About This Issue

In March of this year, blood bankers from across the U.S. and several from Canada and Europe gathered outside of Chicago for a one-day symposium: Plasma Transfusion: Current Status and Future Directions. This was sponsored by the Stroger Hospital of Cook County (the new name of the famous Cook County Hospital) and the Illinois Association of Blood Banks, in honor of Dr. Bernard Fantus. The occasion marked the 75th anniversary of the first U.S. hospital “blood bank,” a term coined by its director, Dr. Fantus in March of 1937. In keeping with the importance and medical and economic impact of plasma products, the symposium was supported by a broad range of blood service organizations and the entire program was recently published in Transfusion by the AABB. The meeting was well-attended and very useful; thus, we’d like to share some of it with you. You can find the original articles online in Transfusion as well. We urge you to look at them, as there are many extremely useful charts and diagrams, as well as some excellent reviews and recommendations on the clinical uses of plasma for you to digest.

Historical Perspective

Not all readers will remember that World War II began in Europe in 1939 with the invasion of Poland, and then of France, Belgium, the Netherlands, Norway, North Africa, Russia and the eastern European and Balkan countries. It grew even larger at the end of 1941, with the attacks on Pearl Harbor, the invasion of Asian and Pacific countries by Japan and the entry of the United States into the war. Prior to that, blood was collected, stored (in ACD, usually) and transfused as whole blood. With a short shelf-life of 21 days, and the difficult logistics of supplying blood to forward areas of combat casualty treatment, it was late in the war before adequate logistics (transport, storage, refrigeration, laboratory management) were in place to get it to where it was most needed. Thus, during much of the war, front line transfusions were accomplished primarily with plasma.

“There is no properly no history; only biography,” said Ralph Waldo Emerson, one of the more noted American writers of the 19th century. But, a bit of history is always in order, and Dr. Paul Schmidt, our transfusion medicine historian, presented some very relevant history at the evening banquet prior to the symposium. And surely enough, it was fittingly biographical. His article leads off the special issue of Transfusion.

In the late 1930s, two separate lines of research had developed liquid plasma, the process developed by John Elliot, who had an honorary doctorate from a small rural college and some U.S. Navy-based laboratory training, and freeze-dried plasma, developed by Dr. Max Strumia, a European-trained academic. Thousands of units of liquid plasma were prepared by the American Red Cross and shipped for use in the Battle of Britain, the aerial bombardment of England in mid-1940. However, the mass production at different laboratories and overseas shipment led to bacterial contamination problems, and the program was halted in 1941. But Dr. Strumia had already developed a process for turning Elliot’s liquid plasma into a sterile powder, and military funding was developed to prepare it in a sterile container with sterile distilled water for reconstitution in a package designed by the two men. After larger pools of plasma were used for production, it became apparent that “serum hepatitis” was a common result of transfusion, and the way was paved for the use of heat-treated serum albumin as a mainstay of non-RBC-containing transfusion support. This was the birth of the process of plasma fractionation, with the eventual development of infection-free coagulation factors and other plasma derivatives, which is another story in itself.

Schmidt, PJ. The plasma wars: a history. Transfusion 2012;52:2S–4S.

In the News

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Cover photo: bone marrow with a megakaryocyte which will form blood platelets or thrombocytes
Several of the articles in this Transfusion supplement have suggested that plasma transfusion is over used, if not, to put it frankly, abused. Drs. Vyas and Pandey, the authors of this paper (see article listing below) note some striking documented increases in FFP transfusion in the United States, from 2.3 million units in 1991 to 3.9 million in 2001, and a whopping 4.5 million in 2008. Why we have doubled our usage in 20 years is a puzzle to some; however, it appears that 30–50% of such transfusions are for non-bleeding patients with—or without—a planned procedure, as is noted in one of the other articles in this issue. They repeat, and we have seen, that there is little to no convincing evidence that such transfusions are beneficial or that modest elevations in standard coagulation factor tests are either predictive of bleeding or that they correct with plasma transfusion. Many studies show that as many as 50% of plasma transfusions don’t follow established guidelines.

