Very small changes in pH levels in the blood may affect renal calcium reabsorption and parathyroid hormone (PTH) secretion, new research suggests. The findings, which are published in the Journal of the American Society of Nephrology, could have important implications for the health of patients with chronic kidney disease (CKD).

“In CKD, calcium and phosphate lost from the bone can end up in the walls of the blood vessels and in other soft tissues, causing potentially serious complications,” said senior author Donald Ward, PhD, of the University of Manchester, in the UK. “The key protein that controls our blood calcium levels is the calcium-sensing receptor, and what we have found is that the mild acidity, or acidosis, that is often seen in CKD is sufficient to impair this protein from working properly.”

In their efforts to uncover the health effects that patients with CKD experience due to the excess release of calcium and phosphate from the bones, Ward and his team found that in both human embryonic kidney cells and bovine parathyroid cells, slightly decreasing the extracellular pH from 7.4 to 7.2 rapidly inhibited intracellular calcium mobilization through the calcium-sensing receptor, whereas raising extracellular pH to 7.6 increased responsiveness to extracellular calcium. “It was known before that large changes in acidity—larger than would normally be seen in human blood—could affect calcium-sensing receptor activity,” Ward said. However, what we have found here is that even relatively mild increases in blood acidity, similar to those commonly seen in CKD, could also inhibit the receptor in cell experiments in our laboratory. Also, pH elevation suppressed PTH secretion from human parathyroid cells, while acidosis increased PTH secretion. The findings suggest that acid-base disturbances may affect the control of parathyroid function and calcium metabolism. While other pH-sensitive membrane proteins may also be involved, the extracellular pH changes had no effect in cells lacking the calcium-sensing receptor, or incubated in low extracellular concentrations of calcium.

Because metabolic acidosis and secondary hyperparathyroidism are both common consequences of CKD, the study’s results point to a mechanistic link between the two. Also, the observation that raising extracellular pH promotes calcium-sensing receptor–mediated suppression of PTH secretion points to a new therapeutic strategy for treating secondary hyperparathyroidism in CKD.

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CKD Prevalence Stable

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CKD remains stable, but higher in older adults

The USRDS is a national data system that collects, analyzes, and distributes information on kidney disease trends. Based on data from the National Health and Nutrition Examination Survey (NHANES), the report suggests an overall CKD prevalence of 13.6 percent.

Saran noted that while CKD prevalence was “certainly stable” during the periods 1999–2004 and 2007–2012, it was about 30 percent higher than in the 1988–1994 NHANES cohort.

“It’s 13.6%, which is a pretty high prevalence,” he said in an interview. “Let’s say conservatively even if it’s 12% . . . that is still higher than the prevalence of diabetes in the general population. That fact is not well-recognized.”

Medicare data suggest an ongoing increase in CKD among Americans aged 65 years or older. In 2012, the most recent year for which data were available, the prevalence of recognized CKD in the Medicare population was 10.4 percent.

That is consistent with recent evidence suggesting that age may be the single strongest risk factor for CKD. “When we look at the risk factors for CKD, we look at diabetes, we look at hypertension, we look at BMI/obesity, the one thing that sticks out and has the highest odds ratio in terms of the strength of that relationship is age,” Saran said. The growing body of evidence on CKD and age has “practical implications for screening, prevention, risk stratification, and treatment,” according to the USRDS report. “Another point I’d like to make is, the prevalence of urine testing leaves a lot to be desired,” Saran added.

“Even in the Medicare data, only about 40 percent of dialysis patients are receiving the urine test. So it tells you that there’s still lots of room for improvement, even among those that have clear-cut, known risk factors.”

Although care patterns are difficult to assess, data suggest that while 91 percent of Medicare patients with CKD see a primary care physician and 62 percent see a cardiologist within a year of diagnosis, only 31 percent see a nephrologist. For patients with stage 3 to 5 CKD, the rate of nephrologist care increases to 55 percent.

All-cause mortality continues to decline among Medicare patients with CKD. But these patients remain at much higher risk of death than those without CKD, a risk that is “multiplied” for CKD patients with cardiovascular disease or diabetes. Cardiovascular morbidity remains very high among Medicare patients with CKD—about 70 percent, compared to 35 percent in patients without CKD.

