In urinalysis, automated microscopy making the difference

Ann Griswold, PhD

March 2014—Traditional urinalysis is messy. It's tedious. It's prone to variability. It's nicknamed the "ugly stepchild" of the laboratory. Many are quick to note that it's just a screening tool—with an emphasis on "just."

But in recent years, urinalysis has been quietly tiptoeing into a new era. "We're in the period of resurgence, using automated urine microscopics and urine chemistry to their full potential," says Keri Donaldson, MD, assistant professor of pathology, medical director of hematology and thrombosis, and medical director of molecular diagnostics at Pennsylvania State University's Milton S. Hershey Medical Center.

While automated methods for urine chemistry aren't all that new, automated microscopy is transforming laboratories by allowing for more accurate, efficient, and standardized results.

But long before the automation, urinalysis once occupied a high position on the medical totem pole. "Even before there were such things as doctors, people were looking at the color of urine, the consistency of urine, the smell of urine," Dr. Donaldson says.

That intense interest in urinalysis lasted well into the 20th century. "Decades ago, we had a golden time when urinalysis was very, very important and people were talking about blood versus urine. But over the years, people took a fair amount of what you could learn from urine for granted," Dr. Donaldson says. "Newer diagnostic tests were introduced that are more descriptive and more specific than some of the findings that were historically available for urinalysis, and the focus on urine slipped away."

The appreciation for urine didn't disappear entirely, of course. It can reveal an array of information about the broad clinical picture.

Herrera

"Our facility is a cancer hospital, so urinalysis ranks really high on the value scale," says Annabelle B. Herrera, CLS, MT(ASCP), hematology supervisor of the clinical laboratory at the University of Southern California's Norris Comprehensive Cancer Center. "Our clinicians monitor the protein content of the urine, for example, to determine if a patient can start chemotherapy. If the esterase is negative and you see a lot of white cells, then you suspect there might be some tumor cells. If they're positive for esterase, you know they're neutrophils and it could be an infection."

Nancy Brunzel, MS, MLS(ASCP), author of Fundamentals of Urine and Body Fluid Analysis and assistant professor of clinical laboratory science at the University of Minnesota, calls urinalysis a "fluid biopsy of the kidney."

"Urine is valuable, wonderful. There's no other biopsy of an organ that we can get that's noninvasive. In fact," she says, "urinalysis gives you a good overview of what's going on in several organ systems."

One of the most valuable components of urinalysis—microscopy—continues to be performed by hand at many

institutions, even large medical centers. Manual urine microscopy can be a long and tedious process with results that vary by laboratorian.

“As laboratorians, we need to more carefully adhere to the microscopic protocol written for our laboratory so that we’ll get the same result regardless of whether I’m doing the urinalysis or it’s done by a brand-new laboratorian, fresh out of school,” Brunzel says.

Individual labs strive to standardize urinalysis results by establishing reference ranges for their patient populations, reporting the number of blood cells per high-powered field. “The problem is that the number of cells you’re going to see per high-powered field depends on the method you use to get to that microscopic examination,” Brunzel says. “That varies all over the place.”

“When I got into the profession in the mid-’70s, urine was collected at the patient’s bedside. It might sit there for a couple hours, or it might get out to the nursing station and sit there even longer. When it got to the laboratory and back into the area that did the urinalysis testing, it might sit on the counter or get stuck in the refrigerator,” Brunzel recalls. “Then you took a well-mixed urine sample, plopped a drop on the slide, put a coverslip on it, and looked at it under the microscope. It was all very qualitative.”

Not much has changed in that regard, she worries. It’s still tricky to standardize the results of manual microscopy across institutions, given the myriad variations in the volume of urine being spun down, the speed and duration of centrifugation, and the volume of supernatant used to resuspend the sediment.

