 |

**Table 1** Comparison of patients who developed contrast-associated acute kidney injury (CA-AKI) and those who did not (no CA-AKI)

| | No CA-AKI | CA-AKI | *P* |
|---|---|---|---|
| Number (%) | 659 (83.5%) | 128 (16.5%) | |
| Data at time of ICU admission | | | |
| Age (years) | 59 (46.0, 69.8) | 64 (50.1, 73.9) | 0.009 |
| Male gender | 416 (63.1%) | 74 (57.8%) | 0.256 |
| Diabetes | 82 (12.4%) | 14 (10.9%) | 0.634 |
| Hypertension | 166 (25.2%) | 38 (29.7%) | 0.288 |
| Heart failure | 55 (8.3%) | 20 (15.6%) | 0.010 |
| Cirrhosis | 81 (12.3%) | 23 (18.0%) | 0.083 |
| $Creatinine_{admission}$ (mg/dL) ($n = 681$) | 0.86 (0.66, 1.22) | 1.01 (0.73, 1.58) | 0.016 |
| $eGFR_{admission}$ (mL/min/1.73 $m^2$) ($n = 681$) | 84 (55.6, 113.6) | 70 (41.6, 96.3) | 0.006 |
| $eGFR_{admission}$ <60 mL/min/1.73 $m^2$ ($n = 681$) | 165 (28.7%) | 46 (43.4%) | 0.003 |
| Chronic kidney disease stages ($n = 681$) | | | |
| CKD 1 ($eGFR_{admission}$ >90 mL/min/1.73 $m^2$) | 249 (43.3%) | 33 (31.1%) | 0.045 |
| CKD 2 ($eGFR_{admission}$ 60–90 mL/min/1.73 $m^2$) | 161 (28.0%) | 27 (25.5%) | |
| CKD 3 ($eGFR_{admission}$ 30–60 mL/min/1.73 $m^2$) | 105 (18.3%) | 30 (28.3%) | |
| CKD 4 ($eGFR_{admission}$ 15–45 mL/min/1.73 $m^2$) | 44 (7.7%) | 12 (11.3%) | |
| CKD 5 ($eGFR_{admission}$ <15 mL/min/1.73 $m^2$) | 16 (2.8%) | 4 (3.8%) | |
| APACHE II score | 17 (13, 23) | 20 (16, 25) | 0.004 |
| ICU unit | | | 0.015 |
| Surgical ICU | 515 (78.1%) | 85 (66.4%) | |
| Medical ICU | 125 (19.0%) | 34 (26.6%) | |
| Cardiac surgery ICU | 16 (2.4%) | 7 (5.5%) | |
| Pediatric ICU | 3 (0.5%) | 2 (1.6%) | |
| Burn ICU | 0 (0%) | 0 (0%) | |
| Data at time of contrast administration | | | |
| Radiography examination | | | 0.939 |
| CT scan | 518 (83.7%) | 101 (16.3%) | |
| Angiography | 141 (83.9%) | 27 (16.1%) | |
| LOS ICU before contrast administration (days) | 2.5 (1.4, 6.0) | 2.8 (1.4, 7.0) | 0.485 |
| Creatinine (mg/dL) | 0.77 (0.55, 1.09) | 1.10 (0.58, 1.73) | <0.001 |
| Creatinine > 1.5 mg/dL (%) | 95 (14.4%) | 44 (34.4%) | <0.001 |
| Urea (g/dL) | 0.41 (0.28, 0.73) | 0.61 (0.38, 0.95) | <0.001 |
| Urine output (L/day) | 2.16 (1.56, 2.94) | 1.39 (0.80, 1.89) | <0.001 |
| Volume balance (L/day) | 0.8 (0.55, 1.14) | 1.16 (0.59, 1.77) | <0.001 |
| Positive volume balance | 501 (76.4%) | 113 (88.4%) | 0.003 |
| Urine $Na^+$<20 mmol/L | 90 (13.7%) | 32 (25.0%) | 0.001 |
| CA-AKI prevention | | | |
| *N*-acetylcysteine | 165 (25.0%) | 44 (34.4%) | 0.029 |
| $NaHCO_3$ | 209 (31.7%) | 59 (46.1%) | 0.002 |
| *N*-acetylcysteine or $NaHCO_3$ | 241 (36.6%) | 66 (51.6%) | 0.001 |
| *N*-acetylcysteine and $NaHCO_3$ | 133 (20.2%) | 37 (28.9%) | 0.028 |
| *N*-acetylcysteine, no $NaHCO_3$ | 32 (4.9%) | 7 (5.5%) | 0.770 |
| $NaHCO_3$, no *N*-acetylcysteine | 76 (11.5%) | 22 (17.2%) | 0.076 |
| Minimum blood glucose (g/L) | 1.23 (1.06, 1.43) | 1.24 (1.03, 1.44) | 0.755 |
| Treatment with insulin | 420 (63.7%) | 92 (71.9%) | 0.077 |
| Insulin administered (U/day) | 28 (13, 50) | 31 (18, 56) | 0.116 |
| Maximum rate of insulin infusion (U/h) | 2.5 (1.5, 4.0) | 2.8 (2.0, 4.0) | 0.142 |
| Hemoglobin (g/dL) | 9.0 (7.8, 10.6) | 8.2 (7.2, 9.9) | <0.001 |
| $Na^+$ (mmol/L) | 140 (137, 144) | 142 (138, 145) | 0.017 |
| $MAP_{low}$ (mmHg) | 72 (64, 83) | 65 (57, 77) | <0.001 |
| Vasoactive therapy | 204 (31.0%) | 64 (50.0%) | <0.001 |
| Mechanical ventilation | 333 (50.5%) | 81 (63.3%) | 0.008 |
| Diuretic therapy | 169 (25.6%) | 51 (39.8%) | 0.001 |
| ACEI or ARB | 49 (7.4%) | 12 (9.4%) | 0.453 |
| Aminoglycosides | 2 (0.3%) | 2 (1.6%) | 0.067 |
| Amphotericin | 0 (0%) | 0 (0%) | |
| NSAID | 0 (0%) | 0 (0%) | |
| Administration of drugs that ↑ risk CI-AKI[a] | 199 (30.2%) | 56 (43.8%) | 0.003 |
| Kidney outcomes | | | |
| Duration CA-AKI ≤2 days | | 34 (26.6%) | |
| AKI class | | | <0.001 |
| No AKI | 585 (88.8%) | 27 (21.1%) | |
| Class 1 | 50 (7.6%) | 47 (36.7%) | |

