Too few studies to steer test protocols for pediatrics

Ann Griswold

August 2014—Are children equivalent to miniature adults? Common sense and years of research on age-related differences in microbiota, immune system development, and infectious disease susceptibility point to a resounding no.

But in clinical microbiology practice, if not in theory, pediatric patients are too often worked up as miniature adults, says Jennifer Dien Bard, PhD, D(ABMM), FCCM, director of the clinical microbiology laboratory and acting director of the clinical virology laboratory at Children's Hospital Los Angeles, and an assistant professor of clinical pathology at the University of Southern California's Keck School of Medicine.

The disparity is far from intentional, she notes. Standardized protocols for microbiological workup, susceptibility testing, and interpretation largely rely on studies performed in adult populations, and evidence-based guidelines for pediatric lab testing are difficult to come by.

"We need more compelling studies and evidence to help us determine whether we should modify a procedure or protocol based on the patient's age, whether it's a neonate versus an infant or toddler," Dr. Dien Bard says. "There is talk of how the clinical microbiology community could put together guidelines and protocols specific to this patient population. But as of now, those talks have been limited."

Three areas of clinical microbiology—blood cultures, urinalysis, and respiratory virus testing—are particularly devoid of information when it comes to pediatric patients. Advances in these areas offer promising opportunities to better serve young patients. But until more research is done, the value of these advances remains uncertain.

The sparse literature devoted to pediatric clinical microbiology practice is hardly a secret, but the implications of this data gap hit home two years ago, when Dr. Dien Bard transitioned from a laboratory that served adults and children to one that serves an exclusively pediatric population.

"With pediatric patients, you're almost more cautious. You might think it behooves you to identify everything that can be recovered from a specimen, even more so because it's a pediatric patient and you're afraid to miss something," she says. "But without studies to support the practices, it is difficult to overcome the traditional cautious approach" that can lead to overtesting.

Dr. Bien Bard

Dr. Dien Bard set out to modify her laboratory's standard operating procedures for pediatric patients to better align with the literature. The problem was, the literature didn't exist. Or parts of it did, but not nearly enough to build the guidelines she argues should exist.

"On many clinical microbiology issues, there's no consensus at all. I think everybody's at a loss as to the best practices for pediatric patients. There's no right field versus left field. We're all just kind of in the middle," Dr. Dien Bard says. "I think the majority of hospitals in the United States are probably in the same boat."

There are exceptions, however. The American Academy of Pediatrics has issued a number of guidelines, such as limiting or rejecting specimens for *Clostridium difficile* testing in patients younger than 12 months. About half of children age two and younger are asymptomatically colonized with *C. difficile*.

“Testing pediatric patients less than 12 months of age just directs physicians down the wrong path, because it might distract them from finding the real cause of a child’s diarrhea,” Dr. Dien Bard says. “Likewise, if you’re screening an adult patient for, say, streptococcal pharyngitis, it’s not recommended to follow up any negative rapid test with culture. But in a pediatric patient, it is recommended that all negative cases be confirmed by culture, as you’re expecting a lower bacterial load that may not be picked up by a rapid test.”

Despite existing guidelines, further studies are needed.

“We need to publish more pediatric-specific, evidence-based guidelines that can be used within either a freestanding children’s hospital or a hospital that caters to both the adult and pediatric populations,” Dr. Dien Bard says. “Because right now, it’s all dependent on who is running the lab and what that person thinks is appropriate.”

Hospitals like Children’s in Los Angeles do offer one major advantage over other institutions: The person running the lab is likely to be adept at serving the institution’s uniform population. Nearly all patients are 18 years or younger, allowing the laboratories to adapt guidelines based on their extensive experience with children, notes Romney Humphries, PhD, D(ABMM), section chief of clinical microbiology at the University of California, Los Angeles, Medical Center, and an assistant professor in the Department of Pathology and Laboratory Medicine at UCLA.

At the American Society for Microbiology annual meeting this spring, Drs. Humphries and Dien Bard debated the pros and cons of adapting various clinical microbiology practices to a pediatric population.

Given the desire to order a gamut of tests in pediatric patients, Dr. Dien Bard says, it’s somewhat paradoxical that phlebotomists and nurses often shy away from collecting the necessary volumes of blood from infants and children.

“If you have a neonate who’s five pounds, you might be afraid to even collect 1 mL of blood,” Dr. Dien Bard says.

That poses a dilemma, considering that the typical blood collection bottle, used for pediatric and adult patients alike at many institutions, requires a minimum sample volume of 10 mL. Insufficient volume can render a sample useless, which is why many children’s hospitals use smaller pediatric collection bottles that require a minimum of 1 mL of blood, and no more than 5 mL.

