

Clinical pearls in hospital nephrology

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ABSTRACT

Hospitalized patients who have established kidney disease and those who have acute kidney injury in the hospital, along with patients with electrolyte disturbances tend to be some of the most complex to care for. Through working closely in nephrology consultation in the hospital with patients and providers, in both private and academic settings, we have come to encounter certain common presentations and recurrent themes that are worthy of emphasis, and of which a good understanding can translate into improved patient care. For the provider who works closely with such patients, many of these aspects are important to recognize and understand. In this review, we present 10 questions that address some of the highly relevant aspects of nephrology for the provider in the hospital. Through a MEDLINE database search, we reviewed the most pertinent studies as we then go through the explanation of management decisions in an evidence-based methodology with an up-to-date approach based on the current literature on the subject.

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1. Question 1

A 76-year-old man, nursing home resident, with a history of quadriplegia, was sent to the emergency department (ED) for evaluation of erythema and odor from a large decubitus ulcer in his sacral area. Due to the pain of the ulcer, he was given two tablets of ibuprofen on presentation. His past medical history (PMH) also includes chronic kidney disease (CKD) stage 3 (baseline creatinine 1.8 mg/dL). His medications are omeprazole and aspirin. Examination of the skin showed a 9-cm diameter ulceration in the sacral area with erythema and malodor. Initial blood work showed a creatinine of 1.8 mg/dL, blood urea nitrogen (BUN) of 22 mg/dL, and white blood cell count (WBC) of $17 \times 10^9/L$. The admitting provider started vancomycin and piperacillin/tazobactam. Omeprazole was continued. Three days later his creatinine was noted to be 2.6 mg/dL. Complement levels were normal. His urinalysis with microscopy revealed 3–5 hyaline casts/hpf but was otherwise bland.

Which of the following is the *most likely* to be predominantly responsible for the worsening kidney function?

- (A) Vancomycin
- (B) Omeprazole
- (C) Ibuprofen and omeprazole
- (D) Vancomycin and piperacillin/tazobactam
- (E) Infection-associated glomerulonephritis

1. Discussion

This patient developed acute kidney injury (AKI) with the rise in serum creatinine from 1.8 mg/dL to 2.6 mg/dL. His risk factors for AKI include multiple nephrotoxic medications and current infection. Although vancomycin use can be associated with increased risk of AKI mainly when elevated therapeutic levels are present, the combination of vancomycin and piperacillin/tazobactam (VT) has been recently recognized to be associated with significantly increased risk of AKI compared to other vancomycin antibiotic combinations [1]. In a meta-analysis of 24,799 patients receiving this combination, VT had a significantly elevated risk of AKI compared to vancomycin monotherapy with an odds ratio of 3.4 [2]. Another study found AKI occurred in 33% of patients from the cohort receiving VT, with associated risk factors including gram-positive infection, receipt of a vancomycin loading dose and receipt of any concomitant nephrotoxins [3]. Although omeprazole and ibuprofen have been associated with AKI mostly in the form of interstitial nephritis, it is unlikely to be the predominant cause of AKI in this patient given bland urinary sediment, with absence of any degree of pyuria or proteinuria, absence of other associated findings such as rash or fever, and relative infrequency of this association. Similarly, infection-associated glomerulonephritis is unlikely in the absence of active urinary sediment, and with normal complement levels.

2. Pearl

The combination of vancomycin and piperacillin/tazobactam is associated with increased AKI risk and should be avoided if possible, especially in patients who have other risk factors for AKI.

3. Question 2

A 61-year-old woman is admitted to the hospital with a one-week history of worsening lower extremity edema, dyspnea, and orthopnea. She has PMH of hypertension, CKD stage 3, and heart failure (ejection fraction (EF) 35%). Her blood pressure (BP) is 112/62 mmHg, heart rate (HR) is 98 bpm, and respiratory rate (RR) is 24 bpm. Her examination is remarkable for increased jugular venous pressure, bibasilar crackles, and peripheral pitting edema. Her medications include losartan 50 mg daily, metoprolol 25 mg daily, and furosemide 20 mg daily. Initial laboratory investigation showed a serum sodium of 139 mEq/L, potassium of 5.2 mEq/L, and creatinine of 1.6 mg/dl.