**Table 1** continued

| | No CA-AKI | CA-AKI | *P* |
|---|---|---|---|
| Class 2 | 12 (1.8%) | 23 (18.0%) | |
| Class 3 | 12 (1.8%) | 31 (24.2%) | |
| RRT ≤10 days after contrast administration | 30 (4.6%) | 21 (16.4%) | <0.001 |
| Duration of RRT (days) | 11 (4, 23) | 9 (2, 22) | 0.655 |
| Number of RRT treatments | 7 (2, 13) | 7 (2, 17) | 0.850 |
| RRT at time of hospital discharge | 0 (0%) | 1 (4.8%) | 0.227 |
| $Creatinine_{discharge}$ (mg/dL) | 0.57 (0.43, 0.78) | 0.91 (0.52, 1.90) | <0.001 |
| $eGFR_{discharge}$ (mL/min/1.73 $m^2$) | 134 (92.2, 183.7) | 77 (30.6, 145.6) | <0.001 |
| $Creatinine_{discharge}$ > creatinine before contrast | 121 (18.4%) | 63 (49.2%) | <0.001 |
| Patient outcomes | | | |
| LOS ICU (days) | 11 (5.9, 22.5) | 16 (8.5, 29.4) | 0.001 |
| LOS ICU after contrast administration (days) | 8 (4.2, 16.2) | 12 (5.1, 24.1) | 0.002 |
| LOS hospital after contrast administration (days) | 29 (15.1, 60.8) | 26 (7.9, 58.0) | 0.030 |
| ICU mortality | 72 (10.9%) | 45 (35.2%) | <0.001 |
| Mortality 28 days after contrast administration | 86 (13.1%) | 46 (35.9%) | <0.001 |
| Mortality 60 days after contrast administration | 113 (17.1%) | 57 (44.5%) | <0.001 |
| Mortality 90 days after contrast administration | 123 (18.7%) | 61 (47.7%) | <0.001 |
| Mortality 1 year after contrast administration | 158 (24.0%) | 71 (55.5%) | <0.001 |

