Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

Mr. Mac Uladensa, a visiting medical student, enters the room along with L.O. Henle to present a case.

Nephron *(with surprise)*: My apprentice, what do you have for me? And who do we have here?

Henle and Mac look at each other.

Henle This is Mac, a visiting medical student, here to learn about nephrology.

Nephron *(with a smile)*: Glad to have you on board. Nephrology is a fun field of medicine and probably the most enigmatic. There is a lot of physiology, pharmacology, and pathology to learn in nephrology. The kidney is a smart organ!

Mac Glad to be on board. I just played NephMadness online and learned a lot of fun facts about nephrology.

Henle We have a case of a bicarbonate level of 60 MEq/L.

Nephron The patient is likely vomiting. What do you want me to do?

Mac The arterial blood gas determination shows a pH of 7.60 and pCO_2 of 66 mm Hg. Serum chloride is 68 mEq/L.

Henle So the patient has a metabolic alkalosis with good compensation.

Nephron I am still confused. Why are you presenting this to me? This sounds like a case of vomiting with some degree of volume depletion leading to metabolic alkalosis.

Mac Why is the urinary sodium not lower than 10 MEq/L? It is 45 MEq/L.

Nephron *(happy)*: Ah! There is an interesting and commonly asked question, but poorly understood. Let's start from the basics. What happens during vomiting?

Mac Vomiting removes gastric fluid from the stomach, although the parietal cells in the stomach still continue to produce hydrogen ions and release bicarbonate into the blood. Because this bicarbonate is not neutralized, this generates metabolic alkalosis.

Nephron What happens in the kidney?

Mac There is increased filtration of this bicarbonate, and it meets the proximal tubule. Given that there is no need to reabsorb this bicarbonate, it will just get excreted.

Henle But doesn't it need a cation to get excreted with?

Mac *(with a smile)*: Likely sodium….hence making urinary sodium high in the state of vomiting.

Nephron Good work, my friends. Normally, in the absence of volume depletion, metabolic alkalosis is corrected by the excretion of excess bicarbonate in the urine. To maintain electroneutrality, sodium gets excreted in the urine. But what do you think happens when there is volume depletion?

Mac Hmmm, does volume trump everything?

Nephron What is this patient's urinary pH? It has to be alkalemic.

Henle Suggesting loss of bicarbonate and hence urine sodium being high.

Nephron *(with a wink)*: Now let's assume this patient's systolic blood pressure drops because of excessive vomiting. What happens then?

Henle A tug of war between metabolic alkalosis and volume. There might be times when sodium will be taken back to maintain blood pressure but can fluctuate. Volume will win most of the time. So, if volume rules, the reabsorption of sodium with bicarbonate continues and maintains the metabolic alkalosis.

Nephron Bingo! Not only have you explained that volume trumps everything, but also you have mentioned one of the key components that maintains metabolic alkalosis, which is hypovolemia. So vomiting in this case is generating and maintaining metabolic alkalosis.

Henle Let's get back to our patient. So does urinary chloride help us in this situation?

Nephron The spot urine chloride is always appropriately low: below 20 MEq/L in metabolic alkalosis because of vomiting, and that can help in the diagnosis. The spot urine sodium might be low if the patient is in a volume-depleted state, or it can fluctuate as you mentioned, based on who is winning: volume or alkalemia. But the urine chloride will be low.

Let me ask you, then: what else will maintain this metabolic alkalosis besides the hypovolemia?

Mac *(confidently)*: Well, low volume will maintain it by stimulating aldosterone, and excess mineralocorticoid activity would then be the second way to maintain it. Aldosterone will enhance the activity of the H^+-ATPase pumps in the intercalated cells and lead to reabsorption of bicarbonate. Aldosterone also increases sodium absorption in the principal cells, leaving the lumen negatively charged, promoting hydrogen ion secretion leading to bicarbonate generation.

Nephron Good points. Anything else that maintains this?

