Trials show no benefit from fresher red cells

Anne Paxton

September 2015—Whether transfusion recipients are better off receiving fresher red blood cells has probably been the most pressing and controversial question in blood banking in the past several years. So much so that enormous randomized, prospective trials involving patients in the U.S., Canada, Europe, Australia, and Africa have been comparing outcomes from RBC units of different duration in a variety of patient subpopulations. One of the goals of these trials was to test findings of a Cleveland Clinic retrospective study, published in 2008, that older blood did seem to produce worse outcomes.

The results of two trials were announced this spring, and the findings have taken at least a few blood bankers aback. Shattering preconceptions on the part of some, results published in the April 9 *New England Journal of Medicine* from pivotal studies in the U.S. and Canada indicate that whether patients requiring transfusion receive fresh red blood cells or standard-issue cells that may be up to 42 days old, there is no difference in clinical outcome in the populations studied.

The RECESS study looked at the duration of red cell storage and cardiac surgery patients' changes in the Multiple Organ Dysfunction Score, or MODS, and found duration was not associated with significant differences in MODS (Steiner ME, et al. 2015;372[15]:1419–1429). The Canadian ABLE study assigned critically ill adults to receive either red cells stored for less than eight days or standard-issue red cells, and found that fresh red cells did not decrease the 90-day mortality of critically ill adults (Lacroix J, et al. 2015;372[15]:1410–1418).

"These were really large and well-done studies that didn't even give a hint that storing blood cells for a longer time period would be detrimental," says James AuBuchon, MD, president and CEO of Bloodworks Northwest in Seattle. "The prospective, objective data speak very loudly, and those data do not indicate that the storage period of red cells is a concern, at least in most circumstances."

With such apparently definitive results, there is wide agreement that storage duration of red blood cells is no longer the front-burner blood banking issue. Yet, as blood researchers interviewed by CAP TODAY suggest, many burning questions remain open, key differences in blood centers' policies on RBC storage duration are likely to persist, and intriguing and unexpected discoveries during the trials will ensure that debate continues to simmer over several issues.

RECESS and ABLE were well carried-out studies, but they have not answered every question about possible risks created by older RBCs, says Harvey G. Klein, MD, chief of the National Institutes of Health Clinical Center's Department of Transfusion Medicine.

"RECESS and ABLE did precisely what they were designed to do, and their conclusions were very closely based on the data they have," Dr. Klein says. "But I think what the studies say—which is sometimes misinterpreted—is that there is no advantage to transfusing blood that's fresher than the standard-issue blood that is transfused. These studies were not designed to look, nor did they look, at the issue of whether there's any toxicity in the 'old' blood that has been 36 to 42 days in storage." Nor did the studies address every clinical situation, he adds—only cardiac surgery and critical care patients.

"First in, first out" is the strategy of blood banks for inventory control. "So ordinarily, you use the oldest blood that you have. Having said that, in most large metropolitan centers, blood is turned over so quickly that the national mean average of blood that's transfused is about 17 to 18 days on the shelf."

That may partly explain why the retrospective studies had different findings than the most recent randomized

prospective trials. In fairness, Dr. Klein notes, the retrospective studies looked at blood that was older than the blood in the randomized, controlled trials. “Retrospective studies really are only generators of hypotheses,” he says. “The Cleveland Clinic published data from two groups, one of which they noted as being fresher and one older, and older was not in the last week of storage; the median storage age was 20 days. That doesn’t mean their conclusion is necessarily correct, but they are looking at something a little different than the randomized trials are looking at.”

“The issue that has been resolved, at least to my satisfaction, is when someone in the civilian sector requests fresher blood than is the standard for transfusion, there is no evidence that it brings benefits—at least to cardiac surgery patients and to patients in critical care. Whether it does in other settings hasn’t been specifically studied, but I think it’s unlikely that fresher blood in most circumstances is going to be better.”

