Lining up for low titer O whole blood in trauma care

Charna Albert

June 2022—For many blood suppliers, there is more enthusiasm for low titer O whole blood than there is an ability to make it, especially with the pandemic having made it harder than ever to collect. With greater use and a stocking of multiple sites versus one central site, "there are lots of folks lining up for the product," said Julie L. Cruz, MD, senior medical director at Versiti Blood Center of Indiana.

Dr. Cruz spoke last fall in a CAP21 session about the product, the donors, the titer, and the supply. With her was Julie Katz Karp, MD, associate professor and director of transfusion medicine at Thomas Jefferson University Hospital, who presented on its use in trauma-induced coagulopathy and at Thomas Jefferson.

Dr. Karp

"Half of it is just thinking about it. The other half is figuring out how you're going to use it and getting it," Dr. Karp said of low titer O whole blood (LTOWB). (The Thomas Jefferson experience with LTOWB will be reported in the July issue.)

There is no standard definition for trauma-induced coagulopathy, a term established in 2010, but it refers to "abnormal coagulation capacity attributable to trauma," Dr. Karp said. It manifests with a spectrum of phenotypes—anything from hypocoagulation to hypercoagulation (**Fig. 1**) (Moore EE, et al. *Nat Rev Dis Primers.* 2021;7[1]:30). What results is a function of many interactive factors, she said. "Things like tissue injury, the presence or absence of shock, and time from injury."

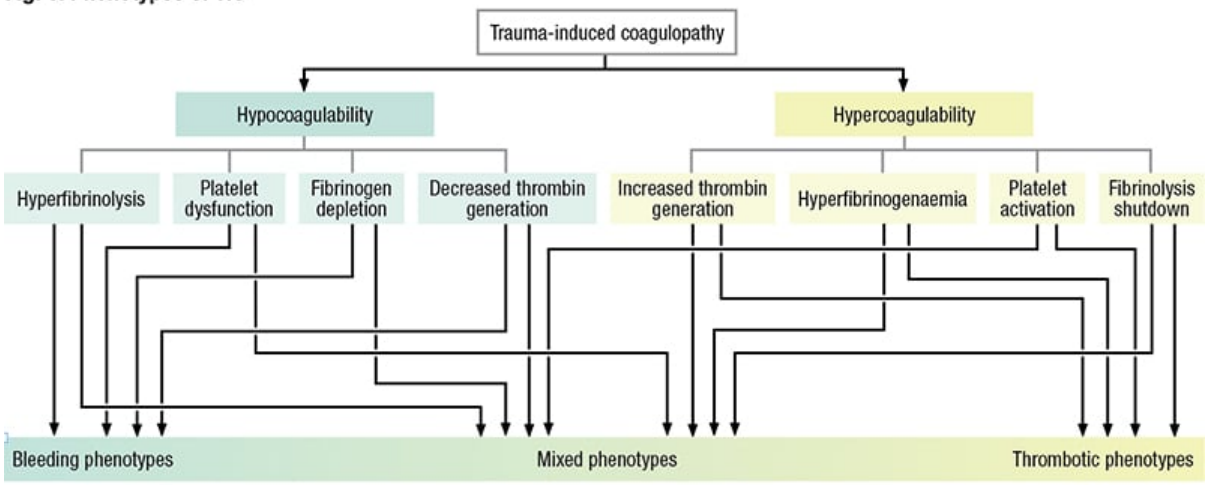
In general, bleeding phenotypes and hypocoagulability are associated with early trauma-induced coagulopathy, and thrombotic phenotypes and hypercoagulability are more associated with later trauma-induced coagulopathy, "probably after initial resuscitation, to some degree." But coagulopathy is a continuum, she noted. "Resuscitating people is not a straight line, and everyone is a little different."

