

Hospital-acquired nephrotoxic exposures in the precipitation of acute kidney injury – A case series analysis and a call for more preventative nephrology practices

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ABSTRACT

The frequency of hospital-acquired acute kidney injury has been increasing in recent years. It is associated with higher patient mortality, increased length of stay, increased cost of hospitalization and potentially is linked with an increased risk of developing chronic kidney disease and end-stage renal disease over time. Decreased renal perfusion, nephrotoxic medications, surgery, and radiographic contrast media remain the most common causes of hospital-acquired acute kidney injury. We present some recent cases of hospital-acquired acute kidney injury managed in the Renal Unit, Mayo Clinic Health System, Eau Claire, WI, USA and make a strong case for more preventative nephrology practices to mitigate, if not eliminate, the scourge of hospital-acquired acute kidney injury.

Implication for health policy/practice/research/medical education:

The increasing incidence of hospital-acquired acute kidney injury remains a challenge to the practicing nephrologist with increasing patient morbidity and mortality, as well as escalating healthcare costs. Preventable causative factors such as decreased renal perfusion, exposure to nephrotoxic medications and iodinated radiographic contrast, and surgery especially the neglected role of intraoperative hypotension were identified. A strong preventative nephrology paradigm could potentially limit, if not totally eliminate, hospital-acquired acute kidney injury. This imperative is even more mandatory in resource-poor countries and communities.

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Introduction

The frequency of hospital-acquired acute kidney injury (AKI) has been increasing in recent years (1,2). Using data from the Nationwide Inpatient Sample, a nationally representative dataset, to identify cases of dialysis-requiring AKI using validated International Classification of Diseases, Ninth Revision (ICD-9) codes, from 2000 to 2009, Hsu et al demonstrated that the incidence of dialysis-requiring AKI had increased from 222 to 533 cases per

million person-years, averaging a 10% increase per year (incidence rate ratio=1.10, 95% CI=1.10-1.11 per year) (2). Decreased renal perfusion, nephrotoxic medications, surgery, and radiographic contrast media remain the most common causes of hospital-acquired AKI (1).

We will present five inpatients with hospital-acquired AKI who were managed in the Renal Unit, Mayo Clinic Health System, in Northwestern Wisconsin, to demonstrate the multifaceted roles of nephrotoxic exposures in the

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pathogenesis and propagation of this syndrome. We end with addressing common sense preventative nephrology practices to mitigate if not eliminate the scourge of hospital-acquired AKI.

Case Series

Case I

A 44-year-old African American morbidly obese hypertensive diabetic male patient, with stage III chronic kidney disease, was evaluated for four days of lower abdominal pain, associated with nausea, vomiting and anorexia. Past medical history was significant for morbid obesity, uncontrolled hypertension, and uncontrolled diabetes mellitus with HbA1c of 9% early in March 2017. He had experienced transient AKI requiring nearly a month of hemodialysis in April 2011 following severe left lower extremity necrotizing fasciitis that required surgical management at the time. Following this event, his baseline serum creatinine had shifted upwards from 0.8-0.9 mg/dL to about 2 mg/dL (Figure 1). About a year ago, in early 2016, he had undergone a bariatric surgery procedure with a gastric sleeve resection after which he lost about 100 lb. He subsequently has experienced loose stools. A day prior to his admission in our hospital, he had been evaluated at an outside hospital with intravenous contrast-enhanced CAT scan using 150 mL of iohexol iodinated contrast (350 mg/mL). The CAT scan revealed a right lower quadrant peri-appendiceal abscess collection around the tip of the appendix. Notably, both kidneys were unremarkable by the CAT scan images. At that evaluation uncontrolled hypertension was evident (135/117 mm Hg). He received a dose of IV Ketorolac 30 mg for pain late that evening prior to the CAT scan in the outside hospital. At the patient's request, he was then transferred to our hospital. At our facility, he appeared stable, temperature of 36 degrees C, heart rate of 89/min, respirations were 24/min, blood pressure was 134/71 mm Hg, with O₂ saturation at 97% on room air. Body mass index (BMI) was 44.8 kg/m². There was right lower quadrant tenderness with some guarding. Laboratory tests revealed a hemoglobin of 10.7 g/dL, hematocrit of 32.6%, white blood cell (WBC) 13.4 thousand with a left shift, and platelets were 122 thousand/ μ L.