Should hospitals with heterogeneous populations follow suit? Despite the obvious benefits of using smaller bottles for smaller patients, the answer is complicated.

“If you’re in an institution where you have both adults and pediatrics, it’s challenging to make sure the pediatric groups are the only ones using the pediatric bottles, and the adult groups are the ones using the adult bottles,” Dr. Humphries says.

Providing a second type of collection bottle can create confusion, especially in the emergency department, where there’s no time to debate the pros and cons of various bottle sizes or collection volumes.
Moreover, a literature search turned up scanty evidence of increased bacterial yield from pediatric versus adult collection bottles.

“The perfect blood-to-media ratio should allow for the ultimate recovery of bacteria. But in reality, there are very few data to show that you’re going to get a better yield using a pediatric versus an adult bottle,” says Dr. Humphries, noting that an older study did show improved recovery with pediatric bottles, but the result likely reflected the presence of proprietary yield-boosting resins that were not included in adult bottles at the time of the study.

One of the biggest hurdles, though, may be the amount of training required to introduce the new bottle type. A poll of UCLA nurses revealed the widespread and mistaken belief that the newly introduced pediatric bottles required a sample of 1 cc, regardless of the patient's size.

"They seemed to think there was a magical property about these smaller bottles that would allow us to recover anything under the sun, even if they just put in 1 cc of blood," Dr. Humphries recalls. "That's the wrong message, because for pediatrics, just like for adults, the amount of blood you put in directly impacts your recovery of organisms. If you have a baby, maybe 1 cc of blood is appropriate. But if you have a 16-year-old football player, he can probably give a lot more blood, and he should, to have ultimate [bacterial] recovery."

Setting the record straight requires ongoing education, notes Dr. Dien Bard, who has encountered similar misconceptions at Children's. "Once you educate the nurses and phlebotomists, and blood collection improves, it's inevitably going to decline again. And so you're just going to have to continually educate them about the appropriate volume they need to draw, regardless of whether they use a pediatric bottle or an adult bottle," she says. "We weigh every bottle and follow up with the house staff on any patients who have had less than 1 mL of blood collected."

Given the pros and cons, Dr. Humphries is hesitant to recommend the smaller bottles to hospitals that treat both adults and children, particularly with the vaccination-related decline in traditional pediatric pathogens like *Haemophilus influenzae* and *Streptococcus pneumoniae*.

"Do we really need to go to that effort to ensure that the pediatric patients have their blood drawn in a pediatric bottle? I'd argue that this is not something you need to worry about if you're not already doing it, because the bottles are likely not making that much of a difference," Dr. Humphries says.

Answering these questions could prove tricky. "Obtaining consent from parents to have extra blood collected from a peds patient would not be the easiest thing to do. But I think it would be very valuable to help us answer some of these questions," Dr. Humphries suggests.

strong>Whether laboratories should require a urinalysis before a urine sample is cultured remains a topic of debate, even more so in pediatric patients.

In an informal poll posted for the online ClinMicroNet discussion group, few clinical microbiologists reported that they require a urinalysis before they accept a urine specimen for culture.

"In pediatrics, the historical sentiment was that it didn't matter if the patient had asymptomatic bacteria or a true infection—bacteria in the urine of a pediatric patient was considered important and should be treated," Dr. Humphries notes. "If that were true, it wouldn't be appropriate to do a urinalysis screen before you did a culture. You would just culture everything."

Dr. Humphries

But guidelines from the American Academy of Pediatrics disagree, noting that if a patient's UA is negative, the likelihood of an infection is slim. Indeed, a series of studies performed in the 1970s examined the long-term outcomes of healthy school-age girls with routine urine cultures that were positive and found no differences in

bacterial recurrence, renal growth, reflux, or pyelonephritis in treated versus untreated girls.

“This suggests asymptomatic bacteriuria is something that happens in kids, and just like in adults, it’s not significant and does not need to be treated,” Dr. Humphries says.

Despite the availability of data to support UA as a preliminary step in pediatric patients, the practice has not been adopted widely in the clinical microbiology community. At UCLA, for example, physicians routinely place simultaneous orders for the UA and a urine culture.

“They’d just rather get both results at the same time,” says Dr. Humphries. “The unfortunate problem with that is even if the UA is negative but something grew on the culture, they kind of feel obliged to treat it.”

Instead of ordering both tests simultaneously, Dr. Humphries advocates an algorithmic approach in which the presence of pyuria is incorporated into an initial UA screen, followed later by a urine culture. The algorithm, she argues, could potentially save money and prevent over-reporting of catheter-associated urinary tract infection rates by screening out patients with negative UAs and asymptomatic bacteriuria.