Dr. Klein

What hasn’t been settled is whether blood that has been stored for 36 to 42 days (the maximum storage duration under Food and Drug Administration rules) is riskier in terms of mortality or morbidity than is standard or fresher blood, Dr. Klein says. NIH studies using animal models suggest patients who have established infections might be at risk from the oldest blood. “We’re continuing to study the pathophysiology of what happens when we give animals the oldest blood, but even large animals’ red cells are not exactly like humans’ red cells. So our studies don’t tell you exactly what happens in the human setting, but I think they certainly suggest we need to be concerned about this.”

The United Kingdom and the Netherlands, and several other countries, Dr. Klein notes, do not use blood older than 35 days. “They don’t have supply issues at all, so they’ve already taken the position that they don’t need to use the oldest blood and they simply don’t.”

In the U.S., for the past five years, supply has not been a problem either and many blood centers have cut back on their recruiting, so he does not think shortages would result from adopting the U.K. policy here. “That doesn’t mean if you changed a storage date, you wouldn’t have to do something about increasing recruiting and probably the cost of blood.” Although hard national figures are not available, Dr. Klein estimates that between eight and 20 percent of blood transfused in the U.S. is in the last week of storage.

That’s not the case at NIH, however. “For more than a year, we have not used blood in that last week of storage. We’ve not discarded it; we’ve put it on a shelf called ‘36-Plus,’ and if a unit on there is unusual and is needed, then it becomes a risk-benefit calculation whether to use it. Obviously, if you need a rare unit, it’s better to have a 36-Plus than no unit at all. So it’s important to realize all blood units are not the same.”

As far as he knows, NIH is the only hospital in the U.S. that has adopted this policy.

“We made the determination based first of all on our own pre-clinical studies. It’s a strategy we feel is safe and can be done without a big impact on patient care since we collect our own blood.”

Dr. Klein does not consider the RBC storage question to be resolved. “We know that during storage, dramatic changes take place in the red cell. The cells ‘run down,’ but we don’t know to what extent and what the timelines are. The question is: Are the changes clinically important?” Although fresh versus standard-
issue blood appears to have been addressed, he notes, “For ethical reasons the clinical studies have not been powered to specifically compare the oldest blood and the freshest blood, and in animal models we’ve found a dramatic difference.”

What is known with certainty is that blood donors are different. “Your cells store differently than my cells. Our red cells store differently because of our genetics. So it’s been known for 40 years that some donors are actually better for the blood supply.” The degree to which this occurs is of increasing interest, Dr. Klein says.

In the future, he predicts, with the information systems now available, “you can see a time when red cells will have a molecular profile for their antigenicity so that we can tell you all about the compatibility at the molecular level and perhaps their storage capability, and our computer would be able to tell us what the best cell is for the individual patient and their disease condition. We might be able to personalize red cell transfusion to a much greater degree than we do today.”

One of the best examples of precision medicine since the beginning of the 20th century, he notes, has been transfusion where blood is selected based on antigens. “Today we can do that based on the molecular profile, and tomorrow perhaps we’ll base it on the storage characteristics of the red cells as well. It will be much more precise than it is today.”

A study comparing the very oldest blood with blood in the first week of storage could find a difference, Dr. AuBuchon agrees. But he questions the wisdom of undertaking such a study. For one thing, “We know that transfusing all units within the first week of storage is not feasible, and it’s rare for someone to be transfused only with the oldest chunk of blood.”

Mounting such a prospective study would also have ethical and logistic hurdles. “Ethically, one would be challenged because researchers would be positing that the oldest blood was detrimental to recipients, and anyone already transfused is already in a difficult situation, and you would potentially risk giving them the ‘worst’ blood possible. It would also be challenging to have the inventory for such a study.”

When RECESS and ABLE were funded, Dr. AuBuchon adds, “We truly didn’t know if older blood was worse for a patient than younger; in fact, some data suggested the opposite, so it was a comfortable situation to propose engaging in the study. Once you know which way was better, it becomes much more difficult to promote participating in the study.”