Sodium was 137 mmol/L, potassium 4.5 mmol/L, chloride 99 mmol/L, bicarb 19 mmol/L, blood urea nitrogen (BUN) 27 mg/dL and serum creatinine was 1.99 mg/dL (eGFR = 44 mL/min/1.73 m² BSA), close to his baseline. Glucose was 131 mg/dL, lipase 15 U/L and the liver panel was normal. Urinalysis showed 30 mg/dL of proteinuria and only the occasional WBC on urine microscopy. Outpatient medications included baby aspirin, loratadine and lovastatin. Notably, at the time of this admission, he was not taking any outpatient antihypertensive agent nor was he on insulin or any oral hypoglycemic for his diabetes mellitus. A repeat intravenous contrast-enhanced CAT scan using 150 mL of iohexol iodinated contrast (350 mg/mL) was carried out to enable a decision as to whether an imaging guided drainage of the abscess by interventional radiology would be possible. This again confirmed the previous finding of an abscess that measured 6 × 6 × 8 cm in the right lower quadrant adjacent to the tip of the appendix consistent with an appendiceal abscess. IV Piperacillin-Tazobactam 3.375 gm every 6 hours was started. Since there was no adequate CAT-guided window to allow for percutaneous drainage of the abscess, it had to be evacuated surgically. He underwent exploratory laparotomy with evacuation of a complex abscess with peritoneal toilet, appendectomy and placement of a wound vac under general anesthesia. There was no significant intraoperative hypotension. By the next day, serum creatinine had doubled from 1.92 mg/dL on the day of surgery to 3.81 mg/dL, associated with hyperkalemia of 5.4 mmol/L and worsening metabolic acidosis (Figure 2). He soon became oliguric, and our nephrology service was consulted. By the third postoperative day, the patient experienced nausea and vomiting, further reduced urine output and hypervolemia. Hemodialysis was started on the fourth postoperative day via a right internal jugular vein tunneled dialysis catheter. He was dialyzed daily for three days and was then switched to thrice weekly outpatient dialysis. Increasing urine output was reported by the patient during the first week of April 2017. His pre-dialysis serum creatinine progressively improved with increasing urine output. Currently his pre-dialysis serum creatinine is 2.32 mg/dL, down from a peak serum creatinine of 7.62 mg/dL, and it remains the hope that he would once

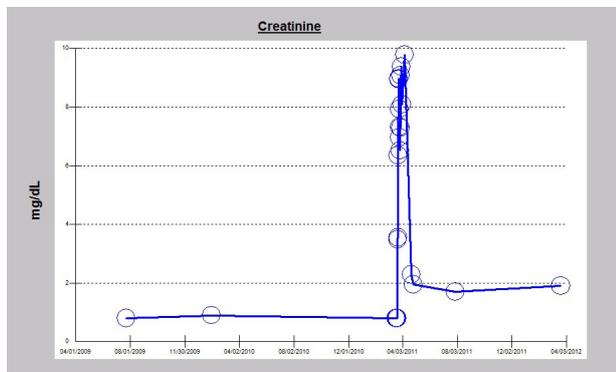


Figure 1. Change in baseline serum creatinine from 0.8-0.9 mg/dL to about 2 mg/dL following recovery from dialysis-requiring acute kidney injury in April 2011.

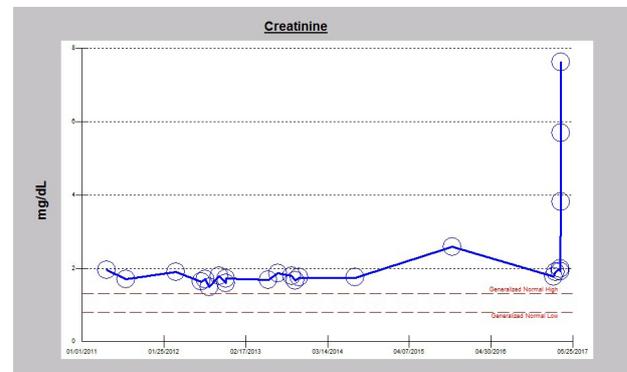


Figure 2. Rapidly rising serum creatinine trajectory following complications of laparotomy with evacuation of a complex peri-appendiceal abscess in March 2017.

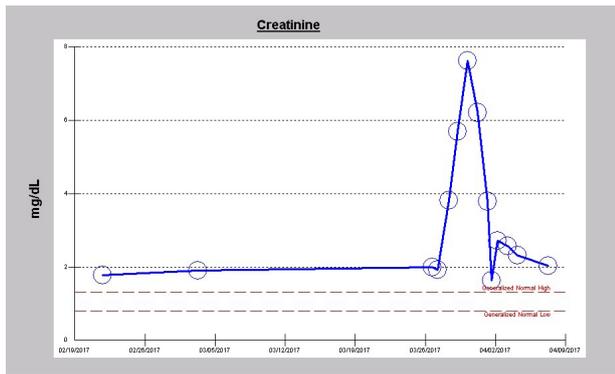


Figure 3. Falling serum creatinine trajectory in early April 2017 following partial renal recovery while still needing outpatient hemodialysis support.

