Urine preanalytics guideline effort highlights data need

Anne Paxton

February 2016—When it comes to recommended practices for preanalytic handling of urine specimens for the microbiology lab, Alice S. Weissfeld, PhD, D(ABMM), has a blunt and colorful take: “I call it ‘running our lab based on urban legend.’”

“The way I learned it and the way I taught it was after two hours, then either use refrigeration or boric acid, women must clean, and so on. There was no way around it.” But the foundation for those standards has been largely anecdotal experience. “The people we looked to—and they were some of the giants in the field of urine cultures—said, ‘Here is the best way to collect; here is the best way to store,’ but they basically never had any data,” says Dr. Weissfeld, president and CEO of Microbiology Specialists in Houston.

Addressing that need with an evidence-based guideline was one of the goals of a collaboration between the American Society for Microbiology and the Centers for Disease Control and Prevention whereby studies of commonly used collection, storage, and preservation methods for urine samples would be reviewed and recommendations made based on a meta-analysis of the studies.

Part of an initiative to write “Laboratory Medicine Best Practices” (LMBP) guidelines, the collaborative project used the CDC’s A-6 systematic review method to develop recommendations based on the “body of evidence.” The method is a “whole new approach” that shifts the focus from the laboratory to the patient, where it should be, to assess quality improvement practices and develop evidence-based practice guidelines, says Dr. Weissfeld, who served as an expert panel member of the Urine Collection, Preservation and Transport Working Group.

Dr. Weissfeld

The two parameters the panel measured were reduction of urine culture contamination and increased accuracy of patient diagnosis. A January 2016 article, “Effectiveness of preanalytic practices on contamination and diagnostic accuracy of urine cultures: a Laboratory Medicine Best Practices systematic review and meta-analysis,” describes the study authors’ findings (LaRocco MT, et al. *Clin Microbiol Rev.* 2016;29[1]:105–147).

The results of the study reflect the relatively weak evidence to support a comprehensive guideline. Of 12 urine preanalytic practices reviewed, only three were recommended, three were not recommended, and the most frequent finding—in six cases—was “No recommendation for or against based on insufficient evidence.”

The available research does justify recommending midstream collection with cleansing for children’s urine specimens, as well as for women’s and men’s specimens, the study authors found. For women’s and men’s specimens, the authors do not recommend for or against midstream collection without cleansing. But for children’s specimens, they recommend against collection in sterile urine bags, from diapers, or midstream without cleansing. The authors also found enough strong evidence to recommend against first-void urine collection from men. As to whether urine should be stored at room temperature, refrigerated, or preserved in boric acid for delayed processing, the authors found the evidence was not strong enough to justify recommendations.

These findings don’t mean laboratories should abandon their customary practices to ensure preanalytic quality, Dr. Weissfeld stresses. And the report notes that its lack of recommendation does not preclude the use of refrigeration

or chemical preservatives in clinical practice. But a key take-away message of the collaborative effort and the paper is that microbiology laboratories need to collect more data on urine preanalytics.

LMBP was one of the projects that resulted from a meeting the CDC convened several years ago. The outcome of the meeting was published in May 2008 as "Laboratory Medicine: A National Status Report," also known as the Lewin Report. The ASM and the CDC started working together on the LMBP studies in 2011.

Dr. Cornish

Nancy E. Cornish, MD, medical officer, CDC's Division of Laboratory Systems, and scientific and technical lead on the urine preanalytics study, joined the LMBP team four years ago when she started working at the division. Six papers have been published using the CDC LMBP method of systematic review. "But since it's still a fairly new process, we're all learning, and improving the process, as we go."

It's been a while since urine has actually been studied, Dr. Cornish notes. "We're in a new age of medicine and we have different circumstances than they did 30 years ago, so I think it's time to re-evaluate, to see if we can build an evidence base to have us feel confident in selecting, collecting, and transporting urines."

Urine cultures are the largest portion of many hospital-based microbiology laboratories' workload, and some hospitals are performing hundreds of cultures a day, Dr. Cornish points out. If the specimens are poorly collected or poorly transported, culture results can be erroneous. But poor selection is just as important. "For example, if the patient doesn't have signs and symptoms of a urinary tract infection, collecting that urine could result in growth of bacteria because patients can be colonized with bacteria periodically without infection, so you are bound to find positives.