She received furosemide 40 mg orally on admission. Next morning electrolytes and kidney function are stable but her shortness of breath and fluid overload are persistent.

Which of the following is the *best* course of action for this patient?

- (A) Increase furosemide to 80 mg PO
- (B) Increase frequency of furosemide to BID and titrate to TID if needed
- (C) Restrict salt intake
- (D) Assess response to the diuretic within few hours of dose
- (E) Add metolazone to furosemide

2. Discussion

This patient presents with decompensation of her heart failure. Loop diuretics are an essential component of the management of heart failure. Oral furosemide has variable bioavailability with a range of 10–100% (average 50%) with wide variability [4,5]. The peak natriuretic response for furosemide is seen within 3 h after administration [6]. As such, prompt and timely assessment of response to diuretic is essential. Measurable clinical parameters should be used in making dose adjustments to loop diuretics such as urine output and accurate weight (standing scale). Lack of timely communication between the clinician and bedside nurse about response to diuretics leads to significant delays in timely adjustment of diuretic dose and frequency. Although restriction of salt intake and other measures such as a thiazide diuretic may become necessary, ensuring adequate diuresis takes precedence in this significantly fluid overloaded patient.

4. Pearl

In patients admitted to hospital with acute heart failure, every effort should be made to assess response to loop diuretic within the first few hours after administration. This allows titration to proper dose quickly leading to faster volume and symptoms control along with decrease hospital stay.

5. Question 3

For the patient in the preceding question, after considering all the available data, she is given 40 mg of intravenous (IV) furosemide and nurse calls with urine output 5 h after the dose of furosemide was received and it was approximately 30 mL/hour

What is the *best* next step for the management of this patient?

- (A) Increase furosemide to 80 mg IV
- (B) Increase frequency of furosemide to BID and titrate to TID if needed
- (C) Restrict salt intake
- (D) Restrict fluid intake
- (E) Add metolazone to furosemide

3. Discussion

The diuretic response in this patient is clearly sub-optimal and further adjustment of dose is needed. Loop diuretics exhibit threshold pharmacokinetics [7]. This means that the full drug effect will only be seen when the concentration of the drug at the site of action reaches a certain threshold. If the dose of the loop diuretic is less than the needed threshold, then the effect of the drug will be small and clinically insignificant. Once the threshold is reached, diuretic full response will be in effect. One approach would be to double the current dose and reassess response. In the case at hand, increasing the dose to 80 mg would be the best next step. A common mistake is to increase frequency of the dosing despite not reaching the threshold which often delays clinical improvement. The threshold for the same individual may be different for different levels of kidney function [7]. Adding a thiazide diuretic or restriction of salt intake is important, but effective early management of loop diuretics in this setting takes precedence.

6. Pearl

Loop diuretics have a threshold effect that should be reached before full effect can be seen. Timely titration to the proper dose is important in the management of patients with heart failure.

7. Question 4

A 77-year-old woman was brought to the ED for generalized weakness and recurrent falls over 3 weeks. Her PMH includes hypertension, hypothyroidism and dyspepsia. Home medications consist of hydrochlorothiazide, levothyroxine, and omeprazole. Her BP was 121/72 and HR 99 bpm. Physical examination showed dry mucus membrane, normal neurologic and cardiovascular examination and no edema. Her clinical investigation showed a serum sodium of 118 mEq/L, glucose 110 mg/dL, creatinine 0.7 mg/dL, serum osmolality 248 mOsm/kg, potassium 2.6 mEq/L, and normal thyroid function. Her urinalysis was bland. Her urine sodium was 84 mEq/L, urine potassium 26 mEq/L, and urine osmolality 410 mOsm/kg. She was started on 0.9% saline at 75 mL/hour with oral fluid restriction. Patient also received aggressive potassium supplementation (total of 80 mEq intravenously and 80 mEq orally in 12 hours). Twelve hours later, her serum sodium increased to 127 mEq/L and her serum potassium to 3.3 mEq/L. Her urine output was approximately 0.7 L in 12 hours.

