[MUSIC PLAYING]

PAUL FADAKAR: My name's Paul Fadakar, I am one of the pediatric nephrologists here at Children's Hospital of Pittsburgh. And today, we're going to be talking about the outpatient evaluation of hematuria and proteinuria.

So we'll start with hematuria. And the main branch point or the big branch point in evaluating hematuria is obviously going to be microscopic versus gross hematuria. Thinking about gross hematuria, aside from the obvious bright red blood in the urine, it's important to suspect gross hematuria when dark red or brown urine is present.

Importantly, though, you should note that dark red or brown urine can be present due to causes other than blood, including pigments from certain drugs, such as rifampin, or foods, such as beets. Also, free hemoglobin or myoglobin in conditions like rhabdomyolysis can also present with dark red or brown urine. Confirmation of blood in the urine is critical by urine centrifugation. And we'll see a picture on the next slide of what this looks like.

If the sediment is red or brown after centrifuging the specimen, then the etiology is most likely blood. If the supernatant is red or brown and the sediment is not discolored, this is actually likely caused by free hemoglobin or myoglobin. And it's also important to note that in patients with gross hematuria, the color change of the specimen does not necessarily reflect the degree of blood loss. As little as one milliliter of blood per liter of urine can induce a visible color change.

So this slide essentially just shows you-- perhaps the graphic on the right of the slide is more indicative of what a spun versus an unspun urine may look like. So on the left, an unspun urine, versus on the right, a spun urine. So you can see, after spinning, when the supernatant becomes clear and the sediment is dark red, then that is indicative of gross hematuria. Versus the supernatent staying red. That is from either free hemoglobin or myoglobin.

The etiology of gross hematuria can be diverse. So it can include anything up to and including UTI, irritation of the external genitalia, trauma, nephrolithiasis certainly glomerular nephritis is a big one. Malignancies, while rare, obviously need to be ruled out, including things like Wilms tumor or bladder cancer.

Hemorrhagic cystitis, either from an infectious cause or from a side effect of drugs, such as cyclophosphamide. UPJ obstruction or rupture of a cyst in a patient with autosomal dominant polycystic kidney disease can cause gross hematuria. As well as angiomyolipomas in patients with tuberous sclerosis or sporadic angiomyolipomas.

The timing of hematuria during voiding, which can be obtained by history, can also be very helpful in the evaluation of gross hematuria. So initial hematuria, or blood in the urine at the onset of urination, is most likely due to urethral bleeding. Continuous hematuria, or blood in the urine throughout the stream, is a little bit less specific and could be coming from any part of the urinary tract, from the kidneys all the way down through the urethra. Whereas terminal hematuria, or blood in the urine at the end of the stream, can be consistent with bladder disease, such as the cystitis or urinary tract infection.

And the color of urine will also potentially help distinguish between glomerular hematuria non-glomerular hematuria. So brown or dark red urine, historically referred to as coca-cola colored urine is associated with glomerular nephritis. Whereas pink or even bright red blood in the urine, or pink or bright red urine color, potentially even accompanied by blood clots, is more typically associated with lower urinary tract bleeding.

Additional history that can be helpful in the evaluation of gross hematuria would be pharyngitis two weeks prior to the onset of gross hematuria would be potentially consistent with post-streptococcal glomerular nephritis. Whereas an upper respiratory or GI infection one to two days prior to the onset of hematuria might be potentially suspicious for IgA nephropathy. Certainly, exposure to drugs known to cause hemorrhagic cystitis, such as cyclophosphamide should be delineated from the history.

Urinary symptoms, including dysuria, flank or superpubic pain, might be found in UTIs or nephrolithiasis. Excuse me, pyelonephritis. Whereas flank pain with radiation to the groin might be more common in nephrolithiasis or UPJ, ureteropelvic junction obstruction. And then certainly, a trauma history should be elicited in cases where the history is not pointing to a more clear etiology.

These graphics illustrate the differences between different actual conditions, all presenting with gross hematuria. On the far left is the appearance of brown or dark red urine consistent with glomerular nephritis. So this is the so-called coca-cola colored urine. In the middle is the bright red blood that you might see with more lower track bleeding, which can be from a number of sources as we just discussed.

And then on the right, you can see there are actual clots, blood clots in the urine specimen. So these are pretty distinct. And it can be challenging for patients or families to describe these. But it can be useful if they're either able to recall it or maybe even potentially show a picture on their cell phone.

