Platelet transfusions: safety, cost, and workflow

Anne Paxton

October 2022—The jury may no longer be out on whether pathogen reduction of platelet units reduces the risk of a septic transfusion reaction enough to replace culturing of platelet units. Nor is there doubt that pathogen-reduced platelets have a shorter hold time before they can be released for transfusion and the potential for a longer shelf life. These merits have helped convince the American Red Cross to switch, over the next year or two, to supplying only pathogen-reduced platelets to its client institutions that need platelets.

“There’s nothing that’s all good or all bad, though,” says Ralph Vassallo, MD, chief medical and scientific officer of blood supplier Vitalant, Scottsdale, Ariz. “We use pathogen inactivation technology and most blood centers have an option to provide pathogen-reduced platelets.” However, the expense of such platelets—commonly an additional $150 for each unit—can’t be ignored.

“The great thing about platelet pathogen reduction is that bacteria present at collection are not going to grow in that unit. As many as one in 2,000 units have bacteria in them, but only one in 10,000 grow to levels high enough to hurt someone. But one in 10,000 when there are 2.2 million transfusions a year is a lot. So pathogen reduction significantly enhances bacterial safety,” Dr. Vassallo says.

The FDA approved the use of Cerus’ Intercept pathogen-reduced platelets (PRP) in the United States in 2014.

Dr. Vassallo

Nonbacterial pathogens are also proactively inactivated by pathogen reduction, which Cerus estimates has proven efficacy against more than 40 clinically relevant pathogens. That means unknown, emerging viruses may be caught in many cases. “We didn’t recognize West Nile or dengue and chikungunya viruses and other potential pathogens that have emerged,” Dr. Vassallo says. “So if something’s in your blood supply and you’re not aware of it yet, pathogen reduction may take care of that.”

Since pathogen inactivation also acts like radiation, “you don’t have to irradiate to prevent transfusion-associated graft-versus-host disease.” Pathogen inactivation also eliminates the need for a cytomegalovirus test as well as some tests for other infectious diseases, although, he adds, “the FDA hasn’t yet gotten to the point where we can cease doing many of them.”

“But the cons are significant,” Dr. Vassallo says. “Pathogen reduction is twice the additional cost of units that we culture more aggressively for bacteria,” so to replace culturing with pathogen inactivation would cost an additional $165 million a year across the United States. “However, we’re talking about 220 people who were harmed each year from bacterial transmissions before enhancement of culturing techniques.”

In addition, pathogen reduction is an exacting process, Dr. Vassallo says. “You can’t have too many platelets. You can’t have too much suspension medium, which is generally plasma or an additive solution, because if you do that, the UV light doesn’t penetrate well enough. So what you end up doing is setting your collection device in a way that you collect fewer platelets. Worse, you may collect in too little volume and have to throw the entire collection away.”

The American Red Cross has opted to focus on Intercept pathogen reduction for a number of reasons, says Pampee

Young, MD, PhD, chief medical officer, biomedical services, American Red Cross. “While it gives the second longest shelf life, it is the earliest available product so that hospitals have the freshest platelet possible. The other products can only be tested at 36 hours or 48 hours, and the hospital can’t get them until 12 hours after that at the earliest, whereas a Cerus product is available 24 hours after collection.”

By safeguarding against so many pathogens, pathogen inactivation technology gives PRPs a great safety profile, Dr. Young says. “But the main reason we like pathogen reduction exclusively is that it increases availability of products for hospitals. What happens when a blood center produces 30 percent non-PR and 70 percent PR, or some other mix? When you’re trying to deal with a mixed inventory, it invariably results in inefficiency and discard and ultimately fewer units available to patients. Our data showed the greatest efficiency can be achieved by having a single technology that provides a safe product with a good shelf life.”

Clinical studies have shown that patients’ platelet counts rise less with PRP, on the whole, than with non-PRP, she says. But clinically, this difference is not significant. “There’s no increase in platelet use or increased risk of bleeding,” as a result of using PRPs. So in terms of efficacy, “We feel comfortable that this is a noninferior product, and that’s the basis on which the FDA approved this product in this country.”

The expense of the PRP technology does not discourage smaller hospitals from wanting to take advantage of it, says Claudia Cohn, MD, PhD, chief medical officer of the Association for the Advancement of Blood and Biotherapies (AABB) and director of the blood bank laboratory, associate director of clinical laboratories, and professor of laboratory medicine and pathology, University of Minnesota.

“The smaller the hospital, the more they want to be taken care of,” she says. Non-specialists don’t want to deal with the complications and nuances that are part of transfusion medicine, Dr. Cohn says. “The American Red Cross will hand you this pathogen-reduced platelet that is super-safe and super-easy to use and it takes care of your needs.”

