Supplemental Material: Table of Contents

Case 1: Use of the fractional excretion of sodium in a patient with pre-existing chronic kidney disease

A 52 year old man with known diabetic nephropathy and a baseline serum creatinine concentration of 2.2 mg/dl (eGFR 33 mL/min/1.73 m²) presents with a 3 day history of nausea, vomiting, and diarrhea described as 4-5 loose watery stools per day. Physical examination is significant for orthostatic changes in blood pressure and pulse, dry mucous membrane, and no peripheral edema. Laboratory studies show (mEq/L): Na^+ 142, K^+ 3.6, Cl^- l06, HCO_3^- 22 and serum creatinine concentration 2.8 mg/dl. The urinalysis shows 1+ protein but no cells and occasional hyaline casts. Urine output over the first 6 hours of evaluation is 500 ml. The urine sodium concentration is 55 mEq/L and the urine creatinine concentration is 75 mg/dl.

How does one utilize the fractional excretion of sodium in patients with chronic kidney disease?

The fraction excretion of sodium measures the percentage of the sodium filtered by the kidney that is excreted in the urine. When the glomerular filtration rate is normal (180 liters/day) and the filtered load of sodium is 27000 mEq/day (180 liters/d x plasma water sodium concentration of 150 mEq/L), the fractional excretion of sodium will always be <1% whenever dietary intake is <270 mEq/day, a value above the average dietary salt intake. The FE_{Na} would need to be <0.1% in order to reduce urinary sodium concentration to <25 mEq/day, indicating an appropriate response to a prerenal state. For this reason, the fractional excretion of sodium is most useful in distinguishing between prerenal azotemia from acute tubular necrosis when the glomerular filtration rate is markedly reduced. In a patient with a glomerular filtration rate of 20 liters/day, the filtered load of sodium would be only 3000 mEq/day. In this case, the fractional

excretion would only need to be <1% to indicate an appropriately reduced daily urine sodium excretion assuming a prerenal cause was the only problem.

Since baseline urine chemistries are not available in the described patient, one has to estimate the initial FE_{Na} based on the known eGFR and an estimate of dietary sodium intake. Assuming the patient was in balance on a dietary sodium intake of 175 mEq/day, the fractional excretion of sodium can be estimated to be 2.4% at baseline:

$$FE_{Na} = \text{daily sodium intake} / [\text{GFR (in liters/day)} \times \text{plasma water sodium content})$$

or

$$(175 \text{ mEq/day} / (33 \text{ ml/min} \times 1440 \text{ min/day}) \times 150 \text{ mEq/L}]$$

Upon presentation, the fractional excretion of sodium is 1.4%:

$$FE_{Na} = (U_{Na} \times P_{Creatinine} / P_{Na} \times U_{Creatinine}) \times 100\%$$

$$FE_{Na} = (55 \text{ mEq/L} \times 2.8 \text{ mg/dl} / 142 \text{ mEq/L} \times 75 \text{ mg/dl}) \times 100\%$$

Even though the urine sodium concentration is not less than 20 mEq/L and the fractional excretion of sodium is >1%, the clinical findings in this case are consistent with some degree of intact tubular function as reflected by the decrease in fractional excretion of sodium from 2.4% at baseline to the current value of 1.4%. Sodium balance is maintained in patients with chronic kidney disease through increases in the fractional excretion of sodium that can reach values of 25-30% when the glomerular filtration rate is approximately 10 ml/min. In chronic kidney disease, the kidney's

response to dietary sodium restriction or development of a prerenal state is delayed and not maximal but eventually the urine sodium concentration and fractional excretion will decrease over time in patients who are not at end stage (1,2). In addition to the change in fractional excretion of sodium, the history, clinical examination, urine microscopy, and, when appropriate, response to volume resuscitation, should be utilized in assessing the volume status of these patients.

Case 2: Distinguishing prerenal azotemia from acute tubular necrosis in the setting of diuretic therapy

A 58-year-old man with a history of heart failure with reduced ejection fraction is admitted with a 3-day history of worsening shortness of breath and edema. His past medical history is significant for a prior myocardial infarction and benign prostatic hypertrophy. He is found to be in pulmonary edema and requires intubation and mechanical ventilation. Medications on admission include aspirin, lisinopril, carvedilol, atorvastatin, and furosemide. On physical examination, he is afebrile, blood pressure is 92/60 mm Hg, and pulse rate is 112/min. There is jugular venous distention, an S3 gallop, diffuse crackles throughout both lung fields, and lower extremity edema to the knees. A urinary catheter is inserted and intravenous furosemide is given. Urine output over the next 4 hours is 300 ml. Laboratory evaluation shows the following (mEq/L): Na^+ 140, K^+ 4.8, Cl^- 103, HCO_3^- 22, creatinine 3.0 mg/dl (baseline 1.9 mg/dl), blood urea nitrogen 76 mg/dl. Urine chemistries show a Na^+ 64 mEq/L, creatinine 72 mg/dl, urea 159 mg/dl. Urinalysis shows 1+ protein, 1-2 RBC/hpf, 2-4 WBC/hpf, and occasional hyaline and fine granular casts.