Which of the following factors was the *most likely* cause of the rapid rise of serum sodium from 118 to 127 mEq/L?

- A. Fluid restriction
- B. 0.9% saline infusion
- C. Potassium replacement
- D. 0.9% saline infusion and potassium replacement
- E. Emergent diuresis

4. Discussion

This patient has hyponatremia secondary to hydrochlorothiazide use. Normal saline, which contains a sodium concentration of 154 mEq/L will be hypertonic in comparison to this patient's serum tonicity. Cessation of thiazide diuretic and infusion of normal saline will increase serum sodium in this setting. Potassium depletion results in a shift of sodium into the cell with equal exit of potassium from the cell into the extracellular fluid. The opposite phenomenon occurs during potassium repletion as described by Laragh [8]. Potassium contributes to body tonicity similar to sodium, and body electroneutrality is maintained by water shift and cations exchanges between compartments. Because the majority of the potassium is intracellular, replacing potassium to treat hypokalemia can raise serum sodium and osmolality especially in hyponatremic patients, likely due to sodium movement out of cells in exchange for potassium through sodium/potassium pump (Na-K-ATPase) and other mechanisms [9]. The increase in serum sodium level caused by 1 mEq/L of potassium supplement is equivalent to that caused by 1

mEq/L of sodium and as such, for example, giving 20 mEq of oral potassium chloride is roughly equivalent to giving 40 mL of 3% saline (each 1 mL of 3% saline has 0.5 mEq of sodium) [9,10].

8. Pearl

Hypokalemia associated with potassium depletion can be associated with hyponatremia, and potassium repletion increases serum sodium and is a risk factor for hyponatremia overcorrection.

9. Question 5

A 43-year-old man is sent to the hospital from his clinic for abnormal kidney function check. Two weeks ago he was seen for sinusitis and was prescribed amoxicillin/clavulanic acid for 10 days. Serum creatinine checked 1 month ago was 0.9 mg/dL. On blood work today, his serum creatinine was 6 mg/dL. Patient is asymptomatic except for some malaise. He is otherwise healthy with no PMH. He does not take any regular medications. Vitals were unremarkable. Physical examination was normal including cardiac, pulmonary, and skin. An ultrasound of the kidneys was normal.

Based on the given history, which of the following is unlikely to help find the cause of renal dysfunction?

- (A) Urinalysis with microscopy
- (B) Finding of WBCs and WBC casts on urine microscopy in the absence of urinary infection
- (C) Peripheral eosinophilia on blood count along with physical examination findings of fever and rash
- (D) Urine stain for eosinophils
- (E) Kidney biopsy

5. Discussion

This patient developed AKI after initiation of a penicillin pointing to the high possibility of acute interstitial nephritis (AIN), however, more data would be needed to make the diagnosis. Urinalysis with microscopy would be the first step to assess the urinary sediment. Finding of sterile pyuria and WBC casts in the absence of infection support the diagnosis of AIN in the right clinical setting [11]. The combination of eosinophilia on blood count along with physical examination findings of fever and rash, if present, make AIN more likely, although it is only found in a minority of confirmed AIN patients [12]. Kidney biopsy is the gold standard for diagnosis of AIN. A study from the Mayo Clinic looked at urine eosinophils and correlated this finding with kidney biopsy findings over an 18-year period [13]. Urine eosinophils were seen in a variety of biopsy-proven diseases. Using a 1% urine eosinophils cutoff, the

comparison of all patients with AIN to those with all other diagnoses showed 30.8% sensitivity and 68.2% specificity, giving positive and negative likelihood ratios of 0.97 and 1.01, respectively. Urine eosinophils were no better at distinguishing AIN from acute tubular necrosis compared with other kidney diseases.

