Buzz, prospects build for heparin-induced thrombocytopenia test

Darcy Lewis

January 2017—U.S. physicians and laboratories are anticipating the early 2017 launch of the HemosIL HIT-Ab(PF4-H) assay, which detects antibodies associated with heparin-induced thrombocytopenia. The new test from Instrumentation Laboratory, Bedford, Mass., is the first fully automated, on-demand assay for HIT.

The stakes are high. HIT, a prothrombotic disorder caused by antibodies to complexes of platelet factor 4 (PF4) and heparin, has historically had a 20 percent mortality rate. About five percent of HIT patients require limb amputation, and 50 percent experience other major morbidity, such as deep-vein thrombosis, pulmonary embolism, stroke, or myocardial infarction.

Fortunately, HIT is not common: Current estimates are that 0.2 to two percent of patients who receive prophylactic or therapeutic doses of heparin during their hospitalization will go on to develop HIT. But this is enough to make HIT one of the most common adverse drug effects due to the large number of patients who receive heparin therapy (12 million patients annually in the U.S.). The disorder is especially common among patients who receive prolonged postoperative thromboprophylaxis after coronary artery bypass, cardiac valve replacement, or various orthopedic surgeries.

A physician suspects HIT when a patient's platelet count drops by half or more (usually to below 150 per cubic mL) beginning five through 14 days after starting heparin. At that point, a diagnostic test, either an immunoassay or a functional assay, follows. "You must pay very close attention to the platelet count and how it changes over time," says Majed A. Refaai, MD, associate professor in the Department of Pathology and Laboratory Medicine at the University of Rochester School of Medicine and Dentistry, Rochester, NY. "If you have any suspicion that you are dealing with HIT, you absolutely must stop heparin and test for it immediately."

The gold standard for HIT testing is the serotonin release assay (SRA), which measures the platelet-activating capacity of PF4/heparin-antibody complexes in the presence of heparin. Platelets from normal donors are radiolabeled with carbon 14 (14 C)-sero-tonin and washed. These washed platelets are then mixed with the patient's sample with low and high heparin concentrations. The test is considered positive if the sample causes a 20 percent or greater serotonin release at a low heparin concentration of 0.1 U/mL. The SRA's specificity and sensitivity for HIT diagnosis, "in our hands," is high, write Theodore E. Warkentin, MD, and colleagues (*Am J Hematol.* 2015;90[6]:564–572).

"The SRA cleans up the high false-positive rate typical of the commonly used HIT assays: It sorts out the true positives from the true negatives," says Russell A. Higgins, MD, chair of the CAP Coagulation Resource Committee and associate professor and pathologist at University of Texas Health San Antonio. "The SRA's specificity may be as high as 100 percent," he adds.

The problem with SRA testing is that few centers have the expertise or resources to perform it, which means an unavoidable delay in obtaining test results. Moreover, SRA testing is often batched, introducing additional delays. Dr. Warkentin, a professor in the Department of Medicine and the Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, has studied HIT for 25 years. "My own center only performs HIT assays on Tuesdays and Thursdays, with results reported on Wednesdays and Fridays," he says. "And I should note that McMaster does the SRA testing for all of Canada, a country of 35 million people."

Enzyme-linked immunosorbent assays (ELISA), which detect antibodies against PF4/heparin complexes, are easier to perform than the SRA and are currently the most commonly performed test for suspected cases of HIT in the United States. They are widely available and have a sensitivity of 99 percent. Their specificity, however, is only 30

percent to 70 percent.

“Most tests are negative, but when there is a positive result it is a flip of a coin as to whether the antibodies are functional,” Dr. Higgins says. “Many patients produce antibodies to PF4 complexes that do not cause clinical HIT.”

The enzyme immunoassays currently available take about two hours to perform, and some laboratories end up batching tests due to resource limitations. Until the HemosIL HIT-Ab(PF4-H) assay is launched, Dr. Higgins notes, the U.S. will not have a rapid test for HIT with “sufficient sensitivity.”