“It’s the largest centers”—the biggest users of platelets—“that have the greatest concerns about the choices that blood centers have made to satisfy the FDA requirements, and about how heavy-handed some blood centers can be in terms of providing only one kind of platelet,” she says.

Dr. Cohn’s own contracts specify that her laboratory is not allowed to go to another blood center to seek blood if there’s a shortage. “It is up to my blood center to seek that blood for me. That’s fine with me and it works.” But other hospitals have contracts that are more open, and they may not be able to rely on predesignated blood units. She says she has heard horror stories that reveal what can happen to midsize hospitals without a primary contract with a blood center. “If there’s a shortage, they can call the blood center and say we need 10 units and the blood center will say, ‘Sorry, we don’t have it for you’—because the blood center is holding it for its larger clients.”

Dr. Cohn

That can aggravate the tendency of hospitals, in a time of shortage, to hoard. “A lot of hospitals take in more than they need so they have enough for their patients in case the blood center says no to them. Of course, the more they hoard, the more waste there is. And that’s unfortunate, but that is the environment in which we function.”

AABB Bulletin No. 21-02 (June 2, 2021) says “blood center decision drivers should include the preferences of their hospital partners although the logistics and cost of providing multiple mitigation strategies may also be a factor.”

The smaller hospital will prefer a platelet product that doesn’t require subsequent testing, agrees Alyssa Ziman,

MD, medical director for Ronald Reagan UCLA Medical Center clinical laboratories and medical director of transfusion medicine and professor of pathology and laboratory medicine at UCLA. “Non-pathogen–reduced units may require a secondary culture or a point-of-issue test. The responsibility of additional testing falls on the blood bank, and [in the smaller hospitals] they lack the expertise or staff to manage the inventory like that.”

At UCLA, 95 percent of platelets are pathogen-reduced, she says. “To me, pathogen reduction provides the safest product as it further minimizes the risk of transfusion-transmitted infections when coupled with standard donor infectious disease testing. In addition, our hospital-based donor center can release the platelet units to our blood banks at day two or as soon as standard donor test results are available.” This is important for patient care, she says, especially during times of shortage.

That process contrasts with platelet culture at the time of collection or shortly after, which is another of the bacterial risk control strategies the FDA approved in its 2019 Guidance for Industry, along with testing before transfusion. The FDA guidance required blood centers and transfusion services to implement one of the three strategies by October 2021.

With culturing, there are concerns about false-positives as well as false-negatives. “There may not be sufficient bacterial load when 8 mLs of the platelet unit are used to inoculate the culture bottle,” Dr. Ziman says. “So a residual risk with the culture strategies remains when bacterial loads do not reach a critical mass in the unit until day four or day five. When considering a strategy that uses the point-of-issue test, there are concerns with false-positives and the resulting impact on the platelet supply, as well as the fact that this testing requires technologist time.”

A recent paper reported that about 80 percent of positives found by culture are false-positives and about 20 percent are true positives (Corean J, et al. *Transfus Med Rev.* 2021;35[3]:44–52).

Amid staffing shortages, additional testing becomes problematic, Dr. Ziman notes. “Blood bank staff would not only have to perform blood typing and antibody screen tests, but they’d also have to do this other test to get the platelet unit to the patient.” When her laboratory at UCLA considered this testing several years ago, “We talked about performing point-of-issue testing in batches once a day rather than at point of issue in order to not delay patient care. This would result in testing our entire inventory on day four and day five.”

“While this ties up staff to test the entire inventory, it ensures there are no delays when platelets are needed emergently or for patients who are getting an outpatient platelet transfusion.” These are all reasons why she believes pathogen reduction provides the safest product for patients and the most efficient product from a workflow and staffing standpoint. Even accounting for the savings in staff time needed for other methods, “pathogen-reduced platelets are still a more expensive product. But I believe it’s the best product available for our hospitals and our patients.”

Contamination of a platelet product during collection is rare. But “another source we’re increasingly recognizing” is “there are opportunistic environmental bacteria that may sneak in through tears in the bag,” Dr. Vassallo says (Gammon RR, et al. *Transfusion.* 2021;62[3]:641–650).

Within the past year, “the FDA issued a warning about a few cases of pathogen-reduced platelets that were actually growing bacteria” because of such tears, says Glenn E. Ramsey, MD, chair of the CAP Transfusion, Apheresis, and Cellular Therapy Committee and medical director of the blood bank, Northwestern Memorial Hospital, Chicago, and professor of pathology, Northwestern’s Feinberg School of Medicine.