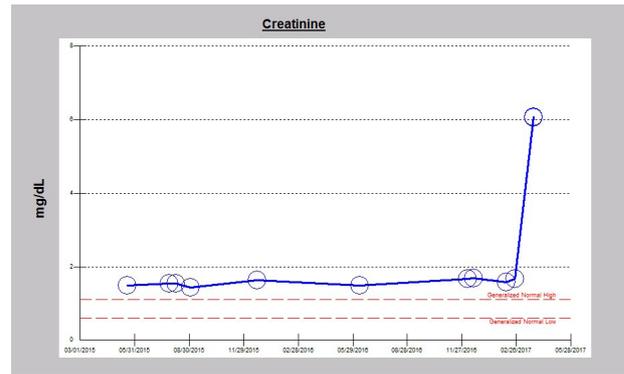


Figure 4. Serum creatinine trajectory following back-to-back double exposure to intravenous iodinated contrast in late March 2017.

again come off dialysis and the need for renal replacement therapy (Figure 3).

Case II

In March 2017, a 77-year-old type 2 diabetic Caucasian female patient with known ischemic heart disease, hypertension, previous myocardial infarction, 2-vessel coronary artery bypass procedure in 2006, chronic kidney disease stage IIIB with serum creatinine of 1.57-1.67 mg/dL (eGFR = 30-32 mL/min/1.73 m² BSA), atrial fibrillation on anticoagulation, biventricular congestive heart failure with severe right-sided heart failure, and severe tricuspid regurgitation presented to us with worsening renal failure. She had been evaluated the week prior to admission in our hospital at a tertiary healthcare institution, for consideration for entry into a percutaneous tricuspid valve intervention study because she was otherwise a very high surgical risk. She had a transesophageal echocardiogram that showed right ventricular enlargement, reduced right ventricular systolic function and severe tricuspid regurgitation with annular dilatation. The estimated left ventricular ejection fraction was 50% with moderate mitral regurgitation. She had undergone a CAT scan with iodinated contrast followed the next day by a cardiac catheterization which showed that all 3 native coronary arteries were occluded, and a right ventriculogram was performed apparently to confirm the tricuspid regurgitation and she then was subsequently discharged home. After three days at home, she began to feel unwell. By the weekend, she was experiencing increasing weakness, somnolence, some nausea, and had noticed a fall in her urine output. She also subsequently developed generalized pruritus which was very uncomfortable. The nausea got worse with occasional retching and vomiting. She then became more somnolent, more tired, and by the next evening she notified her daughter who called Emergency Medical Services and she was taken by ambulance to the emergency department. Outpatient medications included Spironolactone 12.5 mg daily, torsemide 100 mg daily, metolazone 5 mg 2x/week, simvastatin 40 mg at bedtime, baby aspirin 81 mg daily and warfarin.

Blood pressure was 136/66 mm Hg, pulse 66/min, temperature 36.3 C; she weighed 66.6 kg. Examination revealed a prominent right ventricular heave, with a 3/6 blowing quality murmur at the left lower sternal border consistent with tricuspid regurgitation. A blowing quality murmur was also audible at the apex and axilla. She had minor ankle edema and noticeable chronic venous stasis changes in both lower extremities. Laboratory results demonstrated renal failure with serum creatinine of 6.08 mg/dL (Figure 4), high anion gap (22 mmol/L) metabolic acidosis with serum bicarbonate of 17 mmol/L and mild proteinuria (30 mg/dL). She was mildly anemic, hemoglobin was 11.5 g/dL, WBC was 3.9 and international normalized ratio (INR) was 1.8 on Coumadin. Initially, she appeared to be in urinary retention so a Foley catheter was placed and the urine was blood tinged. The Foley catheter was subsequently removed when it became obvious that she was not in retention but was simply oliguric. Our nephrology service was consulted. Renal ultrasound showed left kidney measuring 9.6 cm, the right kidney 10.6 cm, both with thinned cortex, no hydronephrosis and both with elevated resistive indices at 0.87 and 0.90, respectively. The working diagnosis was severe oliguric AKI on chronic kidney disease secondary to contrast-induced nephropathy associated with high anion gap metabolic acidosis, increasing hypervolemia, nausea, anorexia, fatigue and falling urine output. She required initiation of renal replacement therapy and quickly consented to hemodialysis. A tunneled right internal jugular vein dialysis catheter was placed and hemodialysis was started the same afternoon. She then dialyzed daily for the next three days and since then has continued thrice weekly outpatient dialysis following discharge from the hospital. By the end of the first week of April 2017, at evaluation in the outpatient setting, she described increasing urine output and the dose of her diuretics, torsemide and metolazone, were increased. Current baseline serum creatinine, pre-dialysis, is 2.34 mg/dL, and with increasing urine output, it remains the hope that there would be subsequent recovery of kidney function for her to potentially come off renal replacement therapy in the future (Figure 5).