But there is a flip side to every argument, and Dr. Dien Bard notes that a pediatric-adapted algorithm would not be appropriate for all young patients.

“I would argue that it’s appropriate to culture all urine specimens, regardless of the urinalysis result,” says Dr. Dien Bard, whose tertiary care hospital has a large population of oncology patients. “Immunocompromised patients, for example, are not eliciting a sufficient immune response to flag for criteria like white blood cells in the urine.”
Seemingly unremarkable urinalysis results in immunocompromised patients could potentially hide urinary tract infections and place patients at greater risk of serious complications like urosepsis or renal dysfunction, she argues. In such a situation, Dr. Dien Bard does not see a strong reason to stray from adult protocols.

“A pathogen is a pathogen, regardless of how old the patient is,” she says. “The quantity may change. A lower quantity of bacteria may be considered more important in a pediatric patient than it would in an adult patient. But there just aren’t a lot of studies out there right now to support a pediatric protocol.”

In particular, the debate might benefit from studies that examine UA with reflex to culture in hospitalized pediatric patients or studies that explore the parameters of a UA that best reflect a urinary tract infection.

In the past few years, a number of studies have suggested that multiplex respiratory viral panel testing can limit antibiotic use and reduce the duration of hospital stays. But access to viral multiplex panels remains a topic of debate.

“When we talk about algorithms as a means of restricting highly multiplexed respiratory virus testing, the first thing everybody will say is, ‘Oh, but except for pediatrics. You run everything for a peds patient,’” Dr. Humphries says. “There’s not very much literature out there to say one way or another if that’s true.”

Whether reflex testing is warranted in children remains unclear.

“I’d argue that we should allow multiplex testing for any patient—inpatient or outpatient, pediatric or nonpediatric—whenever a physician determines it’s appropriate to order the tests,” Dr. Dien Bard says.
She points to acute respiratory infection—more likely to be viral than bacterial in origin but tricky to evaluate on initial presentation.

“It’s all about limiting antibiotic use,” she says. “Why not give the primary care physician access to multiplex respiratory viral panel testing that can be done within an hour or two, so they can rule out a viral etiology and then possibly give an antimicrobial agent if required?”

Dr. Dien Bard recalls when a colleague’s daughter was diagnosed with respiratory syncytial virus in the primary care physician’s office using a multiplex molecular panel. The test took about an hour, and the young patient was

sent home without a prescription for antibiotics. “That was actually quite amazing, as an alternative to sending the patient home with a script and then following up later to say the antibiotic could be discontinued,” she says.

While the benefits seem clear, the literature remains divided.

“A lot of people will say that you always want to do the full respiratory viral panel for kids, because they could have multiple infections,” Dr. Humphries says. “But there are probably an equal number of studies that say co-infections are associated with worse outcomes versus studies that say there’s no difference in outcomes. So the jury’s still out, if you look at it from an objective perspective.”

In particular, she notes, more data are needed to fully characterize the impacts of respiratory virus panels in outpatient and inpatient settings. “If you’re in the outpatient domain, would a full respiratory virus panel actually help prevent antimicrobial treatment or would it just reveal a better sense of what’s going on with the kid? Does it really make a difference, or should we focus instead on better education to prevent the treatment of viral respiratory infections with antimicrobials?” Dr. Humphries asks.

Data from the Centers for Disease Control and Prevention suggest that the use of antimicrobials in outpatients is significantly high, and Drs. Dien Bard and Humphries suspect that many of the drugs are used to treat pediatric patients who come in with the sniffles. “If we could give physicians a better answer to what’s causing the infection, that would be helpful. But multiplex tests would have to be much cheaper for us to use them in that way,” Dr. Humphries says.

They have a few ideas for further studies.

“Depending on your institution, if you’re not cohorting patients during respiratory virus season, you might be able to do some algorithm testing,” Dr. Humphries says. “You could do a flu A/B and RSV test first, and if that’s negative, move on to the respiratory virus panel.”

Of the three issues—blood cultures, urinalysis, and respiratory virus testing—the most controversial by far is the respiratory virus test, she says. “There’s definitely a camp that wonders why you would withhold information. Why wouldn’t you use that test routinely if it’s ordered, and not restrict it in some way for cost reasons?”

Until further research brings a better understanding of pediatric populations, professional opinions will remain just that.
Says Dr. Dien Bard: “I recommend that anyone in this position look for studies, textbooks, or other material to support what they think are the correct practices. And if the evidence doesn’t exist, that’s when we need to think about carrying out these studies ourselves.”
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