Data are presented as *N* (%) or median (interquartile range)
*CA-AKI* Contrast-associated acute kidney injury, *eGFR* estimated glomerular filtration rate on basis of the modifying diet in renal disease (MDRD) equation, *CKD* chronic kidney disease, *LOS* length of stay, $MAP_{low}$ lowest mean arterial blood pressure, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *NSAID* nonsteroidal anti-inflammatory drugs
[a] Diuretic therapy, ACEI, ARB, amphotericin, or NSAID

**Table 2** Variables associated with development of contrast-associated acute kidney injury according to a multivariate logistic regression analysis

| | Odds ratio | 95% CI | P |
|---|---|---|---|
| Creatinine at time of contrast administration (per mg/dL) | 1.258 | 1.040, 1.522 | 0.018 |
| Diuretic therapy (yes) | 1.659 | 1.073, 2.564 | 0.023 |
| Vaso-active therapy (yes) | 1.890 | 1.205, 2.965 | 0.006 |
| Lowest MAP at time of contrast administration (per mmHg) | 0.978 | 0.961, 0.995 | 0.013 |
| Goodness of fit (according to Hosmer and Lemeshow): $\chi^2 = 7.874$, df = 8, $P = 0.446$ | | | |
| Percentage with correct prediction: 82.7% | | | |
| Area under the curve for the ROC curve = 0.69 (0.631, 0.741) | | | |

*CI* Confidence interval, *MAP* mean arterial blood pressure, *ROC* receiver operating characteristic

without preventive measures in the cohort of patients with CKD stages 3 or greater.

## Outcomes

Compared to no CA-AKI patients, CA-AKI patients were at greater odds for needing treatment with RRT in the 10-day period following contrast administration [odds ratio (OR): 4.12, 95% confidence interval (CI): 2.27–7.45] (Table 1). They also had worse kidney function at discharge, a greater proportion had a higher creatinine concentration at discharge compared to creatinine concentration at time of contrast administration, they had a longer length of stay, worse hospital survival (Fig. 2), and a higher mortality, up to 1 year after contrast administration [OR (95% CI) for mortality in the ICU = 4.42 (2.85–6.85), at 28 days = 3.74 (2.44–5.73), at 60 days = 3.88 (2.59–5.81), at 90 days = 3.97 (2.66–5.91), and at 1 year = 3.95 (2.67–5.84)]. Medical ICU patients had a nonsignificant trend for higher mortality between the 28-day and 1-year follow-ups (medical ICU 19.2% vs. surgical ICU 13.7% vs. cardiac surgery ICU 11.1%, $p = 0.267$). The KDIGO definition for CA-AKI was associated with similar differences in short- and long-term outcomes (Table 1 of the ESM). When stratified by eGFR on admission (higher or lower than 60 and 45 mL/min/1.73 $m^2$), mortality was significantly higher for CA-AKI patients in both strata (data not shown).

## Association of CA-AKI and mortality

In univariate analysis, nonsurvivors were older, had a greater severity of illness at time of ICU admission and at time of contrast administration, were more often medical ICU patients, and had worse kidney function (Table 3). Nonsurvivors also had a greater prevalence and severity