The more common risks of plasma transfusion include transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and allergic, sometimes anaphylactic, transfusion reactions (ATRs). Rarer occurrences include the transmission of infectious diseases, WBC-associated risks (febrile non-hemolytic transfusion reactions), RBC alloimmunization and even hemolytic transfusion reactions. How so these, you ask? Keep reading!

Much has been written of TRALI lately, but since it has emerged in the last decade as the most common cause of transfusion-related mortality, it must be briefly reviewed. It occurs generally within 6 hrs of transfusion and is characterized by non-cardiogenic pulmonary edema (normal central venous and atrial pressure) and severe hypoxemia. Data from the United Kingdom showed it is 7 times more likely to occur after transfusion of FFP than RBCs. Most patients recover with respiratory support, but 5–25% of cases have been reported as fatal. There appear to be recipient factors, such as liver disease, alcoholism, hematologic malignancy and coronary artery bypass grafting that predispose to the occurrence, and the transfused cause is the presence of donor-related HLA Class II or neutrophil antigen (HNA) antibodies. The result is damage to the respiratory endothelium and increased permeability to blood fluids leading to pulmonary edema and severe respiratory distress. Most donors implicated in such cases were multiparous women and a significant decrease in TRALI incidence has accompanied strategies to prohibit, limit or test donations where such antibodies might be present, including those of plateletpheresis donors.

TACO looks similar to TRALI except that it is due to primary circulatory overload, and thus development of “traditional” acute pulmonary edema with elevated central venous pressure due to right ventricular failure. In the 2010 FDA report on transfusion fatalities, TACO was the second most common cause of mortality related to transfusion, occurring as frequently as in 5–15% of TACO cases. Older age or small-body habitus, such as in children, are risk factors, along with pre-existing cardiac or renal dysfunction. Large volumes of transfusion and rapid infusion rates may be involved as well as occurs when FFP is ordered for coagulation reversal.

ATRs are estimated to occur in 1–3% of transfusions, and most are mild with itching and/or urticarial wheals. The more severe anaphylactic reactions present with bronchospasm, angioneurotic edema and often a significant drop in BP. Most commonly they are seen with FFP or platelet transfusions, sometimes related to the presence of IgA antibodies in the recipient, who is usually genetically IgA deficient and has IgG class-specific antibodies to IgA. A registry of IgA deficient donors has been developed by AABB and the American Red Cross for use in defined recipients.

Infectious disease risks from transfusion in more developed countries have been greatly reduced by testing in the last 25 years, which is a big part of the reason TRALI and TACO have

Risk vs. benefit: plasma transfusion redux

Continues on next page
How many times has your blood bank been asked to thaw 2 units of FFP to correct a prolonged prothrombin time/INR in a patient so that a liver biopsy, or spinal tap or some other invasive procedure, perhaps an operative one, could be performed? My guess is...a lot! In this special Transfusion supplement, two experts from the blood transfusion service at Oxford University Hospitals in England took a close look at this practice, and...guess what? No surprises here; they found it to be lacking in soundness.

In this paper, Drs. Desborough and Stanworth used FP as the common designation for FFP or FP24. They discuss pathogen inactivated plasma, but it isn’t clear if such units were included in their discussion, and it likely would make no difference.

Prepared for the invasion

They note that the use of FP has increased in many countries over the past few years, including the U.S. and the U.K., and they note that the production of FP reported in the U.S. in 2005 was 22% greater than in 2004. One of the more common indications for use has been prophylaxis. In England, in 2009, 43% of FP units were given for prophylaxis, in the absence of documented bleeding. In still another British study, 30% of the patients had an INR >1.5. In this study, half of the patients transfused with FP had no recorded bleeding as an indication for transfusion.

