Enough is enough! Or too much?

Two papers, both published in the first week of this year, deal with the major problem of transfusion and upper-gastrointestinal (UGI) bleeding, a very common emergent condition associated with both high morbidity and mortality all over the world. Both papers are from first-rate European medical centers, the first from Barcelona, Spain and the second from Milan, Italy. The first paper, from the New England Journal of Medicine of January 3, 2013, is clearly a seminal study that addresses just when to pull the transfusion trigger for red blood cells. The second paper (see “De liver us reduced complications” on page 4) is more of a thoughtful review of the status of the use and value of coagulation factor interventions in patients with severe liver disease and UGI bleeding. Both are very deserving of thorough review.

In Barcelona, Dr. Villanueva and co-authors enrolled 921 patients with severe, acute UGI bleeding and randomized them into two treatment groups; 461 were treated with a restrictive strategy (transfuse for hemoglobin (Hgb) <7g/dl) and 460 with a liberal one (transfuse for Hgb <9g/dl). They also stratified the groups based on the presence or absence of liver cirrhosis. Fifty-one percent (225) of the patients in the restrictive group received no transfusions, as compared to 15% (65) in the liberal group. Six-week survival probability was higher in the restrictive group (95% vs. 91%, p=0.03). Further bleeding occurred in 10% of the restrictive group vs. 16% in the liberal group (p=0.01). In the subgroup of patients with bleeding from peptic ulcer disease, the probability of survival was slightly higher in the restrictive group. In patients with mild–moderate (Class A or B) cirrhosis, the restrictive group had significantly higher survival rates, but in severe cirrhosis no differences were noted. Portal-pressure gradients increased significantly in the liberal group, as opposed to the restrictive one.

Admission Hgb levels were equal in the two groups, average 9.5 g/dl, and each group received a similar amount of IV crystalloids. All patients had emergency gastroscopy upon admission. If there was a non-variceal lesion with active arterial bleeding, a visible vessel or adherent clot, the patients were treated endoscopically with adrenaline injection and electrocautery or endoscopic clips, followed by IV omeprazole (a protein pump inhibitor) and then oral therapy with the same. When portal hypertension was suspected, a continuous infusion of somatostatin and prophylactic antibiotic therapy were given for 5 days. Varices were banded or sclerosed. (Somatostatin’s gastric effects are to reduce GI release of gastrin, cholecystokinin, vasoactive intestinal peptide and secretin. It decreases gastric contractions and intestinal blood flow.)

Significant differences in favorable outcomes (p<0.05) for the restricted treatment group included: death from any cause within 45 days; further bleeding, overall as well as with Class A or B cirrhosis; number of hospital days; any adverse event; TACO (transfusion-related acute circulatory overload); and cardiac complications. The paper is replete with graphs delineating specific data regarding laboratory values, treatment comparisons, treatment outcomes and randomization.

In the news

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Cover photo: Human red blood cells, activated platelets and white blood cells.
methodology. The details of their statistical analysis are provided in clear and helpful, understandable fashion.

The study is consistent with the results of previous, smaller observational studies in the last few years, some of which excluded patients admitted with acute bleeding. But this paper is unique in its value because it did not exclude patients, except for a small number deemed to be unlikely to have more bleeding, or those who had massive exsanguinating hemorrhage. Clearly transfusion increases blood volume, increases splanchnic blood flow and increases portal hypertension, potentially aggravating blood loss. The blood that was transfused, in both groups, averaged 15 days of shelf-life when transfused. Transfusion decisions other than related to Hgb levels were made by attending physicians when symptoms of severe anemia developed, when massive bleeding supervened or when surgical intervention was required. Violations of the transfusion protocol occurred more often in the restrictive group, but in neither group was it 10% or more of the patients. The authors conclude the article with a mention of the limitations of the trial, such as its applicability to patients with severe cardiovascular disease who may need a higher Hgb threshold. These are nicely summarized, as well, in an editorial comment in the same issue. Overall, this is a terrific piece of work that deserves wide discussion and will undoubtedly lead to changes in our transfusion practices. At least it should!


Or maybe less is best!

You may be aware of a series of papers in the Journal of the American Medical Association (JAMA) under the heading “JAMA Clinical Evidence Synopsis.” The JAMA, of course, is a widely circulated weekly, general medical journal. The synopses are designed to answer important clinical questions, using the best and most recent available studies. In the first week of January 2013 yet another major message on blood transfusion, an updated version of Cochrane evidence related to red cell transfusion, was published. Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care. They investigate the effects of interventions for prevention, treatment and rehabilitation. They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting. They are published online in The Cochrane Library.

Dr. Jeffrey Carlson and colleagues, who have published previous meta-analyses on transfusion thresholds, updated their material with 9 additional studies, bringing their summary to include 19 randomized, controlled trials involving more than 6,000 patients comparing strategies using higher vs. lower Hgb/Hct thresholds for red cell transfusion. The lower thresholds used in the studies varied between 7.0 to 10.0 g/dl; Hgb levels in the comparison groups were commonly maintained between 9.0 to 13.3 g/dl.

A lower Hgb threshold was associated with reduced RBC transfusion, by an average of about 1.2 units. Hospital mortality was lower in patients randomized to the low threshold group; however, there were no differences in all-cause mortality at 14 days or 60 days follow-up, or in ICU mortality rates. There were no differences in cardiac events or in myocardial infarction (MI), although in the two largest studies MI rates were lower in the low threshold groups. The lower Hgb threshold was not associated with major differences in significant complications, such as infection, pneumonia, stroke, pulmonary edema or length of hospital stay.

