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When a Patient with CKD Needs Contrast Radiography

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Case

A 70-year-old woman is hospitalized after a fall that resulted in a right femoral neck fracture. Her medical history includes obesity, type 2 diabetes mellitus, hypertension, and chronic kidney disease (CKD). She has smoked a pack of cigarettes daily for 40 years. Results of the patient's initial workup in the emergency department demonstrated the right femoral neck fracture, serum creatinine of 1.8 mg/dL, and a negative noncontrast head CT. She was admitted to the hospital and the following day underwent surgical repair. The procedure was uncomplicated. However, on postoperative day 4 the patient is developed sudden onset chest pain and shortness of breath. The acute coronary syndrome work-up is negative. Current medications include prophylactic subcutaneous heparin, insulin glargine, omeprazole, and paracetamol. Temperature is 37.8°C, blood pressure is 110/65 mm Hg, pulse is 116/min, and respirations are 30/min. Pulse oximetry is 88% on room air. Lung auscultation revealed decreased breath sounds at the bilateral bases. Cardiac rhythm is regular with normal S1 and S2. The surgical incision shows no surrounding erythema or purulent drainage. The patient follows commands and moves all extremities except the left leg. Laboratory results are as follows: Complete blood count: Leukocytes 12,000/mm^3, Hemoglobin 11 g/dL, Platelets 250,000/mm^3, Serum biochemical tests: Sodium 135 mEq/L, pH: 7.48, pCO2: 30,mmHg, pO2: 85 mmHg, Bicarbonate 24 mEq/L, serum creatinine: 1.8 mg/dL, Glucose 170 mg/dL, Troponin T is undetectable. Chest x-ray shows slight bibasilar atelectasis without focal consolidation, pleural effusion, or pulmonary edema. ECG shows sinus tachycardia but is otherwise unremarkable.

Which of the following is the most appropriate next step in management of this patient?

○ **a)** IV antibiotics ○ **b)** IV furosemide ○ **c)** IV nitroglycerine infusion

○ **d)** Ventilation perfusion scan ○ **e)** Computed tomography (CT) pulmonary angiography

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This patient likely has an acute pulmonary embolism (PE). Recent surgery and immobilization, tachycardia, and absence of a more likely alternate diagnosis indicate likely a prediagnosis of PE. Hypoxemia that is out of proportion to chest x-ray findings and active smoking further increases the probability of an acute PE. Although receipt of prophylactic heparin reduces the risk of acute PE, it does not preclude the diagnosis. CT angiogram of the chest is typically preferred for diagnostic confirmation of acute PE; however, according to our knowledge and routine clinical practice, due to impaired renal function, intravenous contrast should be avoided. Therefore, ventilation-perfusion scan is the most appropriate diagnostic test. A high-probability ventilation-perfusion scan can confirm the diagnosis. However, in our hospital setting particularly on night shifts it is not possible to reach and perform a ventilation-perfusion scan in case of emergency. At this point, her eGFR is 28 mL/min/1.73m^2 and you are wondering if the contrast needed for the CT will cause an acute kidney injury (AKI) and if so, can you do anything to prevent contrast induced AKI?

Is the use of CT angiogram absolutely contraindicated in patients with AKI and severe CKD ?

Although the reply is yes for most of clinicians and this conclusion is consistent with many published researches, there are recent reports against this conclusion. There has been a huge increase in the number of CT

scans performed in our daily clinical practice. Some scans require intravenous contrast while in other cases contrast media may improve image quality. Contrast media also used for life saving procedures like coronary angiography. There has been a lot of studies and reviews about contrast-induced nephropathy and its prevention. However our clinical approach to contrast induced nephropathy mostly build from case reports and non-controlled studies. Historically the CTs were done with high osmolar contrast material and these non-controlled studies showed a rise in AKI. However, we now use iso-osmolar or low osmolar contrast and we are not seeing contrast induced AKI more often as a result. The value gained and the risk incurred by imaging studies in general, and radiocontrast-enhanced imaging studies in particular, remain critically important questions in general medical and surgical care, cardiology, oncology, and other medical and surgical subspecialties. Let's focus on the recent literature. Multiple observational studies have been published recently demonstrating that contrast induced AKI in the modern era does not exist. Part of the difficulty with this topic is the inconsistent definition of contrast-induced AKI. A common definition is an increase in creatinine level by 25% or an absolute increase of 0.3 to 0.5 mg/dL within 3 days. These are all disease-oriented outcomes like change in laboratory values but not patient-oriented outcomes like death or need for dialysis.

