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ACUTE KIDNEY INJURY

What We Used to Call Acute Renal Failure. . . . . Level II

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INSTRUCTOR'S GUIDE TO CHANGES IN THIS EDITION

CASEBOOK

Learning Objectives

- One objective revised.

Patient Presentation

- Case modified, so the cause of the patient's UGI bleeding is from a new gastric ulcer secondary to combined NSAID and antiplatelet use (i.e., aspirin plus clopidogrel). The HPI, PMH, medication list, and other objective information have also been modified.

Clinical Course

- Dobutamine was added to treat the patient's cardiogenic shock.
- The source of bleeding was altered, and some lab values were changed.

Clinical Pearl

- Changed to highlight incomplete recovery of kidney function in the recovery phase of acute tubular necrosis (ATN) and possible continued need to modify medication doses.

Self-Study Assignments

- First assignment modified to make students aware of two accepted definition and classification systems for acute kidney injury (AKI).

INSTRUCTOR'S GUIDE

Problem Identification

- Answer to question 1.a. revised to include naproxen and amlodipine as additional contributing medications to AKI in this patient. Famotidine removed as part of the answer as it is no longer part of the patient case.

Desired Outcome

- Answer revised to include additional nephrotoxins and to address the drug interactions with clopidogrel that are possible if this patient is started on a PPI.

Therapeutic Alternatives

- Answer updated to include discussion of the debate surrounding the optimal method of renal replacement therapy (RRT) in patients with AKI.

Optimal Plan

- Discussion of vasopressor use in AKI revised and updated.

Outcome Evaluation

- Minor revisions made to match updates to patient case.

Patient Education

- Added that the patient should also monitor for changes in his urine output and urinary frequency.

References

- Two references removed and two new references added.

CASE SUMMARY

A 72-year-old man with a history of HTN, CAD, CHF, and RA is admitted to the hospital with an acute UGI bleed resulting in prerenal AKI from hypovolemia and hypotension. After an unsuccessful attempt to stop the bleeding during an EGD, the patient is taken for emergent surgery where hypotension continues requiring the start of norepinephrine. Postoperatively, the patient remains hypotensive and experiences oliguric ATN that fails to respond to IV hydration and furosemide. Subsequently, he experiences acute pulmonary edema from volume overload and worsening heart failure and is started on dobutamine and continuous venovenous hemodiafiltration (CVVH-DF). Students are asked to create a list of the patient's drug therapy problems related to the patient's AKI on admission and develop pharmacotherapy goals. They are also asked to discuss the nondrug therapies used in the case and pharmacotherapeutic alternatives that have been studied.

QUESTIONS

Problem Identification

1.a. Create a list of the patient's drug therapy problems as they relate to his AKI.

- Acute UGI hemorrhage resulting in prerenal AKI from hypovolemia and hypotension.
- Anemia secondary to the acute UGI hemorrhage.
- He is taking medications that may potentially worsen his kidney function.
  - ✓ Furosemide may lead to further volume depletion in the setting of hypovolemia and worsen AKI due to prerenal azotemia.
  - ✓ Enalapril may also worsen this patient's AKI by further decreasing BP leading to a decrease in renal blood flow and causing a decrease in glomerular hydrostatic pressure through efferent arteriolar vasodilation.
  - ✓ Naproxen may also lead to further kidney injury by decreasing glomerular filtration secondary to decreased production of vasodilatory prostaglandins in the cells surrounding the afferent arteriole.
  - ✓ Metoprolol and amlodipine may decrease BP even further and lead to a further decline in kidney function from decreased kidney perfusion.

1.b. What information (signs, symptoms, laboratory values) indicates the presence or severity of hypovolemia and AKI in this patient?

Hypovolemia:

- Patient complains of lightheadedness and weakness.
- Patient feels cold (may indicate poor perfusion).