But even if all of those variables were held constant, Brunzel notes, other confounding factors exist. The microscope’s field of view may vary in size, for one. “Unfortunately, the oldest microscope in the lab is going to be in urinalysis. The scope that hematology no longer needs: ‘Oh well, it can go in urinalysis; they don’t need the greatest microscope.’”

Moreover, the number of high-powered fields observed can differ depending on how much time a laboratorian devotes to the slide. “If you’re sitting there with a rack of 20 urine samples, you’re not going to spend as much time on each one as if you had only three urine samples,” says Denise Gordon, MT(ASCP), hematology supervisor at Holy Name Medical Center, Teaneck, NJ. “You might hurry through it; you might not look at as many fields as you should.”

Automated urine microscopy has helped to achieve that goal. In recent years, automation has had a tremendous impact by allowing labs to standardize and improve the accuracy of urinalysis results. “We don’t have to worry about differences between techs reading a specimen, or the area of the slide they’re reading,” Gordon says.

Until recently, Gordon’s lab relied on a manually loaded Clinitek 500 instrument for urine chemistry, and performed labor-intensive manual microscopics on every positive specimen. A 1,000-bed medical center in a neighboring town continues to perform manual urine microscopy, she says, but at Holy Name, the workload became unsustainable. A single laboratorian was responsible for the coagulation and urinalysis workbenches, and he couldn’t keep up with the barrage of urine samples, especially when the hospital partnered with a large courier service. “We were processing about 90 urine samples a day. We were literally drowning in urine,” Gordon says. “As a manager, I found myself helping at the bench on many, many days, because it just wasn’t feasible for one person to do it all.”

Her lab purchased an AUWi system, which links the Clinitek Atlas Automated Urine Chemistry Analyzer to the Sysmex UF-1000i Urine Particle Analyzer. Racks containing urine specimens can be loaded into the Atlas, which automatically pipettes samples onto dipsticks and prints the urine chemistry results. Positive samples are sent to the UF-1000i, where the specimen is aspirated and subjected to flow cytometry. The system has transformed how her lab operates, she says. “Automating urinalysis has been the biggest change in my department in the past 10 years.”

“It’s been a godsend, because one person can now handle that bench easily. They can do the work and not be

frustrated and overworked. It's manageable," she says. The system's autoverification steps have proved particularly helpful. "Even lowering a turnaround time by one to two minutes can be instrumental."

The application of flow cytometry to urinalysis was a game-changer, Gordon says. "Whoever took that next step was a genius."

Though flow cytometry has been used in hematology assays for many years, it took a long time for the technology to transfer to urinalysis. Many hematology instruments offer body fluid analyses but are highly impractical to use for urinalysis, says Lorraine C. Smith, MBA, SH(ASCP), hematology technical leader in the Department of Pathology and Laboratory Medicine at the Medical Center of Central Georgia./p>

"Body fluid analysis is done in the urinalysis area. If you have a fairly decent-sized laboratory, it can get tedious for the urinalysis person to interrupt their workflow by going all the way over to the hematology instruments to run a fluid," she says. "The second thing is that hematology instruments are meant to count thousands of white blood cells and thousands of red blood cells, but body fluids can have very few numbers of cells."

Having a body fluid module on the urinalysis instrument means one person can perform both urine analyses and body fluids, and the system can be designed to detect and count very few cells.

Hein

"We had it in hematology, why didn't we have it in urinalysis?" asks Darryl Hein, SH(ASCP), hematology supervisor at Children's Hospital Central California. "It's a no-brainer. If you want better accuracy, precision, and reproducibility, you can get them with flow cytometry," he says.

Though the capability exists, not all urinalysis instruments are FDA approved to run body fluids, he notes. "I would prefer running body fluids on our Arkray AU-4050 Hybrid, but it is not FDA approved for that specimen type. It would be nice just to be able to run them and get an answer right away rather than having to run them on a hemocytometer."