The authors go on to pose, and discuss, three related questions. 1. What is the evidence that abnormal results for standard coagulation tests predict bleeding? 2. What is the evidence that administration of FP improves such abnormal tests? 3. What is the evidence that FP use improves such clinical outcomes, including bleeding, to the degree that it outweighs the known risks of transfusion?
With regard to the first question, they cite details from the 2005 review by Segal and Dzik, which was based on a controlled trial in liver biopsies and two dozen observational studies. In addition, they review numerous other reports involving physical interventions, such as: central venous catheter insertion; lumbar puncture; angiography, liver biopsy; thoracentesis; abdominal paracentesis; tracheostomy; and even cardiac surgery. They conclude that the standard coagulation tests have little value in predicting bleeding in these circumstances, but point out that there are very few randomized controlled trials addressing this question, and that other information—clinical conditions such as renal failure, thrombocytopenia, nutritional status—need to also be considered.

Looking at question 2, it was found that FP almost never significantly reduced a prolonged INR or PT, especially at the “standard” dose used in most studies, 10 ml/kg, 2–3 units of FP. The longest INRs or PTs were those most likely to correct somewhat, as we might conclude from the graphs in the paper by Dr. Dzik discussed in this issue. Incremental gains at higher doses were not seen unless the abnormality was pretty severe to begin with.

With regard to question 3, evidence for and/or against the use of prophylactic FP on actual clinical outcomes is hard to come by, given the lack of randomized clinical trials such as are required for a new drug to come on the market. In reviewing almost 80 such trials, there was no consistent evidence supporting the prophylactic or even therapeutic administration of FP along the range of “traditional” indications that we use. The results failed to document effectiveness, either clinical or in laboratory tests, for such prophylactic use, including neonatal, cardiac surgical and other conditions noted above.

When weighed against the measurable risks of TRALI (transfusion-related acute lung injury) and TACO (transfusion-associated circulatory overload), allergic reactions and the diminished but not absent risk of infectious disease transmission, alternative approaches to the prophylactic—and perhaps even therapeutic—uses of FP are in order. A more systematic approach to evidence-based medicine would reduce the over use of this product, and likely reduce costs. The use of tranexamic acid (see following article) and/or other pharmacologic agents, such as DDAVP and aprotinin, need further evaluation in clinical trials. But it seems pretty clear that the knee-jerk use of FP to treat mildly to moderately abnormal coagulation tests in the absence of actual significant bleeding is an unhealthy practice and a habit from which we ought to swear off. Or, as Sir Winston Churchill would have put it, “...a habit from off of which we ought to swear.” But that’s another story.

Everyone knows that blood clots. Cut yourself, and it bleeds; then it stops. And that over the next few days the clot gets reshaped and eventually reabsorbed as healing and new tissue growth occur. But almost everyone also knows that, sometimes, blood doesn’t clot. Surgeons and blood bankers are probably more aware of this than anyone else, except for patients with bleeding disorders and their families. How the blood coagulates—and the many reasons why it sometimes doesn’t—is a very old, gradually unraveling mystery that is one of the most fascinating subjects in science. And then there is the whole business of why it clots at times when there is absolutely no apparent reason for it, with severe results. There is a delicate and multi-factorial balance between clot formation and clot dissolution; loss of this balance can lead to thrombosis or to a bleeding diathesis.

The development of safe and effective plasma derivatives for treatment of specific coagulation defects, and replacement of immune globulins, is a recognized accomplishment of the last quarter of the 20th century. This special supplement of Transfusion focuses on the use(s) of plasma components in transfusion, and the first article by Drs. Benjamin and McLaughlin reviews the properties and traditional uses of these products. Currently, plasma components are used for treatment/replacement of multiple coagulation factor deficiencies, such as in DIC, or severe, massive bleeding; for treatment of single clotting factor deficiencies when there is no factor concentrate, such as Factor XI deficiency; and, as replacement fluid for therapeutic plasma exchange, such as for treatment of thrombotic thrombocytopenic purpura (TTP). The four major products currently in use include fresh frozen plasma (FFP), plasma frozen within 24 hrs of phlebotomy (FP24), cryoprecipitate-poor plasma (CPP) and thawed plasma. Thawed plasma is prepared from FFP or FP24 by thawing at 30–37°C and can be stored at 1–6°C up to four days after thawing.

