# PCT leads the way in antimicrobial stewardship

## Anne Paxton

August 2019—Antibiotic treatment of sepsis patients often has to rely on clinical observation and educated guesswork as clinicians wait for a culture to determine whether the infection is bacterial, viral, or possibly fungal. But with the FDA's recent approval of automated platforms for procalcitonin assays and mounting evidence of PCT's value as a biomarker, hospital laboratories are turning to PCT to diagnose sepsis and guide antimicrobial stewardship.

[showad block=5]Europe has been 10 or 20 years ahead of the U.S. in adopting PCT to help with antibiotic stewardship, says John Boreyko, PharmD, a clinical infectious disease pharmacist and co-director of the antimicrobial stewardship program at Duke Regional Hospital, Durham, NC. He watched PCT's widening use in Europe to guide antimicrobial therapy in recent years, and in 2014 he wanted his hospital to be an early U.S. adopter of PCT for the same purpose.

It didn't happen overnight. "It took me almost two years to get through the process of filing a business plan and showing that we have enough patients who will benefit from the test." But since early 2016, Duke Regional has been using PCT, and he sees other hospitals making the same move. PCT is still not mainstream but the ball is rolling, Dr. Boreyko says. He estimates that close to 50 percent of hospitals are now using this biomarker in addressing sepsis.

The other two hospitals in the Duke University Health System plan to implement PCT by the end of this year, he says.

"I think PCT testing is growing rapidly because we have so much data out there to support that PCT decreases the antimicrobial burden, yet it doesn't cause any adverse reactions as far as injury or mortality."

One new study points also to cost savings. Published April 23 in *PLOS ONE*, the study used a health economic decision model to compare the costs and effects of PCT-guided care for hospitalized patients with suspected sepsis or lower respiratory tract infection. It found that such care is associated with a reduction in antibiotic days, shorter length of stay on the regular ward and intensive care unit, shorter duration of mechanical ventilation, and fewer patients at risk for antibiotic-resistant or *C. difficile* infection. Total costs of sepsis care for the PCT group compared with standard care were 26 percent lower—$11,311 per patient. For patients with LRT infections, costs were lower by 17.7 percent (Mewes JC, et al. 2019;14[4]:e0214222).

In contrast with the initial PCT studies, which were done in Europe, "I would say probably 75 percent of all PCT studies in the last five years have been either multinational or conducted in the U.S."—a necessary stage for the biomarker to win acceptance here, Dr. Boreyko says. "We need to start doing more studies in the U.S. to see if the European findings are generalizable."

Duke Regional's laboratory uses PCT for sepsis patients, first to establish a baseline and, second, as a way to de-escalate antibiotics in culture-negative patients. "If a patient has a high PCT and high risk of sepsis from a bacterial source at baseline, when we get a second PCT level, based on the half-life, it should be 50 percent below baseline. If it's close to that, we know the antibiotic we're using is correct and we don't have to look for another source of infection. In the third and final test, if it's 80 percent below the baseline, then we know we can start de-escalating or stopping antibiotics and that's a culture-negative patient." If the PCT is negative, "That's just another piece of evidence that the patient is having viral respiratory symptoms and not bacterial."

Caveats apply to this algorithm, of course. For example, "There are patients who have sepsis in addition to lung cancer and if their renal dysfunction is from the sepsis, then they will have a markedly elevated PCT. If you are a dialysis patient or have chronic kidney disease stage three or four, we'd expect your PCT to be elevated even though you won't be infected. The algorithm does not take this into account. We just have to train physicians that

you can get a PCT if you want, but you need to take the value with a grain of salt."

In fact, training of clinicians is crucial and has to be ongoing, he emphasizes. "There's always going to be overuse or misuse of procalcitonin and you just have to continually educate," he says. "When we did our education, we let clinicians know what the limitations were and that PCT should be drawn only in certain populations. For the most part they do pretty well, but they may need reminding that sometimes they shouldn't have ordered PCT because we can't assess it."

As clinicians gain more experience, Dr. Boreyko believes they will come to trust the test as fully as he does. "You're only going to trust the test by seeing scores of patients and understanding that there were no adverse reactions based on using the test to make clinical decisions. But you need to see for yourself."

Dr.Boreyko

His hospital tracks antibiotic consumption to make sure it is at the same level or declining. However, "It's too early to say," he says, whether antibiotic use is dropping in the ICU at his hospital. "It's sort of hard to prove you can reduce length of stay, use less antibiotics, or extubate the patient earlier" by introducing a test like PCT, "because most patients have some other comorbidity that's causing them to be in the ICU." And a significant number of patients are lost to follow-up.