Trauma-induced coagulopathy can be treated with blood component therapy or LTOWB. Overall, a one-to-one-to-one ratio of blood components yields a dilute blood mixture compared with LTOWB, due primarily to the presence of anticoagulants and red cell additive solution in the individual components, and that's problematic from a resuscitation perspective, Dr. Karp said. The one-to-one-to-one ratio of platelets, plasma, and red blood cells in blood component therapy "gets you something like reconstituted whole blood," but compared with LTOWB, it has a lower hematocrit (29 percent versus 35 to 38 percent), a lower platelet count (90,000/µL versus 150,000–200,000/µL), and a lower whole blood concentration of coagulation factors (62 percent versus 85 percent).

Cold storage platelets are an emerging topic in trauma resuscitation, she said. "There's a building body of evidence that refrigerated platelets are superior to room temperature storage platelets for acute hemostasis" (Cap AP, et al. *Mil Med.* 2018;183[suppl 2]:44–51). If kept cold, they may be more useful for patients who are actively bleeding, she said. "And that's where we are with low titer O whole blood. These are patients who are actively bleeding," so there's a growing movement to keep platelets in cold storage. There's evidence to suggest, too, that the hemostatic function of platelets in LTOWB is retained in refrigerated storage.

Should low titer O whole blood be leukoreduced? Though the majority of blood components in the U.S. are leukoreduced, Dr. Karp said, it isn't required. The same dynamic applies to LTOWB—some is leukoreduced and some is not. Historically, whole blood has not been leukoreduced. But leukoreduction of blood components has become common in transfusion medicine and has been shown to have important benefits: lower rates of alloimmunization, fewer febrile non-hemolytic transfusion reactions, and less cytomegalovirus transmission.

Fig. 1. Phenotypes of TIC



"It's a logical next step that we would leukoreduce low titer O whole blood when so much of our blood supply, blood-component wise, already is leukoreduced," she said. When LTOWB is leukoreduced and isn't transfused as whole blood, it can be further manufactured into leukoreduced red cell units (if leukoreduced before storage). "So leukoreducing low titer O whole blood sets you up to be able to make leukoreduced red cells, which is potentially a desirable thing from an inventory management perspective." To leukoreduce LTOWB, there are data to support the use of platelet-sparing filters versus non-platelet sparing filters, and they're now more commonly used in manufacturing LTOWB, she said.

A 2018 paper reported on an in vitro randomized controlled study that examined leukoreduced and non-leukoreduced whole blood and its respective hemostatic parameters (Remy KE, et al. *J Trauma Acute Care Surg.* 2018;84[6S suppl 1]:S104–S114). The authors measured median platelet concentration in 21 leukoreduced (with platelet-sparing filters) and 20 non-leukoreduced whole blood units stored at 4°C over 15 days. On day zero, immediately after leukoreduction, platelet concentration was lower in the leukoreduced whole blood. "What's interesting is that at all other time points, out to day 15 plus, there were no differences in the median platelet concentration between the leukoreduced and non-leukoreduced whole blood," Dr. Karp said. There's a difference early in storage, but it eventually diminishes.

In another finding from the same study, on days zero and five, the leukoreduced whole blood units had decreased maximum clot firmness (measured with rotational thromboelastography) compared with the non-leukoreduced whole blood. "So similar to what we saw in the platelet count, but once again, there was no difference in percent reduction [of ROTEM-MCF] from day zero to day 15 between leukoreduced and non-leukoreduced whole blood."

The authors also measured maximal amplitude by thromboelastography, finding no statistically significant difference between the non-leukoreduced and leukoreduced units on each day tested except for day zero, when maximal amplitude was reduced in the leukoreduced whole blood compared with the non-leukoreduced whole blood. Again, there was no difference in the percent reduction of maximal amplitude from day zero to day 15 between the leukoreduced and non-leukoreduced groups.

Leukoreduction performed with platelet-sparing filters, then, caused a reduction in some measures of hemostatic potential. “This reduction was most prominent in days zero to 10 of storage,” she said. “But those differences were gradually superseded by the effects of storage itself.” And at the end of the 15 days of storage, “all of these products look more or less the same.”