10. Pearl

Urine eosinophils are unlikely to be helpful as a diagnostic test for acute interstitial nephritis

11. Question 6

A 55-year-old man was brought to the ED for nausea and vomiting that started last night. He felt quite fatigued during the day today and was unable to get up from bed. He does have history of diabetes mellitus managed with oral agents and hypertension. His medications are irbesartan, metformin, sitagliptin, empagliflozin, and ibuprofen. His BP on presentation was 95/68, HR 110 bpm, RR 24 rpm, O₂ saturation was 95% on room air. Pertinent physical examination findings were dry mucus membranes, tachycardia, and no lower extremity edema. His blood work revealed a sodium of 144 mEq/L, chloride 106 mEq/L, glucose 245 mg/dL, Creatinine 1.3 mg/dL, bicarbonate 14 mEq/L, lactic acid 1.2 mmol/L, and beta-hydroxybutyrate 9 mmol/L. His arterial blood gas analysis showed a pH of 7.28, pO₂ of 111 mmHg, and pCO₂ 28 mmHg.

Which one of the followings is *most likely* responsible for his presentation?

- (A) Metformin
- (B) Ibuprofen
- (C) Empagliflozin
- (D) Irbesartan
- (E) Sitagliptin

6. Discussion

Sodium-glucose transporter 2 inhibitors (SGLT2i) constitute a newer class of medications for the treatment of hyperglycemia in type 2 diabetes mellitus. They work by reducing blood glucose levels by increasing urinary glucose excretion. In a recent meta-analysis of randomized, placebo-controlled, cardiovascular outcome trials, SGLT2i significantly reduced risk of cardiovascular death or hospitalization for heart failure and risk of progression of renal disease [14]. One of the reported complications is diabetic ketoacidosis (DKA) [15] and a number of euglycemic ketoacidosis cases have been reported [16]. The mechanism for euglycemia, although possibly complex, may be facilitated by the urinary loss of glucose which lowers serum glucose [17]. This can

delay recognition of DKA given the lack of hyperglycemia. In one series in such patients, the range of glucose level at presentation was 96–233 mg/dL [16]. A high index of suspicion is needed and consideration for checking serum anion gap and ketones in a diabetic patient taking an SGLT2i presents with nausea, vomiting, or generalized malaise symptoms in absence of obvious etiology.

12. Pearl

Consider euglycemic ketoacidosis when a diabetic patient taking an SGLT2 inhibitor presents with nausea, vomiting, or malaise in absence of obvious etiology even if blood glucose levels are normal or mildly elevated.

13. Question 7

A 67-year-old woman presents with cough, shortness of breath, and fever for the past 3 days, and on evaluation in the ED, she was found to have left lower lobe lung infiltrate on chest x-ray consistent with pneumonia. Her PMH is significant for obesity. Her vital signs show a BP of 132/78, HR 92 bpm, RR 24 bpm, O₂ saturation 93% on room air, and a temperature of 38.2°C. Her weight on admission was 140 kg and height 160 cm. BMI was 55 kg/m². Clinical investigation revealed a creatinine 1.1 mg/dL with an estimated glomerular filtration rate (GFR) 50 mL/min/1.73 m². Her urinalysis was bland and microscopy showed no RBCs, WBCs, or casts. Given her eGFR, you inquire about personal or family history of kidney disease which she denies. Ultrasound of kidneys is unremarkable. On review of records, 6 months ago her creatinine was 1.1 mg/dL. As you document her pertinent medical problems, you noted the possibility of ongoing CKD based on her eGFR.

Based on the findings, which of the following would *best* characterize her kidney disease?

- (A) CKD stage 2
- (B) CKD stage 3a
- (C) CKD stage 3b
- (D) CKD stage 4
- (E) No CKD

7. Discussion

CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, according to KDIGO (Kidney Disease Improving Global Outcome) widely accepted definition [18]. These defining abnormalities can be seen with abnormal histology such as on kidney biopsy, evidence of proteinuria, urinary sediment abnormalities, among others. In the absence of such abnormalities, a GFR

less than 60 mL/min/1.73 m² establishes CKD [18]. The diagnosis of CKD carries health implications and it is important to accurately diagnose and label CKD. The most commonly used equations for estimating GFR currently are the CKD-Epi and MDRD equations [19,20]. Both equations report eGFR values normalized to standard body surface area (BSA) of 1.73 m². Kidney size is proportional to BSA and kidney function is proportional to kidney size. However, patients who have very large or very small weight or height or both will have a BSA that clearly deviates from the normalized value. It is recommended if using eGFR in very large or very small patients, that the reported eGFR is multiplied by BSA to obtain eGFR in units of mL/min [21]. For example, if BMI is larger than 40 or less than 18, consider making this adjustment. In the current patient in the given question, estimated BSA is 2.3 m². Her eGFR without adjustment is 50 mL/min/1.73 m². When accounting for body surface area, her eGFR is 66 mL/min (50 mL/min/1.73 m² * (2.3/1.73)). This clearly makes a difference with medication dosing and also reclassifies her as not having CKD, as she otherwise does not have any other findings of kidney disease.