Case III

Early in the spring of 2013, a 46-year-old morbidly obese hypertensive Caucasian male inpatient, stage II CKD, baseline serum creatinine of 1.21 mg/dL (eGFR = 70 mL/min/1.73 m² BSA), had developed accelerated AKI after an elective right hip arthroplasty, that was complicated by perioperative hypotension and anemia. Outpatient medications before the elective procedure included lisinopril 40 mg daily and hydrochlorothiazide 25 mg daily, both taken for hypertension. Furthermore, he had received an oral preoperative Orthopedic Unit analgesic protocol dose of 200 mg celecoxib (a Cox II inhibitor). The latter medication, celecoxib had completed the “triple whammy” circle. His serum creatinine had within 36 hours more than doubled to 2.58 mg/dL (eGFR 28 mL/min/1.73 m² BSA) (Figure 6). There was also associated metabolic acidosis. Lisinopril and Hydrochlorothiazide were promptly stopped. Hypotension was rapidly corrected with intravenous normal saline infusions. He subsequently needed intravenous Furosemide for worsening oliguria. Urine output then improved and serum creatinine started to decrease (Figure 7). After hypotension was corrected, he become hypertensive again and required the initiation of antihypertensive therapy – this time with oral amlodipine and Furosemide. His serum creatinine continued to improve post-discharge, and had reached a level of 0.99 mg/dL (eGFR = 85 mL/min/1.73 m²

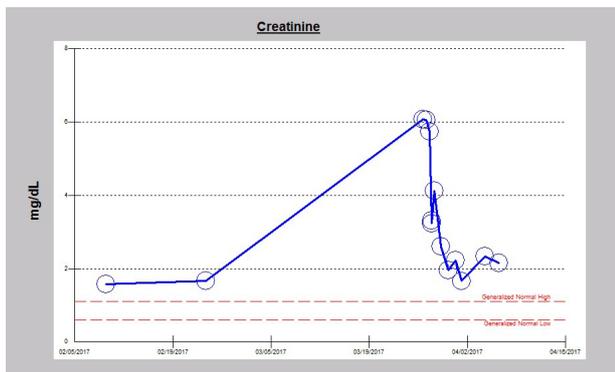


Figure 5. Falling serum creatinine trajectory in early April 2017 following partial renal recovery while still on thrice weekly outpatient hemodialysis.

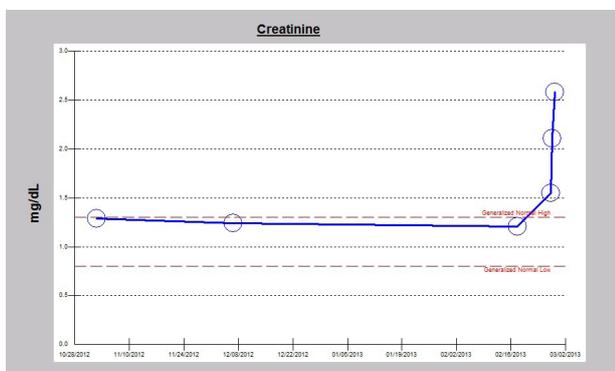


Figure 6. Accelerated acute kidney injury within 24 hours of the elective right hip arthroplasty.

BSA), about one month later, an improved level of kidney function when compared to that before the right hip arthroplasty procedure (Figure 7).