Dr. Ramsey

“The vendor for the pathogen-reduced platelets issued more information to blood centers and hospitals about how to store these products to avoid damage to the platelet bags,” he says. “So there’s still a small chance of contamination. I don’t know to what extent that result has helped resolve the problem, but that was the first time I was aware there could be still some issue with contamination of a treated product.” While he hasn’t seen that at Northwestern, the hospital is aware of it. “In some cases when we get a patient with an unusually severe febrile reaction, we continue to culture the products to make sure there is no bacteria in them. We’re still doing that sometimes with pathogen-reduced platelets just to make sure.”

A December 2021 FDA memorandum said “it is important for blood establishments and transfusion services to recognize the residual risk of bacterial contamination of platelets, including pathogen-reduced platelet components.” Since 2018, the FDA said in the memo, the seven cases of reported platelet septic transfusion reactions are “associated with *Acinetobacter* species and certain other bacterial species seen in combination, and where additional genetic testing indicates relatedness of the organisms.” No source has been identified, it said, and the FDA and CDC continue to investigate.

Those residual risks aside, the availability of PRPs has increased the discussion of possibly using paid platelet donations, Dr. Vassallo says, noting there are several proposals on the horizon to extend platelet shelf life as well as find new donors. “Paid donations have historically been a little less safe. We have very good testing, but there’s still a window period and a pathogen-reduced platelet from paid donors would probably be a very, very safe product.” It’s one more way to deal with shortages.

Cold storage of platelets immediately after donation would produce a 14-day product, Dr. Vassallo explains. “It’s generally out within two days so it has about 12 days’ shelf life. The problem is that when you put platelets in the cold, they express ‘eat me’ signals to the immune system, which quickly removes them from circulation. Nature never meant us to put platelets in the refrigerator. But these more active platelets should be very good at stopping bleeding in a person who is actively bleeding,” he says, though they would not be effective for prophylaxis.

Transitioning room-temperature–stored platelets to cold storage after five days—then refrigerating them for the next nine—would also extend platelet availability for certain patients. “The problem is during those five days you have to have some mechanism to prevent bacteria from growing, and that is either pathogen reduction or a retest on day five to make sure bacteria haven’t grown in those five days.”

Frozen platelets could become available in the next five years or so, he says. “In an emergency when someone has an accident, half of the frozen platelets rush to the wound and the other half circulate. So frozen platelets will be a game changer for patients as well,” Dr. Vassallo says. “If hospitals stock a frozen platelet, we don’t need to collect as many platelets to have just-in-case stock.”

Under the FDA’s guideline for mitigating bacteria in platelets, Dr. Ramsey says, “the two most common pathways are delayed sampling, where the platelets are held for 48 hours and then sampled and cultured. Then they could be stored up to seven days. With pathogen reduction, the platelets are treated up front and they wouldn’t need to be cultured.” At Northwestern, about half of the platelets are pathogen-reduced and half are culture. “It depends on the supplier to some extent, but there’s still a fair mixture of both in the blood supply,” he says.

PRPs are still a five-day product at this point, he notes, while some of the large-volume blood sampling protocols can go up to seven days. “The pathogen-reduced platelets do have a slightly reduced response and the patients do not get quite as good a post-transfusion platelet count increment compared with untreated platelets.” Moreover, the circulation time of those platelets is a little shorter than that of untreated platelets.

“There’s been conflicting data on whether that leads to more usage of platelets,” he says. “Some studies found more usage at hospitals that were converting to pathogen-reduced platelets, and in other studies in other countries there was not such a difference. But there is at least a small effect on the platelet quality from treating the product.”

The academic medical centers have led the way in adopting PRP in California, says Patricia Kopko, MD, professor of pathology and director of transfusion medicine, University of California San Diego Medical Center. “The California experience has been that a large group of the centers, including the UCs, Stanford, and Cedars-Sinai, switched to pathogen-reduced platelets. Then the bigger community hospitals began switching.”

Dr. Kopko 

Alongside this trend, “The American Red Cross decided to go to pathogen-reduced platelets entirely over the next year or two, because when you’re talking about manufacturing, two streams is much more costly than putting everything into the same workflow.”

But there should be little debate, she says, about whether the added assurance of safety justifies the use of PRP, because risks of a septic transfusion reaction are still high. Without intervention, the rate of contamination occurrence—at least one in 10,000 and possibly higher—remains a shocking number, Dr. Kopko says.

“We transfuse over 10,000 platelets a year here, so that means once a year we would be giving somebody a reaction. If you’re on the receiving end, would it seem reasonable to you or your family that the hospital saved $75 on your platelet unit but your wife, daughter, mother, or whomever, died of a septic transfusion reaction?” Using PRP to avoid such outcomes, she says, is well worth the cost to hospitals.

Anne Paxton is a writer and attorney in Seattle.