The report also highlights the ongoing, age-related increase in hospitalizations for acute kidney injury (AKI)—a diagnosis associated with declines in both renal and functional status. Less than 20 percent of patients see a nephrologist within one year of AKI hospitalization, even though more than 90 percent undergo follow-up serum creatinine testing.

Continued declines in ESRD incidence

For the third consecutive year, new cases of ESRD declined, with 114,813 new cases in 2012. In that year, the adjusted incidence rate was 353 per million per year—the lowest since 1997.

The population prevalence of ESRD continued to increase, although there were encouraging signs that the rate of growth may be slowing. “[T]he percentage increase in 2011 and 2012 was the lowest recorded over the last three decades,” according to the USRDS report. At the end of 2012, there were a total of 656,905 dialysis and transplant patients receiving treatment for ESRD.

Analysis of Healthy People 2020 goals showed that about one-third of patients see a nephrologist at least one year before the start of renal replacement therapy. Nearly all mortality targets have been met, including promising trends in overall and cardiovascular mortality among dialysis and transplant patients.

Clinical indicators of hemodialysis care are also improving—nearly 80 percent of patients now have an arteriovenous fistula or graft for dialysis. Although mortality rates continue to decline, they are up to eight times higher than for matched Medicare patients without ESRD.

Transplantation rates have decreased, while the percentage of dialysis patients wait-listed continues to increase. In 2012, nearly 29,000 patients were added to transplant waiting lists. For those who do receive a transplant, one-year survival rates are excellent: 96 percent for deceased donor transplant recipients, and 99 percent for living donor transplant recipients.
For many patients with gout, emerging science suggests that chronically elevated sUA and the resulting monosodium urate crystal deposition can be more serious and widespread in the body than we ever thought, leaving inflammation, bone erosion, and organ damage in its wake.1-5

Isn’t it time to take a deeper look at gout?
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The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2014.

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Blood Acidity

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receptor function. What distinguishes this paper from previous work is that not only does it demonstrate an effect of extracellular pH on calcium-sensing receptor signaling and PTH release, but it demonstrates that in human parathyroid tissue, changes in extracellular pH within the physiologic range are capable of causing measurable changes in PTH secretion,” said R. Tyler Miller, MD, who was not involved in the experimental system.

The calcium-sensing receptor is expressed in a variety of tissues and organs including the kidney, brain, intestine, bone, and skin where extracellular pH could also affect its function.

Miller noted that other work indicates that alterations in human pH that occur with kidney disease, high altitude, and possibly with diets of varying composition can alter metabolism, muscle mass, and bone structure, but the mechanisms for these effects are unclear. Also, the physiologic effects of PTH are complicated and involve not just the level of PTH, but also the frequency of its release. “A long-term effect of pH on parathyroid function via PTH release is a reasonable possibility for some of the physiologic consequences of altered extracellular pH,” Miller said. “Precisely how PTH secretion is affected by extracellular pH will be interesting and valuable to learn as well as determining how pH and PTH secretion relate to long-term nutrition, body composition, and bone biology.”

Ward stressed that additional studies are needed before any clinical applications might be realized. “Firstly, we would need to confirm that this effect is true not only in human cells in the laboratory, but also in live patients. However, if confirmed, then this might reveal a novel mechanism by which acidosis and bone mineral changes might be related in CKD patients,” he said.

Article: “Pathophysiologic Changes in Extracellular pH Modulate Parathyroid Calcium-Sensing Receptor Activity and Secretion via a Histidine-Independent Mechanism” http://jasn.jasn.org/content/early/2015/01/01/ASN.2014070653.long
Patiromer Reduces Potassium in CKD Patients Taking RAAS Inhibitors

The new oral potassium binder patiromer effectively lowers serum potassium levels in patients with chronic kidney disease (CKD), who are being treated with renin-angiotensin-aldosterone (RAAS) inhibitors, reports a trial in the New England Journal of Medicine.

The multicenter study included 243 patients with stage 3 or 4 CKD who were taking RAAS inhibitors and had a serum potassium level of 5.1 to less than 6.5 mmol/L. All received 4 weeks of treatment with patiromer. The starting dose was 4.2 or 8.4 g twice daily. Patients whose potassium level decreased to the target range (3.8 to less than 5.1 mmol/L) were eligible for an 8-week randomized withdrawal phase, with one group continuing to receive patiromer and the other switching to placebo. Changes in potassium level were compared between groups.

