D-dimer trifecta: clarity on units, values, and use

Karen Titus

January 2020—D-dimer has a problem. Several problems, in fact. Many, some might say.

Let's start with the basics regarding D-dimer assays: unit and magnitude.

Setting up the equation is easy, and the digits are small: 2 × 4. When applied to D-dimer testing, however, the answer often means far-flung problems for laboratories and clinicians.

Parsed out (for fans of James Thurber, this means channeling schoolmarm Miss Groby), D-dimer has two different units of measure. Some assays report fibrinogen equivalent units (FEU), and others measure D-dimer units (DDU). The amount of fibrin degradation products can be reported four ways based on the CAP Survey results: ng/mL, g/L, g/mL, or mg/L. "That's eight different combinations of results coming out of the laboratory," says Andrew Goodwin, MD, associate professor at the University of Vermont Larner College of Medicine, medical director of the coagulation laboratory, and CLIA medical director for the University of Vermont Medical Center Laboratory.

Dr. Andrew Goodwin at the University of Vermont with Kristin Lundy, CLS, technical specialist in coagulation. Dr. Goodwin and others suggest that laboratories would do well to provide more clarity to clinicians around D-dimer testing and reporting. [Photo: David Seaver]

Not that we need him to do the math. But Dr. Goodwin and others suggest that the equation demands deeper thought, and that laboratories would do well to provide more clarity to clinicians around D-dimer testing and reporting, which may include, at some point in the future, a new calculation.

Unlike the persnickety Miss Groby (for whom Marc Antony's funeral oration was less about ambition and more about metonymizing ears), laboratories and clinicians are eager to consider the meaning behind the details. How should D-dimer be used to care for patients? Where does it shine? Where does it fall short? How can we do better?

To lend that broader view, however, they must consider a tidy sum of steps along the way. Or, less tidily, "This

means really getting into the weeds," says Karen Moser, MD, assistant professor of pathology at the University of Utah School of Medicine and co-medical director of the hemostasis/thrombosis laboratory, ARUP Laboratories.

Is the assay being used to evaluate deep vein thrombosis or pulmonary embolism? If so, it requires a clinically validated cutoff—but which one? The DDU versus FEU unit type should be stated clearly in the package insert, but, Dr. Moser says, "it can be a source of confusion when you're looking at reports from different laboratories." As she noted in her CAP19 presentation last fall, using the FEU cutoff for a DDU assay can cause false-negative results. And, Dr. Goodwin says, the D-dimer used to exclude venous thromboembolism (VTE) is valid only in patients determined by a scoring algorithm to have a low or intermediate pretest probability of VTE.

When D-dimer is used to evaluate disseminated intravascular coagulation, the results are compared to a reference interval. "That can also cause confusion," says Dr. Moser, who was a member of the CAP Hemostasis and Thrombosis Committee through Dec. 31.

Dr. Moser

At her institution, "We have two different D-dimer test codes," she says. "So you can order a D-dimer for VTE exclusion, and that will report the D-dimer value for the patient, as well as the D-dimer cutoff for VTE that was provided by our manufacturer and clinically validated. So you get a report that's pertinent to that use case." A separate D-dimer test code is used in evaluating DIC.

There is a downside to that seemingly straightforward approach. "We're relying on people to order the correct D-dimer test for the specific clinical indication," she says with a laugh.

"These are some of the issues that come up with the D-dimer. There are more," she says brightly.

D-dimer harmonization issues have burbled up again with relatively recent guidelines calling for use of age-adjusted D-dimer (AADD) for evaluating patients with suspected acute pulmonary embolism, says Dr. Goodwin, also of the Hemostasis and Thrombosis Committee.

For years, he says, laboratories that reported in FEU used a cutoff of 500 in some measurable unit. For laboratories that measured D-dimer in DDU, the cutoff was somewhere between 230 and 250.

So far so good. And then: "As these age-adjusted D-dimer equations started coming out, it became very obvious that people didn't know if they were measuring D-dimer unit or fibrinogen equivalent unit," Dr. Goodwin says. "And that completely changes the mathematics."

Drs. Goodwin and Moser, along with others on the committee, began to notice that the literature was filling up with studies that failed to report what units were being used for measuring, and applying the published AADD could lead to mathematical and/or interpretive errors should a D-dimer result be reported in DDU. As they poked around on popular clinician decision support sites, they found further evidence that units of measure were missing in action.

