Poor testing, dosing dog fetomaternal bleeds

Karen Titus

September 2013—If Mark Brecher, MD, were compiling a greatest hits list of medical successes of the 20th century, there's one advance he'd be sure to include: the introduction of Rh immune globulin in the late 1960s to prevent the Rh sensitization of Rh-negative mothers who deliver an Rh-positive baby.

The number of patients affected may be small, but it's not insignificant, says Dr. Brecher, chief medical officer, LabCorp, and adjunct professor, University of North Carolina, Chapel Hill. If the mother's immune system becomes sensitized to the Rh-D antigen, the result can adversely affect a current pregnancy or the mother's ability to carry a future pregnancy safely to term. In the United States, some 13 percent of mothers are Rh-negative, while the chance that they'll deliver an Rh-positive baby is about 60 percent, says Dr. Brecher, a member of the CAP Transfusion Medicine Resource Committee. With Rh immunoprophylaxis, the risk of the mother being alloimmunized by a D-positive fetus dropped from roughly 13 percent to less than 0.1 percent.

A typical dose of RhIg, 300 µg, covers 30 mL of whole blood or 15 mL of red cells spilled by the baby. When a larger fetomaternal hemorrhage occurs, however—as it does in about 0.3 percent of cases—physicians can't rely on the standard dose. In these cases, laboratories need to determine the volume of fetomaternal hemorrhage and calculate how many vials of RhIg need to be given.

If only they could get it right.

Arriving at the correct dosage would, in Disney parlance, "be a dream come true." But a dream it remains. Laboratories continue to have difficulty with fetomaternal hemorrhage, or FMH, primarily because they make calculation errors and use a test—usually the acid-elution Kleihauer-Betke—that does a poor job of quantifying fetal red cells in maternal circulation.

For fetomaternal hemorrhage, proficiency testing finds
flow cytometry and an online RhIg dose calculator to be underused, says Dr. S. Gerald Sandler, here with Helain Landy, MD, professor and chair of the OB/GYN
department at MedStar Georgetown.

Not that clinicians are rising up in protest. "The average OB-GYN has no clue," says Kenneth Moise Jr., MD,

professor of OB-GYN and of pediatric surgery, University of Texas Medical School at Houston. “The average obstetrician, when asked about fetomaternal hemorrhage, says, ‘That’s a lab problem. I expect them to educate me on what to do.’”

Unfortunately, plenty of data have demonstrated ongoing failure to manage FMH more precisely.

In 2009, the Transfusion Medicine Resource Committee analyzed data on FMH testing from the 2006 and 2007 CAP Surveys. The results did not inspire confidence. The main finding, as noted in a *Transfusion* commentary by three committee members (published online Feb. 27 and scheduled for print publication in September), was that even though nearly 67 percent of participating labs used the standard method, found in the AABB *Technical Manual*, for calculating RhIg dose, almost 21 percent recommended an incorrect dose (11.5 percent too much, 9.2 percent too little).

“We kept getting these crazy responses. Either people were dosing too high or too low,” says Dr. Brecher, who at the time was the chief editor of the manual. “When we tried to focus in on what the problem was, we would tell people to calculate it using the [AABB recommendations]. We found people were *still* making mistakes.”

The committee then tried to take test error out of the picture. Even when labs had the equation set up for them—they were given figures for the percent of red blood cells detected and for the maternal blood volume—“we still had about 16 to 17 percent of people who could not do the calculation right,” says Dr. Brecher.

“Which was in some ways frightening,” he adds.

The Transfusion Medicine Resource Committee, in an effort Dr. Brecher led, responded by creating an online RhIg Dose Calculator. It’s a Microsoft Excel program that requires only that users plug in the numbers—the dose is then calculated automatically. The calculator is posted on the CAP Web site (www.cap.org, under Committees & Leadership, Transfusion Medicine Resource Committee, and then Transfusion Medicine Topic Center), and it does not require validation as LIS software, says S. Gerald Sandler, MD, a TMRC member and lead author of the *Transfusion* commentary. Most importantly, he says, the calculator works.

If you use it.

TMRC analysis, also in 2009, of subsequent Surveys (which are done twice a year) found that nearly 45 percent of laboratories ignored the new tool and continued to calculate RhIg dosing manually; of these, almost 17 percent recommended an erroneous dose. Only 1.6 percent of labs that used the calculator, in contrast, submitted a dosing error.

Dr. Brecher

The calculator appears to be growing in popularity, Dr. Brecher says, noting that it shows up regularly in literature citations. In addition, “We know that it’s been downloaded thousands of times from the CAP Web site”—in the last 12 months, almost 1,500 times. Dr. Sandler, however, says that “a significant” number of laboratories in the Survey group don’t use it. “I can’t explain why,” says Dr. Sandler, who is also professor, pathology and medicine, and medical director of the blood bank, Department of Laboratory Medicine, MedStar Georgetown University Hospital, Washington, DC.

Even when the calculator is used, it’s only as good as the numbers that are plugged into it. Unfortunately, those numbers are overwhelmingly the product of the Kleihauer-Betke test.