Whenever possible, deficiencies of single coagulation factors should be treated with pathogen-reduced or recombinant-produced concentrates, such as in hemophilia A and hemophilia B (Factors VIII and IX, respectively). Cryoprecipitate, although not generally pathogen-reduced in the U.S., is an excellent source of Factor VIII, fibrinogen (Factor I), Factor XIII and von Willebrand Factor (vWF).

FFP can be prepared from a single unit of whole blood, in a volume of 200–250 ml, or by apheresis, in a volume of 400–600 ml. It contains near-normal levels of all the stable and labile clotting factors, as well as all the other plasma proteins. FP24 comes only in single unit size and is comparable to FFP, except for Factor VIII and Factor V, which are slightly reduced over the extra few hours before freezing occurs. Detailed levels are given in the article’s graphs. It does contain vWF multimers, useful for the treatment of TTP. CPP differs from FFP and FP24 in that it is deficient in Factors VIII, XIII, I (fibrinogen) and vWF; however, CPP can be used like FFP in many situations. Thawed plasma will have relative deficiencies of the more labile clotting proteins, but has good levels of Factors II, VII, IX, X and I (fibrinogen) and adequate levels of the vWF antigens, multimers and protease.

The subject of pathogen-reduced plasma components (not derivatives) is very complex and is discussed at some length in this article. Although several products are in use in Europe, currently none are licensed for use in the U.S. Many studies have shown effectiveness equivalent to FFP of solvent-detergent (S/D) treated plasma, methylene blue treated plasma and UV treated plasma, but some problems have been noted in a few case reports, thrombosis and anaphylaxis in particular. However, they are virtually free of viral or retroviral pathogen transmission, except for the non-enveloped viruses, which include B19 parvovirus and the hepatitis A virus.
Massive blood loss, and its attendant coagulation and transfusion problems, is an important, vexing and often poorly understood phenomenon. A great deal has been written about it, and a variety of protocols have been instituted by a variety of civilian and military institutions in attempts to bring order to chaos and to maximize resuscitative success for our patients. But, write our authors from Toronto, Canada, “...the coagulation disturbance in trauma patients is more than just the result of consumption of clotting factors at sites of injury and dilution from the infusion of intravenous fluids and red cells.” They point out that fully 25% of trauma patients have abnormal coagulation values even before large amounts of fluids are administered.

In addition to clotting factor consumption and dilution, some of the other mechanisms that lead to this coagulopathy in such patients en route to care are: hypothermia (which impairs thrombin generation and fibrinogen synthesis); metabolic acidosis (which also impairs thrombin generation and promotes fibrinolysis); protein C activation (impairs clot generation by inhibition of Factors V and VII and promotes clot lysis); and, hyperfibrinogenolysis (depletion of fibrin and of fibrinogen). Such patients may present with prolonged PTs, aPTTs and thrombin times upon reaching the hospital by helicopter, and have a high death rate (46%) even after full attempts at treatment, compared to an 11% overall rate, according to a major study from 2003. The incidence of severe coagulopathy was strongly associated with the degree of tissue injury and presumed hypoperfusion, and no association was found with the volume of resuscitative fluids given.

Several studies recently have noted in particular the activation of protein C and the resulting anticoagulant effect in major trauma patients. Protein C is activated by thrombin, which—since thrombin also converts fibrinogen to fibrin—demonstrates how nature works to balance the pro- and anti-coagulant mechanisms in our blood. But hypoperfusion leads to more thrombomodulin activation of Protein C. And, of course, the role of fibrinogen in all this turns out to be more complex than we realized, historically.

Fibrinogen is known to participate in primary hemostasis (formation of the platelet plug) by forming bridging between platelets, as well as secondary hemostasis, the generation of an insoluble fibrin clot. Fibrinogen has also been shown to be the first factor to reach a critical level (<100 mg/dl, or 1.0 g/L) at 142% of total blood volume loss, as contrasted with platelets at 230% of total blood volume loss. Fibrinogen decreases rapidly in severely injured patients due to consumption, dilution, minimal total body reserve supply and increased fibrinolysis. In studies of trauma patients, those with hyperfibrinolysis comprised a small (2.5–7) percentage of patients, but had mortality rates from 67–87%. The hypothermia and acidosis associated with severe trauma and shock exacerbate these deleterious effects.