Case IV

A 52-year-old hypertensive diabetic Caucasian male patient was evaluated for bright red blood per rectum which started in the middle of April 2014. Past medical history was significant for acute right temporo-occipital lobe ischemic stroke, left vertebral artery complete occlusion, type 2 diabetes, hypertension, previous kidney stones and dyslipidemia. BMI was 30.5 kg/m². Digital rectal examination showed a rectal mass. At colonoscopy, two cecal polyps were removed. A third lesion, a 3 cm appearing wide-based polyp about 5 cm above the anal verge was observed and an attempted polypectomy was not completed due to the wide base. Pathology demonstrated the cecal polyps as sessile serrated adenoma but the rectal lesion revealed invasive adenocarcinoma arising in a tubular adenoma. Subsequent magnetic resonance imaging (MRI) staging in May 2014 demonstrated a 10 mm × 10 mm mucosal lesion, 5-6 cm superior to the anal verge, but no evidence of perianal, perirectal, pelvic, iliac, or inguinal lymphadenopathy. After confirming the staging to be T1 N0, on June 18, 2014, he underwent preoperative cystoscopy with temporary bilateral ureteral stent placements. This was followed by a low anterior resection of the rectum using the total mesorectal excision technique and mobilization of splenic flexure with diverting loop ileostomy. Mean arterial blood pressure (MABP) generally was maintained at >80 mm Hg in the operating room under general anesthesia, but there were as many as 14 5-minute periods with recorded MABP <80 mm Hg. There were indeed two instances of MABP of only 60 mm Hg, the first of such had occurred only 7 minutes into induction of anesthesia. Serum creatinine was normal, 0.84 mg/dL on May 5, 2014. It had risen to 1.17 mg/dL on June 17, 2014, a day after the surgical operation. Notably, he had a CAT scan with iodinated contrast on May 5, 2014. Outpatient medications included enalapril 40 mg daily, hydrochlorothiazide 25 mg daily.

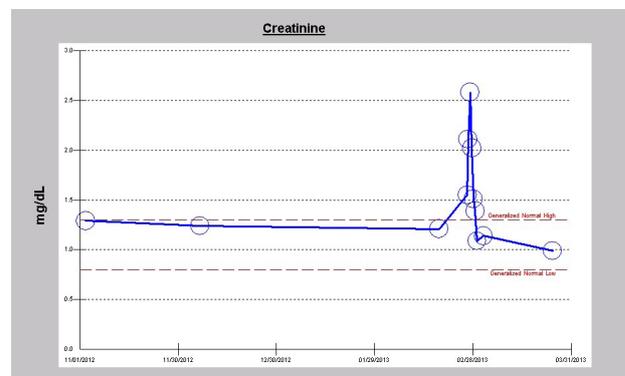


Figure 7. Serum creatinine trajectory showing improved serum creatinine, one month following right hip arthroplasty, and with the patient off the ACE inhibitor (Note that new baseline serum creatinine was lower than the pre-morbid baseline)..

Postoperatively, he experienced significant hematuria down the Foley catheter and reduced urine output was evident despite infusion of intravenous fluids. Forty-eight hours after surgery, his creatinine had nearly doubled to 1.94 mg/dL (Figure 8). He was not hypotensive. Temperature was 37.4 degrees centigrade, heart rate 58 per minute, respiratory 16 per minute, pulse ox 90% on room air and blood pressure was 142/71. He had received intravenous ketorolac, 30 mg every six hours, for a total of 7 doses for pain management. Following nephrology consultation, ketorolac and enalapril were promptly discontinued but his creatinine continued to rise (Figure 8). He received intravenous Furosemide 20 mg once and 80 mg once for oliguria. Together with the hematuria, the patient had also experienced significant low back pain, similar to a previous episode of nephrolithiasis. A renal ultrasound showed only mild right hydronephrosis but subsequent cysto-ureteroscopy was negative for any overt urinary tract obstruction.

Following the cystoscopy, his serum creatinine quickly improved to reach a normal baseline of 0.87 mg/dL by June 21, 2014 (Figure 9). His urine output was also appropriate but his hospitalization was extended due to ileus. He was tolerating solid food and adequate fluids. His ileostomy was functioning well and he was voiding without difficulty. Discharge medications included enalapril 40 mg daily. The ileostomy was finally taken down with re-anastomosis, uneventfully, in September 2014.

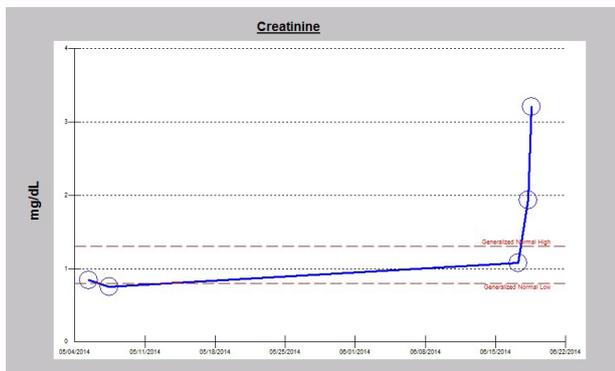


Figure 8. Accelerated acute kidney injury within 48 hours of the anterior resection of the rectal mass..