- BP is low, and patient has orthostatic hypotension.
- Patient has tachycardia.
- Patient's skin is pale, cold, and has poor turgor.
- Patient's conjunctivae are pale; mouth and tongue are dry.
- Pulses are weak.
- BUN:serum creatinine ratio is greater than 20:1.
- Hemoglobin and hematocrit are low.

Acute kidney injury:

- Decrease in urinary frequency in the last 24 hours.
- Elevated BUN and serum creatinine.
- The potassium is elevated despite the fact that the patient is on a loop diuretic. This may be an early indication of the kidney's inability to excrete potassium.

Desired Outcome

2. What are the goals of pharmacotherapy in this case?

- Stop the acute bleeding. This is the root cause of the patient's symptoms and complications. If hemostasis cannot be achieved, the patient's morbidity and mortality will be high.
- Restore and maintain hemodynamics and organ perfusion. The patient's intravascular volume needs to be restored in order to prevent further complications from his UGI bleed. Because hypovolemia from the bleeding is the most likely cause of his hypotension, restoration of intravascular volume will likely increase his BP and restore his kidney function.
- Correct anemia. The patient has a history of CAD and CHF and will likely benefit from transfusions that will increase his hemoglobin level above 10 mg/dL. However, caution should be observed because aggressive transfusion, along with volume repletion, may put the patient at risk for acute decompensated heart failure.
- Avoid or withhold medications that have the potential to worsen this patient's AKI (metoprolol, furosemide, enalapril, amlodipine, and naproxen).
- Avoid drug interactions. The patient will likely be placed on a proton pump inhibitor as part of therapy for the upper GI bleed, and careful consideration should be given to the choice of agent due to interactions with clopidogrel.

Therapeutic Alternatives

3.a. What nondrug therapies were used to manage this patient's AKI? Discuss the evidence that supports their use.

- *IV normal saline.* Repletion of intravascular volume for patients with prerenal azotemia is the most effective therapy for rapid resolution of this cause of AKI.[1] However, patients experiencing decreased renal blood flow for prolonged periods may progress to ATN before fluids are administered. Also, although the transfusions the patient received add to the repletion of intravascular volume, crystalloids are considered the primary therapy for rapid repletion of intravascular volume.[1] Postoperatively, the patient's prerenal azotemia had progressed to ATN due to prolonged hypovolemia and hypotension with subsequent hypoperfusion of the kidneys. At this point, further use of IV fluids should have been used with caution once adequate repletion of intravascular volume had been established.[2] Due to the continued aggressive IV hydration this patient received postoperatively, he experienced an exacerbation of CHF because of volume overload. In patients such as this who are experiencing oliguric ATN, intravascular volume and total daily intake and output should be monitored closely to avoid complications from hypervolemia.[2]
- *RRT with CVVH-DF.* This was necessary because the aggressive volume resuscitation and transfusions this patient received ultimately led to an exacerbation of CHF with resultant pulmonary edema. Severe pulmonary edema, hyperkalemia, uremic acidosis, and severe uremia are all indications for RRT in the setting of AKI.[1] A continuous mode of dialysis (CVVH-DF) was chosen due to this patient's hemodynamic instability (i.e., low BP). Continuous modes of RRT allow for slow, controlled ultrafiltration and dialysis.[2] However, traditional intermittent hemodialysis given for an extended period (6- to 12-hour sessions for several days), also known as sustained low-efficiency dialysis (SLED), can still be used in hypotensive patients when continuous methods are unavailable.[2] Debate exists over which mode of RRT produces the best outcomes in patients with AKI.

3.b. What pharmacotherapeutic alternatives have been studied for the treatment of AKI?