14. Pearl

When using estimated GFR in very large or very small patients, it should be adjusted to the estimated body surface area.

15. Question 8

A 71-year-old woman presented to the ED with persistent cough for past 10 days. A chest x-ray showed a large irregular mass in right upper lung concerning for malignancy. She is being admitted to the hospital for workup of this finding. Her PMH is significant for hypothyroidism and takes levothyroxine. She has a 45-pack-year smoking history. Vital signs were normal. Pertinent physical examination findings were crackles noted in right upper lung fields, moist mucus membranes, and no lower extremity edema. Her neurologic examination was normal. Her clinical investigation revealed a sodium of 120 mEq/L, glucose 121 mg/dL, Creatinine 0.8 mg/dL, serum osmolality 255, serum uric acid 2.1 mg/dL, TSH 2.1, and normal free T4. Her urine sodium was 40 mEq/L, urine potassium 18 mEq/L, and urine osmolality 280 mOsm/kg. Her urine output was 1.1 L in 24 h. Recognizing that syndrome of inappropriate diuresis (SIAD) is the likely cause for her hyponatremia, and given she is asymptomatic, you decide to restrict her oral fluid intake as the initial treatment.

Which of the following will be the *best* indicator of whether fluid restriction will be effective in improving her serum sodium?

- (A) Serum osmolality
- (B) Serum sodium and potassium
- (C) Urine osmolality
- (D) Ratio of urine sodium and potassium to serum sodium
- (E) Ratio of urine osmolality to serum osmolality

8. Discussion

This patient has a clinical presentation and serum and urine indices consistent with SIAD. Total daily fluid restriction is a major component of the correction of hyponatremia in this case. Total and not just 'free water' restriction should be implemented [22]. However, the effect of fluid restriction on correction of hyponatremia is variable and as a sole measure may not be effective in some. The ability of fluid restriction to correct hyponatremia, can be predicted using ratio of sum of urine sodium and potassium to that of serum sodium [23]. If this ratio is less than 0.5, the serum sodium concentration is likely to rise with fluid restriction, whereas if the ratio is greater than 1, then fluid restriction as a sole measure is unlikely to change serum sodium and other measures should be added. In the given question, the ratio is calculated as (40 + 18)/120 which is <0.5 and hints that fluid restriction alone in this patient may allow for gradual rise in sodium.

16. Pearl

In hyponatremic patients, a useful indicator of likely response to fluid restriction is the ratio of sum of urine sodium and potassium to serum sodium; a ratio <0.5 indicates a likely positive response and rise of serum sodium with fluid restriction.

17. Question 9

An 81-year-old woman presented to the hospital with palpitations that she noted for past 3 weeks. She has hypertension and end stage renal disease (ESRD) and is maintained on in-center hemodialysis. She also had a history of stroke 1 year ago with residual right lower extremity weakness. In the ED, an EKG showed evidence of atrial fibrillation (AF) with rapid ventricular response, rate at 130 bpm. Her BP was 110/69. She was admitted to the hospital for further management. Her medications are aspirin, nifedipine, and calcium acetate. Her clinical investigation showed a serum creatinine of 4.5 mg/dL, BUN of 49 mg/dL, potassium of 4.9 mEq/L, magnesium of 2 mg/dL, hemoglobin 12.7 g/dL, and normal thyroid function. An echocardiogram showed an EF of 65% and no

evidence of valvar disease. Metoprolol was initiated and given a high CHADsVasc score of 6, the hospitalist decided anticoagulation will be in her best interest despite recognition of paucity of evidence in dialysis patients, after a careful discussion with patient on risks and benefits.