How can one distinguish between prerenal azotemia and acute tubular necrosis in the setting of diuretic therapy?

This patient presents with acute kidney injury in the setting of decompensated heart failure. The worsening azotemia during the hospitalization is most likely due to decreased effective blood volume causing a prerenal state. Acute tubular necrosis from hypotension and urinary obstruction from prostate disease also need to be considered in assessing the change in kidney function. The fractional excretion of sodium is a useful test to distinguish between a prerenal cause of acute kidney injury from acute tubular necrosis. This test becomes less reliable in the setting of diuretic

therapy because the urine sodium may not accurately reflect attempts by the kidney to retain sodium. Under condition of low flow to the kidney, there is increased urea reabsorption by the proximal tubule accounting for the disproportionate rise in the blood urea nitrogen compared to the serum creatinine concentration. The fractional excretion of urea will be unaffected by loop diuretic therapy since the site of action of these drugs is in the downstream thick ascending limb. In this patient, the fractional excretion of sodium is higher than expected in a prerenal state at 1.9%, but the fractional excretion of urea is only 8.7% (<35%), suggesting an underlying prerenal state.

The use of FE_{Urea} and FE_{Na} do have limitations as discussed in the main text. The initial report establishing a value <1% for a prerenal etiology and >3% to indicate tubular injury came from a small study of highly selected patients excluding those on diuretics and patients with chronic kidney disease, glomerulonephritis, and urinary obstruction (3). A larger subsequent study validating the use of FE_{Na} also excluded the use of diuretics within 24 hours of study entry (4). More recent studies have reported a sensitivity and specificity for the FE_{Na} of 78% and 75% in patients not administered diuretics and 58% and 81% in those administered diuretics (5,6). By comparison the sensitivity and specificity of the FE_{Urea} is 48% and 75% in patients not administered diuretics and 79% and 33% in patients administered diuretics. These observations emphasize the need to use the FE_{Urea} and FE_{Na} as an adjunct to the clinical history, physical examination, urine microscopy, and, when appropriate, response to volume resuscitation in the assessment of the azotemic patient.

Case 3: Distinguishing whether metabolic acidosis is due to kidney disease or not

A 19-year-old woman is transported to the emergency room after being found on the floor of her apartment unable to move. The patient states she was in her usual state of health up until 36 hours ago when she noticed the onset of episodic but progressively worsening generalized weakness. There was no history of bladder or bowel incontinence or loss of consciousness. Past medical history was unremarkable and the patient denied ingestions, however, the roommate who accompanies her says she has been acting "a little crazy" recently. Vital signs on admission showed: temperature of 37 C, blood pressure of 110/60 mmHg and pulse 95. Physical exam is remarkable for erythematous discoloration around her lips and nose and erythema of the oral and pharyngeal mucosa. Conjunctival injections are present. There was 2/6 weakness in both upper and lower extremities and generalized hyporeflexia. Laboratory data show: (mEq/L) Na^+ 136, K^+ 1.5, Cl^- 105, HCO_3^- 10, creatinine 1.4 mg/dl, BUN 32 mg/dl, pH 7.1, pCO_2 35 mmHg, pO_2 110, Urine (mEq/L): Na^+ 42, K^+ 38, Cl^- 65, pH 6.0, urea 38 mg/dl, creatinine 62 mg/dl, osmolality 610 mOsm/kg.

How can one determine whether the metabolic acidosis is due to kidney disease or not in this patient?

This patient presents with severe hypokalemia and a triple acid-base disturbance to include an anion gap metabolic acidosis, hyperchloremic normal gap metabolic acidosis, and respiratory acidosis. This determination can be made by taking a systematic approach to the basic metabolic profile (7). Examination of the plasma sodium concentration suggests a mild increase in total body water. Normally changes in hydration status will lead to a similar change in chloride concentration, however, in this case the chloride concentration is increased. A change in chloride

concentration in a direction opposite or disproportionate to the change in plasma sodium suggests an acid-base disorder is present. The two causes to consider when the chloride concentration has increased relative to the sodium are chronic respiratory alkalosis or normal anion gap metabolic acidosis. One should always calculate the anion gap when given a basic metabolic profile. In this case, the anion gap is 21, thus identifying the presence of an anion gap metabolic acidosis as at least one of the acid-base disturbances in this case. In general, the serum bicarbonate concentration will fall by an amount equal to the increase in anion gap. In this patient the anion gap has increased by nine assuming a normal value of 12. As a result one would predict the plasma bicarbonate should be approximately 15 mEq/L (24 – 9 = 15). Since the measured value is 10 mEq/L, one can conclude a normal gap hyperchloremic metabolic acidosis is also present which was suggested by the disproportionate rise in plasma chloride concentration noted above. The expected degree of respiratory compensation for a bicarbonate of 10 mEq/L in the setting of metabolic acidosis is a pCO_2 of approximately 25 mmHg. The measured value of 35 mmHg indicates an insufficient respiratory response confirming the presence of respiratory acidosis.

