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AABB ramps up donor screening to help stem TRALI

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When it comes to the blood supply, the tradeoffs between safety and availability are a tightrope that blood centers walk with extreme care.

For several years now, TRALI (transfusion-related acute lung injury) has topped the list of causes of transfusion-related mortality in the U.S. Defined as acute lung injury that occurs during or within six hours of transfusion of a blood product, TRALI is fatal to six to 10 percent of the patients it strikes.

As with all quality and safety initiatives in blood banking, risk reduction on behalf of patient safety can bring new risks in the area of availability. The trick is how to screen out the sources of TRALI without creating shortages of blood products for transfusion.

In 2006, the AABB recommended that its members adopt measures to address TRALI in plasma by November 2007, and TRALI in platelets by November 2008. The specific steps to take were left up to the blood centers, but large numbers opted for predominantly male plasma (meaning males plus never-pregnant females), though AB plasma was often excepted from this policy. Soon, TRALI cases showed a significant decline. But since 2009, reports by the Food and Drug Administration show, the number of TRALI deaths from all blood products has stopped dropping and leveled off.

This year, spurred by its TRALI task force, the AABB turned up the pressure in its campaign against TRALI. The AABB's new standard 5.4.1.2 includes screening of women plasma donors who have had one or more pregnancies for the presence of human leukocyte antigen (HLA) antibodies, or anti-HLA, the major known TRALI risk factor. People develop anti-HLA antibodies because they're exposed to foreign antigens, and exposure is usually due to pregnancy, transplant, or transfusion. Less common are human neutrophil antigen (HNA) antibodies, or anti-HNA. They are also a risk factor and are more commonly associated with fatal TRALI.

As of this April, the AABB started requiring that blood centers it accredits manufacture transfusable plasma from whole blood donations only if the donations are from males, never-pregnant females, or screened by an HLA antibody test and found negative. Blood centers are not required to be accredited by the AABB, but the large majority are.

Most blood centers had already been producing male-predominant plasma, with one significant exception: Donations from women with type AB blood sometimes continued to be used for transfusable plasma because it was thought there would be severe shortages of crucial AB plasma if half of the potential donor population could not be used for this purpose.

Under standard 5.4.1.2, the exception for AB plasma will be ended. So the new standard is likely to have significant effects on blood centers, hospitals, and possibly the nation's plasma supply.

Although TRALI was first described in 1985, most people did not really know what TRALI was until early 2000, says Manish J. Gandhi, MD, associate professor of laboratory medicine and pathology and consultant in the Mayo Clinic's Division of Transfusion Medicine.

"Unfortunately, a lot of patients needing blood transfusion may have an acute lung injury. And it was not being picked up that this could be associated with transfusion. The 2004 consensus conference, where experts agreed on a definition of TRALI, made it easier for people to recognize these sorts of transfusion reaction," Dr. Gandhi says.

A four-year prospective study, which began in 2005 and was led by Pearl Toy, MD, provided further information about anti-HLA's role in TRALI. Funded by the National Heart, Lung, and Blood Institute, the study was conducted at two surveillance sites, the Mayo Clinic and the University of California, San Francisco (Toy P, et al. Blood. 2012;119[7]:1757–1767).

Dr. Gandhi was a coauthor of the study. "The whole idea of it was to have clinicians who would prospectively monitor patients who received transfusion within a window of six hours. If there were any symptoms, then all the vital signs and other patient data would be looked at by a panel of three physicians who were completely blinded

to what they were looking at, and they would make the diagnosis of whether it was TRALI or not on the clinical side," Dr. Gandhi says.

The study tested for several factors implicated in TRALI. "We would test for everything that was available," including anti-HLA, anti-HNA, and some bioactive substances, Dr. Gandhi says. The study established that reducing exposure to plasma from female donors was concurrent with a decrease in TRALI incidence, which dropped, after risk reduction, from one in 4,000 blood component exposures to about one in 12,000 blood component exposures.