Which of the following would be *the best* oral anticoagulation choice(s) given her ESRD?

- (A) Warfarin or Dabigatran
- (B) Warfarin or Apixaban
- (C) Warfarin or Rivaroxaban
- (D) Warfarin and any of the factor Xa inhibiting direct oral anticoagulants is safe
- (E) Warfarin is the only safe choice

9. Discussion

Patients with advanced kidney disease were mostly excluded from large clinical trials evaluating newer oral anticoagulants. A recent study showed that among patients with ESRD and atrial fibrillation, apixaban use was associated with a lower risk of major bleeding compared with warfarin, and was also associated with reductions in thromboembolic and mortality risk [24]. The more recent 2019 American Heart Association update on atrial fibrillation recommends that for patients with AF who have a CHA₂DS₂-VAsc score of 2 or greater in men or 3 or greater in women and who have advanced CKD (GFR <15 mL/min) or are on dialysis, that it might be reasonable to prescribe warfarin or apixaban for oral anticoagulation [25]. Although this a weak recommendation, it is a new recommendation and reflects the growing evidence of safety and effectiveness in this group of patients. More studies are needed to evaluate whether this applies to other direct oral anticoagulants.

18. Pearl

Although more data is needed, evidence to support use of Apixaban in advanced CKD patients is favorable

19. Question 10

A 57-year-old man was transferred from outpatient dialysis unit to the ED for fever and abdominal pain for 2 days. His PMH consists of ESRD, hypertension, and anemia. Home medications include carvedilol, amlodipine and calcium acetate. His physical examination showed left lower quadrant tenderness with localized guarding and rigidity. His clinical investigation showed a serum creatinine of 4.7 mg/dL, BUN 47 mg/dL, potassium 3.7 mEq/L, and WBC $21 \times 10^9/L$. Abdominal CT with intravenous contrast showed diverticulitis of the

descending colon with few air foci outside the colon. Patient was admitted to hospital for intravenous antibiotics along with surgical consultation. He usually receives dialysis 3 times weekly and his full dialysis run was this morning. The radiologist recommended that the patient undergoes dialysis as soon as possible today to clear the iodinated contrast.

Which the following is the *best* next step in this setting?

- (A) Provide dialysis now to remove contrast and prevent contrast accumulation
- (B) Resume dialysis per outpatient schedule and no need for urgent dialysis today
- (C) Provide dialysis now to prevent volume overload
- (D) Provide dialysis now for correction of electrolyte abnormalities
- (E) Plan for dialysis to remove contrast within 24 hours since he already had dialysis earlier today

10. Discussion

Despite the theoretical concerns, there is no need for urgent dialysis after iodinated IV contrast administration in ESRD patients who are on dialysis. The patient should be able to wait until their next scheduled dialysis session. There are two major concerns regarding IV contrast exposure in ESRD patients: (a) delivery of excessive solute load causing volume overload and (b) loss of residual renal function [26]. Multiple studies have examined the issue of volume overload and the majority of studies did not show that IV contrast increases the risk of volume overload [26,27]. A group of investigators retrospectively reviewed outcomes of 1,287 ESRD patients receiving 100 ml of Iohexol for CT who also only received dialysis at usual scheduled times and did not receive any extra sessions after contrast [28]. None of the patients developed side effects that needed urgent dialysis. In regard to the second concern, the loss of residual renal function, Janousek et al. did a prospective study comparing 42 patients with ESRD and residual urine output greater than 500 ml/day who received iodixanol for different endovascular interventions with a control group with ESRD patients without contrast. There was no statistically significant difference between the two groups in daily urine volume or creatinine clearance [29].

20. Pearl

Intravenous iodinated contrast can be given safely to most patients with ESRD who are maintained on

hemodialysis. Immediate post-contrast dialysis is unnecessary as a routine practice.

Disclosure of Interest

The authors report no conflicts of interest

Disclosure statement

No potential conflict of interest was reported by the authors.

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Answers: 1:D, 2:D, 3:A, 4:D, 5:D, 6:C, 7:E, 8:D, 9:B, 10:B