Is there a breakpoint when older blood is definitely worse? “We have no indication that the age of red cells has any impact on patient outcome. Most of the biochemical changes that occur in red cells over 42 days of storage are gradual; they do not occur precipitously, and so a dichotomous label such as young versus old or good versus bad does not seem to apply.”

“It was always possible that the accumulation of some analyte or loss of some compound of red cells might render the cells not as helpful to a patient, or potentially harmful to a patient. And again, whether that was at a definable single point does not seem to be the question at the moment.”

Is there any interest in extending the current FDA-approved shelf-life limitation of 42 days? “Most of the blood units that outdate today are Group AB, and if you doubled the storage time, there would still be outdated AB blood; it’s just a factor of the ABO group.” Still, he says, researchers are interested in understanding the changes that occur with storage. At the Bloodworks Northwest Research Institute, the focus is on identifying why the red cells of some donors appear to survive the storage period better than those of other donors.

“We would like to develop a simple test we could apply to a donor unit to identify the duration of storage most appropriate for that unit, and it might be less or more than 42 days. It might be theoretically possible to identify units that were better for patients in certain conditions. But the research has not progressed to that point yet.”

When he did research on red cell recovery and survival at Dartmouth College, where he worked previously, “It was easily observable that some of our subjects always gave superlative recoveries on the reinfusion, while others always had lower than average recoveries. We didn’t know why,” Dr. AuBuchon says. “But now we’re upon the point of unlocking that mystery, and we may be able to apply it to optimize the length of storage of each particular

donor's contribution."

The idea of a "storage lesion" in reference to red blood cells may be on the way out, Dr. AuBuchon believes. "'Storage lesion' is a common shorthand that really reflects our ignorance as to what of importance is happening in red cells. We learn every day that there are so many things that change, yet we don't really know which combination of these changes is potentially important to the survival of the cell or the outcome for the patient."

To his knowledge, no one is considering altering the standard first-in, first-out usage algorithm, except for transfusing neonates. "It is common practice in most institutions to give the very youngest patients the youngest red cells, but they're small and they usually don't need very much. The approach commonly used is to dedicate a fresh unit to a patient, then take aliquots from that unit over the next five or six weeks, so the unit is aging as the patient is aging. That reduces exposure early." This practice began when blood centers were dealing with concerns about HIV and it just continued, Dr. AuBuchon says.

At least potentially, as more study is directed to the metabolic profile of red cells during storage, "we may find some red cells are better able to carry and offload oxygen than others, or they may have capabilities in that regard only for a certain time. So it certainly might be possible that we end up segmenting our red cell inventory to offer red cells of different age and different capabilities in different situations. But it's not going to happen anytime soon."

Research might also show that donors, after a simple test, should be considered as better donors of one component, such as platelets, rather than another. "At the moment, it's based more on ABO than anything else. But we may become more sophisticated in the future."

The RBC storage controversy occurs as the use of red cells is in sharp decline. "It's fallen quite dramatically over the last five or six years," says Dr. AuBuchon, noting that RBC use has dropped by 25 percent to 30 percent and blood centers have constricted their recruitment and collection operations in response. "There's no point in collecting it if you don't need it."

Heddle

According to the most recent HHS National Blood Collection & Utilization Survey Report (2011), from 2008 to 2011, transfusion in the U.S. decreased by more than 11 percent, and the American Red Cross confirms the trend is continuing. Canada, too, has seen significant declines, says Nancy Heddle, MSc, director of the transfusion research program at McMaster University in Hamilton, Ontario, who is leading the 31,000-person INFORM study (Informing Fresh Versus Standard Issue Red Cell Management), which has recruited patients in the U.S., Canada, Australia, and Israel. "About five to seven years ago, there were a million red cell units transfused in Canada, and now I believe on a yearly basis it's about 890,000, so about a 10 percent drop, which is pretty dramatic considering that the population is aging," Heddle says.