This was concerning, though not surprising. "There are so many different ways the results can be reported that it's hard for clinicians and laboratorians to keep up with it," Dr. Goodwin says.

He and his CAP colleagues see evidence of this in CAP proficiency testing data, with labs reporting the wrong value because they were confusing DDU with FEU. Though the data are somewhat old (Olson JD, et al. *Arch Pathol Lab Med.* 2013;137[8]:1030–1038), close to 13 percent of laboratories reported changing type and/or magnitude of

units.

Fortunately, Dr. Goodwin says, matters have improved. “It’s gotten a lot better, because we’ve been working hard to educate laboratories on this. We contacted individual laboratories” with the message that they needed to pay attention to what they report.

Another step was updating the CAP accreditation program checklist, adding a requirement and evidence of compliance that instructs the inspector to compare a patient’s final D-dimer report to the manufacturer’s product insert, making sure the units of measure and reporting values match.

“That’s driven some of the improvement we’ve seen,” Dr. Goodwin says. “But there’s certainly room for continued improvement.”

What would that improvement look like? One longtime object of desire has been a calibrator to standardize assays. For many reasons, this has remained an only half-told Hero’s Journey—those who’ve tried to push for a calibrator have found conflict but not triumph.

Perhaps a Hero’s Getaway would work better. Members of the committee are ratcheting up discussions of how to standardize the process, ideally trimming that eight down to something smaller. For now, Dr. Goodwin says, they intend to play the cards they’re already holding. “Can we use what we know?” he asks.

What they know is that multiplying a DDU by a conversion factor of 1.74 (FEU = DDU × 1.74) will provide the equivalent FEU. It’s been well studied and validated, Dr. Goodwin says. Could the committee, with the assistance of the CAP, come up with an FDA-approved postanalytic conversion factor for laboratories to use? This could standardize reporting and reduce confusion.

This approach would also remove the onus on both vendors and clinicians.

The committee initially considered asking vendors to modify how they develop and market their assay kits. That idea collapsed about as quickly as the Russian Democratic Federative Republic. “I don’t think the vendors are going to want to change,” Dr. Goodwin concedes. “Why would they? They’ve got clinically validated, FDA-approved kits that work. It costs money. It’s not changing anything as far as patient care. The kits provide accurate results.”

Though the various D-dimer assays look similar, subtle differences abound. Each manufacturer has its own proprietary antibody, and each has its own R&D processes. And once a manufacturer sends its kit through the FDA approval process, Dr. Moser says, “It’s difficult to go back and resubmit, to say, ‘Actually, we want to use a different unit.’ That would require a lot of repeat studies and time and expense.”

“It’s hard to argue with that,” Dr. Goodwin acknowledges. “So we rethought our process,” turning to the idea of education and working with the FDA. These have their own challenges. The latter step will take time, he says. And vendors would still be required to take some steps—changing their product insert, for example.

Hence the appeal of having the lab handle any proposed postanalytic calculation, although labs, too, might resist, he says: *We’re reporting the D-dimer, doing exactly what the manufacturer says, and now you’re telling us to add a calculation and do a calculation verification every six or 12 months, depending on the regulation.*

“It does put responsibility on the lab,” Dr. Goodwin says, “but I think in the long run that’s probably the best solution. The laboratory is really good at doing postanalytic calculations. We do it for INRs.”

An FDA-approved postanalytic calculation would allow every laboratory to report in a single unit and quantity. “No matter where a clinician is practicing, the result will be the same,” says Dr. Goodwin.

There’s real value in that, he continues, including better patient safety. He says he gets calls from UVM colleagues who trained elsewhere who don’t always realize from the lab report that the D-dimer is being measured differently. (Vermont reports DDU.) “I get worried sometimes that if somebody is working through a case and accidentally overlooks what our cutoff value is, versus what they’re used to seeing—FEU in the literature, for example—they

could prematurely exclude a VTE in somebody."

Likewise, the many reporting options can be disorienting for physicians who work in different hospital systems or laboratories. "There's a tendency, as we get comfortable with tests, that we just sort of look at the number and say, 'Oh, yeah, I know what that means,'" Dr. Moser says. "But if you don't pay careful attention to the unit, magnitude, and type, there's potential to make a significant misjudgment if you're comparing to a cutoff that isn't appropriate for that test. And I'm not certain our clinical colleagues are totally aware of those sources of variation."