The acid test for reduction of massive bleeding

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Since the middle of the first decade of this 21st century, the pros and cons of clinical trials with fixed 1:1 ratios of plasma and red cells for trauma resuscitation have been debated, and a variety of results reported. The U.S. Army, quite expectedly, has been heavily involved. Arguments for keeping already-thawed FFP on hand at trauma centers have been developed and disputed. Not all trauma patients need plasma transfusion, and in one study there was a significant increase in respiratory distress syndrome in the plasma vs the control patients. There were also reports of an increase in TRALI and multiple organ failure. This relates, of course, to the over use of AB plasma and the need to obtain it from only male donors, and the very difficult task of blood suppliers to provide adequate resources for such activities. (See article by Benjamin and McLaughlin, and the brief article by Dr, Darrel Triulzi—not reviewed here—about AABB and plasma in this Transfusion supplement.)

Finally, the authors present the compelling data for the use of tranexamic acid, an inexpensive and effective antifibrinolytic agent. In a study of more than 20,000 trauma patients randomized to receive tranexamic acid or a placebo at the initiation of resuscitation, the treatment arm showed a strongly significant reduction in death and in death from hemorrhage. There was no increase in thrombotic events. It also appears that active fibrinogen replacement therapy, monitored by thromboelastography (TEG) in some studies, may play an additional useful role, although controlled, randomized studies of this are not yet available.

There’s no such thing as a solution, only new problems

The title above is a piece of old folk wisdom, so to speak, probably common in many cultures. I always thought it summed up the status of many aspects of modern “progress.” Dr. Walter “Sunny” Dzik, from the Massachusetts General Hospital, helpfully (and wittily) develops this point in this Transfusion supplement on plasma in a discussion of the reversal of warfarin’s effect on clotting by vitamin K, plasma, prothrombin complex concentrates and recombinant Factor VIIa. The percentage of populations in the more developed and wealthier countries of the world that are older than 65 years is increasing, he notes, and that segment of the U.S. is expected to double by 2050, from 40 million to over 80 million people. Heart disease, stroke, diabetes and hypertension will increase concomitantly, along with elderly patients with atrial fibrillation, for which warfarin is a mainstay of therapy. Warfarin represents a market of over $7 billion in the industrialized world, but newer anticoagulant drugs have been licensed and represent a huge potential market for pharmaceutical manufacturers.

Warfarin, brand name Coumadin, was isolated from moldy clover in the hay of cows in Wisconsin and identified as the cause of severe hemorrhage in these animals. The mechanism of action was the inhibition of vitamin K, needed for the synthesis of Factors II, VII, IX and X. A team of chemists at the University of Wisconsin performed the work at the Wisconsin Alumni Research Foundation in Madison, which led to the name “warfarin.” Subsequent sales of the drug have
funded a huge number of research products at this large, mid-western university. It was introduced to the market as a rat poison in 1948, and after a suicidal induction of massive bleeding in a depressed patient was reversed successfully with vitamin K, it was realized that—properly dosed and administered—Coumadin could induce controllable and reversible anticoagulation. There are documented genetic alterations in susceptibility to Coumadin that account for the variability in dosing that is required to achieve therapeutic anticoagulation.

