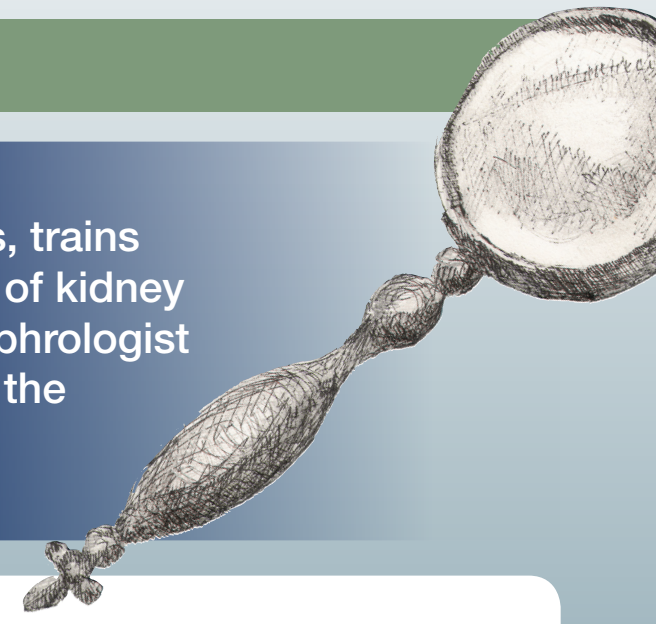
Detective Nephron

Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Wildly waving a stack of paper records, budding nephrologist L.O. Henle and medical student Ms. Curious Tubule run down the hall toward Detective Nephron's office.



Henle (*with a smile*): A case for you sir!

The detective sits facing the window. He has been experiencing some gastric reflux lately and has given up coffee. He is disgruntled as he misses it.

Nephron (*curious*): Finally, something that might put an end to this utter boredom.

Henle It's a case of acute kidney injury (AKI).

Nephron (*smiling*): Ah yes. That's what they call it these days. Gone are the days of renal failure and kidney failure. God forbid that we use big words like "failure" these days. "Injury"… oh well.

Tubule So this is a 70-year-old male with really no past medical history and now noted to have some elevation in serum creatinine for the past 3 months or so. It's 2.3 mg/dL. It was apparently normal 5 months ago with a level of 0.8 mg/dL per records.

Nephron (*interrupting*): I don't need any of that information. Do you have a urinalysis?

Tubule He was found to have a serum bicarbonate of 8 mmol/L. His sodium was 140 mmol/L, chloride was 103 mmol/L. That gives him a serum anion gap of….

Nephron (*surprised look*) …

Tubule . . . Yes, it's bland, no red cells, no white cells, no casts, nothing at all.

Henle Also, we even went ahead and did a spot urinary protein/creatinine ratio and it was 0.2. Fractional excretion of sodium (FeNa) was >1%.

Nephron Interesting. So let's start from the basics!

Tubule Usually, AKI can be looked at from three angles—pre-renal, intra-renal and post-renal.

Nephron Remember there are only two body systems in my nephrocentric mind … renal and extra-renal. So is the problem in the kidney or out of the kidney?

Tubule Well, FeNa points toward an intrinsic pathology.

Henle (*stepping in*): Precisely.

Nephron Is the patient an oliguric Caucasian man?

Tubule (*not chuckling*): Huh?

Nephron (*laughing loudly*): The original studies in which a condition was called "pre-renal" based on FeNa were done by Schrier et al. They were in oliguric Caucasian men. So if a case involves chronic kidney disease, women, or non-oliguric AKI, the value of FeNa is not known. But we still use it in practice… as long as you know its limitations.

Pause.

Nephron Volume exam?

Tubule (*happy*): Euvolemic.

Nephron Trial of fluids?

Tubule Yes, of course. It would be too easy for you otherwise! And no improvement with volume repletion.

Nephron So in a patient who is not fluid overloaded, a fluid challenge and no improvement in kidney function rules out pre-renal. This is even better than the FeNa!

Henle He also has no post-renal issues because he has no post-void residual and no hydronephrosis on my bedside point-of-care ultrasound exam.

Nephron (*jumping in*): Good work on the point-of-care ultrasound exam, Henle. It's about time nephrologists do their own imaging. How small or big are his kidneys?

Tubule 13 cm on the right and 12.5 cm on the left.

Henle (*confident*): Well, given he is 5 feet 6 inches tall, those kidneys sound a bit too big to me. He is not a diabetic and he has no known HIV disease to my knowledge. To me that size is concerning!

Nephron So what is your differential for large kidneys?

Henle As I mentioned, diabetic nephropathy, HIV-related disease, acute interstitial nephritis (AIN), and/or infiltrative diseases of some kind such as leukemias or amyloidosis.

Tubule He is not on any medications except a multivitamin. He denies taking any nonsteroidal pain medications (NSAIDS). His last HbA1c was 5.4. He has a normal white count, normal hemoglobin, and does not endorse bone pain.

Nephron So let's end this confusion once and for all. He is not a diabetic, nor does he have any signs of a malignancy. He is not on any obvious medications causing AIN, nor does he have any chronic viral diseases such as HIV.