“A rapid particle immunofiltration assay is commercially available but has not produced favorable ROC curves when compared to SRA testing,” he says.

What about timing of testing? “In theory the ELISA [test] can be performed shortly after sample collection, but the samples are almost always tested in batches, at most once daily and often not at all on weekends,” Dr. Warkentin says. “In practice, that means the results are often not available to the clinician until one to four days later, even at large centers.”

Meanwhile, how should the clinician manage the patient with suspected HIT while waiting for test results? All heparin products, including IV catheter and heparin flushes, should be discontinued immediately. The patient should then be started on a different anticoagulant. “The paradigm has been if you strongly suspect HIT, you should treat for it. That might sound easy, but it isn’t,” Dr. Warkentin says. “If you switch the patient to argatroban, you’re switching from heparin, which is a well-understood, inexpensive agent, to one that costs about $1,000 per day.”

Dr. Refaai

Dr. Refaai, who participated in IL’s studies to support the application for FDA 510(k) clearance of the HemosIL HIT-Ab(PF4-H) assay, agrees, noting that changing anticoagulation is a delicate balance because most anticoagulants don’t have adequate reversal agents, if needed. “Heparin does, so I hesitate to change the anticoagulation until I’m sure,” he says. “Otherwise, the patient may keep bleeding until a few half-lives go by, which could be disastrous.”

Then there’s the fact that few patients suspected of having HIT actually do. Dr. Warkentin, in an editorial in *Thrombosis Research* (2016;140:163–164), wrote that only five to 10 percent of patients investigated for HIT with laboratory testing are ultimately shown to have this diagnosis. He also notes that the thrombosis rate is about five to 10 percent per day for at least the first two or three days if heparin is discontinued in a patient who is later confirmed to have HIT by SRA. This adds more pressure to the clinician to make the right call.

This is the clinical atmosphere into which the HemosIL HIT-Ab(PF4-H) assay is entering. All of these circumstances combine to set the stage for unsatisfactory outcomes and unnecessary expense. “Our current treatment paradigm all but guarantees there is a lot of overdiagnosis and overtreatment going on,” Dr. Warkentin says. “A rapid assay dramatically improves your ability to get the patient on the right treatment approach quickly.”

To help quantify whether and how having an on-demand HIT immunoassay would help clinicians, IL provided funding to a research team at The Economist Intelligence Unit in London. The resulting research was published in *Thrombosis Research* (Caton S, et al. 2016;140:155–162).

The authors, who noted that IL did not influence study design or analysis, concluded that on-demand HIT testing has the potential to have a positive clinical and economic impact. “Rapid testing enables earlier informed treatment based on high-performance tests, rather than speculative treatment or delayed decision making,” they wrote. “This could potentially improve clinical outcomes in HIT patients by enabling earlier appropriate treatment and reduce costs by preventing expensive complications.” In addition, they say the budget impact model estimated that on-demand testing reduced alternative anticoagulation costs from $39,616 to nearly $13,000 per patient.

Dr. Warkentin

In his accompanying editorial, Dr. Warkentin writes that he found the conclusions of Caton, et al., “likely to be correct.” He noted that a negative result using an on-demand assay would avoid unnecessary expenses and bleeding risks “provided that the diagnostic sensitivity of the on-demand assay is sufficiently good to ensure a high negative predictive value.”
A positive result would justify the expense and risk of alternative anticoagulation “provided that the false-positive rate is not excessively high,” Dr. War-kentin wrote. (He was not involved with the development of HemosIL HIT-Ab (PF4-H), though he has received honoraria from IL, according to his editorial’s disclosure statement.)

Dr. Higgins, Bradley Brimhall, MD, and colleagues at UT Health San Antonio have been following with interest the HemosIL HIT-Ab(PF4-H) development process. “We happen to have an IL TOP instrument and realized early on that there is a tremendous amount of downstream savings to be had for a hospital in the form of decreased argatroban use, so we set out to quantify the savings,” he says.

