Labs seeing the light on practice guidelines

CAP TODAY

August 2010
Feature Story

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In 1989, a woman in North Carolina named Gina Burns was devastated when her one-week-old son died from a preventable disease: Group B Strep. But her response to that tragedy was to have a long-term impact. She launched an intense lobbying effort in favor of national standards for routine antenatal GBS screening. By 2002, her initiative helped lead the Centers for Disease Control and Prevention to adopt a national consensus guideline recommending universal GBS screening for pregnant women, which in turn contributed to a 70 percent drop in annual infant infections and deaths from GBS nationwide.

Gina Burns is a hero in the public health world, and in the microbiology world the GBS screening guideline is a powerful model for clinical practice guidelines, says Peter H. Gilligan, PhD, professor of microbiology-immunology and pathology-laboratory medicine at the University of North Carolina School of Medicine, and director of the clinical microbiology-immunology laboratories at the UNC Hospitals. "It's well-constructed, it has positive outcome data, and it has definitely influenced the practice of laboratories and clinicians."

Like the GBS guideline, which continues to evolve, a range of other clinical microbiology practice guidelines are increasingly meeting more rigorous standards and being applied in health care settings. Dr. Gilligan was one of a panel of experts at the American Society for Microbiology general meeting in May who explored how such guidelines are advancing patient care. At the ASM meeting and in interviews with CAP TODAY, the panelists confirmed that, while much work lies ahead, the nation's heightened interest and investment in evidence-based medicine can help clinical microbiology practice guidelines have a significant and measurable effect on patient outcomes.

Clinical practice guidelines have been developed over the last half century at least. The Institute of Medicine defined them in 1990 as "systematically developed statements to assist practitioners' and patients' decisions about appropriate health care for specific clinical circumstances," says Daniel Amsterdam, PhD, an ASM panelist who is clinical director of the Department of Laboratory Medicine at Erie County Medical Center, Buffalo, NY, and professor in the Department of Microbiology and Immunology and professor of medicine and pathology, University at Buffalo School of Medicine.

But in microbiology, the development of clinical practice guidelines has lagged behind. He points out that the government-sponsored National Guideline Clearinghouse lists more than 1,000 practice guidelines, including 27 posted by the Infectious Diseases Society of America (IDSA), that relate mostly to diagnosis and treatment, but the ASM has not posted any guidelines. "Most of the clinical practice guidelines that are published deal with what happens after you get the lab information—what are the drug therapeutic approaches that you're using—rather than with the preanalytic and analytic information itself," Dr. Amsterdam says.

The ASM's Cumitech series—consensus reports on topics of interest to clinical microbiology labs—covers many of the 360 procedures in microbiology, with the goal of "providing consensus recommendations regarding the judicious use of clinical microbiology and immunology laboratories and their role in patient care." But Dr. Amsterdam notes that the ASM does not have reference documents that can be considered clinical practice guidelines.

Medical groups' practice guidelines in general have not always been evidence-based, he points out. A 2009 *JAMA* article looked at 23 years' worth of cardiovascular clinical practice guidelines of the American College of Cardiology and American Hospital Association, including more than 7,000 recommendations, and found that most were based on the lowest standard of evidence: expert opinions or case studies of the standard of care. The authors also concluded that "the proportion of recommendations for which there is no conclusive evidence is growing. These findings highlight the need to improve the process of writing guidelines and to expand the evidence base from which clinical practice guidelines are derived" (Tricocci P, et al. *JAMA*. 2009;301:831–841).

Clinical microbiologists within the ASM would like to see the organization engage in more formal development of clinical practice guidelines, and a statement from the organization's president, issued in April, calls on ASM colleagues to move forward in this effort. The first step has now been taken, Dr. Amsterdam says: formation of a practice guidelines committee.

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In the field, meanwhile, the issues of practice guide- lines tend to be the more practical ones of agreeing on guidelines and getting everyone to comply with them, as Nancy Cornish, MD, director of microbiology at Nebraska Methodist Hospital and Children's Hospital in Omaha, illustrated in her presentation at the ASM meeting.