Henle Hmmm. Could he have amyloidosis? But he has no signs of nephrotic syndrome? He has no edema on exam, and he has normal albumin, normal cholesterol, and no signs of proteinuria.

Nephron (*with a smirk*): Could he have vascular amyloidosis?

Tubule (*relieved*): Well, he could but his free light chain ratio and serum immunofixation are in range for his kidney dysfunction.

Nephron What is his urine glucose?

Henle (*jumping in*): Not elevated and his electrolytes don't suggest any signs of Fanconi syndrome either.

Nephron What do we think?

Tubule With all of the above workup negative, I feel lost and confused. Perhaps we have to move to a kidney biopsy?

Nephron Let's go back to an older technique we call "history taking." I think that he is not telling us everything … or "we" are not asking the right questions. Take a more detailed history on any new medications, herbals, over the counter medications, and so forth.

Tubule and Henle leave the room.

Tubule (*returning*): Nothing. The only symptom he had a few months ago was some gastric reflux, for which he took some over the counter omeprazole and calcium carbonate with some relief. He takes them occasionally and in some cases daily. But no real nephrotoxic medications.

Henle (*jumping in*): Really? He is taking a proton pump inhibitor (PPI)?

Tubule So?

Nephron (*excitement in his eyes*): PPIs are increasingly being associated with AKI from AIN and eventually CKD as well.

The detective's eyes brighten as he suddenly looks up at Ms. Tubule for a split second, then backs down again.

Nephron Fascinating.

Henle and Ms. Tubule appear puzzled.

Nephron Please get a kidney biopsy!

Tubule and Henle return a day later.

Tubule It is AIN!

Henle We told him to stop the omeprazole.

Nephron So you are sure it is the PPI causing his AKI or CKD?

Tubule I think so!

Nephron (*continues on*): While PPIs have an excellent overall safety profile, concerns have been raised about recent adverse renal events, specifically their association with AIN and hypomagnesemia. While only a small proportion of patients develop AIN from PPIs, these drugs are now a common cause of drug-induced AIN in the developed world due to their widespread and prolonged use. PPI-induced AIN is often subtle and without systemic allergic manifestations; subclinical, leading to gradually progressive kidney failure; delayed, median time from drug initiation to AIN diagnosis often exceeds 6 months; and often unsuspected prior to a biopsy.

Henle (*showing off from a review article he just read*): It is not until recently that new studies performed by many around the world have demonstrated this association. First, two population-based studies described a higher risk of AIN and AKI in patients prescribed PPIs as opposed to H2 blockers such as ranitidine. Second, evidence suggests that on intermediate to longer term follow-up, patients have a lower estimated glomerular filtration rate (eGFR) after an episode of PPI-induced AIN and patients prescribed PPIs have higher CKD risk.

Tubule *(curious)*: Is it a class effect?

Nephron Yes. Possibly.

Nephron Yes, I think it is a class effect. Moreover, new users of PPIs in comparison to H2 blocker users had a higher risk of eGFR less than 60 mL/min/1.73 m^2, had a greater than 30% decrease in eGFR, and end stage kidney disease (ESKD) with greater than 50% decrease in eGFR after adjusting numerous factors and co-morbidities of participants.

Henle Why does this happen? Is it just allergic?

Nephron The purported mechanism of PPI-induced nephrotoxicity is either from impaired lysosomal acidification and proteostasis or due to hypomagnesemia, both of them causing increased oxidative stress, dysfunction, and accelerated wear and tear damage in human renal endothelial cells.

Tubule So if I had to summarize, PPIs can cause AIN, CKD, and if continued and not interrupted, can lead to ESKD as well. In addition, we know the electrolyte disorder of hypomagnesemia is linked with it as well.

Nephron Precisely!

Henle In causing AIN, how do PPIs compare to antibiotics and NSAIDS?

Nephron Excellent question! Let me take you on a historical adventure. If the year was 1965, probably the only known AIN-causing medication class was antibiotics. If the year was 1978 or 1981, NSAIDS started to trickle in. In the late 1980s to early 2000s, NSAIDS overtook antibiotics as the number 1 cause of drug-induced AIN. And if you take the years from the mid-2000s until now, PPIs and antibiotics lead the way in the number of drug-induced AIN cases followed by NSAIDS. Keep in mind that "evidence based" or "not evidence based," many patients are placed on PPIs from hospital discharges, as it is part of some form of "prophylaxis." Unfortunately, perhaps some never discontinue their use. Be vigilant my detectives! When needed, these agents are a great treatment for ulcers, *H. pylori*, and gastric reflux, but so are NSAIDS for severe pain. Like everything, we have to watch for any known effects on the kidney in our nephrocentric minds!

Tubule Fascinating.

Nephron Very well then. And so, yet again, the kidney is a bystander here and commonly used drugs can be a missed cause of CKD and ESKD. Good work my pupils. Let's go before this drug causes a stress ulcer in all nephrologists out there.

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The concept of Detective Nephron was developed by Kenar D. Jhaveri, MD, Professor of Medicine at Hofstra Northwell School of Medicine and an Attending nephrologist at Northwell Health System, NY. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.