The mean reduction in serum potassium during the initial treatment phase was 1.01 mmol/L, and 76 percent of patients reached the target range by 4 weeks. Among 107 patients enrolled in the withdrawal phase, potassium levels increased by 0.72 mmol/L within 4 weeks for those switching to placebo, compared with no change for those continuing to receive patiromer. The rates of recurrent hyperkalemia (potassium level 5.5 mmol/L or higher) were 60 percent in the placebo group and 36 percent in the patiromer group.


dataref:6

References:


For the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

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• Each AURYXIA tablet contains 210 mg ferric iron, equivalent to 1 g ferric citrate

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References:


Drug Interactions: Doxycycline should be taken at least 1 hour before AURYXIA. Consider separation of the timing of the administration of AURYXIA with drugs where a reduction in their bioavailability would have a clinically significant effect on safety or efficacy. Please see Brief Summary on following page.

You may report side effects to Keryx at 1-844-44KERYX (844-445-3799).

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INDICATIONS AND USAGE
AURYXIA is a phosphorus binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

WARNINGS AND PRECAUTIONS
Iron Toxicity: Iron overload may lead to elevations in iron stores, which may increase the risk of iron-related complications. Iron overload has not been demonstrated in patients treated with AURYXIA.

PATIENT COUNSELING INFORMATION
1. AURYXIA may cause diarrhea, nausea, constipation, and vomiting. Advise patients to report severe or persistent gastrointestinal symptoms to healthcare professionals.

2. Concomitant medications that should be dosed apart from AURYXIA must be identified and the timing of drug administration adjusted, if necessary, to avoid decreased bioavailability of medications that have a narrow therapeutic range, or increased levels of medications that are highly dependent on gastrointestinal absorption.

3. Assess iron parameters (eg, serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving IV iron may require a reduction in dose or discontinuation of IV iron therapy.

4. Iron Overload: Assessment of iron overload in patients treated with AURYXIA and concomitant IV iron is used.

5. Assess iron parameters (eg, serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving IV iron may require a reduction in dose or discontinuation of IV iron therapy.

6. No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease on dialysis, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant IV iron is used.

7. Iron Overload: Assessment of iron overload in patients treated with AURYXIA and concomitant IV iron is used.

8. Patients with Gastrointestinal Bleeding or Inflammation: Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials. Safety has not been established in these populations.

ADVERSE REACTIONS
Adverse reactions are most readily ascertained by comparison with placebo, but there is little placebo-controlled experience with AURYXIA. Safety has not been established in these populations.

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. It is not known whether AURYXIA can cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted.

AURYXIA has been studied in 219 children (14% of the total study population) from 2 to 16 years of age who received AURYXIA at the time of randomization. The safety and efficacy of AURYXIA have not been established in pediatric patients.

Nursing Mothers: AURYXIA is excreted in breast milk. Because of the potential for serious adverse reactions in the nursing infant, breastfeeding should be discontinued while taking AURYXIA.

Labor and Delivery: No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease on dialysis, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant IV iron is used.

Antacid Use: Do not take an antacid (eg, aluminum- or magnesium-containing products) within 2 hours of AURYXIA administration.

Drug Interactions: AURYXIA is an oral drug that has to be taken at least 1 hour before AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA include acetaminophen, diphenhydramine, ibuprofen, naproxen, oxymorphone, oxycodone, parecoxib, propoxyphene, quinapril, rimodulin, ritonavir, trimethoprim, and zafirlukast.

Surgical Robots Linked to Increased Rates of Partial Nephrectomy

Hospitals acquiring surgical robots are more likely to perform guideline-recommended partial nephrectomy in patients with renal cancer, reports a study in Medical Care.

The researchers used payer data from seven states to identify nearly 21,600 nephrectomies performed in 2001, 2005, and 2008. Hospital-level rates of partial nephrectomy were analyzed in relation to the hospitals’ acquisition of a surgical robotic system. The association was adjusted for nephrectomy volume, year of surgery, and other hospital factors.

