Navigating the quandaries of coagulation testing

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January 2019—Naming the things about coagulation testing that most perplex clinicians isn't easy for Michael Laposata, MD, PhD. But there's a good reason for that: He finds confusion to be pervasive. New drugs with untoward effects on traditional coagulation tests, revamped clinical guidelines, and assays that can be difficult to interpret have been among the more recent contributors to clinicians' bewilderment. Dr. Laposata, however, sees a more basic problem: "All of coagulation testing is confusing for the average physician in all specialties."

It's been that way for some time, says Dr. Laposata, chairman of the pathology department at the University of Texas Medical Branch at Galveston—and he should know. He's been a faculty member at different institutions since 1985, but even earlier, on his first encounter with clinicians as a resident, he saw there was a knowledge gap. "I realized that the doctors on the floor didn't know how to interpret even the simplest coag test result—even the brightest doctors. To me, that was a shock." He found they needed to know not only which test to order but also what the results meant and what the recommended next steps would be.

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But saying "Here is what I recommend for the next step" was stepping out of bounds for pathology, he says. "Historically, what we did [in clinical pathology] was generate results and give them back to doctors and hope they knew what to do."

Coagulation testing could use an interpretive approach, he thought at the time, similar to that used by anatomic pathologists for breast biopsies, for example. When he tried it at his first faculty job, the results were not what he expected. "We would provide a patient-specific, expert-driven interpretation of the lab data. We did this for several months and it was so well received that I was told to stop it. They told me we were giving the doctors the diagnosis too quickly and it meant fewer consults and less revenue."

The reaction at Massachusetts General Hospital, where he became the first division chief of clinical pathology, was different. "I said we were going to interpret every single coag test panel that is more than the simplest test and say what it means and what you're going to do next. We started doing that in 1995, and it was a big hit."

From then until 2008, Dr. Laposata gave more than 100 talks about providing advice for coagulation test results, a process that evolved into what is known as a diagnostic management team, or DMT. His colleagues over time and at more than one institution expanded the teams to other areas. All are modeled on the original DMT in coagulation; that was the "primordial cell," Dr. Laposata says.

The purpose of the coagulation DMT is "ending the problem of ordering 20 tests when you need five, or ordering just one when you need the other four," he says. "As coag specialists, we help doctors get the right tests. Our requisitions say things like 'Evaluate my prolonged PTT'—they don't have to pick any tests, we pick them—or 'Evaluate my patient with a blood clot.'" By doing this in coagulation, "We can stop the process whereby doctors are given bits of information and cannot explain it to their patients, through no fault of their own," he emphasizes. "It's not because they don't study or were poor students. It's just because those small bits of information about coagulation have multiplied by the hundreds."

For example, "Back in 2013 we didn't have as many blood thinners, and they were a source of serious medical errors that could cost you your life. Now we have a half-dozen anticoagulants that are in common use, and at least as many that affect platelets." But choosing the right drug is crucial to preventing adverse outcomes.

Dr. Laposata

His diagnostic management team for coagulation provides recommendations on how to avoid such outcomes for specific patients. With support from the Centers for Disease Control and Prevention, Dr. Laposata spent two years with Marisa Marques, MD, of the University of Alabama at Birmingham, writing a software application called "Anticoagulation Manager" that steers users through the pertinent questions (for example, What does your patient have? Is your patient over 18? Is urinary function impaired?), gives options for drugs, and then provides the exact dose to be prescribed. "We built dozens of algorithms for use of anticoagulants in different settings to create the app," he says, noting it has been downloaded by several thousand users. (The Anticoagulation Manager is available free for IOS mobile download from Apple's App Store.)

"The application is constantly changing because now we have new drugs appearing that are either blood thinners or reversal agents of blood thinners, and the reversal agents are very expensive. For example, the most recent reversal agent of the drugs Eliquis or Xarelto usually costs $10,000 or more for a single dose. So if someone doesn't know what they're doing, you've wasted $10,000."

One source of clinicians' confusion in coagulation are the American College of Physicians' clinical guidelines for ruling out pulmonary embolism with D-dimer testing. The guidelines set new age-adjusted D-dimer cutoffs, but they are not widely known.