Physical exam findings that can be useful when evaluating gross hematuria include hypertension, which can be associated with the renal dysfunction that comes with glomerular nephritis in more severe cases. Weight gain or peripheral edema can be seen in a mixed picture of nephritis and nephrotic syndrome. Rash, which you might find in a case of lupus or HSP nephritis. Certainly, external genitalia irritation would be worth noting on a genitourinary exam. And then an evaluation for abdominal masses to rule out Wilms tumor or other potential neoplasms.

A study done back in 2005 looked at the clinical significance of asymptomatic gross hematuria in children. So this study reviewed 228 patients presenting to a single center for evaluation of asymptomatic hematuria. These patients had a thorough evaluation, including blood and urine studies, renal ultrasound, and in some cases, even a renal biopsy.

And the etiologies detected for the gross hematuria were quite variable. But interestingly enough, in more than 1/3 of the cases, there was no identifiable cause. And the next two most common causes were hypercalciuria was seen in a little bit over 20% of these patients, and then IgA nephropathy in 16%.

In patients presenting with asymptomatic gross hematuria, a full evaluation for any of these potential etiologies is warranted. Certainly starting with a urinalysis, which would include microscopic examination of the urine, specifically to look for red blood cell casts, which are pathognomonic for glomerular nephritis. It's important to note that the urine dipstick will often overestimate proteinuria in the presence of a large number of red blood cells in the urine.

Measurement of serum creatinine will help identify renal dysfunction, which certainly may occur with acute glomerular nephritis or a mixed nephritis nephrotic picture. Serum complement levels are very important to potentially differentiate between causes of acute glomerular nephritis. Low C3 with a normal C4 is a typical pattern seen in post-streptococcus or membranoproliferative glomerulonephritis. Versus a low C4 and a low C3, which is often seen in lupus nephritis.

Whereas the C3 and C4 both being normal is associated with a more diverse potential array of GN conditions, including IgA nephropathy, Alport syndrome, your ANCA vasculitides, anti-glomerular basement membrane disease, and thin basement membrane disease. Measurement of the urine calcium to creatinine ratio is helpful to potentially detect hypercalciuria. And a renal ultrasound is also useful to detect congenital anomalies of the kidneys or urinary tract, including polycystic kidney disease, potentially angiomyolipomas, possibly even UPJ obstruction, as well as kidney stones or masses.

In the case of gross hematuria with symptoms, the patient's symptoms and clinical findings should direct the evaluation. So certainly, a trauma history would warrant further evaluation with imaging, including possibly a CT scan. Urinary symptoms such as dysuria or frequency, urgency, might prompt an infectious evaluation with a UA and urine culture.

Dysuria associated with abdominal pain, flank pain, nausea, vomiting might prompt you to look for kidney stones or obstruction, for which you would start with a renal ultrasound. And signs or symptoms of glomerular disease, including edema, proteinuria, and hypertension would prompt referral at that point to a pediatric nephrologist. You certainly could consider additional evaluation in the primary care or other outpatient settings, including CBC serum complement levels, serum albumin level, ANA and ASO titers.

So microscopic hematuria, to shift gears a little bit, technically defined as greater than or equal to 5 RBCs, red blood cells, per high-power field on urine microscopy. Urine dipsticks will detect red blood cells, but will also detect free hemoglobin or myoglobin. So it's important to keep in mind that you can get false positives. But the dipsticks are highly sensitive for RBCs in the urine.

The gold standard for detection in microscopy, or microscopic hematuria-- excuse me-- is urine microscopy. And as pediatric nephrologists, when we evaluate these patients in our clinic and look at their urine under the microscope, the appearance of the red blood cells themselves can actually be helpful from a diagnostic perspective to differentiate the glomerular from non-glomerular hematuria, as the red blood cells themselves will have what's called a dysmorphic appearance, showing that they likely pass through the glomerulus. And certainly, we would expect to see red blood cell casts as well.

Here we see a nice graphic showing the difference between eumorphic and dysmorphic red blood cells. Now ironically, the picture on the left, while showing mainly eumorphic RBCs has arrows pointing to cells that are not actually RBCs. So you'll have to forgive me for that. And on the right, arrows pointing at dysmorphic red blood cells, or sometimes referred to as acanthocytes with those disruptions of the membrane that are characteristic of these are RBCs passing through the glomerular basement membrane.

The etiology of microscopic hematuria can also be variable. There are cases of transient microscopic hematuria that can be seen with simply fever, UTI, even exercise induced, and certainly trauma. While more persistent causes or the ones that will likely require more of your attention include the chronic glomerulonephritities, these were listed earlier, if you may recall, under the normocomplementemic hematuria category. So it includes IgA nephropathy, it includes Alport syndrome, as well as thin basement membrane disease. And certainly, nephrolithiasis or hypercalciuria may present with microscopic hematuria.