Within the application of flow cytometry to urinalysis, evolution is occurring on a smaller scale. Different dyes are used, separate channels are created, and more companies are getting into the game—meaning greater competition and likely even better technology.

Digital imaging, another option for automated microscopy, tends to have a lower positive predictive value compared with flow cytometry. But it makes up for that in other ways. Urinalysis is routinely performed on inpatients before admission to help determine, for billing purposes, whether the patient arrived with a UTI or acquired one during the hospital stay. "Having the pictures from digital imaging, and being able to save the pictures, is valuable from a teaching perspective and an accountability perspective," Smith says. "I can go back and see how the staff classified cells. Before, when we were manually looking at abnormal urines under the scope, once we'd discarded the microscope slide, it was gone forever. But on the Iris, I can say, 'He called this one a red blood cell.'
For me, the 'look-back' has been a game-changer."

Automated systems don't eliminate the need for manual microscopy, but they greatly reduce the lab's

burden. “We don’t do microscopics on 80 percent of the urine samples because either they were negative or the instrument does the microscopic for us,” says Gordon of Holy Name Medical Center. “So if we’re processing 100 urine specimens a day, only 20 of those require us to sit down and look under a microscope.”

Though some laboratories don’t perform urinalysis often enough to justify an automated instrument, other laboratories stick to manual microscopy for different reasons. “People like to put value on rare things they find with manual microscopy, but day in and day out we have lots of patients with UTIs,” Hein says. “We want to know which of those patients are going to yield a positive culture, so we need something that does a better job of counting bacteria. That’s what flow cytometry does, versus some of the other methods.”

In a small study, Hein’s laboratory looked at casts and epithelial cells from patients with known kidney disease, comparing the results from automated versus manual urine microscopy. The results were interesting, he recalls.

“The analyzer flagged for renal tubular epithelial cells—it called them ‘small round cells’ because they’re in the epithelial area of the flow cytometry, so you have to confirm that on a slide. When we looked at them on a slide, the original tech said they were just squamous. But on closer observation, there actually were renal tubular epithelial cells.” That wasn’t a surprise, he says, because the patient had known kidney disease. But if that patient had presented in the ER, the automated results would have prompted the laboratory to scrutinize the slide a bit more carefully. “The flagging feature [in the automated instrument] is a good thing,” Hein notes.

Last June, Smith’s laboratory had a similarly positive experience when it switched to the iChem Velocity urine chemistry system and the Iris iQ200 urine microscopy system. The lab had previously used a semiautomated system.

The new workflow is simple: A sample is delivered to the laboratory, poured into a tube, and placed in a rack on the instrument. The laboratorian need not return until the instrument indicates that the dipstick is negative or the microscopy is complete.

“The iQ200 uses digital imaging to look at the entire urine sample and count how many red blood cells are there, how many white blood cells are there, if there are crystals or anything pathological,” Smith says. The digital imager is remarkably accurate, she adds. “It takes really beautiful pictures of the cells. It does a pretty good job categorizing them, but the whole point is that we make sure that what the instrument is calling white blood cells are actually white blood cells, what it’s calling red blood cells are red blood cells, and so on. Once everything looks the way it’s supposed to look, we release it, and it crosses the interface, goes to the patient’s chart, and then we’re done.”

One of the best parts, Smith says, is that the laboratory’s rules are programmed into the instrument. “With their middleware solution, we were able to set up autoverification. So once results are verified, they leave the instrument. Our techs don’t have to type anything in and there are no chances for clerical errors.”

As more and more labs switch to automated urine microscopy, however, the University of Southern California’s Herrera urges them to think carefully about operator training.

“All of us know the basics of manual urinalysis,” she says. “Some people might think, ‘Oh, even a monkey can run automated urinalysis,’ but that’s not true. You still have to correlate. You still have to think about what makes sense, what’s compatible with life. The instrument is not going to tell you that. If we’re going to go with automation, we have to train people to do it properly.”