So it’s unclear if LTOWB should be leukoreduced, she said. There may be logistical reasons to do so, though it may not improve standard of care. “But in the end, it seems like it’s a wash. There’s no clear, better answer as far as hemostatic function,” though other factors may tip the scales.

In the same study, Remy, et al., looked at agitation of whole blood stored at 4°C and found that agitation is not needed to maintain hemostatic function.

Another study, reported in *Transfusion* in 2019, compared five type O positive whole blood units leukoreduced with platelet-sparing filters to five units leukoreduced with non-platelet sparing filters (Haddaway K, et al. *Transfusion.* 2019;59[5]:1809–1817). The authors measured four TEG-derived hemostatic variables: R time, K time, alpha-angle, and maximal amplitude. They found that in vitro hemostatic function of whole blood prepared with a platelet-sparing leukoreduction filter appears to be superior to whole blood prepared with a non-platelet sparing filter.

“What I take away from this is fairly obvious—platelets are important for hemostatic function,” Dr. Karp said. “And that’s what we’re after for our trauma patients.”

Haddaway, et al., also looked at how storage duration affects coagulation testing of whole blood leukoreduced with platelet-sparing and non-platelet sparing filters, measuring prothrombin time, activated partial thromboplastin time, factor V activity, and chromogenic factor VIII. For each day of storage over a two-week period, no significant difference was seen in PT and PTT between the units leukoreduced with a platelet-sparing filter and those leukoreduced with a non-platelet sparing filter. “And that makes sense because platelets generally don’t contribute to PT and PTT measurements,” Dr. Karp said. More important, she added, for each day of storage no significant difference was seen in PT and PTT. Coagulation factors other than labile factor VIII were preserved at 1° to 6°C for 14 days or more.

In sum, Dr. Karp said, these studies support the premise that LTOWB retains hemostatic function throughout storage, and that platelet-sparing filters, if leukoreduction is performed, are critical to maintaining that function. And leukoreduction may have some impact on hemostatic function, particularly early in storage, “but these changes are gradually superseded by the effects of storage itself.” What isn’t clear is whether these findings are clinically relevant. “Again, these are just laboratory in vitro studies.”

Finally, she said, “Treatment for trauma-induced coagulopathy, particularly soon after injury, can be accomplished with low titer O whole blood. We’ve seen that clinically, and we now have the laboratory testing to support the use of these products.”

The blood center will need information from customers interested in LTOWB about what the customer considers an acceptable titer, as well as massive transfusion protocol activations and component use, the makeup of the customer’s massive transfusion protocol coolers, and the leukoreduction preference, Dr. Cruz said in her talk on blood center perspectives. The trauma and transfusion services considering LTOWB use should ask their supplier if they already offer LTOWB. “If so, what are its attributes?”

And what is the available donor population? For LTOWB, donors must be group O, aspirin free, and transfusion-related acute lung injury (TRALI)-reduced risk. “Many centers don’t routinely test female whole blood donors who have ever been pregnant for human leukocyte antigen antibodies, so that population may be excluded from available donors,” said Dr. Cruz, a liaison to the CAP Transfusion, Apheresis, and Cellular Therapy Committee.

Rare units, antigen-negative units for treating patients with sickle cell disease, and pediatric units must be protected to ensure they’re available for patients who have no other options. And only Rh-positive units may be available if the blood center doesn’t have a consistent source of Rh-negative units. Many centers enroll a group of

donors recruited specifically for LTOWB, but targeted recruitment is less efficient and more costly.

The anticoagulant or bag that is used will determine expiration, she noted, and whether leukoreduction is done can determine the bag. “You have to have a platelet-sparing filter, and there’s only one approved in-line leukoreduction filter available, so that determines the bag you’re using as well.” Logistically, if the collection bags are different than those used for routine donors, Dr. Cruz said, “you have to ensure the bags are available at the collection center when the appropriate donors are present.”

The blood center will discuss titer cutoff with the transfusion service, she said. “What are you requesting? What are your concerns? Can our donor population support a titer? The lower the titer you choose, the more donors you’re going to exclude.” Early studies used a titer cutoff of 50, but as evidence of safety has accumulated, isoagglutinin titer cutoffs of 200 or 256 are commonly selected. The method for determining the titer sometimes can also impact the level of donors excluded.