Within a couple of years, he expects that "at least for lower respiratory tract infections, we will have at least 500 patients we can use to compare two cohorts that are following a PCT guideline." An early "snapshot" study of admissions to the ER for LRT infection at his hospital already suggests the effect of PCT might be dramatic. Before adoption of PCT, 550 LRT infection patients had a 30-day same-cause rate of readmission to the ER of 5.4 percent. He compared those patients with the LRT infection patients admitted in the first year of the hospital's use of PCT for LRT infection.

"After PCT was implemented, the same 30-day rate of re-presentation to the emergency room or same-cause readmission dropped to 0.4 percent—approximately a 92 percent decrease" in that measure alone. He doesn't predict that a repeat study will have such striking results. In reality, "It's probably closer to a 50 to 70 percent reduction, but that's still a significant difference."

Dr. Boreyko hopes that, by 2020, PCT use will be even more mainstream and available not only in hospitals but also in large clinics and physician offices, where potentially unnecessary antibiotics might first be prescribed for a patient.

But he is not of the view that PCT is playing an increasingly central role in ameliorating sepsis. "Not at all," he says. "All we're doing is hopefully identifying if the patient is septic and decreasing antibiotic use in a culture-negative patient. The main benefit of PCT is conservation of antibiotic use, which we hope is going to reduce resistant organisms that could potentially cause you to have repeat sepsis down the road."

The UC Davis Health laboratory implemented PCT in December 2014, after years of waiting for it to become available on an automated platform, says Nam Tran, PhD, associate professor of clinical chemistry, special chemistry, toxicology, and point-of-care testing at UC Davis Health, which has the largest level one trauma center north of San Francisco. UC Davis previously offered only same-day results because of the available platform but immediately "jumped to the Roche instrument once it became FDA approved to enable stat testing," he says.

UC Davis was such an early adopter of the use of PCT for sepsis recognition and antibiotic de-escalation that most

of the algorithms for the application at the time were theoretical rather than tested. “They were performed in nicely controlled studies, but pragmatic studies were quite limited,” Dr. Tran says.

In the U.S., sepsis is present in more than half of hospital deaths, Dr. Tran says, though sepsis may not be the primary diagnosis. “Sepsis can be caught up front in the ER, but there is still a good number of cases where sepsis was not present at admission and diagnosed later.” At UC Davis, there is a sizable high-risk patient population, including cancer, transplant, and burn patients. “Our burn patients are unique in that regard, since your skin is your primary barrier against the world—without it, your infection risk increases dramatically.”

Burn patients have a higher proportion of fungal infections than the average, which is roughly 10 percent of sepsis cases; however, some studies suggest even higher numbers approaching 25 percent, Dr. Tran notes. Although PCT is not a test for fungi, “If the PCT is low or negative and you still suspect some foreign infection and one possibility is fungi, the negative PCT could lead doctors to realize maybe they should do a fungal culture, for example.” But making such decisions still depends on the skill and experience of the doctors, he adds.

It’s not too early to draw conclusions about the impact of PCT on his laboratory and clinical care at Davis, Dr. Tran says. “We’ve been using PCT for a while. We are seeing trends in decreased antibiotic use, and we are also seeing folks moderate their use of certain molecular tests based on PCT results.”

“We are slowly optimizing algorithms and workflows as physicians get used to a structured PCT testing process,” he continues. “One of the most important things in PCT or any test like this is not just how good a biomarker it is, but how well you educate the staff and implement it. If you have only half your hospital using the guidelines for the test, you are at best 50 percent successful and more likely just a complete failure.”

Dr. Tran recommends engaging the education mission on multiple fronts. “The key is to identify champions in key services like the ED and the ICUs. We did the usual emails, flyers, and blogs, including a Web blog that is publicly available. We even had information posted on Facebook to aid in disseminating best lab test practices. Then we showed up at hospital committee meetings and had our champions continually push these ideas within their respective services. After implementation, we come back and check to see how we are doing, see our weak points, then re-engage, addressing those weak points to perpetually keep the message going.”

The next phase will be a move to full electronic decision support with PCT along with a prediction tool inside the electronic health record to push it even further, he says. “We are going from word-of-mouth education to paper-based algorithmic approaches to, now, electronic implementation with sophisticated prediction tools and beyond. That has been our effort for the last couple of years for many diagnostics, not just PCT.”

Intrapatient variability can bring problems when it comes to interpreting PCT results, he says. “The good news is with the algorithms to de-escalate, we are looking at a percent change relative to the initial value for each patient. So the variability is more or less controlled for by testing serially in a patient.” With that said, “We all know patients are all different.” For example, studies have shown that burn patients’ baseline PCT is higher than that of a normal person; the value would be considered abnormal in a non-burn patient, he points out.