The committee's initial 2009 analysis alluded to this issue, noting that flow cytometry was more precise than the acid-elution assay for quantifying FMH. At that time, 3.8 percent of labs used flow, while almost 74 percent used acid-elution methods. (The remaining 11.5 percent said they used "other" methods.)

The 2012 analysis showed the numbers haven't budged. A whopping 96.1 percent of participants used an acid-elution method, while only 3.9 percent used flow cytometry. Of the laboratories using an acid-elution assay, more than 46 percent recommended an inadequate dose of RhIg, and just over 29 percent recommended an overdose.

Kleihauer-Betke is not a good test, to put it bluntly. "It's not specific enough," says Meghan Delaney, DO, MPH, assistant medical director, Puget Sound Blood Center, and assistant professor, University of Washington, Seattle. "People could have widely variant responses, and therefore don't get the right answer."

Dr. Moise

Most laboratories get very little practice in running the test. So when they "pull out the kit, they're going to be reading the instructions again to figure out how to do the stain," says Dr. Moise. If it's not done correctly, it's difficult to count the adult versus the fetal cells. "It's just not going to be a very accurate test," he says.

The answer would seem to be obvious: Switch from the KB test to flow cytometry. Says Dr. Sandler: "It's not as though we have a virus and no test to detect it."
(What about improving the Kleihauer-Betke test? Says Dr. Brecher: "In theory, anything can be improved, but I haven't seen anything suggesting that this test can be improved.")

A certain torpor has set in, however, which has kept that solution visible but out of reach, like an object in an art museum.

Among FMH cognoscenti, there's agreement that despite troubling data about Kleihauer-Betke's unreliability, most players are unaware there's a problem with the test.
As noted earlier, clinicians aren't demanding flow cytometry. OB-GYNs "all think KB is accurate," says Dr. Moise.

"There's not a lot of attention or understanding that this is even an issue," agrees Dr. Delaney, who is also a TMRC member and one of the commentary authors.

Kleihauer-Betke can also be done quickly, no small consideration given that physicians have a short window—72 hours from when a woman delivers, according to standard practice—in which to administer Rh immune globulin. Flow cytometry, on the other hand, wouldn't necessarily be available when pregnant patients are most likely to need it—that is, 24/7. "I think that's another reason why KB has held on," says Dr. Moise, speaking with the experience of someone whose seen more than his share of weekend births and mothers eager to get home quickly. "It can be done in most hospitals whenever it's needed, even though they're not very good at doing it."

While that has the ringing endorsement of serving tuna noodle casserole for dinner—sure, go ahead and open that can of cream of mushroom soup, but is it really the healthiest meal to prepare?—it can be hard to make a better choice.

Dr. Delaney

Even those who see the problems concede change could be a long way off. Listening to them explore the issue is a fascinating exercise, like observing the same attorney argue both sides of a case. Data and experience show that KB should be dropped, they say. On the other hand, flow is an expensive procedure. Not every lab has the deep pockets or expertise to set it up, especially for such an uncommon event. Indeed, Dr. Delaney, whose blood bank has had several conversations with the flow cytometry lab about doing the test, admits it's been difficult to make the case. The numbers just aren't there. "Bringing in a test is a medical and a business decision," she says.

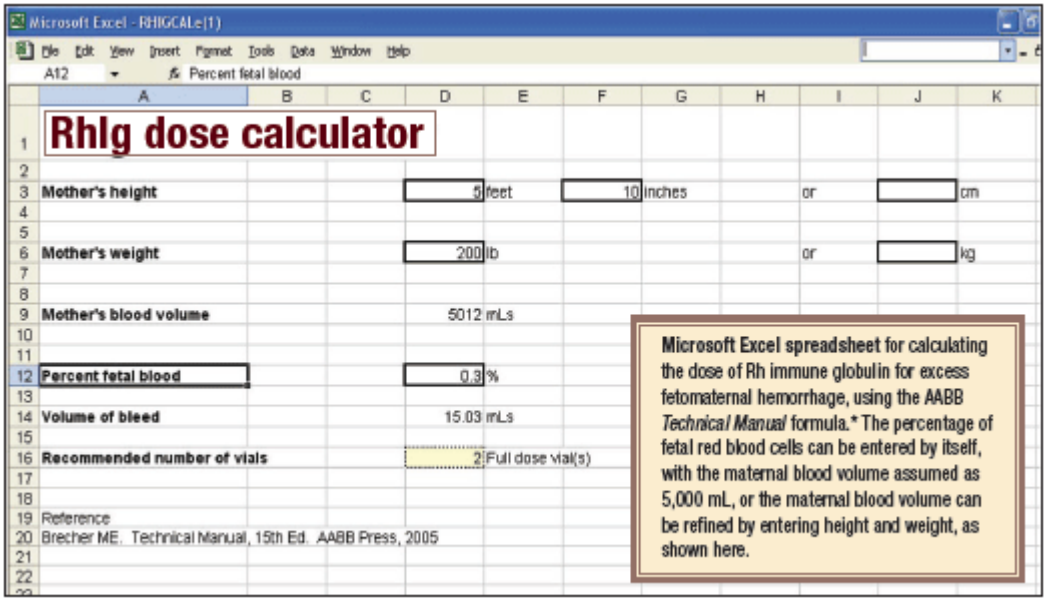
Other numbers argue against moving to flow as well. In clinical practice, Dr. Sandler notes, any time an Rh-negative woman delivers an Rh-positive newborn, she automatically receives one vial of Rh immune globulin, even if there's no evidence of fetomaternal hemorrhage. If there is such evidence, it's standard to add one vial of RhIg into the calculation to ensure a very wide margin of safety. Thus, even with the KB's limitations and calculation errors, the Rh immunoprophylaxis failure rate is almost imperceptible. Ask a physician about the efficacy of current practice, says Dr. Sandler, and the response will invariably be, "I've never seen a case that failed." The failure rate, he says, is roughly one in 10,000; in those cases, the fault is thought to lie with failure to give the injection, not failure of the lab test or the calculation.