Responses to critical questions based on literature review

Critical Question 1: Is contrast used for imaging studies associated with AKI ?

Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the Risk of Radiocontrast-Associated Nephropathy. J Am Soc Nephrol, 2017 (1)

- **Study population:** Adult humans (The entire Nationwide Inpatient Sample (NIS) dataset for 2009 consisted of 7,810,762 hospitalizations. After inclusion criteria 5,931,523 hospitalizations were left for analysis)
  - **Inclusion criteria:** Patients at least 18 years old at the time of admission with an admitting diagnosis other than AKI. Authors limited their study population to those hospitalizations 10 days or fewer in length to reduce misclassification of contrast associated nephropathy.
- **Intervention:** Radiocontrast administration, as determined by International Classification of Diseases, 9th Revision Codes (ICD9) procedure code.
- **Comparison:** Patient not received radiocontrast
- **Outcome:**
  - **Primary outcome:** The primary outcome was AKI, as determined by ICD9 diagnosis code.
  - **Secondary outcomes**: Death or dialysis within 30 days of imaging.
- **Results & authors' conclusions:** "In the entire sample, AKI developed in 5.5% of patients who received radiocontrast and 5.6% of patients who did not. After controlling for comorbidity and acuity of illness, radiocontrast administration associated with an odds ratio for AKI of 0.93 (95% confidence interval, 0.88 to 0.97)."

"In conclusion, the risk of radiocontrast-associated nephropathy may be overstated in the literature and overestimated by clinicians. More accurate AKI risk estimates may improve clinical decision-making when attempting to balance the potential benefits of radiocontrast-enhanced imaging and the risk of AKI."

- **Caution from authors:** "However, we would also extend a word of caution regarding interpretation of these results and results from similar studies: to date there have been no randomized studies of the risk of radiocontrast administration. Even sophisticated analyses may fail to detect the full effect of patient selection on their results and, in that case, may erroneously conclude that there is no real risk to patients, even those previously believed to be high risk such as patients with CKD or diabetes. If physicians are expertly identifying patients truly at increased risk for AKI after radiocontrast administration, that selection bias may mask a true effect of contrast in analyses such as ours. For this reason, we must interpret this study and similar studies with caution, carefully weighing the benefit of a contrast-enhanced study with the risk, likely low but likely not zero, of radiocontrast administration on the kidney."

Aycock RD, Westafer LM, Boxen JL et al. Acute Kidney Injury After Computed Tomography: A Meta-analysis. Ann Emerg Med, 2018 (2)

- **Study population:** Adult humans
  - **Exclusion criteria:** Pediatrics, non-human studies, studies of contrast enhanced procedures (ex: coronary angiography), interventional studies, case reports, review articles, clinical guidelines, other meta-analyses
- **Intervention:** Contrast enhanced CT scans
- **Comparison:** Noncontrast CT scan
- **Outcome:**
  - **Primary outcome:** Incidence of AKI
  - **Secondary outcomes**: Mortality or need for renal replacement therapy
- **Authors' conclusions:** "We found no significant differences in our principal study outcomes between patients receiving contrast-enhanced CT versus those receiving noncontrast CT. Given similar frequencies of AKI in patients receiving noncontrast CT, other patient- and illness-level factors, rather than the use of contrast material, likely contribute to the development of AKI."