Take, for example, the blood culture contamination clinical practice guidelines project that just went live at Children's Hospital. During the three-year planning and discussion process that paved the way, the nursing department and the laboratory disagreed over how long to air-dry antiseptic applied to the skin before drawing blood. It might have seemed that the nurses were upholding a higher standard. "The lab wanted to wait 30 seconds, and nursing wanted a minute," Dr. Cornish says.

But, after they sat down to discuss it, the two departments realized they were operating in different arenas. When nurses drew blood from children on the floors, their patients were not wiggling; either the draw was from a central line that the child didn't feel, or it was a peripheral stick where the child was anesthetized. "All the blood cultures that phlebotomists do are on kids who may be kicking and screaming," Dr. Cornish says. "And a shorter drying time is better." As a result of the meeting, the nursing/lab team decided to adopt a more flexible guideline of 30 to 60 seconds, or until dry.

The incident epitomizes the theme that Dr. Cornish discussed as a panelist on the ASM panel: implementing practice guidelines using a multidisciplinary approach.

The blood culture contamination project all started because the laboratory wasn't getting enough of the volume it needed from child patients to diagnose blood infections, she says. "Getting two sites drawn, so we get adequate volume and can tell the difference between skin contamination or not, is standard for adults. But it often doesn't happen with kids. Parents and nurses and doctors get very anxious when you have to poke a kid multiple times with a needle, and they routinely say, 'Why did you have to do that?' We had nurses and physicians who flat-out refused to follow the guideline. They weren't bad nurses or doctors, but they were concerned about taking too much blood."

On paper, it had always been the laboratory's policy to do two draws and get the proper volume of blood according to the weight of the patient. But "that didn't mean anybody did it," she says. With CBCs, it's not an issue because without the volume the lab can't do the test. "With blood cultures you can draw a mL and stick it in a bottle and we would not reject it. So people didn't learn they couldn't do it." But without sufficient volume, "you may not be able to make a diagnosis," that is, you have a false-negative culture, "because you have very low levels of bacteria circulating in the blood."

By assembling a team of nurses, doctors, and laboratory personnel, Dr. Cornish's laboratory was able to put a policy—which the medical executive committee approved—with teeth in place. The CLSI guidelines, "Principles and Procedures for Blood Cultures," which came out in 2007, "really helped with that because they had all the recommendations, hundreds of references, and they made it easy to present and say this is what we need to do." She is immensely grateful to the people who develop guidelines. "Without the CLSI guideline, I would have had a huge amount of work trying to decide what was relevant and what wasn't."

"All of us—nurses, residents, medical students, and physicians—have lanyards we wear around our necks with our ID cards, and now there are cards explaining how much blood you should draw based on patient weight," Dr. Cornish says. The laboratory-nursing team has also designed posters and 5×7 pocket cards, fact sheets, and a parent educational sheet "explaining why the hospital needs to stick your child twice," she adds. "It's not perfect, but it's a start."

There is a real push now to implement best practices in the hospital, to follow evidence-based medicine. "But to do that, you have to get everybody on board. One place where it's not yet clicking is when doctors order too many tests on a child. They often don't realize how much blood that will take. In the laboratory, we have a point where we say we're not going to take any more blood. If somebody orders 20 tests on a baby who's 10 pounds, we look at it and say the doctor has to select fewer tests, because we're not going to draw more than a certain amount of blood each day." The policy, called the Twenty-four-Hour Maximum Blood Draw Guideline, has been in place for several years, "but the nurses had no idea the lab would stop drawing blood at a certain point. When they found out about it, they thought it was a good idea. They would like to adopt the same policy, but it will take teamwork and time to get it accomplished." She doesn't know if they have adopted the same policy yet.

Dr. Cornish is now working with guidelines of the IDSA for catheter-associated urinary tract infections. IDSA guidelines don't always specify exactly how to collect, store, or transport the specimen, but she tries to find that information from other sources.

Her experience in implementing clinical guidelines for urine cultures demonstrates how unintended consequences can result. "We started it when I realized a lot of our urine culture requests were not properly labeled. We had no idea whether they were foley catheter, clean catch mid-void, or straight catheter specimens." She also noticed the laboratory was growing coagulase-negative staph, a common urethral colonizer, many times from specimens labeled straight catheter, which she found strange because such specimens are supposed to be basically sterile and they had this contaminant at very high levels.