- *Furosemide.* Loop diuretics may have a role in the therapy of intrinsic AKI because they can convert a patient from an oliguric to a nonoliguric state and may decrease the metabolic workload in the tubule.[2] They are used clinically to remove excess intravascular volume in order to avoid the need for RRT due to hypervolemia.[1] However, loop diuretics should be used with caution, because they could further worsen kidney function in patients with prerenal azotemia due to hypovolemia. The use of a loop diuretic to try and maintain euvolemia in the setting of oliguric ATN in this patient was appropriate after adequate intravascular volume repletion. However, an escalating dose of 40 mg IV, then 80 mg IV, and then 160 mg IV is recommended instead of intermittent bolus dosing.[2] If escalating dosing fails to produce an adequate increase in urine output, the diuretic should be discontinued, and intake and output should be closely matched to avoid volume overload.[2]

  The evidence for the use of diuretics in the treatment of AKI is conflicting. A recent prospective epidemiologic study found no significant increase in the risk of mortality when diuretics were used in intensive care unit patients with AKI.[3] Two recent trials that evaluated combined data from several trials of furosemide for prevention and treatment of AKI also found no significant difference in mortality or the need for RRT with its use.[4,5] However, diuretics are still generally recommended in patients with AKI despite the lack of a clear outcome benefit and the possibility of increased mortality.[1,2]
- *Low-dose dopamine (≤2 mcg/kg/min).* Although widely used in the past for prevention and treatment of AKI, the use of low-dose (so-called renal-dose) dopamine has fallen out of favor. Although low-dose dopamine increases natriuresis and urine output, repeated studies fail to show a decrease in mortality or need for RRT when used for prevention or treatment of AKI.[6] Current guidelines and consensus statements recommend against the use of low-dose dopamine for the prevention and treatment of AKI.
- *Atrial natriuretic peptide.* Atrial natriuretic peptide increases urine output by inhibiting sodium and water resorption in the collecting duct.[2] It also increases GFR by dilating afferent arterioles and constricting efferent arterioles. It was initially shown to have potential benefits in patients with ATN but failed to show similar results in subsequent trials.[2] There is no commercial product available in the United States, and due to a lack of supportive data, it is not used for the treatment of AKI.

- *Mannitol.* Due to its diuretic effect, mannitol was initially thought to have potential benefits in patients with AKI. However, clinical trials have failed to show a benefit in the prevention or treatment of AKI except when used in organ preservation solutions during kidney transplantation and possibly early in the course of myoglobinuria secondary to crush injuries.[2]

Optimal Plan

4. Design an optimal therapeutic plan for managing this patient's AKI postoperatively.

- The optimal plan for this patient's postoperative AKI includes maintenance of hemodynamics and renal blood flow, monitoring of intravascular volume and maintaining euvolemia, restoration of urine output, and nutritional support

Maintenance of hemodynamics and renal blood flow:

- Vasopressor therapy was necessary in this patient postoperatively to maintain an adequate BP. This is appropriate because an adequate BP is needed to maintain renal blood flow and perfusion. The choice of vasopressor can be debated because there is no clear support for any particular agent in hypotensive patients with AKI. However, norepinephrine is a good choice due to its ability to increase mean arterial pressure and systemic vascular resistance, and it has been shown to increase urine output in patients with AKI.[7] Other vasoactive agents such as epinephrine and vasopressin may be reasonable alternatives, but available studies supporting their use are limited.

Restoration of urine output:

- Therapy for patients with intrinsic AKI is mainly supportive. There are no options for immediate reversal of dysfunction as in prerenal AKI. The decision to give this patient a diuretic in order to restore urine output was acceptable, but it was initiated without giving consideration to his volume status and was dosed inappropriately. Without an adequate response to diuretic therapy, the furosemide should have been discontinued and the patient's intravascular volume should have been closely monitored. Ultimately this patient needed RRT therapy, which was initiated appropriately for pulmonary edema due to hypervolemia. About 85% of patients with oliguric ATN will require RRT while waiting for kidney function to recover.[2] However, some patients will progress to end-stage kidney disease despite supportive care.