McDonald JS, McDonald RJ, Carter RE et al. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. Radiology, 2014 (3)

- **Study population:** Adult humans
  - **Exclusion criteria:** Patients were excluded if they (a) had preexisting dialysis requirements prior to or on the day of the scanning or (b) underwent additional contrast-enhanced procedures within a 14-day period of the scanning. Patients were also excluded if they had a diagnosis of acute renal failure in the 14 days prior to their scanning, as determined by the date of the acute renal failure ICD-9-CM diagnostic code.
- **Study groups:** A total of 12,508 propensity score-matched patients with contrast-enhanced (contrast material group) and unenhanced (non-contrast material group) scans.
- **Comparison:** Study groups stratified according to baseline eGFR by using Kidney Disease Outcomes Quality Initiative cutoffs for CKD into subgroups with eGFR of 90 or greater, 60-89, 30-59, and less than 30 mL/min/1.73 m^2. Incidence of AKI (serum creatinine increase of ≥0.5 mg/dL [≥44.2 μmol/L] above baseline) was compared in the matched subgroups.
- **Outcome:**
  - **Primary outcome:** Incidence of AKI
- **Results & authors' conclusions:** "The incidence of AKI significantly increased with decreasing baseline eGFR (P < .0001). However, this incidence was not significantly different between contrast material and non-contrast material groups in any eGFR subgroups. Diminished eGFR is associated with an increased risk of AKI following CT examinations. However, the risk of AKI is independent of contrast material exposure, even in patients with eGFR of less than 30 mL/min/1.73 m^2."
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Challenging issues in the existing literature about contrast associated nephropathy:

1) **Quality of studies:** Most of the studies on contrast associated AKI are retrospective, observational and low power studies. A very few randomized controlled trial with inadequate power analysis.
2) **Publication bias:** Publication bias occurred in this topic where trials with significant positive results are published but trials with negative/null results are not.
3) **Selection bias:** Most of the studies are non-randomized and inappropriate selection methods were used in these studies.
4) **Measurement bias:** There were differing definitions of AKI in the included studies and the timing of renal function measurements.

Critical Question 2: Do intravenous sodium bicarbonate or sodium chloride with oral acetylcysteine or placebo prevent AKI and major adverse outcomes in high-risk patients undergoing angiography?

Weisbord SD, Gallagher M, Jneid H, et al; PRESERVE Trial Group. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. N Eng J Med, 2018 (4)

- **Study population:** Patients who were scheduled to undergo coronary or noncoronary angiography and who had an eGFR of 15 to 44.9 ml/min/1.73 m^2 or 45 to 59.9 ml/min/1.73 m^2 among those with diabetes mellitus
  - **Exclusion criteria:** Patients who were undergoing emergency angiography and those with unstable baseline levels of blood creatinine (which was defined as an increase or decrease of ≥25% within 3 days before angiography). A complete list of inclusion and exclusion criteria is in the Supplementary Appendix, available at NEJM.org.
- **Intervention:** IV 1.26% sodium bicarbonate (150 mmol/L) or IV 0.9% sodium chloride (154 mmol/L)
- **Comparison:** Oral N acetylcysteine or Placebo capsules
- **Outcomes:**
  - **Primary outcome:** Composite of death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 to 104 days after angiography and confirmed at subsequent testing within 14 days (defined as persistent impairment in kidney function)
  - **Secondary outcomes:** Contrast-associated AKI, which was defined as an increase in serum creatinine of either at least 25% or at least 0.5 mg/dL (44 μmol/L) from baseline at 3 to 5 days after angiography; death within 90 days; dialysis of any kind within 90 days; confirmed persistent kidney impairment at 90 to 104 days; hospitalization with acute coronary syndrome, heart failure, or stroke within 90 days; and hospitalization for any cause within 90 days.
- **Results & authors' Conclusions:** The sponsor stopped the trial after a prespecified interim analysis. There was no interaction between sodium bicarbonate and acetylcysteine with respect to the primary end point (P=0.33). The primary end point occurred in 110 of 2511 patients (4.4%) in the sodium bicarbonate group as compared with 116 of 2482 (4.7%) in the sodium chloride group (odds ratio, 0.93; 95% confidence interval [CI], 0.72 to 1.22; P=0.62) and in 114 of 2495 patients (4.6%) in the acetylcysteine group as compared with 112 of 2498 (4.5%) in the placebo group (odds ratio, 1.02; 95% CI, 0.78 to 1.33; P=0.88). "Among patients at high risk for renal complications who were undergoing angiography, there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated AKI."
- **Caution from authors:** There is a selection bias in this study that the population in this study was military veterans with stage 3 or 4 CKD of whom 94% were male, 80% had diabetes and most (90%) were getting a contrast enhanced CT scan of their coronaries. This selection bias

may cause external validity problem in female patients without diabetes and those getting other forms of contrast associated imaging studies. Another important issue that may cause validity problem is that the trial was stopped early at the final interim analysis. They included only 5,177 (67.4%) of the patients minus those (4.1 to 9.2%) with missing creatinine levels.