Despite this trend, Dr. AuBuchon says, red cells are still essential to modern health care, and many blood centers are finding it increasingly difficult to recruit adequate numbers of blood donors. "In fact, blood collectors around the world are finding the same thing. Part of the BEST (Biomedical Excellence for Safe Transfusion) Collaborative has been comparing data over the last year, and all developed nations with the exception of Singapore are showing that their donor populations are aging."

The ABLE study (Age of Blood Evaluation Randomized Controlled Trial), a multinational study based in Canada, enrolled 2,430 critically ill patients whose mortality rate was upward of 30 percent, says coauthor Paul C. Hébert, MD, professor of medicine and chief of the Department of Medicine at the Centre Hospitalier de l'Université de Montreal. But when the results came in, "we were unable to document any harmful effects of older blood overall and in any secondary analyses."

Overall, Dr. Hébert was not surprised by this result. "However, it's called 'research' because you don't know what you're going to find," he says. "There were some counterintuitive findings—some small signals suggesting fresh blood might have actually been worse. There were no significant results, but in a few subgroups you would be noticing the fresh side is on the wrong side of the line. Interesting and unexpected."

The authors concluded that fresh blood was definitely no better than standard issue in this population, Dr. Hébert says. "What we don't know is: What about very old blood, stored from 35 to 42 days? It's entirely possible that blood that is stored for over 35 days does more harm than good."

Interestingly, he notes, another study called ARIPI (Age of Red Blood Cells in Premature Infants), on which he was second author a few years ago, found that even with neonates, no difference was detected in outcome between a group that received the assigned unit a quarter unit at a time while the unit "ages on the shelf," and a group that received fresh blood each transfusion (Fergusson DA, et al. *JAMA.* 2012;308[14]:
1443–1451).

The ABLE study provides definitive evidence that fresh blood is no better than standard in the critically ill, Dr. Hébert says. Another large study, TRANSFUSE, is underway in Australia. "It's still recruiting approximately 100 patients a month and will be almost twice as many patients as the ABLE study. However, the TRANSFUSE trial asks whether giving the freshest blood first is superior to giving the oldest blood first. So basically a 'front of fridge' approach versus 'back of fridge.'

"This is a policy study—a different and complementary way of formulating the research question," Dr. Hébert says. "This more pragmatic approach will help blood banks but risks having less of a difference in storage times between groups. In the ABLE trial, we decided to look at fresh versus standard issue. In doing so, that afforded us an 18-day spread in the age of the blood."

Including the ARIPI study of neonates, "Three of the major trials that have been designed over the last 10 years have now been reported," says McMaster University researcher Nancy Heddle. She was involved with a study published in the *American Heart Journal* that retrospectively looked at 2002 to 2006 data, finding that, as blood aged, there was a progressive increase in in-hospital mortality (2010;159[5]:737–743.e1). "So that observation fit with the hypothesis that all of these randomized, controlled trials have based their studies on. Everybody had the sense that old blood was harmful if it had been stored for a long time, and our results were consistent with that."

That the ABLE study found an opposite trend was somewhat surprising, she says. "The 90-day mortality rate in the 'fresh' arm of the study was about 1.7 percent higher. It's not statistically significant, but it's in the wrong direction of what everyone thought it would be, so that was one of the intriguing things."

That result fit nicely with the hypothesis raised in her study published in February on the age of transfused blood and in-hospital mortality in patients with cardiovascular diagnoses (*Transfusion*. 2015; 55[2]:364–372).

"It's a retrospective study, so it can only be hypothesis-generating, but we found this pattern of older blood possibly being more harmful in the data up to 2006. Then, when we analyzed the data up to 2011 and 2012, the signal disappeared. It no longer appeared that old blood was bad; rather, it appeared that fresh blood may have an increased effect in hospital mortality."