After Hershey Medical Center switched from manual to automated urine microscopy, Dr. Donaldson performed a study that revealed the “profound impacts” of automated microscopy on the clinical laboratory’s workflow and on the reproducibility of the results. “All of a sudden, instead of having variability between the amorphous stuff that might be classified as either bacteria present or absent [depending on the laboratorian], we had pretty solid repeated measures between values,” he recalls.

He has since performed other studies in hopes of securing faster, quicker, and more reliable urinalysis results that can inform the best possible clinical decisions without the need to wait for a positive urine culture.

“It’s increasingly important that we leverage our knowledge and have a delivery system that we design that gives physicians what we call ‘just-in-time information’ that’s in front of them and drives the appropriate clinical decision,” Dr. Donaldson says. “We need to make sure that if a person is on a prophylactic antibiotic therapy, it’s appropriate. And if it’s not appropriate, we need to make sure the patient gets off of it as soon as possible.”

A study of Hershey Medical Center’s urine cultures for a three-month period—a total of 13,000 cultures—assessed whether a positive or negative culture result could have been predicted on the basis of urine microscopy and chemistry findings. “We can really predict a negative result,” Dr. Donaldson says. “For a defined patient population, we can predict a urine culture result 99.9 percent of the time, which is great.”

He hopes that some day, rather than being just< a screen, urine might serve as the first portion of a reflex test to provide a quicker and more reliable tool compared with historic methods.

“There are three legs of the stool: being able to do the testing in a very controlled, very reproducible, quality-centric way; being able to report the results efficiently; and being able to guide the physician in using those results. A comprehensive program hits all three,” Dr. Donaldson says. “In urinalysis, it’s imperative to hit all three because urine is so ubiquitous. It’s everywhere. It impacts a lot of patients in a major way, and if we don’t control for the three sets of that process, there’s a likelihood we could be reporting things that may or may not be true.”

Despite the growing popularity of automated urine microscopy, many clinicians likely remain unaware of the change in their laboratory’s urinalysis workflow. “From their side of it, it looks pretty seamless,” Smith says. “The biggest clue is that physicians are receiving the results faster because we’re not waiting for someone to enter results manually into the LIS. Instead, the result pops up on our screen when it’s ready to be validated, it’s reviewed, and then released to the physician.”

As a result, Dr. Donaldson says, some clinicians may continue to interpret urinalysis results with a grain of salt, assuming that the bacterial count is subject to a great deal of variation. “I’ve sent an e-mail out to clinicians to announce that in the last three months, there’s been a huge methodological shift at our institution. I was pretty descriptive, but if they didn’t read it then they probably don’t know that this historic variation in urinalysis results no longer exists.”

Whether or not clinicians are aware of their laboratory’s change in technology, they’re likely to take note when the internal validation studies uncover surprising results. A reference range study performed on the new instruments in Gordon’s lab, for example, revealed that certain particulates long considered abnormal, including protein aggregates known as hyaline casts, occur far more often in healthy people than previously recognized. “Normally you don’t do microscopics on normal people, and you tend to rush through slides that hardly have anything on them,” Gordon says. “Nobody had really bothered to count these things in normal people.”

“Physicians had to get used to the fact that someone can be walking around with 100 epithelials in their urine and it’s okay. Or a couple of hyaline casts—it’s okay,” Gordon says. “It changed our thinking that you should see nothing in urine.”

In the end, however, the importance of a physician’s careful evaluation cannot be overstated.

“It all comes down to the ability of a physician to have a trained eye,” Hein says. “My son is a physician in a little rural clinic, and all he has are his eyes and a dipstick. All other lab work has to be sent out. If he has a person with kidney disease, more than likely when they walk in they’re going to have edema, and they need to get on a diuretic right away, and he can see that.”

“That said, why not give them the best information we can in a hospital setting? If we could reduce patient stays with better urinalysis, I think more people would want to put more effort into getting a better sample.” [hr]

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