Urgent or emergent reversal of Coumadin anticoagulation is often seen from the standpoint of blood bankers as being needed for the convenience of a physician wanting to do an invasive procedure. True emergencies do exist, however, such as intracranial bleeding, where reversal seems essential, even though we have no clear evidence that doing so changes survival outcomes, says Dr. Dzik. The INR has been the traditional way to measure the reversal of anticoagulation, but it has been significantly misinterpreted. Dr. Dzik presents an extremely important and helpful graph that readers should look at and copy for use in their facilities. Adequate levels of the vitamin K-dependent factors (30% of normal) are present at INR levels of 1.8–2.0, and clinicians don’t understand that this test is sensitive to any reductions in factors from normal levels. No one worries about bleeding with a platelet count of 100,000, yet this is considerably lower than normal. But, it is, in both cases, adequate for hemostasis. The graph also shows that INR levels of 2.0–3.0, “anticoagulated” levels, only cover a very narrow zone of anticoagulation, factor levels of about 20%. This means that only modest increases are needed to restore hemostasis. Thus, the infusion of FFP will have little effect on mildly prolonged values, and it means that extremely large volumes of FFP would be required to achieve a “normal,” not just clottable, level of coagulation factors. And since correction is only temporary, vitamin K needs to be administered concomitantly, since levels of Factors VII and IX decline fairly rapidly after infusion.

There are similar, associated reservations concerning the use of prothrombin complex concentrates (PCCs), which in the U. S. contain only Factors II, IX and X, and they do not contain FVII, as do the PCCs licensed in Europe, nor do they contain anticoagulant Proteins C and S. Recombinant Factor VIIa is not licensed for Coumadin reversal, nor does it seem to have such an effect. The key to any successful reversal of Coumadin seems to rely in these studies on concomitant use of vitamin K.

Vitamin K is the specific antidote for Coumadin, but its optimal use has been clouded by two important misconceptions, the first being that it is slow to reverse the drug. This is primarily due to an observational study in which vitamin K was administered subcutaneously, thus getting absorbed by fat and delaying its effect. Further studies have shown that subcutaneous vitamin K is of little use and should be ignored; despite which it is very often administered in this fashion, due to the second misconception. This second misconception is that IV vitamin K administration has a high rate of anaphylaxis. This has not been borne out in practice, and IV administration rates not exceeding 1 mg/min. are recommended by hospitals familiar with the process. It seems clear that we are unclear about what an INR of 1.6–2.0 really means, and overly cautious about the use of the appropriate antidote. Plasma doesn’t seem to be a great deal of use, by itself.

What about the new anticoagulants of the last decade, purportedly safer and easier to reverse than Coumadin? There are two classes: direct thrombin inhibitors, such as dabigatran, and direct Factor Xa inhibitors, such as rivaroxaban and apixaban. Careful analysis of their effectiveness doesn’t appear to show significant benefit over Coumadin, and there are no actual studies in humans that address the question of reversal. Thus, so far, “no solutions, just new problems.” Dr. Dzik concludes as follows: “The ultimate goal for society is the development of an oral anticoagulant that can be taken once a day, that will effectively reduce the risk of stroke or thrombosis in patients with a wide range of thrombophilic disorders, that is inexpensive and non-toxic and that can be promptly reversed should bleeding occur. Sort of sounds like warfarin, doesn’t it?”

Limits of lab testing: POCT and TEG?

We’re all fond of the French saying that, translated, means "The more things change, the more they seem the same."* It fits with many situations, but scientifically it certainly “ain’t necessarily so.” We have seen considerable progress in the last 20 years in our understanding of how blood clots, why sometimes it doesn’t, and in our armory of available diagnostic tests and interventions. Many of these, but not all, are definite improvements. In their paper on point of care testing (POCT) at the plasma symposium, Drs. Tim Goodnough and Charles Hill discuss some of these changes at length, especially as they relate to cardiac surgery, liver transplantation and other massive transfusion experiences. (Massive transfusion is generally defined as the transfusion of 10 or more units of RBCs in an adult in 24 hours or less.)

Once again, the reader is urged to look at the article itself to review the excellent graphs that illustrate the critical points of the authors. The hemostatic abnormalities seen in these massive transfusion scenarios relate to various hemodilution factors; to the consumption and/or destruction of coagulation proteins, platelets and sometimes red cells; and to the activation of procoagulant and anticoagulant moieties by several factors, including those due to exposure to foreign surfaces, tissue injury and white blood cells. Because of the variety and rapidity of development of these several abnormalities, traditional laboratory testing for transfusion decision-making has become less useful and timely. Traditional testing for the PT, PTT, INR, etc., usually requires a delay of an hour or more, and are subject to several caveats in interpretation. Hence, the development of POCT testing performed in, or near, the operating theater, and the use of predetermined fixed ratios of RBCs and FFP, and sometimes platelets, for transfusion. We have seen in other papers reviewed in this issue that these ratios are not foolproof, and can be very expensive in terms of money and resources (available, transfusable blood products).