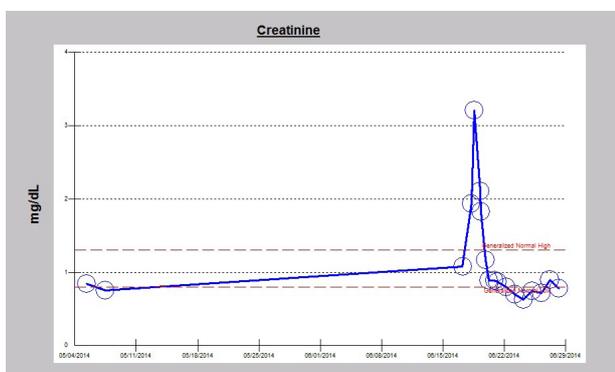


Figure 9. Serum creatinine trajectory showing improved serum creatinine, 4 days following the surgery.

Case V

In early April 2017, a 59-year-old morbidly obese hypertensive, diabetic Caucasian female patient with baseline creatinine of 0.69 mg/dL with additional past medical history for gastric bypass in 1980 and chronic narcotic dependence/methadone substitution therapy for chronic pain syndrome, was evaluated for a painful right groin swelling that had been progressively enlarging for several days. She weighed 93 kg, blood pressure was elevated at 154/90 mm Hg, pulse 102 per minute, temperature was 36.9 degrees centigrade and pulse oximetry was 97% on room air. Her diabetes was uncontrolled due to noncompliance with insulin therapy, as she had discontinued her insulin for about 2 months, with HbA1c of 14%.

Physical examination was otherwise significant for an indurated right groin swelling above the labia majorum measuring at least 8 × 6 cm in size, without fluctuation, not warm to touch, showed no overlying erythema, but was quite tender. Laboratory review showed the following pertinent values: Hemoglobin 13.8 g/dL, WBC 21.5 thousand/L, sodium 128 mmol/L, potassium 4.1 mmol/L, chloride 87 mmol/L, and serum creatinine was 0.69 mg/dL. Random blood glucose was 397 mg/dL. Blood cultures were drawn and she was started empirically on intravenous Vancomycin and intravenous tazobactam-piperacillin. A contrast-enhanced CAT scan of the pelvis utilizing 150 ml of iohexol (300 mg/mL) was performed in the emergency department which showed changes in the labia majorum and adjacent soft tissue consistent with inflammation/cellulitis. Intravenous insulin infusion was started to address the uncontrolled diabetes mellitus.

In addition to methadone and sertraline, she received intravenous hydromorphone for pain. It is unclear whether the patient's drug-seeking behavior contributed to this – she received a total of five doses of intravenous ketorolac (NSAID), which was prescribed for pain every 6 hours, as needed, between admission and early on day 2 of the admission before this agent was discontinued for concerns of nephrotoxicity.

Despite parenteral broad spectrum antibiotics, after 48 hours, there was increasing swelling, discomfort, erythema and tenderness of the right groin swelling with serum creatinine now up to 1.98 mg/dL (Figure 10). Surgery and gynecology specialties were now consulted. Examination at this time revealed that the right half of the mons pubis and the entire right labia majorum and labia minorum, down to the level of the perineum, was equally swollen, exquisitely tender and extremely indurated starting at the level of the pubic bone through the entire labia majorum and toward the perineal body. There were no areas of fluctuance palpable nor were there any open areas or lesions noted. Bimanual exam was not performed due to the exquisite tenderness of the external genitalia. An ultrasound examination of the area revealed a 3.5 × 2.2 × 2.2 cm focus of significant soft tissue edema consistent with severe cellulitis.

Infectious disease consult, three days after admission, replaced tazobactam-piperacillin with ceftriaxone and clindamycin. The vancomycin was discontinued after four days. She in addition also received intravenous cefazolin, 1

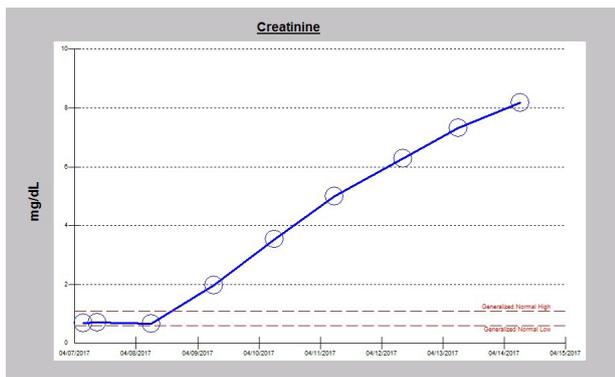


Figure 10. Accelerated acute kidney injury following admission to the hospital with right groin abscess.

gm every 24 hours.