She helped assemble a team including pathologists, lab management, clinical nurse specialists, staff nurses, performance improvement, informatics, and clinical support services, for a two-year process. "Many nurses didn't realize it was important to label correctly because we work it up differently based on how the specimen is collected and where it's from."

The IT department helped the team collect data, and that led to a realization that nurses were doing suboptimal urine specimen collection. "The problem was that on the floors and in the ER, they were using the wrong collection kit. Called 'Quick Cath,' it collects the first 10 mL of urine, and was not approved for collecting for urine culture, which requires a mid-void to prevent the urethral bacteria from contaminating the

specimen." This was not only happening at Methodist but at other hospitals locally and across the country, and it was partly because the company had no label for use on the product, which allowed its inappropriate use for urinalysis and urine culture, Dr. Cornish says.

The nursing solution was to replace the Quick Cath with the proper culture collection kit, one that is labeled for use in urine cultures and happens to be cheaper. So there were cost savings and, in addition, after the switch was made, she discovered the number of laboratory workups of coag-negative staph in urine found in significant numbers decreased by 250 per year. "We saved $35,000 in the laboratory by that simple change." Added to that was the savings from not treating 250 patients with antibiotics: about $750,000. "It may look like a small thing, but when you add it up, it's a huge amount of money."

Implementing guidelines for urine transport to the lab was another project Dr. Cornish's lab undertook. Because bacteria multiply quickly when urine is at room temperature, urine specimens must be kept cold, but many were sitting for more than 20 minutes before being sent to the laboratory. "Many nurses didn't realize that if a specimen sits for two hours at room temperature, it will look like the patient has a urinary tract infection." As a result of considerable group discussion and brainstorming by nurses, a new magnet is now posted at each pneumatic tube station with a reminder to send urine specimens within 15 minutes of collection. In addition, the nursing educators asked the laboratory to reject urines and request re-collection if received past the 15-minute deadline, to document this, and to keep track of the data. "This provides a continuous feedback loop so the process does not fall apart," Dr. Cornish says.

Since the 1970s, there have been notable expert guidelines on blood cultures, including the ASM's regularly updated Cumitech series and the Clinical Laboratory and Standards Institute's "Principles and Procedures for Blood Cultures" in 2007, says Melvin P. Weinstein, MD, another ASM panelist who is professor of medicine and pathology and laboratory medicine, and chief of the Divisions of Infectious Diseases and Microbiology, Robert Wood Johnson University Hospital, New Brunswick, NJ. But the value of these documents has been limited because, despite being referenced extensively, they do not provide a ranking system to indicate the strength of the recommendation (A, B, C) or the quality of the evidence in support (I, II, III).

Microbiologists have hoped that the IDSA's work on clinical practice guidelines would go beyond blood cultures to provide guidance on appropriate and optimal use of the microbiology laboratory for diagnosis of infectious diseases. "That initiative started in the early '90s and it's had a lot of difficulty being brought across the finish line," Dr. Weinstein says.

Everyone can agree on the goal of more rigorous, evidence-based guidelines, he says, but trying to get funding to do good head-to-head comparisons is difficult, as is choosing the best subjects or variables to study. "As an article in the *British Medical Journal* once asked, would anybody ever do a controlled, randomized trial of jumping out of an airplane with a parachute versus without a parachute? There are some things that you just know. So nobody would do a study of surface contamination of the skin, for example, but you certainly could do a study of tincture of iodine versus chlorhexidine gluconate to determine whether one is better than the other for skin decontamination."

There is increasingly high-quality, category I evidence for certain practice guidelines in blood cultures, he says. For instance, "several studies have demonstrated that as you increase the volume of blood you culture, you also increase the relative yield from that culture." In the past, when microbiologists did quantitative cultures, "they would actually take a blood sample and inoculate it onto a molten agar plate, then count the number of colonies that grew. And they found that there may be as few as one bacterial cell in 10 or 20 mLs of blood."

"That means that if you only culture 2 mLs of blood or 5 mLs of blood, the chances the cells will be in that volume of blood and will multiply over a one- or two-day incubation period to the point where you can detect the infection are much smaller than if you culture a 20- or 30-mL sample of blood."