Case Follow up:
Although ventilation perfusion scan could not be performed under emergency night shift circumstances, our patient underwent *CT* pulmonary angiography after receiving parenteral N acetylcysteine and IV 0.9% sodium chloride and pulmonary embolism was detected. CT pulmonary angiogram revealed thrombus in right pulmonary artery, lobar and segmental arteries on both sides. Other notable findings in CT were; dilated right ventricle, dilated right atrium, main pulmonary artery (32 mm), left pulmonary artery (18 mm) and right pulmonary artery (22 mm). The patient is started on intravenous heparin under close monitoring.

Critical Question 3: Do we need to administer these parenteral N acetylcysteine and IV 0.9% sodium chloride before CT pulmonary angiography ?

The answer is "NO". Even it seems logical to use N acetylcysteine, it should be given oral and there is no evidence based on recent literature for IV acetylcysteine and IV 0.9% sodium chloride as a preventive treatment for contrast induced nephropathy. Intravenous acetylcysteine is not suggested also due to risk of serious adverse events (5). The main reason for our reply "No" is the difficulty to ascertain the diagnosis of contrast induced nephropathy in previous clinical studies, because the diagnosis of contrast nephropathy in these studies rely on different criteria and chart reviews. A support for causation effect between contrast media and AKI is needed and our search for this support directs us to review experimental studies. In experimental studies, radiocontrast media are found as direct cytotoxic agents that can induce necrosis and apoptosis of renal tubular cells and disrupt nitric oxide–mediated vasodilation, impairing renal perfusion, particularly in the renal medulla (6). Despite these direct cellular effects, interestingly contrast media only causes AKI in animals that have been presensitized or preinjured with nonsteroidal anti-inflammatory drugs, nitric oxide inhibition, dehydration, etc. Some authors have suggested that this presensitization requirement suggests that radiocontrast is not significantly nephrotoxic in vivo and that the experimental model is, therefore, not clinically relevant. However, the fact that contrast only causes clinically apparent nephrotoxicity in susceptible subjects makes it quite similar to human contrast nephropathy, which rarely occurs in the absence of a concomitant risk factor. Although presensitized or preinjured kidney is needed for contrast nephropathy, the experimental data still seems convincing. Confirmation of evidence for cause-effect relationship of contrast in clinical AKI is more difficult. In our clinical setting we often use the criteria of contrast exposure and subsequent renal dysfunction to make the diagnosis clinically, however we cannot completely rule out the presence of other causative factors.

There may be several explanations for the findings of these recent studies suggesting that AKI rates after contrast exposure found to be no different between matched patients without any contrast exposure. The most likely contributing reason is potential selection bias in these retrospective studies. This is because, despite authors' best attempts at accounting for the most important risk factors, it is impossible to normalize for everything that led the physician to select a noncontrasted CT rather than a contrast-enhanced CT in each individual patient. Indeed, contrast is often withheld in the sickest patients and those with the highest risk of AKI unless absolutely necessary. These factors alone would tend to create different populations. Moreover, there are several important factors that are not accounted for, such as dehydration and medications, and it is impossible to account for the severity of each factor like severity of diabetic nephropathy. Thus, patient selection and preparation by the physicians could influence the overall rates of contrast nephropathy.

In conclusion, in the light of recent studies, now we can say that the risk of AKI related to radiocontrast administration has been overestimated, and we have to take this information into account in our clinical decision-making when we are faced with important decisions regarding the use or non-use of radiocontrast-enhanced imagining studies like emergent coronary intervention or CT angiogram for the diagnosis of PE.

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