Although ultrasound imaging of the lesion failed to demonstrate an abscess, given the worsening symptoms and increasing serum creatinine, a surgical evacuation was recommended. In the operating room, after the right labia majorum was incised with a longitudinal incision over the softest portion, the surgeons had to go through the skin and subcutaneous tissues for at least a centimeter before entering into a large pocket of yellow purulent material which was then evacuated. Operating room time was only about 40 minutes and MABP was generally maintained in the 70-90 mm Hg range.

Postoperatively, WBC improved and had normalized three days after the abscess was evacuated. Nevertheless, she remained oliguric, making only about 200 cc of urine a day, and serum creatinine continued to rise with worsening high anion gap metabolic acidosis (Figure 10). Renal ultrasound demonstrated normal sized kidneys except for a small left renal septated cyst. After initial resistance to starting dialysis, the patient consented to a dialysis catheter and she had her first dialysis treatment four days following the operation. Serum creatinine had reached 8.18 mg/dL, with an anion gap of 21 mmol/L, serum bicarbonate of 16 mmol/L and serum phosphorus of 9.4 mg/dL. She remains oliguric, and as at the time of going to press, she has been dialyzed daily for two days and would continue hemodialysis while we continue to monitor for possible recovery of her kidney function.

Discussion

Hospital-acquired AKI continues to constitute an increasing burden in current healthcare practices (1-3). As noted previously, Hsu et al demonstrated that the incidence of dialysis-requiring AKI had increased from 222 to 533 cases per million person-years, averaging a 10% increase per year (incidence rate ratio = 1.10, 95% CI = 1.10-1.11 per year) (2). Furthermore, renal hypoperfusion syndromes, nephrotoxic drugs, sepsis, surgery, and radiographic contrast media represent the most common causes of hospital-acquired AKI (1,4-6). Evidence for AKI as an independent risk factor for mortality has solidified over the years, with the increasing severity of injury resulting in a progressively higher risk of death (7-10). Despite these

facts, its therapy has not changed significantly for many decades, and currently, therefore, prevention is the only action that can reduce the frequency and consequences of AKI (11).

The following analysis of our five case presentations in this article would highlight the various opportunities for physicians and hospital healthcare providers to have applied preventative nephrology practices that more likely than not would have mitigated if not totally prevented the precipitation of hospital-acquired acute injury in all five patients. It must be acknowledged that even as we go to press, three of them remain on dialysis, with associated increased patient morbidity and concurrent escalating health care costs.

Case I: This 44-year-old African American male patient had CKD stage IIIA with serum creatinine of ~2 mg/dL, eGFR of 50 mL/min/1.73 m² BSA. His uncontrolled hypertension and uncontrolled diabetes mellitus were risk factors for poor renal outcomes. He then received a dose of intravenous ketorolac, a NSAID, and two back-to-back doses of intravenous iodinated contrast (iohexol) during CAT scan examinations. Arguably, an alternate analgesic could have been used in place of the ketorolac such as a narcotic agent. Moreover, the double exposure to iodinated contrast was potentially avoidable as well. Fortunately, during the laparotomy procedure to evacuate the abscess, intra-operative blood pressures were maintained with MABP generally >80 mm Hg and consequently, the patient was saved the additional precipitating factor of intra-operative hypotension. We and several other investigators have highlighted recently, in several publications, the neglected, potent, and yet preventable role of intraoperative hypotension in the causation of post-operative AKI (12-16).

Case II: This 77-year-old Caucasian female patient had CKD stage IIIB with serum creatinine serum creatinine of 1.57-1.67 mg/dL (eGFR = 30-32 mL/min/1.73m² BSA). Besides, biventricular failure and ischemic cardiomyopathy were additional predisposing risk factors for acute renal injury. The back-to-back sequential double exposure to both intravenous and intraarterial iodinated contrast could not come at a worse time for the precipitation of severe dialysis-requiring contrast-induced nephropathy. Arguably, the cardiac catheterization could have been delayed for several weeks, as necessary, following the first exposure during the iodinated CAT scan examination to avoid this double contrast exposure that arguably led to the precipitation of her dialysis-requiring AKI. Although, there is some doubt suggested in the literature whether contrast-induced nephropathy is a significant contributor to hospital-acquired AKI (17,18), the overriding evidence supports such a role, more so with repeated exposure and/or intra-arterial iodinated contrast as occurs during cardiac catheterization (19-21).