In short, the current system, for all its flaws, is, in many regards, successful. But when things go wrong, they go really wrong.

Dr. Moise recounts the case of a recent patient, at regular term, who had an abruption and a 130-mL bleed, which was confirmed by multiple KB tests. "It was confusing to me, because the baby looked fine," he recalls. For its part, the blood bank couldn't figure out how much RhIg to give the patient. "They were scared to give the IV prophylactic—they hadn't done that before for a massive bleed. They were just out of their league," says Dr. Moise.

"I get calls from blood banks all the time, and from perinatologists, saying, 'We don't know what to do.' People are at a loss," Dr. Moise says. If the events are rare, that also means when they occur, people rarely have answers.

In an ideal world, every hospital that delivered babies would make accurate calculations and use flow cytometry. But Plato is not in charge here; Candide is. So while FMH experts consider using a more complex, more expensive test, one with slower turnaround times, to cover rare situations and fix problems that most people don't even realize exist, what, realistically, is the next best thing?



Perinatal issues in transfusion practice. In: Brecher ME, ed. Technical Manual. 15th ed. Bethesda, Md.: AABB, 2005:535–556.

Dr. Moise would like laboratories to give better guidance for determining when enough RhIg has been given after a large bleed. When Dr. Moise gives lectures to obstetricians, he likes to tell them that current recommendations round off the calculation to the nearest decimal point, "then add one to grow on," he says. "They all get a kick out of the 'science' of how much Rh immune globulin to give. But you'll see very poor recommendations in the obstetrical literature, on what to do." As far as he's concerned, "That's another hole in the system," along with poor calculations and poor testing methods.

Likewise, Dr. Moise says clinicians would benefit from recommendations on when to repeat a patient's anti-D titer after she's received multiple vials of RhIg.

At the very least, he says, labs need to refine their calculations. "It's one of my pet peeves, when labs make the calculation based on a maternal blood volume of five liters every time. Obviously we know all women don't have five-liter blood volumes." Why not just use the dose calculator? he asks.

Dr. Sandler, looking beyond hospital labs, would like to see large reference labs step up. "There's a terrific opportunity to capture an entire community's flow cytometry for fetomaternal hemorrhage," he suggests.

So far reference labs haven't taken the bait. Dr. Brecher says he and his colleagues at LabCorp haven't discussed marketing the test on their own. "In the absence of significant demand from clinicians or a practice guideline that would favor it, we would be unlikely to see adoption even if we introduced the test."

Dr. Sandler wonders if the demand is low because the referral channels for FMH testing aren't as well established as they are for, say, viral testing. The first step, a screening test, typically is done at a blood bank; the sample is then sent to a hematology laboratory for the acid elution test. Perhaps, Dr. Sandler theorizes, "We're somewhere in a crack between the blood bank and the hematology laboratory, neither of which are major sources of referrals to reference labs."

Moreover, he continues, switching testing to a reference lab could be an unwelcome change in routine for some, regardless of how fraught that routine is. Sending samples to a reference lab is another way of saying that the sample has left the building, taking with it the hospital's ability to be sure RhIg is injected within 72 hours. "It's easy to understand how some decisionmakers might say, 'We have a patient care deadline that I have control over now that's very important, and I'm concerned about losing control over this chain of the lab sample, the lab test, the injection. I don't want that to happen.'"

Patient advocacy groups, so important in other diseases, are unlikely to push for change. FMH is not front and center in most patients' minds; it doesn't have the apparent urgency of, say, a cancer diagnosis. It's not about the

current pregnancy; it's about a potential problem with a future pregnancy, which isn't going to be uppermost in the minds of women currently busy with a newborn. "An occasional woman who's Rh negative, who's going to get a shot, doesn't present much of a lobbying group," Dr. Sandler says.

Reference labs are more likely to respond if there is a mandate to require a better method, says Dr. Brecher. The push could come from major organizations such as the CAP, AABB, and ACOG.

Even then, the push would have to come from on high. It would not be a grass-roots effort, Dr. Moise says. "An obstetrician might be faced with this a couple times a year, so their interest in having a national guideline is not going to be very profound."

But, as he points out, there's no denying FMH can be a profound problem for the patient when it happens to her, and for those involved in her care. "It's like teenage pregnancy—until it happens, no one thinks it's going to happen to them."

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