"I came back from a flight from Paris to Houston with a swollen right leg and normal left leg, and I was worried I had a blood clot. When the doctor looked at my D-dimer test, she said the result was elevated, and I said no, it's not, because I am 66 years old. She asked, 'Does that matter?' I said yes and showed her the calculation. She said, 'I had no idea. Therefore, we have people in here who are 80 and they have a much different range.'" That was one indication to him that as of yet, the age-adjusted cutoffs are not commonly understood, he says.

But perhaps the most vivid example of how confusing coagulation can be is heparin-induced thrombocytopenia, or HIT, an adverse drug reaction that can occur with heparin. "With this allergy, your platelet count decreases," Dr. Laposata explains. "You would expect, since you need platelets to form blood clots, that you would have a bleeding problem. But in HIT, as platelets decrease in number, they get more activated. So you have to give the patient a blood thinner even though the platelet count is low. It is counterintuitive."

Deciding whether the low platelet count is because of an allergy to heparin is difficult, he notes. "There are at least four or five other reasonable diagnoses for many patients about why their platelet count is low. And the first consequence of calling it HIT and treating it is that we take away heparin because you're allergic to it, and we give you a drug that costs $1,000 a bottle and we have to give that drug every six hours."

Unfortunately, administering that drug makes it easier to develop a bleeding complication. ELISA testing to detect who has HIT has improved, Dr. Laposata says. "But it still is not definitive enough. The confirmatory test, serotonin release assay, is much better but is performed at only a limited number of labs. So you have to send it off and wait up to three days for an answer. If you are spending all this money thinking it is an allergy to heparin, you're giving this drug that could cause much more bleeding, and then three days later you find out the confirmatory test was negative and the ELISA was a false-positive—then you say, gosh, I don't want to do that again."

Direct oral anticoagulants have swiftly become a linchpin of anticoagulant therapy. They are being used more often because they have fewer associated side effects than warfarin and are easier to use, says Dorothy M. Adcock, MD, chief medical officer of LabCorp Diagnostics. "More than 40 percent of all anticoagulant prescriptions in the U.S. are DOACs, and that is a pretty significant increase over the past five years," she points out. In fact,

since DOACs reduce a common danger of warfarin—the risk of serious bleeding and particularly intracranial bleeding—"individuals who previously were not put on anticoagulants are being anticoagulated because of these new drugs."

An important benefit of DOACs is that they eliminate the need for routine laboratory monitoring, Dr. Adcock notes. This probably means there will be a decrease over time in prothrombin time testing because fewer patients will be prescribed warfarin, though to date LabCorp has not seen a significant impact on traditional PT/INR testing.

But DOACs pose a potential patient safety issue because in their presence, APTT and PT assays are often not reliable indicators of a patient's level of anticoagulation. DOACs can also interfere with special coagulation testing, for example with lupus anticoagulant testing, where DOACs can cause false-positive results, and some thrombophilia testing, which can be falsely negative.

Dr. Adcock

"When a patient is on warfarin, you can order a PT/INR and that correlates with the level of anticoagulation, plus the patient has been getting PT/INRs typically on a regular basis," Dr. Adcock says. "Furthermore, a patient on a DOAC can be fully anticoagulated and have a normal APTT and PT result, which can be confusing to clinicians. If a patient is unconscious and you don't know their drug history, you can't just run these coagulation tests at the point of care or in the lab and let a normal PT/INR and APTT assure you that these drugs are not present."

LabCorp is proactive in addressing the potential confusion regarding DOAC impact when providing results of special coagulation assays. For example, in the interpretation it provides with lupus anticoagulation results, "When we suspect a DOAC is present and the result is positive, we state that the positive result could be DOAC interference. A false-positive lupus anticoagulation result may result in a patient mistakenly receiving long-term anticoagulant therapy."
The most common question Dr. Adcock receives is: How can the laboratory determine if a DOAC is present in an emergency situation such as when a patient requires a surgical intervention or thrombolytic surgery due to a stroke, or if a specific reversal agent is being considered to reverse the effect of the DOAC in a situation of bleeding? "Hospitals that serve as stroke centers have reached out to me about what they should do in cases like these, realizing that you can't rely on a PT and an APTT to determine if the patient is anticoagulated nor their level of anticoagulation."