Dr. Tran

For what PCT is used for today, the variability is acceptable, in his view. “As it gets better, we will find out we are missing some part of the big picture, just as with cardiac troponin. As that test became more sensitive, we realized there is a lot of variability; the biomarker is leaking into our bloodstream under different health conditions. Does that mean anything? We don’t fully know—it has brought up new questions today. That is the process of science.”

Automation is key to making PCT testing succeed, Dr. Tran says, adding that smaller hospitals that feel they can't afford an automated system should consider the high value of PCT testing. "PCT has been hypothesized to save half a day to a day, on average, from a hospital stay in the ICU, which the literature says costs $4,000 to $8,000 a day on average. You only have to save a day or a couple of days to pay off an analyzer—and most importantly, improve the quality of care."

"For a small hospital to get an immunoassay analyzer that can do PCT and other high impact things like high-sensitivity troponin . . . we can make a case several times over as to how it would help." And, he says, small hospitals should definitely keep treating sepsis patients. "Every hour delay in appropriately treating severe sepsis increases the odds of nonsurvival by around 7.6 percent. The faster you treat, the more likely they will survive or do better over time."

Sepsis is so complex that finding the best new drugs or new ways to detect it remains challenging, Dr. Tran says. And biomarkers like PCT have been implemented, in some institutions, less than perfectly, which can lead to an inadequate response for patients, "making some clinicians even wrongly think PCT is a poor biomarker."

Dr. Tran has seen both overuse and underuse of PCT. "Some of the misuse of PCT early on was the frequency of ordering. Some clinicians started trending it every two or three hours. We quickly re-educated them to test once a day based on the half-life and imprecision of the assay, which is also now the practice for antimicrobial stewardship de-escalation."

Not ordering procalcitonin when it's called for can also be a problem. "Some folks may not trust or understand it yet, so there's some resistance, plus there are those who have 'bought into' papers that suggest PCT performed poorly, but without reading the whole paper where it showed the PCT implementation was poor."

Some clinicians also sometimes forget PCT is there, Dr. Tran adds. "We had some cases in the past where clinicians suspected an iatrogenic cause of sepsis. Some argued it couldn't be the device and must have been an occult bacteremia that was missed prior to the surgery. However, my group was looped in and we recommended running PCT on residual samples pre- and post-surgery. The pre-surgical PCT levels were near the lower detection limit—very normal—which indicated the patient did not have bacterial sepsis or inflammatory process. Of course the post-surgical PCT levels were sky-high."

Improving sepsis treatment is the  main goal of Berkshire Health Systems' move to a PCT test, says Kari L. Murad, PhD, clinical chemistry supervisor at the 300-bed community hospital in Pittsfield, Mass., who recently completed her laboratory's validation of Thermo Fisher's Brahms assay on the DiaSorin Liaison platform.

"The decision to go with a PCT test was in direct consultation with our infectious disease doctors who were interested in bringing this in-house for use in our inpatient setting, as an additional tool in the toolbox for the diagnosis of sepsis." But antibiotic stewardship was perhaps even more of a driving force, she says.

To prepare the staff, they have had five different educational sessions with ER physicians, the pharmacy department, hospitalists, pulmonologists, and the laboratory department about how to use PCT. "Every floor or department is going to use it differently whether they are in the ED setting, a step-down unit, or the general population. Some of the doctors and practitioners who are more involved in long-term assessment of patients are very interested in the test for any potential to shorten the duration of antibiotics and discontinue their use when appropriate," Dr. Murad says.

The Liaison runs about 10 assays including PCT and much of the laboratory's infectious disease serology. So far, only a handful of PCT tests directly related to sepsis have been performed, she says, and the majority of the results have been in the normal range. So it's too soon to assess the test's impact. "The couple of patients who had a high PCT value and were diagnosed with sepsis were certainly placed on antibiotics, and we'll be following up later on the outcomes for those patients."

Dr. Murad

The test is not yet available stat because the laboratory at Berkshire, a small community hospital, lacks the staff to run 24/7. “We’re hoping to get to the point of being able to offer this around the clock,” Dr. Murad says. For now, “If you draw a sample at midnight and store it correctly to be run at 7 AM, you’re going to have a good indicator at that moment of the person’s PCT level. The doctors are not waiting for this particular test to decide whether or not to treat; they are basing the initial decision of antibiotic use within the complete clinical context.”