The laboratory findings along with the erythema around the mouth and oropharynx are consistent with inhalation of toluene. Metabolism of toluene generates benzoic and hippuric acid which are buffered by endogenous bicarbonate. The subsequent excretion of the sodium or potassium salts of these acids into the urine is equivalent to the indirect loss of bicarbonate from the body. While chronic exposure to toluene can lead to tubular injury and a type 1 distal renal tubular acidosis, examination of urine chemistries demonstrates a normal response of the kidney to the acidosis as manifested by robust excretion of ammonium in the urine.

Calculating the urine anion gap allows for indirect assessment of the amount of urinary ammonium. Metabolic acidosis of extrarenal origin leads to a marked increase in urinary

ammonium excretion and normally would be reflected by a large negative value for the UAG. In this patient, the UAG is 15 suggesting the acidosis is due to intrinsic kidney disease. The UAG is misleading in the setting of toluene exposure due to increased urinary excretion of Na^+ and K^+ coupled to hippurate and or benzoate (8,9). In addition, the stimulatory effect of acidemia and hypokalemia progressively increase the amount ammoniagenesis so that large quantities of ammonium hippurate and benzoate are also present in the urine further limiting the utility of the UAG to accurately reflect urinary ammonium excretion. A similar situation occurs in diabetic ketoacidosis where the UAG may remain positive despite an appropriate increase in urinary ammonium excretion due to the increased urinary excretion of Na^+, K^+, and NH_4^+ ketoacid salts.

The urine osmolal gap is a more useful method to semiquantitatively estimate the amount of ammonium in the urine under conditions of organic acid anion loss in the urine. In this case, the urine osmolal gap is significantly increased at 436 mOsmol/kg indicating large amounts of ammonium in the urine and an extrarenal source of the acidosis.

The severe hypokalemia is due to the poorly reabsorbable anion effect of hippurate and benzoate causing increased distal Na^+ delivery in the setting of increased mineralocorticoid activity, the latter being due to volume depletion. The urine K^+/creatinine ratio of 6.9 (38 mEq/5.5 mmol) indicates K^+ wasting by the kidneys.

Case 4: The use of urine chemistries in the approach to a polyuric patient with hypernatremia and a patient with hyponatremia

A 73 year-old man with dementia is transferred from a nursing home to the hospital with a diagnosis of pneumonia. On admission serum electrolytes were normal. In addition to treating the infection, hyperalimentation with high-protein supplements (solution contains 30 mEq/l each of Na^+ and K^+) is begun in an attempt to improve the patient's poor nutritional status. Five days later it is noted the urine output is averaging 4 liters/d. Laboratory evaluation shows (mEq/L): Na^+ 156, K^+ 4.6, Cl^- 116 HCO_3^- 26, BUN 35 mg/dl, creatinine 1.2 mg/dl. Urine chemistries show (mEq/L): Na^+ 12, K^+ 42, osmolality 505 mOsm/Kg.

How can one use urine chemistries to determine the cause of free water lose in this patient?

This patient presents with a water deficit in association with polyuria. When approaching a polyuric patient one needs to distinguish between a water diuresis and an osmotic diuresis. In the setting of a water diuresis the urine osmolality will be maximally dilute at <100 mOsm/kg. The urine osmolality of 505 mOsm/kg in this patient suggests an osmotic diuresis. Even though the urine is concentrated, calculating the electrolyte free water excretion indicates this patient is losing 2.6 liters of free water per day exacerbating the water deficit. In the setting of a normal diet daily solute excretion averages 900 mOsm. This patient is excreting 2020 mOsm/day (Uosm (505 mOsm/kg) x 4 liters/24 hr = 2020 mOsm). The most likely cause of the polyuria is an osmotic diuresis due to urea excretion derived from the metabolism of protein in the hyperalimentation.

Calculating electrolyte free water clearance can also be useful in the management of patients with hyponatremia. Consider a patient with SIADH who presents with a plasma sodium concentration of 123 mEq/L and has a urine output of 1 liter/day. Urine studies show osmolality

of 550 mOsm/kg, Na^+ 95 mEq/L, and K^+ 58 mEq/L. The daily solute excretion is 1 liter x 550 mOsm or 550 mOsm/day.

$$\text{Electrolyte free water clearance} = U_{volume} \times [1 - (U_{sodium} + U_{potassium} / P_{sodium})]$$

$$\text{Electrolyte free water clearance} = 1 \text{ liter} \times [1 - (95 + 58 / 123)]$$

$$\text{Electrolyte free water clearance} = -240 \text{ ml}$$

The negative value indicates water restriction would not be an effective strategy to correct the hyponatremia. In fact, any water intake in excess of insensible losses would aggravate the hyponatremia. The administration of urea to increase urinary solute excretion or administration of a vasopressin receptor antagonist would be effective treatments in this setting.

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