Hospitals performed more partial nephrectomies after acquiring surgical robots. For hospitals acquiring robots between 2001 and 2004, the proportion of
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- **Cost Savings:** A 23% average savings per year compared with catheters

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**References:**

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Available data support the "cautious expansion" of metformin use for patients with type 2 diabetes and mild to moderate chronic kidney disease (CKD), according to a systematic review in the *Journal of the American Medical Association*. A literature search identified 65 publications providing data on the risk of lactic acidosis in metformin-treated patients with impaired renal function. Since its approval in 1994, metformin has been contraindicated for use in patients with "renal disease or renal dysfunction."

However, the evidence suggested that drug levels generally remained in the therapeutic range for metformin-treated patients with mild to moderate CKD (estimated GFR 30 to 60 mL/min/1.73 m²). Despite renal clearance of metformin, the rates of lactic acidosis were low and in the range of the background rate among all patients with diabetes: about three to ten cases per 100,000 person-years. There were no randomized trials evaluating the safety of metformin in patients with impaired kidney function. Some reports suggested that the guidelines regarding metformin use in kidney disease are "commonly disregarded," with no increase in adverse events. Observational studies suggested beneficial effects on macrovascular outcomes, even in patients with contraindications to metformin use.

On the basis of these data, the authors suggest a change in prescribing guidelines to permit metformin use in patients with mild to moderate CKD. They emphasize that any such strategy would require appropriate dosage reductions and careful monitoring of kidney function [Inzucchi SE, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; 312: 2668–2675].

Surgical Robots

Partial nephrectomies increased by about 30 percent in 2005 and 35 percent in 2008. A smaller increase of 15.5 percent was noted for hospitals acquiring a surgical robot between 2005 and 2008. Hospitals with a higher nephrectomy volume and those in urban locations had higher rates of partial nephrectomy. At hospitals that had not acquired a robotic system by 2008, partial nephrectomy was performed in just 20 percent of cases. Nephron-sparing surgery is a guideline-supported but underused alternative to radical nephrectomy for patients with renal cancer. The new analysis suggests that surgical robots—a costly and controversial use of technology—facilitate the performance of partial nephrectomy in this group of patients. "This is one of the few studies to suggest robot acquisition is associated with improvement in quality of patient care," the researchers write. They discuss the implications for adoption of new technologies, noting that the "earliest adopters" of surgical robots had the greatest increases in partial nephrectomy [Sivaranjan G, et al. The effect of the diffusion of the surgical robot on the hospital-level utilization of partial nephrectomy. *Med Care* 2015; 53:71–78].
New Combo Drug for Hypertension

The FDA approved the drug based on phase III data from the 837-patient PATH trial (Perindopril Amlodipine for the Treatment of Hypertension trial), which demonstrated that the fixed-dose combination in one pill was more effective than either compound taken alone for reducing sitting diastolic and sitting systolic blood pressure after six weeks of treatment. Both drugs alone can cause hypotension, and perindopril can cause swelling of the head and neck. Warnings include not giving diabetic patients aliskiren (a renin inhibitor for primary hypertension) along with ACE inhibitors, including Prestalia, as well as discontinuing Prestalia immediately when a patient learns she is pregnant.

The company has several other combination drugs for hypertension in the pipeline, all containing perindopril perindopril plus atorvastatin, perindopril plus indapamide, and perindopril plus amlopidine (the two drugs in Prestalia) plus indapamide. Its first product, perindopril erbumine (Aceon), is an antihypertensive drug that can be taken alone or in combination with other classes of hypertension-reducing drugs. Aceon is used to treat patients with high blood pressure and to reduce the risk of heart attack.

NephoCheck Test Gauges Risk for AKI

The NephoCheck test system is now being marketed by Ortho Clinical Diagnostics to help identify risk of acute kidney injury (AKI). The urine test is designed to detect both insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases, factors associated with AKI.

The test provides a score within 20 minutes that shows a patient’s risk for the development of AKI, Ortho noted in an announcement. Patients with a positive NephoCheck risk (greater than the defined cutoff point of 0.3) have a one-in-four to a one-in-three chance of developing moderate or severe AKI within 12 hours of assessment, Ortho reported.

The U.S. Food and Drug Administration (FDA) approved the test, manufactured by Astute Medical, in September 2014.

The test has shown that it gives a positive result in about half of patients who do not have AKI, according to Medscape. Two studies compared NephoCheck results with the diagnoses in more than 500 critically ill patients at 23 hospitals: the test accurately detected 92 percent of AKI patients in one study and 76 percent in the other.

