Tuning in to hypotensive transfusion reactions

Ann Griswold, PhD

April 2014—Most pathologists are trained to think of hypotensive transfusion reactions as rare events, and for the most part they are. But one pathologist's experience suggests these reactions may be underreported, and perhaps on the rise. Greater recognition of these events could provide valuable information and help improve patient outcomes.

Richard Scanlan, MD

"People often report these reactions as possibly related to transfusions, but the challenge to the pathologist is that the transfusion reaction workups are negative, for the most part. So they're in a quandary as to whether the drop in blood pressure was because of the transfusion or other causes," says Richard M. Scanlan, MD, clinical professor, vice chair of laboratory medicine, and director of the transfusion medicine service at Oregon Health and Science University (OHSU).

It's critical that clinicians and pathologists recognize the reactions for what they are—and establish a firm line of evidence linking the transfusion to the reaction—so the event can be reported to blood centers and to the Food and Drug Administration, he says.
"Only then can we get a better handle on how frequent these reactions are and pursue more effective strategies for responding to them," says Dr. Scanlan, who is chair of the CAP Commission on Laboratory Accreditation.

Until recently, Dr. Scanlan was aware of only one hypotensive transfusion reaction at OHSU in all his 20 years as a blood banker. But shortly after agreeing to lecture on the topic at CAP '13, two more cases fell into his hands. In hindsight, Dr. Scanlan wonders if other reactions might have been overlooked.

"Someone has to recognize it on the floor and call it to my attention, and I'm not sure I was always tuned in to these. I might have signed some of them out as symptoms unrelated to transfusion. So now we're trying to keep other people from making that same mistake," he says.
The problem of hypotensive transfusion reactions was first reported in the late 1970s, with the introduction of the first technologies to separate plasma. "Originally, it was that the blood was being filtered and the filters were creating a lot of bradykinin in the bags. It was also seen in dialysis filters. They've more or less engineered that

problem away," Dr. Scanlan says.

But as that problem resolved, similar reactions sprang up in its place. In the mid-1990s, clinicians noticed a spike in acute hypotensive transfusion reactions in patients taking angiotensin-converting enzyme, or ACE, inhibitors, which are increasingly used to treat diabetes.

"When blood from a normal donor is collected and filtered, the act of going through the filter creates a lot of bradykinin in the bag, and then it's just sitting there in storage," he explains. "When it gets infused into the patient, if the patient isn't able to rapidly break that down because they're taking ACE inhibitors, their blood pressure goes down."

Acute hypotensive reactions still occur today, along with three other major types of responses: anaphylactic, acute hemolytic, and septic hypotensive transfusion reactions.

How common these reactions are is difficult to gauge. "They're rare enough that they're not likely to be statistically significant as a public health issue," says Dr. Scanlan, noting that overall mortality figures do not include these data.

Nonetheless, he wonders if the numbers of hypotensive transfusion reactions might be rising due to the burgeoning population with diabetes. After concluding his CAP '13 lecture on the topic, several members of the audience approached him to share their similar experiences.

"They said they'd had reactions like these and didn't really know what they were dealing with at the time," Dr. Scanlan says. "So I think they're common—and a common cause of puzzlement among pathologists."

Sorting out the triggers of hypotension during a blood transfusion isn't always straightforward, but Dr. Scanlan points to several things that should catch the eyes of astute clinicians and pathologists.

"The four hypotensive transfusion reactions have in common a rapid onset of symptoms, and they can be severe enough to cause death if an appropriate intervention is not made," Dr. Scanlan says. "So we're focusing on making the right intervention and then classifying the case correctly."

After ruling out other potential triggers of plummeting blood pressure, such as hemorrhage, pulmonary emboli, and heart attack, additional clues can be found in the timing of the hypotensive response.

"If it happens just after the infusion was started, we want to think of ACE inhibitors or an IgA deficiency," Dr. Scanlan says, noting that symptoms of acute hypotensive and anaphylactic reactions typically begin within minutes of the transfusion being started.

Conversely, acute hemolytic and septic reactions tend to have a delayed onset, causing hypotension 15 minutes to an hour after the transfusion begins. These reactions often occur with other symptoms. A high fever, for example, might herald a septic reaction.

A greater awareness of transfusion reactions won't change how the clinical care team responds—whenever a patient shows signs of a reaction, the transfusion is turned off, no matter what—but reporting them could help amass critical information needed to improve patient care.
Here, Dr. Scanlan shares the lessons he has learned about each type of reaction in hopes that others will join his quest.

Anaphylactic reactions to transfusion are rare, but when they do occur, they can be tricky to resolve. "After I agreed to give the talk, I thought to myself, 'I'll never see one of those,'" Dr. Scanlan recalls. "Within two weeks, I had a patient who almost died from a transfusion."

The patient had leukemia and a known IgA deficiency, and needed to be transfused. In keeping with standard practice, the team at OHSU administered washed blood products, in which the donor IgA had been removed so that

the recipient wouldn't mount an allergic response. "We gave three units of washed red cells that worked wonderfully. She didn't have any symptoms," Dr. Scanlan recalls. "Then we gave her a unit of washed platelets and she just about died."

The patient went into bronchospasm. "She couldn't breathe; we had to call a code on her. Fortunately, we were able to resuscitate her," he says. "What I learned was that washing is effective for red cells, but that the IgA is internalized within platelets and can be released after the transfusion. That was a striking take-home lesson for me."