Because the differential diagnosis is so broad for patients with microscopic hematuria, it can be useful to break it down in terms of whether or not the patient is symptomatic. So asymptomatic versus symptomatic microscopically hematuria. And also breaking down whether or not the patient has protein in the urine.

So in the case of asymptomatic isolated microscopic hematuria, which is the most common presentation of microscopic hematuria, what you often find is a transient presentation that's not associated with clinical disease. The initial approach is most often just observation and repeating a urinalysis to determine if the hematuria has remained. If not, then certainly your evaluation is complete. But if the isolated microscopic hematuria persists, then additional evaluation to consider would be urine culture, urine calcium to creatinine ratio to rule out hypercalciuria.

You can actually test the patient's parents for hematuria, as thin basement membrane diseases is an autosomal dominant inherited condition. And so one of the parents is almost invariably going to have microscopic hematuria in that case. If all studies are negative but the microscopic hematuria persists, then referral to pediatric nephrology is warranted at that point.

In 1979, there was a landmark study that looked at almost 9,000 children between the ages of eight and 15 years who were all screened for hematuria. And microscopic hematuria was found in one or more specimens in 4% of these patients, and in two or more specimens in a little over 1% of these patients. And what they found based on this study was that, in a nutshell, coexisting proteinuria and the degree of hematuria did correlate with the severity of morphologic alterations that were found on renal biopsy in a small percentage of these patients.

In addition, pathologic findings in microscopic hematuria seemed to be less frequent than in gross hematuria. So in most such patients with isolated asymptomatic microscopic hematuria, renal biopsy was not indicated. And in some children, it may be that low grade hematuria represents the upper end of physiologic variation.

So 3% to 5% of normal healthy children may at some point have isolated asymptomatic microscopic hematuria.

In the case of asymptomatic microscopic hematuria proteinuria, the likelihood of significant renal disease increases quite a bit. So in these cases, quantifying the proteinuria by measuring the urine protein to creatinine ratio is vital. And in particular, using a first morning urine sample to do the measurement. We'll talk more about that a little bit later.

The normal value for the measurement of urine protein to creatinine is less than 0.2. If the urine protein value is less than this threshold, then essentially, you'd be following the recommendations at that point for what we just discussed for patients with isolated microscopic hematuria, since you've essentially ruled out the proteinuria. But if proteinuria and hematuria persist, then again, referral to a pediatric nephrologist is indicated. In the case of symptomatic microscopic hematuria, so this encompasses a lot of similar things to the symptomatic gross hematuria that was already discussed before.

So urinary symptoms may suggest UTI versus kidney stones. Exposure to medications may suggest hemorrhagic cystitis. Certainly, trauma-- excuse me. Arthritis and rash may be seen in patients with lupus or HSP. And in younger children, bubble baths can actually cause irritation of the urethra or external genitalia. That can cause microscopic hematuria.

And the physical examination is-- the findings that you are paying attention for are essentially the same, whether gross or microscopic. So blood pressures may be elevated in the setting of GN-associated renal dysfunction. Weight gain or edema in the case of a mixed nephritis, nephrosis picture. And evaluation for abdominal masses is always important to make sure that you're ruling out Wilms tumor or other neoplasms.

And once again, with further evaluation in the cases of trauma history or urinary symptoms such as those you might find in nephrolithiasis or obstruction to perform additional imaging tests. And if signs or symptoms of glomerular disease are present, once again, it is necessary to refer to pediatric nephrology at that point.

Shifting now to talk about proteinuria, we can classify proteinuria in different ways. And that can be helpful in terms of sort of delineating the category of disease. So there is a level of protein excretion in the urine that's considered normal. And in children, this is typically less than 100 milligrams per meter squared per day. It's a little bit more in the neonatal period because the re-absorption of low molecular weight proteins being filtered by the glomerulus is a little bit reduced in neonates while there renal tubular function is sort of coming up to speed.

As far as abnormal protein excretion, nephrotic range proteinuria, where we've become obviously more concerned for clinically significant renal disease, would be anything greater than 1,000 milligrams per meter squared per day. Or perhaps more clinically useful is the measurement of the protein to creatinine ratio, where normal is less than 0.2 and nephrotic range is greater than 2. Certainly, it can be challenging to collect a 24-hour urine specimen in a child. So the ratio is certainly an acceptable and often the most common way that we measure.