The test system may be used along with clinical evaluation in intensive care unit patients who currently have or have had within the preceding 24 hours an acute cardiovascular event, respiratory compromise, or both. The test should be used as an aid in the risk assessment for moderate or severe AKI within 12 hours of patient assessment in patients over age 21.

For more information about the product, visit www.astutemedical.com.

Report Details Nephrology Fellow Demographics, Job Market Concerns

By Kurtis Pivert

ASN’s latest nephrology workforce report provides a detailed portrait of future nephrologists and their perceptions of, and experiences in, the current job market. Findings from the 2014 Survey of Nephrology Fellows is the second in a series of workforce studies authored by George Washington University (GWU) investigators. The analysis of the 2014 ASN Nephrology Fellow Survey provides clues about demand for the specialty and a baseline for future research.

The report confirms recent trends in nephrology training. International medical graduates (IMGs) comprised the majority of respondents (6/4 percent), reflecting the continued decline in the number of US medical graduates (USMGs) choosing the specialty. Despite an increase in women entering nephrology, most of the 1st and 2nd year fellows who answered the survey were men (61 percent). Fellows’ racial and ethnic composition remains unrepresentative of the communities they will serve—only 9 percent of fellow respondents were African American and 8 percent Hispanic.

Distributed to ASN fellow members in June 2014, the survey is an important component of ASN’s ongoing collaboration with GWU to study all aspects of the specialty. Workforce research is one of ASN’s many initiatives to increase interest in nephrology careers. Although this initial survey elicited a low response rate (35.8 percent), the participants’ demographic characteristics were similar to those of all nephrology fellows, according to information from the Accreditation Council for Graduate Medical Education database.

“This kind of survey can provide a good picture of the future supply,” said lead author Edward Salsberg, MPA. “The experience of new entrants into the job market can also provide a valuable snapshot of the regional and national demand.”

Job search experiences and market perceptions differed between IMGs and USMGs. IMGs were more likely to practice in a Health Professional Shortage Area and to report difficulties in finding a satisfactory position. USMGs were more likely to note a lack of jobs in desired locations and to perceive more job opportunities nationally than locally.

A substantial proportion of nephrology fellows looking for employment reported changing their plans because of limited practice opportunities (43 percent). Although nephrology fellows’ perceptions of local job opportunities (within 50 miles of their training site) were disappointing (71 percent said there were no, very few, or few nephrology practice opportunities), a vast majority indicated they would still recommend the specialty to medical students and residents (72 percent).

The report’s release extended a continuing dialogue among the kidney community that started with the disappoigniting nephrology Match for academic year 2015–2016, which has expanded to social media. An ongoing discussion of the report, the Match, and nephrology careers on Twitter—at the NephWorkforce hashtag—has explored many themes. These include the hurdles IMGs encounter in locating employment and research funding, student debt, and the importance of mentorship. ASN encourages all stakeholders to join this discussion using the #NephWorkforce hashtag.

Salsberg, together with Principal Investigator Leah Masselink, PhD, will focus future reports on the effects of changes in care delivery on the specialty, as well as geographic distribution of practicing nephrologists and training programs.

As of press time, ASN announced the Nephrology Match Task Force will be chaired by ASN President-Elect Raymond C. Harris, MD, FASN. Composed of Nephrology Training Program Directors, Division Chiefs, and ASN Councilors, the task force will address issues surrounding the Match, including an assessment of its future viability and identifying ways to ensure its integrity.

The nephrology fellow survey report is available at http://wwwasn.org/online/education/training/workforce/.
ABIM Announces Changes to MOC Program

Responding to concerns raised by ASN, the American College of Physicians, and other medical specialty societies, the American Board of Internal Medicine (ABIM) on February 3, 2015, announced it is suspending the Practice Assessment, Patient Voice, and Patient Safety requirements of its Maintenance of Certification (MOC) program for at least 2 years in order to engage the medical community’s input regarding its MOC program.

Starting a year ago, ABIM changed its once-every-10-years MOC program to a more continuous one. The change generated substantial criticism among internists and medical specialties.

“Some believe ABIM has turned a deaf ear to practicing physicians and has not adequately developed a relevant, meaningful program for them as they strive to keep up to date in their fields,” ABIM President and CEO Richard Baron, MD, MACP, said in a statement. “ABIM clearly got it wrong. We launched programs that weren’t ready and we didn’t deliver an MOC program that physicians found meaningful. We want to change that.”