In 2007—in fact, in the middle of the UCSF/Mayo study—the weight of evidence from available research and from a successful male plasma mandate in the U.K. led the AABB to issue a recommendation that all plasma come from males and never-pregnant females. "For the most part, blood centers had done that, but some had not done it for AB plasma," says Patricia Kopko, MD, professor of pathology and director of transfusion medicine at the University of California, San Diego, and a member of the AABB's TRALI task force.

Since AB type plasma is universal plasma, there is high demand for it. But while hospitals need about 11 percent AB plasma, only about four percent of blood donors are AB. So switching to all male plasma would essentially double blood centers' problems on the supply side, Dr. Kopko explains.

After looking at the data, however, the TRALI task force saw a distinct pattern. "Most TRALI cases from plasma were from AB plasma," Dr. Kopko says. So the task force decided it was time for a standard; it would argue for a requirement that all plasma, regardless of blood group, come from male donors.

According to studies, about 20 percent of multiparous women have anti-HLA antibodies—the more pregnancies they had had, the higher the HLA antibodies, Dr. Gandhi says. This finding had the most implications for plasma. "When we talk about blood products, we tend to refer to the 'red product' and the 'yellow product,' because when we split whole blood into its components, the red cells would have very little plasma, and fresh frozen plasma and platelets would have a lot of plasma. So the yellow products would have much higher antibody levels, even though studies show red cells may also cause TRALI."

In the AABB's guideline, male-predominant plasma was recommended. "Most of the centers did go down that path, and some donor centers stopped taking female donors as plasma apheresis, with the exception of AB plasma because it was difficult to meet the needs," Dr. Gandhi adds.

Meanwhile, improvement started becoming apparent; statistics on incidence of TRALI show that the screening measures were having an impact after 2006. "We could actually show the number of TRALI cases decreased substantially when the policy was put in place," says Steven Kleinman, MD, senior medical advisor for the AABB and chair of the TRALI task force.

When the American Red Cross looked at its numbers for plasma, the risk was significantly decreased with implementation of predominantly male plasma. The ARC is still implementing the policy in AB plasma and a lot of the TRALI they had was AB females, Dr. Kopko says. "That data was part of what led the AABB TRALI task force to say there was enough evidence to go forward with the new standard."

Coincidentally, and unfortunately, these new restrictions on plasma for transfusion have been happening at the same time that use of group AB plasma has increased dramatically because of "massive transfusion" protocols, practiced by the military and extended to the civilian population.

"Over the last several years, based on mostly anecdotal reports from the military that rapid-response protocol patients do better if they get red cells and plasma in a one-to-one ratio, hospitals are just giving lots of plasma in the beginning, rather than waiting to see which patients are coagulopathic," says Dr. Kleinman.

"It's become the norm for every hospital to have such a massive transfusion protocol. That has increased the number of plasma units being ordered," Dr. Kleinman says.

The one-to-one ratio protocol is still controversial, he points out. "Some people say it's not proven, it's all a question of the way the studies are done, and patients who got the most plasma sooner look like they survive better because they got a lot of other early care. So you could question whether there is adequate evidence. But in practice, most of the trauma surgeons have accepted it."

Given the surge in demand for plasma, how widely is the new AABB standard likely to be followed? "I think it will be completely adopted," Dr. Gandhi says. "Most of the donor centers will be AABB-accredited, the standard is already out, and donor centers will have had to set up the mechanics for following it."

There are a number of different commercial tests that can be used for testing HLA antibodies, Dr. Kopko says. But the HLA tests have not been without problems. “The tests weren’t initially designed for donor screening,” Dr. Gandhi says. “They were meant to be used for solid organ transplant patients. So they had some cutoffs that were very sensitive.”

“When the initial studies were done, it was shown that a good proportion of male donors without a history of transfusion or transplantation also tested positive by the HLA test.” Essentially this was considered background noise, but there was a great debate in the HLA community about what would be the right cutoff for blood donation. “AABB does provide some guidance about what the cutoff should be. But that is something the community will have to sort out,” Dr. Gandhi says.

Until now, there hasn’t been widespread anti-HLA antibody testing of plasma or platelet donors. “But with this mandate, there will be widespread testing, and we will get to know what percentage of donors are going to be positive and what that will do to the inventory,” Dr. Gandhi says.