In terms of further classification, so glomerular proteinuria, where what you see is increased filtration of macromolecules, but mostly albumin across the glomerular capillary wall, typically, this is caused by some sort of anatomical or functional lesion of the glomerular basement membrane from glomerular disease. But it can be caused by other things that are not associated with actual renal disease, including fever, posture, which we will talk more about, or even intense exercise.

Conversely, tubular proteinuria refers to micromolecules that are filtered across the glomerular basement membrane, and then largely reabsorbed in the proximal tubule. So these particular proteins are not detected by urine dipstick. And this can be seen in certain conditions, such as tubular interstitial nephritis or Fanconi syndrome. And while not detected by the dipstick, these proteins can be measured with specific lab tests looking for the category of low molecular weight proteins, of which the major ones include beta-2 microglobulin retinal binding protein and alpha-1 microglobulin.

We all are, I think, are familiar with the urine dipstick So there are typically a range of measurements from negative all the way up to 4 plus on the urine dipstick that correspond with an approximate concentration of protein in the urine. It's important to remember, as was just mentioned, that low molecular weight proteins are not detected by the dipstick. And also, false positives can occur in highly concentrated urine specimens.

So when the specific gravity is at least 1.015, you may see a positive dipstick for protein. And this is often caused by dehydration. Certainly, a quantitative assessment of protein is a necessary measurement in cases where you suspect proteinuria by either a 24-hour or a spot-- excuse me, spot urine protein to creatinine ratio.

In terms of evaluating proteinuria, the simplest and most effective way to do so is to measure the urine protein to creatinine ratio on two separate urine specimens. One from a first morning void, and a second specimen obtained in your office or clinic. Certainly, if both specimens demonstrated normal urine protein level, then whatever test was abnormal that prompted the visit in the first place had resolved. And so we would consider this to be a case of transient proteinuria.

And we've discussed reasons why this may occur, including fever, exercise, even stress. And no further evaluation would be necessary at that point. Orthostatic proteinuria, also referred to as postural proteinuria, would be diagnosed based on a normal protein to creatinine ratio on a first morning void, with a second urinalysis during the daytime positive for proteinuria.

This condition is a benign one, not associated with any actual renal disease in which increased protein excretion occurs in the upright position. And when the patient is recumbent, while sleeping overnight, for example, the urine protein levels return to normal. So when this diagnosis is made, once again, no further evaluation is required.

And then certainly persistent proteinuria would be diagnosed by an elevated protein to creatinine ratio level on the first morning urine void, in addition to the daytime specimen. And at that point, certainly referring to pediatric nephrology is indicated. When it comes to the symptomatic child with proteinuria, the goal is to identify this patient as early as possible because this tends to signify significant renal disease, and some sort of intervention is often necessary.

So these patients will present with some version of a characteristic history that is likely to include swelling or peripheral edema. Possibly a recent illness, possibly decreased urine output, or even a foamy urine appearance. And the initial laboratory evaluation for these patients should include certainly a urinalysis with a urine protein to creatinine ratio. Also, renal function tests and serum electrolytes to measure creatinine, sodium, potassium, bicarb.

And then a serum albumin to see whether or not the proteinuria has led to significant hypoalbuminemia. And then a fasting lipid panel can help diagnose nephrotic syndrome, as those patients will have significant hypercholesterolemia. And here's just a graphic showing a patient with significant proteinuria and how foamy their urine specimen is.

So I jumped the gun a little bit and was just describing what the evaluation and potential results look like in a patient who presents with heavy proteinuria and peripheral edema and needs to be evaluated for a nephrotic syndrome. So the nephrotic range proteinuria comes with urine protein to creatinine ratio greater than 2. These patients often have a very low, even undetectable serum albumin level.

Dependent peripheral edema. So the key areas to look for on physical exam include the periorbital region, certainly the extremities, but also the sacral as well as the scrotal or labial area. And then hypercholesterolemia, which is significant hypercholesterolemia sometimes with total cholesterols upwards of 300s and 400s.

Patients with persistent proteinuria, but in the non-nephrotic range with a protein creatinine ratio between 0.2 and 2 should still be referred to a pediatric nephrologist for further evaluation. In particular, concerning findings in these patients would include hypertension, elevated serum creatinine, or an abnormal urinalysis.

These are graphics just illustrating the most common sources or areas of peripheral edema in patients with the nephrotic syndrome. Starting on the left, the periorbital edema. And then in the subsequent two graphics, the genital edema that can often be seen in younger kids.

And here, actually, this is a very good picture of a patient with quite significant lower extremity edema. It's not the best picture, but if you look closely, you can see four fingerprints illustrating just all the subcutaneous fluid that's present. That's the end of my talk. Thank you very much.