"In the lab, we don't know if the patient has signs or symptoms. We do our ID and our susceptibilities based on laboratory criteria for workup. The clinicians get the report with a full ID and susceptibility and may feel they need to treat the patient because the report indicates the patient may have a UTI."

The authors looked at a series of practices, then evaluated the literature in each case to see if there was enough evidence to support a recommendation. But out of 12 questions on practices that the study authors explored, "We only could make recommendations for three of them." Was that surprising? Yes, Dr. Cornish says. "I was trained as a clinical microbiologist and a pathologist, and I thought the guidelines I was following were based on evidence. So then to do a thorough systematic review and discover we actually didn't have enough evidence for some of these guidelines was a surprise."

"That doesn't mean we are not doing the right thing," she adds. "Maybe we are. But we don't have the evidence to prove that."

The CDC's emphasis on "great data" through its systematic review process may, over the long run, help remedy the evidence gap. "To me, great data is the beauty of the CDC method," Dr. Weissfeld says. "You start with a librarian, and it has to be a librarian trained in systematic review, and you say, OK, I need to know how many papers there are on this subject. Then you take key words and strings of words you'd like to search on—say, 'boric acid' and 'preanalytic.' And you actually look at how many articles there are and start weeding them down to ones that will answer your specific question. So everything relates back to this focused question."

You won't necessarily find what you expect, Dr. Weissfeld cautions. "If you can't culture a urine specimen within two hours, does refrigeration help? We know that's what you should do and still think that's what we should do. But

if someone were to say ‘Show me the papers,’ you can’t.”

In fact, after the authors winnowed relevant articles from more than 5,000 to about 75—the group known as the body of evidence—practically every urine preanalytics practice the authors looked at was problematic, Dr. Weissfeld says. On midstream collection in women, however, a lot of work had been done in the United Kingdom comparing cleansing versus the patient’s holding the labia apart and urinating. “I was very impressed with the fact that they spent a lot of time and money looking at urine collection, and it pretty much looks like women really don’t have to clean as thoroughly as we have them clean now before collecting urine specimens.” Unfortunately, there were not enough data to justify a new recommendation regarding this practice, she says.

With midstream collection for men, there were not enough data to recommend cleansing versus non-cleansing; results showed no difference in contamination between the two methods of collection and there was imprecision due to the small effect size in the studies. “You look at 10 different things in a paper to give it a rating. CDC developed the A-6 method and said we need at least three papers rated ‘fair’ to ‘good’ in order to make a recommendation,” Dr. Weissfeld explains. “It doesn’t sound like a lot, but even with thousands of papers to look at, it turns out to be a hard task.”

She is now working on a separate study of *Clostridium difficile*, using the same review process. “One question with *C. difficile* is if you do a rapid test like PCR, is that better for the patient than doing other tests available on the market? Is there an advantage in length of stay or time on antibiotics?” Again beginning with thousands of studies, her team has narrowed the number of relevant studies to 139 to explore the answers.

Microbiology lags somewhat behind clinical chemistry in the quest for evidence-based practices, Dr. Weissfeld says. “The AACC has been active a lot longer than ASM on this, and Rob Christenson, past president of AACC, actually helped CDC design this method. So while we feel at ASM that we’re jumping into the game late, we’re trying to catch up.”

Despite being a worthwhile goal, evidence-based medicine can be expensive to achieve in practice. Theoretically, Dr. Cornish agrees, a randomized, controlled, double-blind study could resolve issues of best preanalytic urine specimen practices. “You would just have to have the resources to do it.”

In the meantime, there are many practices that people believe in, that seem sensible, but for which evidence is scarce. “That’s what I found when I was in clinical practice,” Dr. Cornish says. “I wound up following the established guidelines that everyone followed, and I was challenged by the nursing group I was working with to find the evidence base. But I had difficulty.” On midstream collection, for example, “You’d have to do some well-designed studies with adequate populations of subjects of varying age ranges and backgrounds. You couldn’t just do a study on outpatient college women and apply the results to all women. Elderly women, for example, should be studied separately.”

Dr. Cornish doesn’t know how much it would cost to do the studies that are needed. “But I know it costs a lot of money to do things that are inappropriate. And certainly the rise of antimicrobial resistance is an example of that. If we are selecting, collecting, or transporting urine inappropriately and growing organisms or bacteria that are contaminants or colonizers, and we’re doing susceptibilities, then physicians may think this is a UTI—and the patient may get treated with antibiotics they don’t need.”