The biggest hit from the new standard will be to AB plasma, he agrees. The second impact will be on platelets. “Because we do bacterial testing, the effective shelf life of platelets is three to three and a half days, and we still have nearly 40 percent of platelet donors who are female. Once these tests are implemented, we will realize the effect on our platelets inventory.”

As with any high-complexity test, there are specific requirements for who can perform or supervise the anti-HLA test, and this would have meant HLA experts would have to oversee the testing. “AABB did go to CMS about this, and CMS ruled that if a laboratory is only doing anti-HLA antibody testing for screening blood donors, the test would not be considered high complexity. So that takes care of a lot of the staffing requirements,” Dr. Gandhi says.

In a letter earlier this year, the CMS notified the AABB that “HLA antibody screening for the purpose of TRALI risk mitigation performed in order to qualify blood donors can be classified either as histocompatibility or general immunology,” which also allows the AABB to be an accrediting organization for facilities that perform the testing.

One of the next urgent issues is to develop anti-HNA antibody tests. “It’s the anti-HNA antibodies which are the worst kind. But right now there is no good FDA-cleared test for anti-HNA that can be done on a mass scale,” Dr. Gandhi says. “The available tests take a lot of time and are very cumbersome. With blood donor testing, we are talking about thousands of donations a day, so we need something on a high-throughput platform.”

One specific HNA antigen has been associated with more TRALI cases and greater severity, Dr. Kleinman notes. It’s called HNA3a, and the molecular structure of it was unknown for many years. But it was identified several years ago.

“Because it was unknown, it was not possible to develop a molecular-based test. So to test for anti-HNA right now, you have to combine patient serums with live neutrophils. That’s the historic way HNA antibody testing has been performed. It’s labor-intensive and technically demanding such that only a very few labs in the country do this.”

When the antigen structure of HNA3a was elucidated, there was hope it would lead to an automated test and an end to having to harvest fresh neutrophils from volunteers for use in lab assays. “But it hasn’t panned out,” Dr. Kleinman says. So HNA antibody testing is still not easily available.

Because there were dire predictions about plasma shortages when the new standard was announced in January, the AABB issued a bulletin saying if a blood center thinks adhering to the standard might create problems, there are alternatives one could use, Dr. Kleinman says. For example, a blood center could consider, as an alternative to AB plasma, using group A plasma with low anti-B hemolysis titers for trauma patients.

But in response to the AABB’s new standard, blood centers have adjusted, Dr. Kopko says. The impact of the standard on supply is still not marked. “We’ve not been short since the standard took effect in April.” However, she notes, clinician usage of blood overall in the country has decreased, while plasma usage is up.

“What has happened is they’ve encouraged their hospitals to be more conservative with plasma, plus blood centers have found other ways to collect AB plasma, such as using predominantly apheresis plasma,” she says.

“If you have an AB blood donor, their red cells can only go to people who are AB. So for the most part, blood centers don’t recruit them.” To be a good steward, “The last thing you want to do is collect a red cell and throw it out. What many blood centers have done is use an apheresis machine. That allows them to take the plasma donation and return the red cells to the donor. You actually get more plasma per donation, and the donor can donate more frequently,” Dr. Kopko points out.

"If you're recruiting males and never-pregnant females, or testing donors who are female and have been pregnant, you still mitigate the TRALI risk," she says. "It's the same screening process, but there's additional work to make sure you have enough AB plasma."

With the other blood types, there are more donations from whole blood than needed, so the excess plasma goes to manufacturers for crucial medications like albumin and IVIG, she adds.

Blood centers have been active in making sure their customers are appropriately using plasma. Some small hospitals had continued using only AB plasma because it was universal, but that's going to change now, Dr. Kopko says.

At UCSD, to conserve AB plasma, the procedure for a trauma patient is to start with transfusion of AB plasma for trauma and to switch to type specific plasma as soon as the patient's blood type is available. "If a patient has a gunshot wound to the chest, we want to have plasma available for transfusion as soon as the patient arrives. To do this, you have to useAB plasma, because you don't know the patient's blood type. In order to start using non-AB plasma, you have to determine the patient's blood type. If you work with your trauma service to quickly obtain a sample for blood typing, you can switch from using AB plasma to type specific—usually A or O—plasma quickly. If you're fastidious about getting this done, you can use less AB plasma."