In addition to receiving washed blood products, Dr. Scanlan suggests IgA-deficient patients might benefit from other precautions, including a regimen of steroids or antihistamines of the anti-H1 or anti-H2 types to dampen an allergic response. "And in acknowledgment of the difficulty of these cases, we think some kind of bronchodilator should be given to the patient, or at least be rapidly available when treating an anaphylactic reaction."

Because these reactions are so rare, the link to transfusion is not always intuitive. And even when clinicians suspect an allergic reaction, additional allergy testing often leads to dead ends. "It's unclear whether it's of value to test the recipient for things like peanut allergies or foods that the donor may have ingested but the recipient is allergic to," Dr. Scanlan notes. "It can be very expensive and it usually doesn't get you anywhere."

Even IgA levels can be difficult to interpret, he says. "Generally speaking, we can rule out an IgA deficiency relatively easily," Dr. Scanlan notes. But in the recent case at OHSU, things were a bit more complicated. The patient was thought to have an IgA deficiency based on a previous transfusion reaction at another hospital, but the laboratory reported the IgA levels as less than 50 ng/mL.

"Some people asked, 'She has IgA—how can she be having an IgA deficiency?' But actually, that was the lower limit the lab could measure," Dr. Scanlan explains. "They don't measure down to zero. It takes a special reference lab to absolutely confirm that the IgA is deficient. That was another wrinkle in that case."

Clinicians can screen for risk factors and laboratories can prepare washed blood products, but in the end, Dr. Scanlan says, the outcome is too often determined by chance.

"It's always a surprise for someone," he says. "Even with all the precautions, it still happens."

Like anaphylactic reactions, acute hypotensive reactions happen quickly. One notable difference, however, is that most acute hypotensive reactions spontaneously resolve as soon as the transfusion is stopped.

"We had a reaction occur in the operating room once," Dr. Scanlan recalls. "The anesthesiologist started a transfusion on the table and, within minutes, the patient's blood pressure went down to below 60. She immediately turned off the transfusion and, within a few minutes, the patient's blood pressure came back."

That's typical of the bradykinin mechanism, he says, noting that clinicians often realize in hindsight that the reaction was related to an ACE inhibitor. "If the transfusion is stopped instantly and the symptoms resolve, then you're good."

Pathologists can help mitigate these reactions by educating family practitioners about the potential risks of ACE inhibitors, so that they can recommend that patients with diabetes stop taking the drugs before receiving a high volume of plasma or a plasma exchange.

"I would emphasize that many, many people who get transfusions are on these drugs, and they don't have severe reactions," Dr. Scanlan says. "We're not recommending routinely stopping these drugs in everybody who gets a transfusion with just a few units. But if the patient shows hypotension, stop the transfusion and, going forward, make sure they're not on those drugs when they get transfused."

Acute hemolytic transfusion reactions are notoriously difficult to treat and have a high mortality rate, Dr.

Scanlan notes, but three steps can greatly reduce a patient's risk. "One out of three acute hemolytic reactions ends in death," he says. "So here, an ounce of prevention is worth a pound of cure."

The three preventive measures are key: Obtain a second ABO confirmation, opt for automated ABO testing to eliminate human error, and use bar-code–assisted transfusion administration to confirm the final identity of the recipient and link that recipient to the donor unit in hand.

"By using these three things, you can materially reduce the risk of acute hemolytic transfusion reactions," Dr. Scanlan says. "If you're unfortunate enough to have one, you'll be able to show that you were aware of the problem and took steps to mitigate the risk. That will help in your defense."

Septic transfusion reactions are relatively easy to spot. "The septic transfusion reaction is one marked by hypotension and a high fever. It's fairly characteristic," Dr. Scanlan says. "Stopping the transfusion and starting with antibiotics empirically is the treatment of choice."

About five years ago, he recalls, clinicians noticed an increase in the number of septic transfusion reactions. In response, blood centers started culturing the bags for 24 hours before releasing them for distribution.

"There are some slow-growing organisms that don't show up in the first 24 hours but can occasionally be associated with adverse reactions. So it's not 100 percent effective, but it has reduced the number of problems," Dr. Scanlan says. In addition, a small number of institutions use a point-of-care device that allows the blood product to be sampled and tested for gram-positive or gram-negative organisms.

But identifying a septic reaction is only the start. The next challenge lies in identifying the organism and establishing an effective treatment strategy. Here, Dr. Scanlan says, Gram staining can prove useful.

"Gram stain is not the most sensitive way to detect infection, but it will give you information that is actionable. If the bag is heavily contaminated, it's likely that you're going to find organisms on the Gram stain. That information can then be shared with the attending, and appropriate antibiotics can be started."

The problem is that all too often the bag becomes contaminated during attachment to the transfusion apparatus or during transport to the laboratory. In those cases, a Gram stain of the bag will reveal only limited information.

"The key here is that if you suspect a septic reaction, culture the patient. That's the most effective way to get a clean culture."

Preventing hypotensive transfusion reactions is simple, at least in theory.

"Be lucky," Dr. Scanlan says. "Transfusions are inherently risky. There are going to be complications. But let's go back to the basics: Don't give the transfusion unless it's absolutely necessary."

When luck runs out, he says, logic must take over.

"The main thing is to ensure good communication. When the floor calls and declares there's been a transfusion reaction, the laboratory technologist receiving the call should be absolutely certain that the transfusion is stopped, that the clinician is actively engaged in managing the patient, and that the laboratory director is immediately called on," Dr. Scanlan says.

In addition, the lab and nursing staff should make sure the pathologist is alerted to the problem.

"The challenge is saying, okay, were these symptoms coincidentally related to the transfusion or were they caused by the transfusion? And that's where you earn the big bucks as a pathologist."n

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