“Where PCT will help is when subsequent serum samples are collected from the patient either 24 or 48 hours later and compared to that initial PCT value. That’s when the real strength of this assay comes out. You can see whether you are treating a bacterial infection appropriately and whether the treatment is effective. If the PCT was never high, you can likely rule out a systemic bacterial infection.”

Dr. Murad believes PCT testing is going to be a valued part of sepsis diagnosis and treatment. “It’s never going to be the only marker, obviously, but it does have a strong predictive value, especially when you’re trying to discern the etiology of disease, whether it’s bacterial or viral, and also the appropriateness of the antibiotics that person is placed on.”

When Joshua Hayden, PhD, moved from NewYork-Presbyterian/Weill Cornell Medical Center in New York City last year to become chief of chemistry at Norton Healthcare in Louisville, Ky., the transition to new instrumentation for PCT testing proved trickier than he expected.

At Cornell, Dr. Hayden says, “we had brought in the Roche e411 in large part to perform 24/7 PCT testing. We had switched from the BioMérieux Vidas Brahms, which was run in a batch mode, where we would do testing at defined times throughout the day. Since I have come to Norton, our primary chemistry immunoassay vendor is Ortho Clinical Diagnostics and they don’t currently have an FDA-approved PCT test. So there is a sort of cart-and-horse issue where the test is not as readily available and so it isn’t frequently ordered.”

“But there are growing requests for the PCT test, so we have brought in PCT at one of our sites, which has Abbott Architects. Then just recently at another site we wanted faster turnaround time, and there we are using the Vidas assay.” Dr. Hayden considers it suboptimal to have two different methods, given the lack of harmonization between them (Chambliss AB, Hayden J, Colby JM. *Clin Chem Lab Med.* 2019;57[9]:1414–1421). “I would like to be able to offer this test on existing platforms 24/7, but that is just not an option right now.”

Dr. Hayden

Standardization at Norton is still a priority, he says. The health system is in the midst of evaluating new chemistry platforms. “Our decision is for me to address the PCT issue when we look globally at what new generation of chemistry IA instruments is most appropriate for our health system. PCT will be one of many factors.”

Nevertheless, he says, there is a growing recognition of the need to standardize how to recognize and respond to sepsis. At Norton as well as other health systems, “We are actively moving to make order sets for suspected

sepsis, so that labs are drawn and treatment courses are started when they suspect sepsis and practices are solidified. The order sets include PCT as well as more traditional testing such as CBC." He is hopeful that standards like these will bring improvements in overall survival of sepsis patients.

"PCT is not troponin; it doesn't necessarily have the same diagnostic efficiency. But if your choices are to evaluate a patient just based on clinical assessment or based on clinical assessment plus PCT, I do believe we can see an improvement in recognition and correct decision-making."

The proliferation of platforms has made it much more feasible for labs to offer the testing, Dr. Hayden notes. "The cost has decreased as competition has entered into this, and labs have seen the price to offer PCT going down substantially."

From a laboratory standpoint, he says, it's important to remember that not all PCT assays that have become available have claims for antibiotic stewardship. "You do need to be aware that if your vendor doesn't have claims for antibiotic stewardship, then it would be an off-label use." Beyond that, he says, "You absolutely must have a physician-led protocol for how to do antibiotic stewardship. It should be coming from your antimicrobial stewardship committee so that subject matter experts are making recommendations."

Unfortunately, many health systems are struggling with compliance with the PCT algorithms, Dr. Hayden says. "If you look at compliance to recommended algorithms, it hovers around 50 percent" because, in general, "physicians are very reluctant to de-escalate antimicrobial therapy based on lab tests."

The biggest misuse of PCT that he sees is "nonuse"—not integrating the PCT results into the patient's care path. "This is a challenging one, because providers need to treat the patient and not the lab result." There are times that the care plan should be different from what one single lab test suggests, he says. "Still, ordering PCT and not knowing how to integrate the results into the assessment of the patient is at best a waste of resources—the expense of PCT—and at worst a lost opportunity to optimize the care the patient receives."

Dr. Tran of UC Davis says education remains the cornerstone for the success of PCT and any other test. "The literature is pretty consistent that education is critical for successful implementation. Despite PCT being available for ages now, it is still 'new' in the minds of clinicians, especially those who don't deal with the management of sepsis day in and day out."

Dr. Tran is a believer in and practitioner of implementation science, which is integral to PCT testing's success, he says. "There are not a lot of implementation scientists. I am one; my colleague is one. It just happens at Davis that we have a laboratory and an ED person who are passionate about proper new test and workflow implementation, and that is why we have been successful. How we execute this algorithm and this biomarker is the key to success. That is really what is needed these days."

*Anne Paxton is a writer and attorney in Seattle.*