Clinicians in these hospitals have questions about what to do in an emergency situation because they can't rely on what they have been accustomed to for many years, Dr. Adcock says. "We do have a test, the thrombin time test, although not all labs have it up, that is a very sensitive assay for the presence of dabigatran and would determine its presence, but dabigatran is not used very often anymore."

The other assay to consider for determining the qualitative presence of a DOAC is a chromogenic anti-factor Xa assay calibrated with heparin or low-molecular-weight heparin, she adds. However, using this assay to determine the presence of an Xa inhibitor DOAC is problematic because it is an off-label use. "When the result of a chromogenic anti-FXa assay calibrated with heparin, low-molecular-weight heparin, or a hybrid of both, is below the assay's lower limit of detection, this would suggest that an Xa inhibitor DOAC, if present, is at a concentration of less than about 30 ng/mL." Quantitation of the DOAC would require an FXa assay calibrated with the specific DOAC in question, Dr. Adcock says, and all DOAC calibrators are labeled by the FDA for research use only at this time.

“The FDA has not approved the use of laboratory assays to measure DOAC levels in part because the drugs went through FDA approval without the need for these assays,” she says. “The drugs have wide therapeutic windows and predictable pharmacokinetics, and for the routine patient, therapeutic monitoring is not necessary. And yet we find situations where doctors want to know: Is a DOAC present in the patient’s plasma in a significant concentration?” While clinicians know quantitative assays are not generally readily available, “I don’t think they are always aware of the alternative assays that can be used to determine DOAC presence in the emergent situation.”

Clinicians may not understand that the impact of DOACs on special coagulation assays might be outside their bailiwick. “There is a concern that if you administer an anticoagulant like a DOAC that doesn’t require routine monitoring, then the clinician may think, ‘Oh, it doesn’t impact lab assays. I don’t have to worry about ordering factor activity assays, thrombophilia assays, or lupus anticoagulants.’ But the savvy or experienced doctor may have an inclination and reach out to us. It is the clinician who doesn’t reach out to us that we worry about. That’s why we provide interpretations for many of our special coagulation assays and for all of the lupus anticoagulant profiles.”

A second common source of coagulation-related questions is around the interpretation of testing for von Willebrand disease, the most common hereditary bleeding disorder, which leads to such symptoms as increased menstrual bleeding in women, nose bleeds, easy bruising, and increased bleeding with trauma. “The levels of von Willebrand factor and factor VIII can elevate with stress or in response to estrogen as well as increasing age. Levels can decrease with blood group O and there is a common genetic polymorphism that interferes with the von Willebrand ristocetin cofactor activity assay, leading to a falsely low result,” Dr. Adcock explains.

The assay is ordered frequently, she notes, estimating that LabCorp runs about 10,000 von Willebrand disease tests a month. Not only are there common situations that can alter the von Willebrand assay results but also result interpretation is complex, since von Willebrand disease has three major types and multiple subtypes. Therefore, there is a lot for clinicians to know about making the diagnosis based on laboratory results. For that reason, “we provide an interpretation with our von Willebrand disease panel that is based on complex algorithms.”

When dabigatran came on the market as the first anticoagulant other than warfarin that could be swallowed, “It really opened the floodgates,” Dr. Laposata says. Pharmaceutical companies soon developed an array of other DOACs. “Of course it is a huge patient advantage to not have to come in once a month or more often to be tested if you are on warfarin.”

Putting aside the purchase price of reversal agents for DOACs, he says, “If you look at all the patients on warfarin and look at the worst consequence, bleeding inside the brain, warfarin is much more expensive than all the other DOACs. And that, in my estimation, is the biggest reason to try to use one of the newer DOACs—because the intracerebral bleed has such huge consequences.”