Whether donors will be titered serially is another question. Some evidence suggests it may be unnecessary to titer low-titer donors at every collection, Dr. Cruz said, noting that one study demonstrated anti-A or anti-B IgM and IgG titers for low-titer donors tend to stay low titer (Sprogøe U, et al. *J Trauma Acute Care Surg.* 2017:82[6S suppl 1]:S87–S90). This suggests that for these donors, she said, the titer could be verified at longer intervals such as annually. But that’s difficult to track, “so many centers continue to do it on every donation.”

Many suppliers are concerned about over-collecting LTOWB and then running short for non-trauma patients who need component therapy or single transfusions of red blood cells. Thus, supply potential must be assessed, she said, and that involves tracking the number of O-positive RBC units collected and distributed annually, the number of units imported, and the O-positive RBC apheresis to whole blood collection ratio. “Since we drive our collections toward apheresis, we can get two red cell products in one donation, and that maximizes our red cell supply,” she said, though those units are then not available as whole blood. The percentage of high-titer donors excluded due to the chosen titer and LTOWB expiration date also should be assessed.

The blood center’s logistical challenges include identifying appropriate units for the production lab and product loss. “You may collect from an inappropriate donor,” she said, one who is not TRALI-reduced, for example, or learn of positive infectious disease test results in downstream processing. Though these often are false-positives, she said, the unit still would be unavailable for distribution. More often it would be a new donor exceeding the low-titer cutoff or manufacturing problems for those that are leukoreducing. Ensuring supplies are at the collection sites when they’re needed is another challenge. “This is particularly the case for those who are collecting in a bag that is not their routine bag.” And “collecting on mobiles or a constraint around delivery of supplies,” she said, can be problems when trying unexpectedly to ramp up collection of LTOWB. Timing too is important: The only FDA-approved inline platelet-sparing filter bag requires that the product be filtered within eight hours of collection.

The most efficient way for the transfusion service to ensure regular delivery is to establish a fixed or standing order, Dr. Cruz said. With order changes or ad hoc ordering, lead time considerations come into effect. “I’ve got to be able to get that notice to the site, anticipate donors at the sites and mobiles, ensure that the supplies are in the right place, and potentially put the targeted recruitment machine into place.”

Communication between the blood center and transfusion service is key as production of LTOWB is increased to meet need, she said. “You want to ramp up to your comfort level, but also adjust down to account for seasonality or if you find you’re having wastage.”

So what is the best model for stewardship? Dr. Cruz asked. A blood center stock is possible but requires a critical level of demand and utilization to be reached. “Again, overstock will lead to outdating and wastage.” One option is to reclaim RBCs by spinning the product down at the 14-day mark, for example, and converting it to RBCs, but that product will have a shorter shelf life than regularly collected RBCs, she said. “So where are you in your ability to accept short dates? If your blood supplier is asking you to accept short-dated red cells, how often are you accepting and using those?” The other possibility, she said, and the one that’s preferred—at least from the blood center’s perspective—is just-in-time production.

Dr. Cruz

Returns add cost and labor, and reclaimed red cells add labor and planning in the processing lab for units that can be difficult to place because of their short dates. Some transfusion services reclaim RBCs if they aren't using and transfusing the blood out to the full 21 days. "Some report that they perform a reclamation at the center," she said, and if they're not able to do that, they may do separation via sedimentation. Others identify opportunities where expiring units might be appropriate, such as in the OR.

"Everything was looking good" for LTOWB, Dr. Cruz said of the ramping up of supply. "Then COVID. So we have more challenges than ever to collect donors in the blood supplier space." Transfusion services too have "felt the pinch" of the severe blood shortage and especially of O-positive donors. And all have suffered supply chain and staffing problems. "In any case," Dr. Cruz said, "we continue to move forward."

Charna Albert is CAP TODAY *associate contributing editor.*