TEG stands for thromoelastography, first developed in the late 1940s as a coagulation test using whole blood to produce a tracing, a graph, of the kinetic changes in clot formation; that is, the strength, volume and rate of formation of a blood clot, as well as its dissolution. It allows for an assessment of both coagulation and fibrinolysis that depends on the interaction of the plasma coagulation factors, including fibrinogen, and platelets. It has become widely used in massive transfusion settings to guide therapy. ROTEM (rotational thromboelastometry) is a variation of the primary methodology, and the authors use TEG as the generic term for these tests. In addition, newer technologies for rapid POCT have been developed for the PT, aPTT and platelets and have been demonstrated to be reliable. "Point of care testing (POCT) provides rapid clotting test results and helps link them swiftly to appropriate component selection based on pre-planned algorithms. Thus, patient care can be improved in massive transfusion situations." Sample tracings with details of the process are presented in a graph in the article in the Transfusion supplement.

The authors go on to present details of how this process is used to define defects in clot formation and to link them via sample algorithms to more appropriate blood component therapy. They also point out that a recent meta-analysis of major papers on the process showed that TEG/ROTEM had significant effects in reducing bleeding in massively transfused patients, but the studies failed to show measurable improvements in morbidity or mortality. Studies using POCT for the “standard” coagulation tests (PT, aPTT, fibrinogen and platelets) also resulted in reduced blood loss, especially in cases of severe microvascular blood loss following cardiac surgery.

Thus, POCT as a tool for guiding transfusion practices has been shown to decrease cost. The impact, say the authors, of POCT in the operating theater will expand as the technology for performing the tests improves, along with careful training of equipment operators and other quality control measures. POCT will also be useful in evaluating the other, newer, pharmacologic alternatives for managing patients’ massive transfusion needs.

Goodnough LT, Hill CC. Use of point-of-care testing for plasma therapy. *Transfusion* 2012;52:66S–64S.

* “Plus ça change, plus c’est la même chose.”
Lest we forget: Blood comes from donors; making rabbit stew

The seemingly ever-increasing need for, and use of, blood products has led to a number of developments, and concerns, in donor recruitment and retention, and in ways to garner ever-increasing volumes of valuable resources from them. Though the simile is crudely inappropriate, if one makes rabbit stew, one needs rabbits, and there’s no escaping that fact. One can hunt them down, or one can raise and sustain them as a renewable population and resource. And they should be treated kindly in the process, and their health must be maintained.

Blood donors, which of course include a lot of us, require procedures that leave them intact. Nonetheless, with increasing requests for all of our products, double red-cell apheresis procedures and whole blood donation frequencies of every eight weeks (in the U.S.), it is not surprising that our activities, despite our noble intentions in providing life-sustaining products to patients, have created some health issues for our other clients, our donors. Hematomas, nerve injuries and fainting spells, generally and for the most part improve rapidly. The injury is obvious, the reparative process almost always straightforward. Iron deficiency is more complicated.

Donor recruiters know it is far easier—and cheaper—to recruit seasoned donors than to search for new ones. But the chronic loss of body iron stores can present significant, and not always obvious, problems. Seventy one percent of donations come from repeat donors, some of whom donate several times per year, according to a 2009 report from the Department of Health and Human Services. This fact has risen to the level of a major concern for all of us, and has been the subject of increasing study and numerous recent papers on the subject, especially including those of the REDS II Donor Iron Stores Evaluation (RISE) studies led by Dr. Ritchard Cable, New England Region, American Red Cross, along with 10 physicians from blood centers around the country who are part of the National Heart Lung and Blood Institute’s REDS-II study. (Their most recent report is in this same issue of Transfusion and is cited below.)