However, $40 a month for a prescription for DOACs like Eliquis (apixaban) or Xarelto (rivaroxaban) can be a deal breaker for some patients, and many stay with warfarin, which costs only about $3 a month, for that reason. “We have a number of patients who are taking warfarin instead of a DOAC because of the money.” But they are not taking other expenses into account,

Dr. Laposata points out. “What they don’t quite realize is they are also stuck getting their blood monitored, their diet may change the impact of warfarin, or they are stuck without a medicine they need because they have a cold and it changes the impact of warfarin.”

At ARUP Laboratories in Salt Lake City, a clear trend has been observed to switch patients from warfarin to the DOAC class of drugs, says Kristi J. Smock, MD, medical director of the hemostasis/thrombosis laboratory and associate professor, Department of Pathology, University of Utah. In the process, clinicians have gone from the high comfort level they had with warfarin to “quite a bit of confusion about this new drug class.”

While many patients have been managed fairly straightforwardly on warfarin and consistently achieve therapeutic

INR without a lot of problems, “there is definitely a subset of patients for whom warfarin is a suboptimal therapy because they are hard to keep in the therapeutic range,” she notes.

For these patients, DOACs might be the right answer. “But many people are surprised to learn there can be strong interferences from the drugs in some of the widely used coag tests that can generate an unreliable or erroneous result.” While there is no need for routine laboratory monitoring of those drugs, “there are some circumstances where you would like to measure the presence of the drugs, and there are ways that DOAC measurements can be compared against the drug levels of the clinical trials, despite the lack of true therapeutic ranges. But there are currently not any FDA-approved kits or calibrators for those measurements.”

“That is kind of a sticking point,” Dr. Smock points out, because many labs have anti-factor Xa, for example, available for monitoring heparin, but it is calibrated against heparin. “You can’t just take these new drugs and throw them into that assay and get meaningful quantitative anti-factor Xa results without using a drug-specific calibrator.”

Since a number of new DOACs were approved in relatively short order over the past few years, Dr. Smock says, some physicians may not have encountered all of the drugs. That can cause confusion and potentially delays in care while the doctors investigate what implications a particular drug might have in surgery, for example. She believes the next five years will bring further increases in the number of patients on DOACs. “Luckily, in most centers, pathologists are knowledgeable about the drugs and can be contacted for consultation to help with anticoagulation management and anticoagulation bridging for surgeries.”

As to the age-adjusted D-dimer cutoffs, Dr. Smock believes there are also unsettled questions. “D-dimer levels, even in normal individuals, tend to increase as people get older, so should their cutoff for exclusion of venous thromboembolism be different—in fact, higher—than for younger patient populations?” Some large studies have looked at the question of whether a higher cutoff is feasible and safe, she says. “That’s where all these questions and guidelines are coming from.”

Dr. Smock

But there are mixed feelings about the new cutoffs on the laboratory side. “Of course we want to assist with excluding the proper patients from VTE appropriately, but there is a lot of controversy, I think, surrounding that question.” Adding to laboratories’ reservations, she says, is that the newer cutoffs and algorithms are not included in the labeling of the D-dimer reagents and package inserts.

“Laboratories are struggling over whether these calculations are valid things to do. Are they applicable across all older ages, even for a patient in their 80s or 90s? Probably a lot of patients at those ages may not have been included in the studies. Is there actually a difference with small incremental age increases for patients? There is some intrinsic imprecision in D-dimer measurements, so are these incremental changes and cutoffs valid when you take the imprecision into account?” The calculation laboratories need to make for these age-adjusted cutoffs also depends on what units are used in their D-dimer reporting, and there is a lot of variability in the units used by different assays, she adds. “So there are a number of questions.”

Laboratories can lessen the confusion about coagulation testing, Dr. Adcock believes. “Pathologists and laboratorians need to make themselves readily available to clinicians, and when possible we should provide interpretations with our more complex assays such as lupus anticoagulant and von Willebrand disease profiles.”

“Coag testing has always been a source of confusion,” Dr. Smock says. “It has been a place where sometimes

people have felt they didn't receive a lot of training or exposure to it." As new issues such as DOACs and age-related cutoffs for D-dimer testing are showing, "The conversations we have can change over time. But pathologists who practice in the area of coagulation have always been accustomed to having a lot of interaction with our clinical colleagues who order coag testing."

Anne Paxton is a writer and attorney in Seattle.