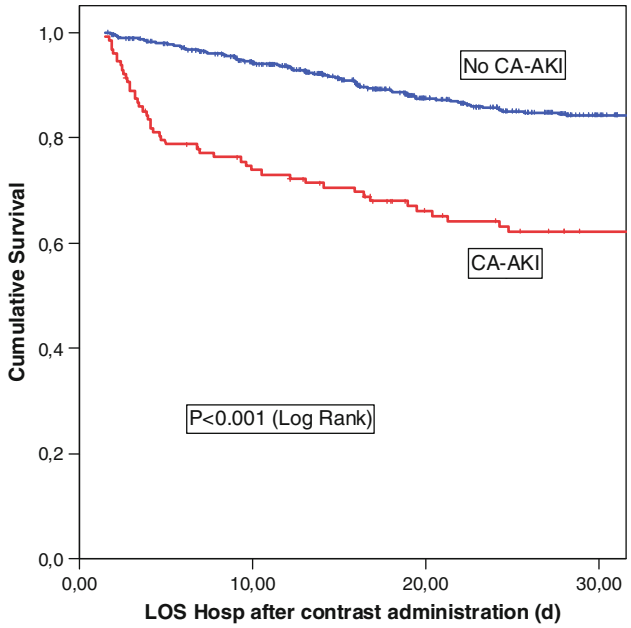


**Fig. 2** Survival of patients without and with contrast-associated acute kidney injury (CA-AKI) *LOS Hosp* Length of stay in the hospital in days

of CA-AKI. When corrected for other covariates, for development of CA-AKI (with a propensity score), and for duration and severity of CA-AKI, we found that CA-AKI was associated with 28-day mortality (Table 4).

## Discussion

CA-AKI developed in one out of six ICU patients who were administered intravenous or intra-arterial radio contrast for a noncoronary angiography or CT scan. This was associated with worse short-term and long-term outcomes. CA-AKI patients were more frequently treated with RRT for AKI and had worse kidney function at ICU discharge. Furthermore, CA-AKI was associated with greater length of ICU and hospital stay, suggesting greater cost and resource use. Finally, mortality was higher in CA-AKI patients for up to 1 year after contrast administration.

The incidence of CA-AKI in this cohort of general ICU patients was higher than that reported in several other studies on this topic [20, 22–24], while others reported a similar or higher incidence [21, 25]. It is very difficult to compare incidences in these studies because different definitions for CA-AKI were used, and specific cohorts were examined. The higher incidence in this study may be explained by the more sensitive definition for CA-AKI used compared to that in others (creatinine increase >25% or 0.5 mg/dL compared to 0.5 mg/dL) [20, 22, 23]. Also, a relative high number of patients had risk factors for development of CA-AKI in our study cohort. On the other hand, the higher incidence of CA-AKI in the study by Huber et al. [21] (61%) may be explained by the higher risk profile for CA-AKI in that study, which included only patients with a baseline creatinine concentration of 2.5 mg/dL.

Sixteen percent of CA-AKI patients were treated with RRT, which is nearly four times as many compared to patients without CA-AKI (16.4 vs. 4.6%). This is much higher compared to the incidence of RRT in non-ICU patients with CA-AKI, which is generally less than 1% in patients without risk factors and may increase to 4% in patients with underlying chronic kidney disease or patients undergoing primary PCI for acute coronary syndrome [4, 15, 16]. This high incidence can be explained by the greater severity of illness and resulting higher incidence of AKI in an ICU cohort. The 4% incidence of RRT in patients without CA-AKI is comparable to that reported in ICU patients [33, 34]. Greater severity of illness is probably also the main determinant for greater severity of CA-AKI with need for RRT. This finding underlines the important impact of CA-AKI on outcome and on ICU health care resources. It also underlines the need for targeted strategies for prevention of CA-AKI in ICU patients.

The alternative definition for CA-AKI, the KDIGO modified RIFLE classification, had a higher sensitivity, which resulted in a higher incidence of CA-AKI, while relevant end points, such as short-term and long-term mortality were similar. This supports the use of this definition for CA-AKI as it may allow more early detection and intervention.

CA-AKI patients had a greater number of risk factors for development of CA-AKI. These included diabetes, hypertension, worse kidney function, lower urine output, prerenal characteristics, lower hemoglobin, and administration of drugs that enhance the risk for CA-AKI. They were also more severely ill on admission and at time of contrast administration (more were treated with vasoactive therapy and mechanical ventilation and blood pressure was lower), and a greater proportion were treated in the medical ICU. Although intravenous administration of radio contrast media probably carries a lower risk for CA-AKI compared to intra-arterial administration, we found that patients who underwent a CT scan (with intravenous contrast administration) carried a similar risk for CA-AKI compared to patients who underwent angiography (predominantly intra-arterial administration).