The problem pops up even within single systems, says Jeffrey Kline, MD, vice chair of research and professor, Department of Emergency Medicine, Indiana University School of Medicine. He says he's pushed for years—unsuccessfully—for a method that would normalize the D-dimer concentration across the IU network. "We have different D-dimers in the stat lab versus the clinical lab upstairs." Perhaps there are good reasons for this, he says, adding that directors will likely say they strive for a standard approach. "But they still have local directors at each hospital who end up clinging to whatever test they use," says Dr. Kline, who spoke about the perils of D-dimer testing at the 2019 annual AACC meeting also.

Obviously clarity is in big demand. Dr. Goodwin suggests an FDA-approved calculation would also offer clarity for those using age-adjusted D-dimer—they would need to use only one equation to determine the age-adjusted cutoff for excluding a VTE: age × 10.

The age-adjusted D-dimer, for those in need of a brief refresher, is based on the observation that as people age, their normal level D-dimer goes up. Those age 50 or younger have a negative value of less than 500 ng/mL FEU. A 60-year-old might have a higher D-dimer based on normal physiology, so their cutoff value would be 600 ng/mL FEU; 70-year-olds would have a 700 ng/mL FEU cutoff.

This being D-dimer, there are caveats. "You've got to be careful," says Dr. Goodwin. "A lot of the data that has been published so far only takes patients up to about 75 years of age. So we don't know if this holds true across the age spectrum, for people in the ninth and 10th decades of life." But for those in their 50s through 70s, "we in theory could exclude a VTE using a D-dimer and not send them for follow-up scans."

Dr. Kline is certainly aboard this train. In his AACC talk, he noted, "Ninety-seven percent of the people we're testing for PE with a CT scan don't have it. This is an astounding number."

For the foreseeable future, however, physicians will continue to practice in a pre-post-analytic conversion world. It's a disheveled world at best.

Spend a little time with the D-dimer literature—particularly articles proposing use of D-dimer in clinical decision rules/guidelines—and another source of confusion quickly pops up, Dr. Moser says. Sometimes the cutoff is stated clearly in terms of both unit magnitude and unit type. Sometimes it's also clear what assay kit was used to arrive at the cutoff. Most often, though, none of this is evident. "So then laboratories are left wondering: If my clinical colleagues are calling and asking, 'Can I use your D-dimer test in this particular clinical application?' it's not always clear, even if the medical director or laboratory supervisor reads the literature in question."

She says she welcomes this proactive approach to such inquiries. On the flip side are the calls the lab receives *after* clinicians have ordered a D-dimer for a use they've read about or heard discussed at a conference. "Then they call and say, 'Your result is goofy. Why is your D-dimer test broken?'"

She cites several articles that illustrate the problem with the literature, including one (Parvizi J, et al. *J Arthroplasty.* 2018;33[5]:1309–1314) that looks at using D-dimer to predict periprosthetic joint infection. The article doesn't state the kit or kits (the article comes from several institutions) used to develop the cutoff proposed in the criteria, she notes, or whether the cutoff is in DDU or FEU. It also refers to serum D-dimer. Since D-dimer is measured on plasma, this is the wrong sample type. "This is just one example of the confusing information out there in the literature regarding D-dimer," she says.

"This makes it hard for laboratories to advise their colleagues: 'Yes, this works with our test' or 'No, it doesn't,'"

she adds.

There's a similar dilemma with the clinical decision rule for identifying women at low risk of VTE recurrence, who might be candidates for discontinuing anticoagulant therapy. The clinical decision rule known as HERDOO2 can help identify these women, and D-dimer is one component of that rule (along with several clinical observations).

But, as Dr. Moser notes, the article describing the HERDOO2 rule validation used a single D-dimer kit to determine the D-dimer cutoff to use, and this was stated clearly in the article (Rodger MA, et al. *BMJ.* 2017;356:j1065). The decision rule received further attention in a subsequent analysis (Rodger MA, et al. *Thromb Res.* 2018;169:82–86), which explored which commercially available D-dimer assays could be used in HERDOO2 and at what cutpoint. Several assays were considered inappropriate for use in HERDOO2, according to the authors.

This may be one of those weedy patches she alluded to earlier, "but it's clinically important," she says. Moreover, "These are the kinds of questions that laboratory directors and laboratory supervisors get. Somebody reads these articles and says, 'Does this work for our patients? Does this work with our test?' And sometimes it's hard to tell."