A review and discussion of this material is provided in an editorial (also cited below) by Dr. Mark Popovsky of Haemotechnics Corporation. In addition to iron deficiency anemia, iron deficiency alone, not yet severe enough to cause anemia, has known health sequelae, such as ongoing fatigue, reduced work capacity, decreased endurance, restless leg syndrome, sleep difficulties, pica and diminished cognitive skills applications. The RISE study aimed to clarify the incidence of hemoglobin deferrals, absent iron stores and iron-deficient erythropoiesis (blood generation) in about 2,500 donors from six geographic and demographic populations. Iron-deficient erythropoiesis begins before total absence of iron stores is detected. Prior donations in the repeat donors were of whole blood or double RBC apheresis. The donors were divided into a total of four groups, men and women who were frequent donors (two to three in the past year), and men and women who were either new donors (first time, FT) or had not donated in the previous two years (reactivated donors, RA).

Among the women who were FT or RA donors, 20% and 51% had absent iron stores and iron-deficient erythropoiesis, respectively, after giving between 2.5–3 donations over a roughly 15-month period of the study. The corresponding proportions for men were 8% and 20%. Of the frequent donors who returned over the study period of about 17 months (4.5–5 donations), the figures for women were 27% and 62%, for men 18% and 47%. Along the way, deferrals for low hemoglobin were more common among women, and most common in women who were frequent donors. Note that the frequent donation rate, 4–5 times per year, is double the rate when averaged around the country as a whole. Note also that many of the women who were in the FT or RA group had iron-deficient blood production at the onset of the study. As has been previously noted, iron deficiency could be predicted based on being a woman, being a young woman, being black and by having a shorter interval since last donation.

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What approaches would improve this situation, especially given that the demand for blood components continues to increase? Four steps are generally discussed: modifying Hgb standards, changing donation intervals, testing for iron deficiency and oral iron supplementation. They all have problems, all have been discussed before, and no consensus has yet been developed for a national approach to the problem. Currently the minimum Hgb level for both men and women is 12.5 g/dl. Some would lower it to 12 for women, since many normal women have that level. There are also advocates for raising the level for men to 13.0 or 13.5. Any need for more donors to make up for this loss would inevitably target younger, first-time donors, who are the hardest to mobilize and include a sizeable, vulnerable population. Increasing the interval between donations—which has some advocates, since eight weeks is not enough to replace the iron loss of a 200+mg/donation—also would require more donors. Testing for iron deficiency using a serum ferritin test is useful, but it is clearly too expensive to implement on a large scale for most major blood collectors. It would provide an accurate guide, however, for replenishing iron with iron supplements.

Why not just provide iron supplements to donors? Iron-rich foods are inadequate for this degree of loss, especially for the repeat donor. Concerns have also been expressed about the possibilities of iron poisoning in small children, should packets of pills be left around a house. Donor compliance with standard iron replacement is likely to be as poor as the compliance noted in our iron deficient patients, since elemental iron is quite irritating to the GI tract. The pills themselves are not all that expensive, and the risk of iron overload is relatively small, with proper use and appropriate supervision. Still, there are identifiable numbers of families/individuals with a gene that provides for excessive iron absorption and consequent disease that can be serious.

All in all, it would seem that thoughtful and donor-friendly means of iron supplementation should work, especially for the motivated frequent donor. Studies have shown that it works, and tolerable formulations of iron deliver the best compliance. A large-scale multi-institutional study evaluating the most effective therapy and monitoring regimens would seem to be in order. We owe it to our donors before they become as scarce as hens’ teeth!


Popovsky MA. Anemia, iron depletion and the blood donor: It’s time to work on the donor’s behalf. Transfusion 2012;52:688–692.

Publications Corner

Recent publications by American Red Cross scientists and physicians:

The REDS-II Donor Iron Status Evaluation (RISE) study: conclusions should not exceed the limitations of the data. Benjamin RJ. Transfusion 2012; 52:1382–3.


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Immunohematology Journal
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