There are both technical and clinical reasons for getting more than one sample from a patient to do a blood culture, Dr. Weinstein points out. "If you obtain a single venipuncture, and that is positive and grows an organism, how do you know that that organism represents a real infection as opposed to skin contamination? We know that most hospitals have contamination rates for blood cultures of about three percent. So if we get a sample from both the left antecubital vein and the right antecubital vein, we have two independent probabilities of three percent. That means that if you do culture both samples and get the same organism, there is less than a one in 1,000 chance that it's skin contamination."

On the other hand, surveys of the available data have also upset traditional ideas about blood cultures, such as the belief that to detect certain fastidious organisms you need to incubate the blood culture for periods longer than five days, Dr. Weinstein says. In fact, if an organism hasn't grown after five days, extending the incubation period does not help. "You need to use other techniques that may detect these organisms."

A balance has to be struck as laboratory medicine employs more clinical practice guidelines, Dr. Weinstein believes. "My concern is, are guidelines just guidelines, or do the guidelines become mandates? Do they become law? Do we say everybody must do something in every circumstance or there will be penalties? There has to be some room and some latitude for physicians to continue to exercise clinical judgment. On the other side, the big issue is always compliance: How do you get the information out there and get physicians to see what the guidelines are and what the rationales for them are?"

Compliance, in fact, is centrally important in evaluating guidelines, Dr. Gilligan of UNC points out. "CDC has published data that really show there has been good compliance with the Group B Strep guideline, and they've also shown there has been continuous reduction in the number of early-onset GBS infections. It's very important that guidelines make very clear what the practice issues should be and present the data to support those practices."

The outcomes of the 2002 GBS guidelines showed dramatic improvements. The rate of screening rose from 48 percent in 1998–1999 to 85 percent in 2003–2004. Eighty-seven percent of GBS-colonized women received prophylaxis, and the number of early-onset cases fell from 1.7 per 1,000 live births in 1993 (an estimated 6,630 cases nationwide) to .32 per 1,000 live births in 2003–2004 (an estimated 1,312 cases nationwide).

Another attribute of well-executed clinical guidelines is "that they address shortcomings of prior guidelines and are updated at least every five years based on current scientific evidence," Dr. Gilligan notes. The modified GBS guideline scheduled for publication later this year has significant laboratory components, he says, including the option for self-collected vaginorectal swabs, clarification about the recommendation for urine culture, the added ability to report positive chromogenic agars and broths as positive, and the option to perform nucleic acid testing, which can be done reliably from enrichment broth culture.

When the University of North Carolina Hospitals had the opportunity to implement universal HIV testing guidelines set by the CDC in 2006, he says, preanalytic and postanalytic barriers had to be overcome, but the results were positive. "At that time, there were two factors that were recognized in central North Carolina: Certain 'sexual networks' had high rates of acute HIV infections, and HIV testing was done only infrequently in our ED because of barriers to testing."

The preanalytic barrier was that by North Carolina public health rules, informed consent and pretest counseling were required before HIV testing. Postanalytically, "the ED wanted nothing to do with followup of HIV testing, nor did they want to get positive patients into care."

The pretest counseling requirement was burdensome, he says. "I don't think anyone should have any lab test where they're not told they're having the test, but the idea that you have to have a prolonged 15- to 20-minute session explaining all the whys and wherefores of HIV testing, that's a real barrier, certainly in our institution and I'd be willing to bet at many others."

Having set the goal of making universal testing more viable in the ED for individuals who fit the profile of those likely to have acute HIV, "in spring 2007 we went to the HIV branch of the state department of health and asked to get the public health rules changed to reflect the new CDC guidelines." The state agreed, and the key change was eliminating separate written consent for HIV testing. By January 2008, opting out of HIV testing became part of the hospitals' general consent to treat, with immediate results: HIV testing in the ED increased 170 percent during the program's first year.

The solution to the postanalytic problem was finding a way to address the ED physicians' needs and patients' needs at the same time, he says. "The ED is seeing a gigantic variety of people, and they need to move patients through the system as quickly as possible. So one of the big concerns the ED doctors have is when their shift is over, they want everything resolved. With HIV testing, that result might not be known for a week, then they have to follow up, and that's not part of their culture."