Preventive measures for development of CA-AKI, such as administration of *N*-acetylcysteine or bicarbonate, were only undertaken in 60% of risk patients and were not associated with a lower occurrence rate of CA-AKI. Selection bias, resulting in administration of preventive therapy in patients who are at greatest risk for CA-AKI, may explain this. However, we cannot rule out that the

**Table 3** Survivors compared to nonsurvivors at 28 days after contrast administration

| | Survivors | Nonsurvivors | *P* |
|---|---|---|---|
| *N* (%) | 655 (83.2%) | 132 (16.8%) | |
| Data at time of ICU admission | | | |
| Age (years) | 58 (44.8, 69.3) | 64 (51.3, 72.4) | 0.001 |
| Male gender | 413 (63.1%) | 77 (58.3%) | 0.307 |
| $Creatinine_{admission}$ (mg/dL) | 0.86 (0.66, 1.24) | 1.00 (0.72, 1.47) | 0.018 |
| $eGFR_{admission}$ (mL/min/1.73 $m^2$) | 84 (55.6, 114.1) | 68 (42.3, 103.7) | <0.001 |
| $eGFR_{admission}$ < 60 mL/min/1.73 $m^2$ | 158 (28.1%) | 53 (40.2%) | <0.001 |
| Diabetes | 81 (12.4%) | 15 (11.4%) | 0.748 |
| Hypertension | 171 (26.1%) | 33 (25.0%) | 0.791 |
| Heart failure | 50 (7.6%) | 25 (18.9%) | <0.001 |
| Cirrhosis | 75 (11.5%) | 29 (22.0%) | 0.001 |
| APACHE II score | 17 (13.0, 23.0) | 20 (16.0, 27.0) | <0.001 |
| ICU | | | 0.006 |
| Surgical ICU | 512 (78.2%) | 88 (66.7%) | |
| Medical ICU | 118 (18.0%) | 41 (31.1%) | |
| Cardiac surgery ICU | 20 (3.1%) | 3 (2.3%) | |
| Pediatric ICU | 5 (0.8%) | 0 | |
| Data at time of contrast administration | | | |
| Radiography examination | | | 0.057 |
| CT scan | 507 (77.4%) | 112 (84.8%) | |
| Angiography | 148 (22.6%) | 20 (15.2%) | |
| LOS ICU before contrast (days) | 2.5 (1.3, 6.0) | 3.1 (1.6, 7.1) | 0.037 |
| Creatinine (mg/dL) | 0.75 (0.54, 1.08) | 1.26 (0.68, 1.75) | <0.001 |
| Urea (g/dL) | 0.41 (0.28, 0.71) | 0.68 (0.42, 1.06) | <0.001 |
| Urine output (L/day) | 2.10 (1.50, 2.95) | 1.49 (0.90, 2.33) | <0.001 |
| Volume balance (L/day) | 0.76 (0.54, 1.09) | 1.26 (0.69, 1.76) | <0.001 |
| Positive volume balance | 494 (75.7%) | 120 (91.6%) | <0.001 |
| Urine $Na^+$ <20 mmol/L | 565 (86.3%) | 100 (75.8%) | 0.002 |
| Treatment with insulin | 413 (63.1%) | 99 (75.0%) | 0.009 |
| Hemoglobin (g/dL) | 8.9 (7.8, 10.6) | 8.7 (7.6, 10.0) | 0.086 |
| $Na^+$ (mmol/L) | 140 (137, 144) | 141 (138, 145) | 0.085 |
| $MAP_{low}$ (mmHg) | 71 (63.0, 83.0) | 66 (58.3, 77.0) | <0.001 |
| Vasoactive therapy | 202 (30.8%) | 66 (50.0%) | <0.001 |
| Mechanical ventilation | 322 (49.2%) | 92 (69.7%) | <0.001 |
| Diuretic therapy | 163 (24.9%) | 57 (43.2%) | <0.001 |
| Administration of drugs that ↑ risk CA-AKI[a] | 193 (29.5%) | 62 (47.0%) | <0.001 |
| Kidney outcomes | | | |
| CA-AKI | 82 (12.5%) | 46 (34.8%) | <0.001 |
| Duration of CA-AKI (% within CA-AKI) | | | 0.611 |
| ≤2 days | 23 (28.0%) | 11 (23.9%) | |
| >2 days | 59 (72.0%) | 35 (76.1%) | |
| AKI class | | | <0.001 |
| No AKI | 544 (83.1%) | 68 (51.5%) | |
| Class 1 | 62 (9.5%) | 35 (26.5%) | |
| Class 2 | 18 (2.7%) | 17 (12.9%) | |
| Class 3 | 31 (4.7%) | 12 (9.1%) | |
| Renal replacement therapy | 27 (4.1%) | 24 (18.2%) | <0.001 |