ABIM plans to institute the following changes:

• Within the next 6 months, ABIM will change the language used to publicly report a diplomate’s MOC status on its website from “meeting MOC requirements” to “participating in MOC.”
• ABIM is updating the Internal Medicine MOC exam. The update will focus on making the exam more reflective of what physicians in practice are doing, with any changes to be incorporated beginning fall 2015. More subspecialty MOC exams will follow.
• MOC enrollment fees will remain at or below the 2014 levels through at least 2017.
• By the end of 2015, ABIM will assure new and more flexible ways for internists to demonstrate self-assessment of medical knowledge by recognizing most forms of continuing medical education approved by the Accreditation Council for Continuing Medical Education.
• Effective immediately, ABIM is suspending the Practice Assessment, Patient Voice, and Patient Safety requirements for at least 2 years. This means that no internist will have his or her certification status changed for not having completed activities in these areas for at least the next 2 years. Diplomates who are currently not certified but who have satisfied all requirements for MOC except for the Practice Assessment requirement will be issued a new certificate this year.

The organization plans to work with medical societies and directly with diplomates to seek input regarding the MOC program through meetings, webinars, forums, online communications channels, and surveys. For more information, please see the ABIM MOC FAQ page.

Kidney Week On-Demand: online access to more than 350 hours of educational content from the meeting. This resource in the ASN Learning Center is complimentary to fully paid Annual Meeting participants with access codes or is available for purchase.

For more information on sessions captured or how to purchase, visit www.asn-online.org/dl/kw.

CME credit will not be awarded for these materials.
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 pCO2 of 66 mm Hg. Serum chloride is 68 mEq/L. So the patient has a metabolic alkalosis with good compensation.

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

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.

Henle 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.

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

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.

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

Henle (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 proximal tubule and reduces bicarbonate reabsorption. In addition, in the state of vomiting, 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?

Nephron (jumping in): Chloride depletion itself in this vomiting state will lead to maintaining the alkalosis. In type A intercalated cells, there is a Cl/HCO3− 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...

Continued on page 14
type B intercalated cells, the Cl/HCO₃⁻ 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 stampeded 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.
Kidney transplantation has been the preferred treatment for people suffering from kidney failure since Dr. Joseph E. Murray completed the first successful kidney transplant in 1954. Although recent advances in transplant medicine have drastically lowered the risk of acute transplant rejection, these advances have failed to deliver an effective treatment for chronic allograft nephropathy (CAN), which remains the leading cause of organ loss following transplantation and limits the 10-year survival rate of a kidney transplant to 54%. If detected early, intervention can minimize CAN, a kidney transplant to 54%. If detected early, intervention can minimize CAN, a kidney transplant to 54%

For Demetri Maxim, a high school junior in Maine, the difficulties of kidney transplants and kidney disease are personal. In August 2004, Demetri’s mother, LeEli, lost both her kidneys to polycystic kidney disease (PKD) and was forced to go on dialysis. Fortunately, she received a kidney transplant in October 2005, just 14 months later. Demetri also has PKD and may someday lose his kidney function as well.

Demetri’s mother experienced four different rejection episodes in the first 18 months of her transplant. Each episode necessitated a painful biopsy that involved removing a small piece of the kidney to test for rejection, a process that further reduces the long-term success of the organ. Demetri knew there had to be another way to tell whether or not she was rejecting her kidney. So the summer before he started high school he set out to invent an alternative method to detect CAN. Two years later, in March 2014, following countless hours of background research and lab work, Demetri’s invention won grand prize at the Maine State High School Science Fair and qualified for the Intel International Science and Engineering Fair.

At Kidney Week 2014, Demetri presented a poster describing the simple, portable, patent-pending device that can be used to non-invasively monitor CAN in kidney transplant recipients. The device works by screening patient blood samples for the biomarker VEGF-C, which is upregulated during CAN. The device is 11 times faster and 16 times less expensive than the current gold standard for biomarker detection, ELISA. He hopes to publish his work.

Demetri currently works in Dr. Joseph Bonventre’s Laboratory of Kidney Injury and Repair at the Brigham and Women’s Hospital and Harvard Medical School.

Demetri's invention: a portable, non-invasive method to detect CAN.
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