One of the important areas where the authors were not able to make a recommendation, due to insufficient evidence, was storage of specimens. It’s commonly accepted that if a specimen is going to be held for delayed processing, it should be refrigerated or chemically preserved. CAP Q-Probes studies performed in 1998 and 2008 found that urine culture contamination rates were substantially affected by post-collection processing, especially refrigeration of the specimen. But the strength of studies analyzed in the review was not strong enough to compare refrigeration with room-temperature storage or boric acid preservation.

This is unfortunate because with the increased regionalization of microbiology, and greater use of reference laboratories, urines are not always worked up close to the patient anymore, Dr. Cornish says. “And it changes how

you do things. If the urine you're collecting doesn't reach the lab until tomorrow, that's really different from urine that reaches the lab in five minutes, so those storage and transport issues have to be considered."

But as the study demonstrates, there is an evidence gap on the question of what those policies should be. So in line with the LMBP project, one of the study authors' goals is to encourage laboratories to do their own research. "What we do in the lab has a big effect on patient outcomes. We have to work with our clinical colleagues and hook our results to outcomes to make that link," Dr. Cornish says. Adopting practices in the laboratory that are expensive and time-consuming makes no sense if they don't make a difference to patients. "It may be some simple things we can do will improve outcomes and should really be continued, but you need an evidence base for that."

Many specimen collection and handling practices are feasible and commonly used today in all settings and patient populations, among them sterile collection cups, cleaning towelettes, boric acid, and other things to aid collection and transport. "Whether they are being used routinely is another question, but they are commonly practiced," Dr. Cornish notes, so laboratories have the opportunity to collect data. "And once we understand the best way of doing things with a good strong evidence base, then we could feel comfortable making recommendations and helping people in various settings to select, collect, and transport specimens properly."

As part of their paper, the authors include a 20-part data collection form for laboratories' use (page 18 in this issue). "We designed the form to include everything we need to make a strong study. The form can be used to collect data for any quality improvement project that examines preanalytic practices associated with urine cultures," Dr. Cornish says. "We want to encourage laboratories to go out and collect data so we can do this systematic review and be able to make firm recommendations for the country to follow."

The data collection form is in the open-access publication, and Dr. Cornish hopes labs use it to provide the data needed. The QA data collected can then be submitted through the CDC LMBP website as unpublished or "grey" data. The systematic reviews the CDC is doing, using such collected data, meet the criteria of the National Guideline Clearinghouse, and the plan is to put them on the Agency for Healthcare Research and Quality website (http://j.mp/ngc_factsheet).

Dr. Weissfeld also hopes that people in microbiology labs all over the world will submit their urine preanalytics data on the LMBP website when the mechanism to do so is set up. "For example, if you had women cleansing, then a subpopulation of women not cleansing, how much contamination did you have? And was it, one, easier for the patient and, two, better because you lowered the amount of contamination?" This is evidence-based medicine "because you're looking at subsets of people, what is happening to them, and the best way to do things."

One facet of the urine preanalytics data collection project that Dr. Weissfeld particularly appreciates is that it will expand the variety of sites being studied. "We'll now have an opportunity to collect data from acute-care hospitals. This will let people see a broader range of raw data than just what's collected by university-affiliated hospitals or large medical centers."

Microbiology laboratories can use the data collection form to collect robust data with all the elements needed and contribute to the collective evidence base, which, Dr. Cornish notes, will help everyone.

Beyond urine preanalytics, the LMBP project continues with clinical practice questions and the hope is that economic analysis can be added as well. The CDC's goal is to include in each manuscript a data collection form that will focus on the data needed to answer the practice questions.

At Microbe 2016, the next annual meeting of the ASM, to be held June 16–20 in Boston, attendees will have the chance to learn more about how they can expand the evidence database for urine preanalytics. "What we hope to do is train a number of people who are interested in how to do these collections," says Dr. Weissfeld, "and we hope they can go back to their hospitals, collect the data, and bring it in to us."

Anne Paxton is a writer in Seattle. The CDC wishes to note that the findings and conclusions in this article are those

of the guideline authors and do not necessarily represent the views of the CDC.