Henle *(jumping in)*: Chloride depletion itself in this vomiting state will lead to maintaining the alkalosis. In type A intercalated cells, there is a Cl/HCO_3^- exchanger in the basolateral membrane. If there is less chloride in the lumen, there is loss of chloride and hydrogen secretion, leading to bicarbonate reabsorption. In addition, in the

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type B intercalated cells, the Cl/$HC0_3$– exchanger is in the luminal side, leading bicarbonate to be retained and not secreted because chloride in the tubular flow is low.

Nephron Sounds as if you know most of this very well. Good work, Henle. This is an important concept to understand.

Mac *(interrupting)*: I think the last factor would be hypokalemia. This is partly due to aldosterone again. The distal nephron hydrogen secretion is stimulated by the low potassium state, leading to increased bicarbonate generation.

Nephron Also, $NH4^+$ is made from glutamine in the proximal tubule. The latter is unregulated in hypokalemia. $NH4^+$ is excreted in the lumen (trapped). Therefore, HCO3– is reabsorbed. This is an additional mechanism.

Henle Now, back to our patient. As we know, this patient has active metabolic alkalosis. But the team is puzzled about the cause of this?

Nephron *(with a bored face)*: Why are they so puzzled?

Mac *(scared)*: Did we mention to you that the patient has ESRD and is receiving hemodialysis?

Nephron *(with a surprised look)*: Ahhh! So now you tell me, after that long discussion regarding urinary losses and urinary bicarbonate generation and so forth, that there is not much urine!

Mac Affirmative.

Nephron Well, that whole discussion is off the table, then, because this patient makes no urine. Am I repeating myself?

Mac Affirmative.

Nephron Nothing gets a nephrologist more excited than seeing metabolic alkalosis in a dialysis patient, because it's not the usual situation.

Henle *(jumping in)*: In a dialysis patient, the increase in serum bicarbonate concentration can be caused only by metabolic alkalosis. Primary respiratory acidosis with compensatory metabolic alkalosis cannot be possible because there is no kidney function.

Nephron Good point—and in this case, it doesn't matter that the urine sodium was 45 mEq/L, because overall the patient doesn't make that much urine.

Henle Also, given that the patient has no kidney function, metabolic alkalosis can occur only if there was excess alkali intake or significant hydrogen ion loss.

Mac So in this case, we don't need to consider mineralocorticoid excess and or other urinary transport problems?

Nephron *(with a smirk)*: Affirmative.

Mac So this has to be a gastrointestinal loss? Should we image the abdomen?

Nephron I would. This could be as simple as a "bad" ulcer or a gastrointestinal outlet obstruction or increased gastrin production producing a tumor?

Mac When we lose hydrogen ion in emesis, how much bicarbonate gets generated?

Nephron One millimole of bicarbonate is generated in body fluids for each millimole of hydrogen ion lost in emesis—although this added alkali is buffered, but given that this patient has no kidney function, the increased bicarbonate is sustained.

Henle and Mac exit to order the suggested tests.

A day later:

Henle A computed tomographic scan revealed a gastric mass, and a biopsy was performed. Hemodialysis was initiated with the goal of helping decrease the alkalosis.

Nephron Isotonic fluids may restore the volume loss here, and it may dilute the body's alkali stores, but it will not correct alkalosis because no bicarbonate excretion is happening. Hence, hemodialysis with a reduced bicarbonate bath is a safe and effective treatment.

Henle and Mac exit to order the suggested tests.

A day later:

Nephron What do we have as the final diagnosis?

Mac A gastrinoma.

Henle The patient was also prescribed a proton pump inhibitor. His electrolytes normalized, and currently he is awaiting evaluation by the hematology and oncology services.

Nephron Mac and Henle, you have stumped me this time with an excellent case of alkalosis in a dialysis patient. Again, nephrologists can always be amazing detectives. With one electrolyte disorder in a patient with ESRD, you made a systemic diagnosis! The problem is not always in the kidney! Let's have some coffee to celebrate!

Detective Nephron was developed by Kenar Jhaveri, MD, associate professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Rimda Wanchoo, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine, for her editorial assistance.