However, it turns out that just at the time of the switch, Canada had changed the way it processes blood. "We

went with a system called ‘buffy coat’ processing that is not used in the U.S. Then, all of a sudden, fresher blood appeared to be worse. So we at least raised the hypothesis that the manufacturing or processing method for whole blood donations might actually have an impact on patient outcomes.”

Buffy coat processing has been common in Europe for the past 10 years, she says, because it produces more plasma from whole blood donations, which helps support the supply of other products, and appears to produce a better platelet product. “But some people just assumed that because the platelet product is better, then the red cell product would be better too, and that may or may not be the case.” (In the U.S., she notes, platelets are produced through apheresis, not from whole blood.)

There are only a handful of centers in the world that are able to link large databases of blood donor, product, and patient transfusion information, Heddle says. “We were fortunate to have one of those databases to look at factors that affect patient outcomes.” It happens that the ABLE study’s finding of 1.7 percent higher mortality in the “fresh” arm fits well with her hypothesis. But “all we can say is over a 10-year period, for the first four or five years there was a higher risk of in-hospital mortality with old blood, and in the last four or five years the risk was higher with fresh blood.”

While she cannot announce the results yet (they will be reported in October), she has compared outcomes for the two processing methods, buffy coat and whole blood filtration, for every unit of blood transfused at her center from 2008–2014.

As for decreasing the storage window, as the U.K. and the Netherlands have done, “To my knowledge there are no discussions of that in Canada,” Heddle says. “The concern is you might not have enough blood supply or you might waste units. I don’t think a week is going to make a difference.” Canada used to allow blood to be stored for only 21 days, she adds. “So it’s doubled in the years I’ve been in the field.”

In the next year and a half, three more large age-of-blood studies will be published, including the INFORM study being conducted at McMaster University. “With over 30,000 patients, that will be the largest of all the studies,” and its results should be available in spring 2016, Heddle says. The ABC PICU study (Age of Blood in Children in Pediatric Intensive Care Units) and the critical care study in Australia, TRANSFUSE, are the two remaining trials.

But there remain a lot of unsettled questions and unexpected discoveries. “The hypothesis we generated—that depending on how different countries make blood, there may be potentially a risk of fresher blood being bad—who would have ever thought of that? You would never think the freshest jug of milk would be bad. So if anything, these additional studies are only going to serve to confirm that stored blood probably does not carry additional risk, but they will also help determine whether fresh blood may cause risk.”

What happens to red cells during storage is only partly understood, and basic research on this subject is likely to get a boost as more questions are raised, Heddle believes. “There certainly is basic science research going on trying to understand the biological mechanisms that might be associated with the storage of blood and patient outcomes. People have hypothesized a lot of things—whether it’s promoting inflammation, or whether the iron coming from red cells may be detrimental. So there are a lot of different frameworks and hypotheses out there. I suspect we’ll see an increase in activity once all the results from these studies come out.”

From here, Dr. Hébert predicts, transfusion research dollars are likely to shift to two other big areas: transfusion triggers in specific subpopulations and studies evaluating the use of plasma. “For transfusion triggers, we still don’t know what to do in certain subpopulations, such as heart attack patients or traumatic brain injury. Maybe people with really acute injuries to the heart or brain are different. These remain unanswered questions with limited high-quality data. Then we also need a lot more research on the use of plasma to determine when it is truly beneficial. This area of research is in its infancy. There is so much to explore.”

For the time being, the RBC storage duration studies completed so far are showing there is no evidence that older blood stored up to 42 days causes harm to patients, Dr. AuBuchon says. “I think the last half decade or longer that this controversy has been swirling—we will look back on it decades from now as indicating how one can be trapped

into an unsupportable belief by retrospective studies.” He believes the blood collectors of the world, who always have to worry about potential shortages, are pleased because, based on these prospective, randomized trials, a strong push to reduce the storage window for red cells will now be unlikely.

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