Dr. Higgins

The HemosIL assay, like other HIT assays, is not meant to exclude HIT without knowledge of the clinical history. “HIT testing should not be ordered on patients with low pretest probability,” Dr. Higgins explains. The UT San Antonio team presented data at the Texas Society of Pathologists 2015 annual meeting that summarized their experience. They quantified the cost savings from avoiding unnecessary testing through the use of the 4Ts scoring system, a pretest probability test calculator for HIT. Utilization figures were collected over a four-year period, from 2007 to 2011. Integration of the pretest probability calculator into the hospital information system lowered annual HIT testing from 224 tests in 2007 to 67 tests in 2011, saving $18,448 annually in laboratory testing variable costs. The subsequent savings related to reduced use of argatroban were much larger. “We saved $220,055 annually by applying the 4Ts scoring system,” says Dr. Higgins.

“If we had a test like HemosIL immediately available, we estimate additional savings,” Dr. Higgins says. “The test’s utility is that it’s rapid, automated, and random access. Anyone who is trained on the machine can do the test so those savings can be realized very quickly.” Waiting two days for negative HIT test results leads to the unnecessary administration of argatroban. He estimates an additional $191,128 in annual savings if the HemosIL HIT-Ab(PF4-H) is implemented in his laboratory.

Fast-forward to July 26, 2016.

That was the day IL announced that the Food and Drug Administration granted 510(k) clearance to HemosIL HIT-Ab(PF4-H) for use on the ACL TOP Family Hemostasis Testing Systems. “Our predicate device was the ELISA, and the HemosIL HIT-Ab(PF4-H) performance is very good,” says Annie Winkler, MD, MSc, Instrumentation Laboratory’s director of medical affairs. “This assay has a negative predictive value of 99.6 percent when used within the context of the American Society of Hematology 2013 guideline, which is what is most important when you are dealing with HIT.”

The assay’s exact entry date into the U.S. market, and other key details that include pricing, have yet to be determined, but early this year remains the target. The test has been available in Europe since 2010 and in China since 2014.

Dr. Winkler believes that the HemosIL HIT-Ab(PF4-H) approval for use on the company’s ACL TOP Family of instruments will help the test come into widespread use relatively quickly. “No additional equipment is required for laboratories that already use an ACL TOP Family instrument,” she says. “HemosIL HIT-Ab(PF4-H) consists of liquid ready-to-use reagents and controls, which means that no reconstitution is required.”

Dr. Warkentin notes that, although the HemosIL HIT-Ab(PF4-H) results are expressed quantitatively, in units per mL, the results are only interpreted categorically as “positive” or “negative” based on the assay cutoff (1.0 U/mL). He would like to broaden the conversation about HIT diagnosis by including research that measures the predictive abilities of the HemosIL HIT-Ab(PF4-H) assay based on the specific quantitative result. “I have done these tests and am now analyzing the numbers,” he says. “I hope to have these results published in the near future.”

In the meantime, Dr. Warkentin calls the introduction of the assay a big deal: “This test harnesses the power of on-demand because, even in emergent situations, you can afford to wait 20 minutes to get this information,” he says. “If you have to wait eight hours, one day, three days, you will have to make treatment decisions for your patient in the meantime. That means you will be wrong some of the time, simply because you don’t have the right information when you need it.”

Dr. Refaai believes the assay has the potential to make substantial improvements in clinical outcomes associated with HIT, though he cautions that the test does have its limitations. “No assay can give 100 percent specificity and sensitivity, of course, but I would rather use an assay that can give me my answer in half an hour in accordance with the patient’s clinical picture than wait longer for some kind of perfect test,” he says. “Getting that information more quickly is what will most help me with my management of the HIT-suspected patient.”
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