Even age-adjusted D-dimer is not without problems. Reports can sometimes be confusing, so to help clinicians, Dr. Goodwin says, "Some laboratories are reporting the manufacturer's VTE exclusion and they're reporting out an age-adjusted VTE exclusion value." As long as they're using an assay that has been reported in the literature to be appropriate for using AADD, that approach is fine. But not every assay has been properly validated or has enough literature to support its use for AADD.

Laboratorians and emergency physicians are natural allies when it comes to clarifying D-dimer. Used appropriately in those patients with low or intermediate pretest probabilities, AADD can reduce the number of patients who need a CT angiogram or high-resolution CT scan to rule out PE. If a 65-year-old patient has a D-dimer value of 550 ng/mL (measured in FEU), the straight cutoff would be considered a positive result, which would warrant an imaging study, Dr. Goodwin says. Using the age-adjusted cutoff, however, the result would be 650 ng/mL FEU, "so now we've excluded PE, and no imaging is needed."

Dr. Moser puts it in a zippy way: Emergency physicians are working through the differential diagnosis of "Clot or not?" Patients with high pretest probability should proceed directly to imaging. "The positive predictive value of D-dimer isn't so great," she says. Where it shines in the ED is in its negative predictive value. It's especially helpful to rule out PE in elderly patients, who often have poor renal function and are best spared unnecessary radiation and contrast exposure. D-dimer should not be used to exclude patients with active malignancies, she adds.

Concurs Dr. Goodwin, "ER physicians are well aware they have to do their pretest probability—they can't just use D-dimer to exclude all patients who walk in."

Not everyone understands what can lead to a false elevation in D-dimer, however. Every once in a while, Dr. Goodwin gets a call from a treating physician who's using D-dimer in a patient for whom the assay can provide no useful information—excluding a PE in a pregnant woman. It is recommended, he said, that the D-dimer not be used in the diagnostic workup of PE in pregnancy.

Such calls don't surprise Dr. Kline, who daily sees the impact of assay variability on his colleagues.

Emergency physicians often grapple with the different thresholds used by different manufacturers, he says. And they don't fully appreciate the regulatory requirements pathologists face when balancing industry cutoffs and the demands of CLIA regarding test validation.

The result is a cognitive dissonance of sorts, Dr. Kline says. "They understand D-dimer perfectly well, but they don't understand why one test has this cutoff and another test has a different cutoff. Then they lose interest."

Speaking from what is clearly an in-the-trenches perspective, Dr. Kline says his colleagues are being neither dim nor unregenerate. "But they only have so many things they can put their attention into." When D-dimer cutoffs become too cumbersome to sort through, "They'll say, 'Forget it. I'll just order a CT scan, and then I don't even

have to think about it.'"

In his AACC talk last summer and his interview with CAP TODAY, Dr. Kline noted that emergency physicians are sometimes reluctant dance partners with pretest criteria. At AACC, he said, physicians "should use pretest probability, but they don't."

Dr. Kline

Moreover, he added, "D-dimer has a very, very mixed reputation [with] emergency physicians because they perceive it as being positive all of the time, because of cancer, injury, infection, old age, pregnancy. And ER docs don't like to wait for their tests. They order things in parallel because everybody is under pressure.

"We've got to get patients moving," he continued. "We see 350 patients a day in the hospital where I work. Decisions have to be made fast. And you wait for the D-dimer to come back, and it can take 90 minutes, counting the blood draw, and it's positive. And now I've got to order the CT scan." That's wasted time for physicians who think D-dimer is plagued by false-positives.

How can labs help? Dr. Kline urges pathologists to use the comments section to remind emergency physicians how to use AADD and pretest probability adjustments with the varying thresholds. "That could be a huge benefit," he says. "I'm talking another 10 to 15 percent of patients [who] get tested for PE can be ruled out with a blood test rather than a CT scan if we use these rules."

Like the lab, the ED is also looking at ways to fine-tune D-dimer testing. If some pathologists view a postanalytic conversion as the next step, Dr. Kline has a goal of his own. "The next frontier," he says, "is to use pretest probability adjustment, where we double the threshold for low pretest probability." A recent article (Kearon C, et al. *N Engl J Med.* 2019;381[22]:2125–2134) hints at the potential of using low clinical pretest probability and D-dimer to rule out PE. The study's authors report that their findings are consistent with investigations that use the YEARS diagnostic algorithm (van der Pol LM, et al. *N Engl J Med.* 2019;380[12]:1139–1149), another approach to adjusting pretest probability.