Nutritional support:

- Patients with AKI have a high rate of protein catabolism secondary to several metabolic factors, but mainly due to hepatic gluconeogenesis from amino acids.[2] Patients who require RRT have even greater protein requirements due to substrate loss, breakdown from proteases, and release of cytokines. Patients requiring continuous RRT usually require 1.5–1.8 g/kg per day of protein but can require intake up to 2.5 g/kg per day. Therefore, the patient in this case should have been started on appropriate early nutrition support that would have provided similar amounts of daily protein.

Outcome Evaluation

5. What clinical and laboratory parameters are necessary to evaluate the therapy for achievement of the desired therapeutic outcome and to detect or prevent adverse effects?

Clinical parameters:

- This patient's intravascular volume should have been monitored to assure adequate volume status and avoid hypervolemia in the setting of oliguria. The choice to continue infusion of IV fluids without proper monitoring was suboptimal and led to this patient's need for RRT. Invasive methods for monitoring intravascular volume include central venous pressure and pulmonary capillary occlusion pressure. Noninvasive methods include monitoring total fluid intake and output, patient weight, and BP. However, these noninvasive methods are less specific to actual intravascular volume because they will also account for fluid in other body compartments.
- The patient's BP, mean arterial pressure, and heart rate should be monitored at least every hour along with his temperature. This is especially true while the patient is receiving RRT.
- The patient's central venous pressure should also be monitored every 2–4 hours. His intake and output should be carefully recorded and totaled every 8 hours. His weight should also be recorded daily.
- The patient's urine output should be recorded hourly and totaled every 8 hours. The amount of replacement fluid administered and ultrafiltrate removed should be recorded hourly and totaled every 8 hours during CVVH-DF.
- Monitor the patient for wound and skin breakdown daily. Consider performing indirect calorimetry weekly if available. (*Note:* Measurement of urinary nitrogen excretion will be inaccurate because the patient has AKI.)

Laboratory parameters:

- Monitor Chem-7, calcium, magnesium, phosphate, complete blood cell count with differential, and arterial blood gases daily (especially while on mechanical ventilation and RRT).
- Assess the hepatic panel (aspartate aminotransferase, alanine aminotransferase, direct and total bilirubin), albumin, and prealbumin weekly.
- Monitoring of appropriate coagulation studies will be necessary depending on the type of anticoagulant used for CVVH-DF (i.e., activated partial thromboplastin time if using heparin).

Patient Education

6. What information should be provided to the patient to help avoid future episodes of AKI?

- Call your doctor immediately or go to the emergency room if you develop dark black stools or blood in your stool, if you are vomiting blood, or if you observe any change in urinary frequency or urine quantity or color.
- It is important that you take your medications as prescribed by your physician. If you miss a dose of one of your medications, take it as soon as you realize you missed the dose. However, if it is halfway to the time of your next dose, wait until the next scheduled dose. Never double up a dose of your medications to make up for a missed dose.
- It is very important that you see your doctor as scheduled and go for all your scheduled laboratory work so the effectiveness and safety of your medications can be monitored.

REFERENCES

1. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005;365:417–430.
2. Gill N, Nally JV Jr, Fatica RA. Renal failure secondary to acute tubular necrosis: epidemiology, diagnosis, and management. Chest 2005;128:2847–2863.

3. Uchino S, Doig GS, Bellomo R, et al. Diuretics and mortality in acute renal failure. Crit Care Med 2004;32:1669–1677.
4. Ho KM, Sheridan DJ. Meta-analysis of furosemide to prevent or treat acute renal failure. BMJ 2006;333:420–425.
5. Sampath S, Moran JL, Graham PL, et al. The efficacy of loop diuretics in acute renal failure: assessment using Bayesian evidence synthesis techniques. Crit Care Med 2007;35:2516–2524.
6. Friedrich JO, Adhikari N, Herridge MS, et al. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005;142:510–524.
7. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. Crit Care Med 2008;36(Suppl):S179–S186.