"I think most major suppliers are adhering to the standard," Dr. Klein-man says. "I don't know whether it's 100 percent. Certainly if a person really needs plasma and the only alternative is plasma that hasn't gone through TRALI risk reduction, I don't think a blood center or hospital transfusion service would withhold that transfusion."

Through its January 2014 association bulletin, the AABB has helped give direction to blood centers about screening. However, says Dr. Kopko, "The HLA test costs about $10, and for plasma donors is probably price-prohibitive, because you can get enough plasma from men and never-pregnant women. I don't know of any blood center that is testing plasma donors."

Blood centers typically collect more plasma than they transfuse, Dr. Kopko says. "But we don't waste it; the rest goes to fractionation. Under the AABB standard, plasma from a donor with a history of any pregnancy may be sent for plasma fractionation without testing for HLA antibodies. The key for plasma is how to balance what's needed for transfusion, and it's really only an issue for AB plasma."

For anti-HNA, "there is really no good commercial test," Dr. Kopko agrees. A couple of labs, including BloodCenter of Wisconsin, do most of the HNA testing through their own laboratory-developed tests. "It is a gap. But I'm not sure how big a gap, because HNA antibodies are not as common as HLA antibodies."

While there's not an absolute correlation between HNA antibodies and HLA antibodies, "if you look at some studies, a number of people with HNA antibodies will have HLA antibodies. So if you test and defer donors with HLA antibodies, you will de facto defer some with HNA antibodies," Dr. Kopko says.

The issue of extending the plasma standard to platelets has been more controversial, says Dr. Klein-man. After considerable debate, the AABB decided to issue a new interim standard, adopting the same policy for apheresis platelets but not making it effective immediately.

Because the platelet supply is so much more fragile than the plasma supply, the task force decided—almost unanimously, Dr. Kopko says—to give blood centers two years to accomplish the new screening and testing policy required by the AABB. So the standard for platelets will likely take effect in October 2016.

"To implement this requirement, they can start with women with three or more pregnancies, then two or more, then ever-pregnant. You end up having to defer some donors, so at the same time, recruitment professionals have to work really hard to recruit more donors or there won't be enough platelets."

"It takes a lot of planning if people are going to lose 10 percent of their platelet apheresis donors," says Dr. Kleinman. But Dr. Kopko says many blood centers have already reached the standard with platelets.

As compared with plasma, which goes for less than $50, platelets sell for more than $400. "So for that product—for which there is not an excess—it's a much better cost-benefit equation to test those donors. Plasma is also good for a year, while the shelf life of platelets is five days, so there's not as much flexibility in the platelet supply."

More platelet units are from men than from women, who she estimates make up only about a third of donors. "Just in general, more platelet donors are male than female because men tend to be bigger. And the bigger you are, the more blood volume you have."

Across the board, awareness of TRALI has risen, and that's improved clinicians' ability to diagnose, Dr. Kopko says. "The subject has moved out of the exclusively transfusion literature and into medical and anesthesia surgery literature, so there's better awareness that TRALI is an entity. I don't know if we catch it all, but I think we're doing better."

However, confusion of TRALI with TACO (transfusion-associated circulatory overload) continues. "It's still happening and always will, because these complications look very much the same. Clinically, you need to distinguish the two, and it's the difference between cardiogenic pulmonary edema [TACO] and non-cardiogenic [TRALI]."

In assessing the measures being taken against TRALI, Dr. Kleinman cautions against comparing TRALI data across different countries. "You have to note how they did case reporting, because everyone monitors TRALI differently." In the U.S., Canada, and Europe, he believes that in the absence of intervention the rates of TRALI are probably similar.

However, he notes, recipient susceptibility is definitely an important factor in whether a patient develops TRALI. "It's not only getting exposed to a unit from a donor, but in almost all cases, the patient has to have something that's caused the neutrophils to be primed." Among different countries, some differences in rates might have developed because the underlying risk factors in recipients vary, and there are also differences in donors undergoing different interventions.