Data are presented as *N* (%) or median (interquartile range)
*CA-AKI* Contrast-associated acute kidney injury, *eGFR* estimated glomerular filtration rate on basis of the modifying diet in renal disease (MDRD) equation, *LOS* length of stay, $MAP_{low}$ lowest mean arterial blood pressure, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *NSAID* nonsteroidal anti-inflammatory drugs
[a] Diuretic therapy, ACEI, ARB, amphotericin, or NSAID

complex and multifactorial pathophysiology of development of AKI in ICU patients precludes the beneficial effects of these therapies. Our data do therefore suggest the need for a prospective study on the effects of preventive measures in this specific cohort of ICU patients.

The strength of this study is that we specifically studied a cohort of ICU patients. ICU patients have a completely different risk profile for development of CA-AKI compared to non-ICU patients. Therefore, epidemiologic data on CA-AKI in, e.g., hospitalized patients or patients who have undergone coronary angiography should not be translated to ICU patients who are administered radio contrast. The epidemiology of CA-AKI in an ICU setting was described in two other studies [20, 24]. Our study is a relevant addition to these. First, the two studies described a total of 470 patients, compared to 787

**Table 4** Association of contrast-associated acute kidney injury and 28-day mortality

| | Odds ratio | 95% CI | *P* | AUC ROC curve |
|---|---|---|---|---|
| Unadjusted | 3.738 | 2.440, 5.725 | <0.001 | 0.61 (0.555, 0.668) |
| Adjusted | | | | |
| Model 1 | 3.449 | 1.962, 6.065 | <0.001 | 0.734 (0.683, 0.785) |
| Model 2 | 3.302 | 1.786, 6.104 | <0.001 | 0.781 (0.733, 0.829) |
| Model 3 | 2.693 | 1.381, 5.251 | 0.004 | 0.795 (0.745, 0.845) |
| Model 4 | 2.742 | 1.374, 5.471 | 0.004 | 0.804 (0.754, 0.853) |
| Model 5 | 3.095 | 1.485, 6.451 | 0.003 | 0.806 (0.757, 0.855) |
| Model 6 | 3.032 | 1.447, 6.352 | 0.003 | 0.807 (0.758, 0.856) |

Covariates used for adjustment were as follows: *Model 1* age, APACHE II score, ICU type; *Model 2* covariates from model 1 + heart failure, cirrhosis, creatinine on admission; *Model 3* covariates from model 2 + propensity score for development of CA-AKI; *Model 4* covariates from model 3 + variables at time of contrast administration (mechanical ventilation, vasoactive therapy, type of radiographic examination, volume balance, sodium concentration, urinary sodium concentration <20 mmol/L, hemoglobin, insulin therapy); *Model 5* covariates from model 4 + duration of CA-AKI ≤2 days; *Model 6* covariates from model 5 + renal replacement therapy

*CI* Confidence interval, *AUC* area under the curve, *ROC* receiver operating characteristic

patients in our study. Including a larger number of patients reduces bias and renders more relevant data. Second, both studies analyzed patients who were administered contrast in the setting of a CT scan examination. We also describe patients who underwent noncoronary angiography. Third, we did not restrict ourselves to reporting of ICU and hospital mortality but also reported on a whole set of kidney outcomes and 28-, 60-, 90-day, and 1-year mortality. Fourth, we are the first to compare the traditional and new definitions for CA-AKI. Finally, we did not restrict ourselves to a univariate comparison of patients with and without CA-AKI but provide on the basis of a very complete set of possible confounders a multivariate analysis for development of CA-AKI and six different multivariate models to evaluate the association of CA-AKI and mortality (including the use of a propensity correction).