So the hospital compromised with a handoff between the ED and the infectious disease clinics. "We agreed that all HIV testing results would be handled by the ID clinics, and that has worked quite well. Patients are given a phone number and can find out the result by calling. If they are HIV-positive, then the people in the ID clinics get them into HIV care."

When the CDC's new universal HIV testing guidelines come out within the next year, Dr. Gilligan would like to see one of the additions be that "if the patient has positive syphilis serology, or perhaps any sexually transmitted infection, and the patient does not have an HIV test documented, there should be a reflex HIV test. I don't participate in the writing of those guidelines, but that seems like common sense."

When Dr. Gilligan recounted this experience at the ASM conference, and asked how many people had general consent for HIV, very few members of the audience raised their hands. "It's sad," he says. "It's been very controversial in our state. People are still really afraid about HIV testing. It's a different world from 1985, but nevertheless there's something about HIV testing that makes people very, very nervous."

The UNC's implementation of the CDC guidelines for shiga toxin-producing *E. coli* (STEC), however, proved to be even more controversial, he says—to the point that UNC Hospitals decided against adopting the guideline. "What CDC was saying was, in patients with acute community-acquired diarrhea, to look at all stools not only for *E. coli* 0157 but also non-0157 STEC organisms."

The big issue is how much it's going to cost to find the few cases of STEC, he says, when there are many fewer cases in the southeastern U.S. than in other parts of the country. "So we'll go ahead and do cultures, and also do shiga toxin detection for non-0157 if there are outbreaks. But just to do them routinely on all stools is something we can't justify from a cost perspective." "You put yourself at a little medicolegal risk by not following the guidelines, but we're pretty comfortable because we have institutional data that we've generated here to explain why we don't, and we also have a pretty low threshold to look for these organisms."

Institutional data, he adds, are "absolutely" part of UNC Hospitals' evidence-based approach to guidelines. "I would say with HIV, because of the long-term care costs of those patients, the cost of a test is very minimal." In a different recent case, cost was a significant factor. "For a year we screened a segment of our patient population using the molecular test for MRSA [methicillin-resistant *Staphylococcus aureus*], and we found the cost of the test was about 10 times what we were using prior to that, and the molecular test had no impact on the rate of MRSA nosocomial infection. So we just dropped it."

By contrast, Dr. Gilligan is optimistic about the recently approved fourth-generation HIV test, Abbott's Ag/Ab Combo assay. "We've been screening all of our patients for acute HIV, which is something done in very few places in the U.S. But in four years I think

we've had four patients who were positive for HIV, and it cost us maybe $50,000 per year. If in each one of those cases we can prevent transmission to one patient, and it costs half a million to take care of an HIV patient over a lifetime, that's a tremendous return on investment. And it's the right thing to do morally, to protect people from getting the disease."

As the country moves toward a more national health care system and trying to figure out more efficient ways of providing care, Dr. Gilligan says, "I think clinical practice guidelines are going to be very important, and we want to make sure the data that is used to promulgate these guidelines is the best data we can get."

In line with that need, Dr. Daniel Amsterdam of the Erie County Medical Center in Buffalo cites the growing role of "electronic textbooks" in helping clinicians convert clinical laboratory data into actionable health care information. "It's something that's interesting and alarming, because so much of what we do is through the Internet now," he says.

DynaMed, for example, is a clinical reference tool used primarily at the point of care, and it claims to be updated daily and to monitor content of more than 500 medical journals. UpToDate responds to inquiries "by laying out all the information, evidence-rating it, and letting the observer or reader make the decision," Dr. Amsterdam says. "Somewhat like a Consumers Union format, it lists different choices and ranks them."

In the UpToDate information service, "they'll have a reviewer and the currency of that review is noted. Usually the reviewer will state, in this condition use drug x, or this condition should lead you to this problem. So it's decided by an expert based on what he knows and a literature review." Dr. Amsterdam was exposed to DynaMed because it was being evaluated at his institution. "I thought it was a very powerful tool." He finds that new house staff frequently ask whether Erie County Medical Center has UpToDate, because they use it as a resource in their daily reports.