Even within the U.S., detecting whether protocol changes are having an impact can be difficult. "The overall number of TRALI cases from transfusion that we actually capture through reporting and surveillance is small," Dr. Kleinman says. "Platelets are not transfused as often as plasma and we have an inability to capture all the cases. The numbers starting at baseline are relatively small. So when we have an organization put a policy in place and they're asked whether the number of cases is being reduced, their answer is that it sort of looks that way," Dr. Kleinman says. "It's the dilemma of small numbers."

"But we made predictions that the plasma policy, based on what we knew, ought to decrease TRALI by 70 or 80 percent, and that's in fact what happened. We were able to use existing data to predict, and then show our prediction was right," he points out.

With platelets, putting together the casework on how much antibody testing should help, plus the correctness of the plasma prediction, "I feel relatively confident about putting interventions in place for platelets and expect a decrease in TRALI of about 60 percent. But as yet there's no proof."

More research is needed on the causes of TRALI besides HLA and HNA antibodies, Dr. Kleinman says. "We are addressing the antibody mechanism of TRALI. But we know there's another mechanism caused by other substances in donor units called biological response modifiers. It involves the products generated by cellular metabolism while the blood component is in storage, and we don't know much about that. It's very hard to get a handle on figuring out what these molecules are or how often they are causing TRALI. There's a strong consensus that the modifier mechanism exists, but beyond that, we need a better understanding of the modifiers."

The blood banking community has continued to reduce the number of TRALI cases thanks to risk mitigation interventions. It's been effective for plasma, and the consensus is that it's worth doing for platelets as well, but interventions have to balance safety with availability of blood products, Dr. Kleinman says. "If you minimize unnecessary transfusion, you'll minimize TRALI. But there is still a lot about TRALI that is unknown."

Complicating the assessment of risk mitigation is the fact that acute lung injury is not all that unlikely in patients who are sick enough to be in the hospital, so tracing the cause to a blood transfusion is not a simple matter. The patient might have been about to contract acute lung injury anyway. "Because it is an uncommon complication, physicians need to be alert for TRALI," Dr. Kleinman says.

As always, utilization must be factored into risk mitigation as well. "The best way to prevent TRALI is to stop unnecessary blood transfusions," Dr. Gandhi says, "and that's another effort that is going on. A lot of major blood centers, and even the smaller centers, are doing blood product management, and they are getting much more proactive about pushing clinicians to use the right product at the right time, and not just use it to treat a number. And in fact a lot of blood centers that have started using blood management have seen a drop in usage, even though the surgeries overall have become much more complex."

It's somewhat difficult to assess the impact of recent protocols and donor screening, because a strong improvement trend has not yet been apparent in the FDA's annual accounting of transfusion-related mortality. Deaths from TRALI fell from 34 in 2007 to 16 in 2008. But despite some fluctuations, TRALI still accounted for an

average 38 percent of deaths associated with transfusion between 2009 and 2013 (Müller MC, et al. Transfusion. Epub ahead of print Aug. 18, 2014. doi:10.1111/trf.12816).

Perhaps that will change with the AABB's new standard for plasma, and eventually platelets. But ironically, as momentous as the new standard may be, it will not affect the main cause of TRALI at all.

"The greatest number of TRALI cases come from red cell transfusion, because even though the risk per red-cell unit is so much less than the risk per plasma unit, we transfuse so many more red cells," Dr. Kopko says.

Unfortunately, blood centers can't afford to turn away female donors of red cells who have ever been pregnant, because it would decimate the blood supply, Dr. Kleinman says. "We could not take out every antibody-positive unit for red cells. We would lose too many donors and too many units."

"We are still working on safety," Dr. Kopko says. "We've done the plasma, we're now doing platelets, but red cells are still the No. 1 cause of deaths. The question is: Is there anything we can do about red cells? And I don't know the answer. It will probably take a similar task force to decide what measures to take." The AABB's new standard is another important step in improving safety, but TRALI has by no means been fully addressed, she says. "Safety is an ongoing process."

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Dr.Kopko

Dr.Kleinman