Case III: The 46-year old morbidly obese hypertensive Caucasian male inpatient, stage II CKD, baseline serum creatinine of 1.21 mg/dL eGFR 70 mL/min/1.73 m² BSA had a relatively low susceptibility to renal injury at the time of the elective procedure. However, the addition of celecoxib, a Cox II inhibitor to his outpatient medications,

lisinopril and hydrochlorothiazide, completed the circle of “triple whammy” exposure, thus raising the ante for the occurrence of nephrotoxicity (22-26). This was then further exacerbated by the super-imposition of peri-operative hypotension, thus constituting the “quadruple whammy” syndrome that we first described in the English literature earlier in 2013 and 2014 (27-29). Obviously, we would posit, that whereas the ACE inhibitor was withheld for 3-5 days before the elective right hip arthroplasty (30), and whereas the patient had received an alternative analgesic other than a NSAID or a Cox II inhibitor, and whereas intraoperative hypotension was avoided in the operating room, the patient would have experienced a smoother postoperative course, no AKI, reduced hospital stay and significantly reduced healthcare costs.

Case IV: The 52-year old hypertensive diabetic Caucasian male patient with normal kidney function in May 2014, serum creatinine of 0.84 mg/dL already had shown some rise in serum creatinine to 1.17 mg/dL before the anterior resection of the rectal mass in June 2014. It remains unclear if the contrast-induced CAT scan in May 2014 played any role in this initial change in kidney function (17-21). Subsequently, the combination of concurrent ACE inhibition (enalapril), concurrent diuretic (hydrochlorothiazide) and the exposure to seven doses of intravenous NSAID (ketorolac) had completed the well described phenomenon of “triple whammy” nephrotoxicity (22-26). To further exacerbate this scenario, the patient during the anterior resection of the rectal mass experienced significant intraoperative hypotension, a factor that has now been acknowledged to be a neglected yet potent factor in the pathogenesis of post-operative AKI (12-16). We dubbed this phenomenon as the previously unrecognized syndrome of “quadruple whammy” (27-29). We would argue that a pre-emptive withholding of the ACE inhibitor before the elective anterior resection of the rectal mass (30), the avoidance of the NSAID agent ketorolac, and a more aggressive prevention of intraoperative hypotension would have obviated the degree of AKI, a much shortened hospital stay and of course reduced healthcare costs. We do acknowledge however that there may have been some contribution from non-overt obstructive uropathy to the AKI and that this may have fortuitously been incidentally resolved following the cysto-ureteroscopy.

Case V: In a similar vein, we would argue that had this patient not received five doses of intravenous ketorolac, a NSAID, had the imaging been an ultrasound scan rather than a contrast-enhanced CAT scan, she would not have experienced dialysis-requiring AKI with all the implications for morbidity, mortality, prolonged hospital stay and escalating healthcare costs. It remains unclear if the pre-admission outpatient chronic exposure to naproxen (NSAID) played any role in the AKI since the admission serum creatinine was normal.

Conclusion

Goldstein has contested that increased physician awareness, daily monitoring of all potentially nephrotoxic exposures must remain standard of care for susceptible inpatients

(31). Moreover, the application of logic and other decision support systems in the electronic health record (EHR) could be leveraged to enhance biochemical surveillance and monitoring paradigms to improve renal outcomes in hospitals (31,32). We have demonstrated that the utility of serum creatinine trajectories in the real-time management of AKI in hospitalized patients cannot be over-emphasized (33). Chaumont et al have suggested that appropriate renal dosing of ACE inhibitors could lead to significantly reduced nephrotoxicity associated with this class of drugs (34). Our recent experiences with the syndrome of late onset renal failure from angiotensin blockade (LORFFAB) would support the pre-emptive withholding of angiotensin blockade before elective surgical procedures and before iodinated contrast exposure (35-37). Finally, it must be acknowledged that no effective treatment for AKI is available, except to institute renal replacement therapy options (11,38). We join the call for physicians and other hospital care providers to aggressively institute specific preventive measures as highlighted in this article, and more, to mitigate and possibly eliminate the scourge of rising hospital-acquired AKI.

Authors' contribution

All authors contributed equally to the manuscript.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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