He did a side-by-side comparison of results from a query about urinary tract infection, and found more recent references on DynaMed; UpToDate had a citation from the *Journal of Clinical Microbiology*, however, which DynaMed was missing. Whichever tool is preferred, he believes the trend is clear. "I'd like to make the recommendation, or plea, that somehow we automatically intersect laboratory information and link it to clinical data by using these electronic textbooks."

The purpose of the CDC's Laboratory Medicine Best Practices Initiative, which the R&D firm Battelle has been developing under contract to the CDC since 2006, is also to conduct reviews of the literature on best practices, but with a focus on a few key principles, says Paul L. Epner, MEd, MBA, a consultant in Evanston, Ill., who was another panelist in the ASM session.

"First, the systematic review of the evidence is truly systematic. It is comprehensive, the inclusion and exclusion criteria are articulated carefully, and the search terms are transparent. We also grade the literature according to the study design—two independent reviewers score each study by four different categories. So we have a body of evidence graded as good, fair, or poor, and we submit it to expert panels." For example, in a study of methods to reduce blood culture contamination, he says, the Laboratory Medicine Best Practices Initiative started with 1,677 total references and eliminated all but 30.

That study is now being submitted to peer review and its conclusions have not been released. But it looked at the use of dedicated phlebotomists versus nursing care technicians and others to draw blood, the use of venipuncture versus using a line draw like a central line catheter, and the use of commercially prepared collection kits versus homebrew kits. "The work group did find good evidence for several of those practices," he says. "People may intuitively know that phlebotomists get better results, but that by itself does not constitute evidence. In many cases we may determine what others think they already know, but now we have established that it is evidence-based."

Until recently, "In laboratory medicine there have not been a lot of good evidence-based recommendations," Epner says. "I think you'll struggle to find things that go beyond consensus- and expert-panel-based findings."

The gold standard for evidence—the use of placebo-controlled, randomized trials—is difficult to apply in laboratory medicine because the patient-oriented outcomes are difficult to measure. "The trials don't fit the kinds of operational models we have, nor are they required by the regulatory agencies, so the kinds of evidence that other health care fields use is really not available in lab medicine." The LMBP Initiative has tried to find methods that are still rigorous even if they are not randomized controlled trials. But the research landscape is shifting, Epner says, as increased funding for comparative effectiveness research will be part of health care reform. "And over time payers and policymakers will latch onto results, and accreditors like the Joint Commission and presumably CAP will start to say there's evidence, for example, that using bar codes reduces specimen ID errors, and if you don't use them we will write you up. And that's when behavior will really start changing."

Epner says individual hospitals have a role to play here too. "For years now, many hospitals have been doing continuous quality improvement projects and applying tools of Lean and Six Sigma to improve methods. And they can state that for them locally, it is evidence-based. That does not mean it would stand the test of NIH or the Agency for Healthcare Research and Quality scrutiny for national standards. However, with a little additional planning, the locally important study can become suitable as evidence in a systematic review, he says. "In the coming year, LMBP expects to provide training on how to accomplish just that."

In his 31 years at Abbott Laboratories, Epner developed the "Labs Are Vital" program, which brought him into contact with many people who were collecting such locally based but unpublished evidence. As a result, when he started working on the Best Practices Initiative with Battelle, he was able to uncover some of that unpublished literature on good laboratory practices. "I think we were pleased with the amount we found."

The Best Practices Initiative, like all evidence-based medicine, focuses on not accepting the concept of "intuitively obvious." "For years, hormone therapy for postmenopausal women was considered to produce improvement, and there was evidence to support it," Epner points out by way of example. "But that's the problem with small studies or too few studies or studies that aren't well designed, because when you had a large, statistically significant, well-designed study, the evidence contradicted all the anecdotal stuff that had previously been collected."

He believes that clinical practice guidelines development is putting laboratory medicine on the right track. "What we think we know for sure isn't always necessarily proven, as we've seen with hormone therapy. And laboratory medicine in particular seems to suffer from a lack of large, well-controlled studies about what are best practices. But if we engage the profession and upgrade the evidence base of what we do, that will change."

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