"This is the next thing that's going to move the needle in terms of using D-dimer," Dr. Kline says.

Dr. Goodwin says his philosophical belief is that the laboratory needs to ally itself with clinicians. "We work hard at that because they are the end users of our results." That includes ensuring that the data are timely and actionable.

"When age-adjusted D-dimer first came out," Dr. Goodwin recalls, "we put a newsletter together to communicate to the clinicians. I visited the clinicians in our emergency department; I discussed with our hematology group the differences between a fibrinogen equivalent unit and a D-dimer unit and what we report in our laboratory. And I talked to them about the pros and cons of using age-adjusted D-dimer."

Slow, antiphonal steps are rewarding, Dr. Goodwin says, allowing him to share with his clinical colleagues what he understands about the assay and its strengths and weaknesses, but also to learn and understand from them what they need. "I don't want to be an obstructionist. I don't want to say, 'Oh, you cannot use it that way.' I want to say, 'What can we do to get the data you need to treat your patients?'"

The biggest challenge for him—apart from a recent LIS upgrade that sent every other initiative ducking for cover temporarily—is that when AADD first emerged, much of the literature looked at assays that used FEU. Since Vermont uses DDU, "There were a fair number of requests to switch our assay. I had to explain to them that it's

not just as easy as buying a different box of reagent." His colleagues understood, and he was recruited by an ED colleague to study how well their assay performs regarding AADD—a study Dr. Goodwin embraced but which moved to the back burner because of competing issues. "I suspect it is going to be fine, but we haven't finished the study yet."

His situation hints at another problem with D-dimer. The guidelines are clear, says Dr. Goodwin. To use D-dimer to exclude a VTE, the standards indicate running at least 200 to 300 patients in the low- to intermediate-risk groups. "You have to follow those patients with a negative D-dimer for three months and demonstrate that the cutoff value has to have a negative predictive value of around 98 percent," he says. "It's pretty challenging to do that."

As age-adjusted D-dimer has taken root, physicians have looked to meta-analyses of studies that have performed that type of rigorous evaluation. In fact, Drs. Goodwin and Moser were authors, with members of the CAP Hemostasis and Thrombosis Committee, of an article (Goodwin AJ, et al. *Ann Intern Med.* 2017;166[5]:361–363) that includes a table listing the various D-dimer assays (and their manufacturer, methodology, etc.) used in clinical studies of AADD cutoffs. "You'll notice they're all fibrinogen equivalent units," Dr. Goodwin says. Adding up the patients studied in each of the papers, "many of the ones that use [FEUs] actually exceed the 200 patients followed for three months.

"So I think that's where most of the practice is coming from," Dr. Goodwin continues, "collating data from multiple papers."

More immediately, those who use AADD have to decide who's going to do the math. It may be simple, but it's still easy to stumble. Some laboratories will choose to report out the age-adjusted cutoff based on a calculation made in their LIS, Dr. Moser says. Some give a more general comment or blanket statement, providing the cutoff published in the package insert and the reference interval. "Then they'll have an interpretive statement that says, 'For patients over 50, here's how you calculate the age-adjusted cutoff.' And they leave it to the receiving physician to make that calculation."

Always, there's worry, she says. Labs need to state clearly what they're doing, so physicians don't mistakenly adjust twice, like a baseball player caught unawares on camera. "I'm not sure there's one best way to go. There's just some different options."

The take-home from all this, Dr. Goodwin says, is that laboratories need to know what assay they're running. It sounds obvious, but the detail is crucial, and as Dr. Goodwin has learned from his talks with colleagues and phone calls he's fielded, not everyone knows the basics. Labs need to know what unit they're reporting. They need to make sure their clinical colleagues understand the cutoff for the assay. And lab and clinician alike need to know if the AADD is applicable to their kit.

Those three things are the most common challenges Dr. Goodwin sees with D-dimer testing. And if the proposed conversion happens, that would clear away a wide swath of weeds. "That would allow clinicians to stop worrying: *What unit are they reporting in?*"

That would then free everyone to worry about other weeds. This is D-dimer, after all.

Karen Titus is CAP TODAY contributing editor and co-managing editor.