Limitations include the single-centre retrospective design. Selection bias was a consequence of the gradual introduction of the PDMS. CA-AKI had a higher incidence in the medical ICU, which also had a shorter study period. The reported data therefore probably underestimate the true incidence of CA-AKI in a general ICU. Also, it is not certain if the occurrence of AKI in this cohort of ICU patients was caused by contrast administration or was the result of the underlying disease state (e.g., sepsis) or was the consequence of both. Especially in critically ill patients, many other factors may play a role, and AKI is most likely of heterogeneous origin. Future studies should aim to demonstrate that preventive measures that are specific to one of the possible underlying etiologies (e.g., contrast exposure) also impact on these outcomes in a cohort of ICU patients. In addition, despite the extensive dataset included in this database, we could not evaluate the effects of the volume of contrast administered. Further, long-term survival was based on administrative hospital data. These are accurate because the majority of our patients have in-hospital follow-up. However, we cannot exclude that there was loss of follow-up in a small minority of patients, which may have led to an underestimation of the reported long-term mortality. Finally, the retrospective data collection also precluded recording of data on the exact amount and type of contrast media administered.

## Conclusions

CA-AKI occurred in one out of six ICU patients who underwent a contrast-enhanced noncoronary radiography examination and was associated with both short- and long-term worse outcomes such as need for RRT, worse kidney function at discharge, increased length of stay in the ICU and hospital, and mortality. Preventive measures were only used in two-thirds of risk patients and did not result in a lower incidence of CA-AKI. Increasing the sensitivity of the definition for CA-AKI by use of the KDIGO modified RIFLE classification renders equal relevant outcomes and may thus help in early detection and preventive measures.

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# Contrast-induced acute kidney injury: what is the prevalence of prevention protocols?

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Dear Editor,

We read with interest the study by Hoste and colleagues [2] and the accompanying editorial by Joannidis and Wiedermann [1]. Hoste has shown the incidence of contrast-induced acute kidney injury (CI-AKI) to be much higher in the critically ill patient and associated with a three-fold increase in mortality. Those most at risk of renal injury appear to be patients with chronic renal disease, especially if they are hypotensive or on vasopressor therapy. The currently recommended treatment to optimise peri-procedural renal function is crystalloid volume loading. However, there is no consensus on which fluid to use and in what quantity—a state of affairs that could leave some clinicians sceptical as to whether an intervention is worthwhile at all. To assess current levels of practice in the UK, we performed an electronic survey to estimate the use of protocols and preventative therapies.

We directed the survey at all UK intensive care units (ICUs), as defined by the most recent UK Critical Care Directory (2008), via the Intensive Care Society website and by emailing individual hospitals.

We received responses from 117 individual ICUs from a possible 329—a 36% response rate. From these, 32 (27.4%) claimed to have a protocol while 85 (72.6%) did not. Protocols were more likely to have been implemented in cardiac or neuroscience ICUs (10/17 units; 58.8%) than in teaching hospital ICUs (8/32 units; 25%) or district general ICUs (14/68 units; 20.6%). Of the 32 units that claimed to have a protocol, 18 (56%) used *N*-acetylcysteine (NAC) in a variety of dosing regimens, and the remaining 14 (44%) did not use NAC. In units with a protocol, 1.26% sodium bicarbonate was the preferred fluid type (11 units; 34%), followed by Hartmann's solution (10 units; 31%) in a wide variety of volumes and regimen timings. Only five units (16%) with protocols did not use fluid boluses. Of the 85 units that did not have a protocol, no consensus on the available evidence was stated as the reason by 48 units (41%), while 20 units (17%) felt this is a decision taken by radiology. Of these units without formal protocols, 17 (20%) still gave NAC, whereas 68 (80%) did not. A fluid regimen was used by 39 units (46%), while 46 (54%) did not give fluid boluses at all. Themes from free text comments included the feeling that the evidence is not yet convincing for the widespread use of standardised preventative measures as well as that taking a "risk benefit" approach, rather than using specific creatinine cut-off values, ought to determine contrast use.

Protocols for the prevention of CI-AKI are not commonplace on ICUs in the UK. However, it appears that many clinicians are thinking about CI-AKI and freely prescribing some form of prophylaxis. We think this adds weight to Joannidis and Wiedermann's claim that more evidence, ideally in the form of a randomised control trial, is needed to convince the majority of ICU physicians that to follow a standardised approach in order to prevent renal injury from contrast media is worthwhile.

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