In summary, the lower Hgb threshold was associated with fewer transfusions without any apparent harm, but one assumes with demonstrable savings, although cost was not analyzed. A problem with the analysis is that the lower thresholds in some trials were equivalent to the higher ones in others. The lower threshold in the largest trials was 7 g/dl in ICU patients and 8 g/dl in surgical patients. The most commonly used higher threshold was 9.5 to 10.0 g/dl. Findings from this systematic review are consistent with other recently published guidelines using lower Hgb values of 6–8 g/dl as thresholds for transfusion and incorporating the presence of critical symptoms into the red cell transfusion decision. The data are not adequate, however, to provide specific recommendations for such high-risk patients as those with acute coronary syndrome or acute brain injury.

De liver us reduced complications

Advanced liver disease is associated with a myriad of coagulation defects and major clinical—and surgical—problems. Bleeding from esophageal varices occurs in up to 25% of such patients, and 15–20% of these die in a large age range. Major blood loss occurs alone, or with minor or major surgery, including hepatectomy and liver transplantation. Severe liver disease is associated with a multitude of coagulation defects, in no small part because almost all of the procoagulants are manufactured there. Thus, it has become common practice in severe liver disease to treat or attempt to prevent major bleeding using all sorts of promoters of hemostasis, including plasma derivatives, frozen plasma and recombinant clotting factors, including rFactor VIIa, prothrombin complex and anti-fibrinolytic agents. The use of most of these is based on their relationship to lab coagulation tests that are used for clinical diagnosis, originally, and subsequently as a guide to correct hemostasis. In general, there are few, if any, randomized controlled trials to validate such treatment.

Drs. Mannuci and Tripodi, from a well-known clinical center at the University of Milan that focuses on blood coagulation, look at the host of coagulation problems in severe liver disease patients in view of recent evidence that questions whether bleeding in these patients is causally related to the laboratory tests we use and whether the use of “traditional” agents are useful in treating their bleeding. The entire paper is available to all online. Fresh frozen plasma, in large enough doses, does shorten the prothrombin time but does not affect or increase the amount of thrombin formation. It does, however, significantly increase volume and portal hypertension, aggravating more bleeding. Platelet concentrates are used to supplant the low-circulating numbers generally seen in patients with liver disease, portal hypertension and splenomegaly, but there are no critical data as to proper dose and such administration does not usually increase counts dramatically or normalize more global coagulation tests, such as thromboeleastography and thrombin generation.

Recombinant Factor VII (rFVIIa) has been used off-label, but studies show no effect on clinical outcome, and it is not recommended for bleeding or prophylaxis in this setting. Prothrombin complex concentrates of the Vitamin K dependent factors (II, VII, IX, X) in large doses do correct the prothrombin time, but without consistent improvement in clinical bleeding, and at some real risk of an increase in thrombosis, emphasizing what we have recently learned about the poor relationship between bleeding and coagulation factor deficiencies. Tranexamic acid, the “premier” antifibrinolytic drug du jour that blocks the binding of plasminogen to fibrin so that it can’t convert to plasmin, a fibrinolytic, has not been helpful in variceal bleeding, but has a role in hepatic transplantation. The authors go on to review thrombotic complications in liver disease, but emphasize that our improved treatment protocols derive generally from better anesthesiologic and surgical treatments, vasoconstrictors and endoscopy, as noted by the paper from Barcelona.

It's not just for grownups anymore!

And, actually, it never was, but when most of us think of therapeutic plasma exchange (TPE) procedures, we think of them as adult treatments, which they were at first, of course. The authors, all from The Children’s Hospital of Pennsylvania, in Philadelphia, have had considerable experience with the procedure and with pediatrics, and decided to review available data from 42 children’s hospitals across the U.S. to see to what degree pediatric experience mirrored the recommendations of the American Society for Apheresis (ASFA). ASFA assigns conditions to 1 of 4 categories, based on the quality of published evidence and the strength of recommendations based on that data. Classification as an ASFA Category I condition means that TPE is considered a first-line therapeutic option. Examples of such would include Guillain-Barre syndrome, TTP and myasthenia gravis. TPE is accepted as supportive or adjunct treatment for Category II conditions, such as familial hypercholesterolemia, anti-neutrophil cytoplasmic antibody (ANCA) and multiple sclerosis. The use of TPE for the remaining 2 categories is either not established (III) or discouraged (IV). The problem is that the accepted guidelines are all based on adult patient studies. The data reviewed represented 70% of all free-standing children’s hospitals and 85% of major metropolitan areas.

During the 7 years of the study, between 2003 and 2010, there were 3,142 admissions for an ASFA Category I condition. TPE was performed during 13.4% of Category I hospitalizations and its use was highest, 63.4%, for TTP, followed by Goodpasture’s syndrome (42.3%) and myasthenia gravis (15.9%). The proportion of subjects for each condition increased substantially when comorbidities, such as respiratory or renal failure, were present. The TPE rate remained basically the same over the study period. There were 918 admissions for Category II conditions, and TPE was performed during 9.3% of these. Familial hypercholesterolemia and ANCA-positive vasculitis were the most common Category II diagnoses for which TPE was performed.

Overall, TPE was performed at least once during 4,190 total admissions for 3,449 patients. Excluding Category I and II conditions, the most common primary diagnoses for which TPE was performed included complications of cardiac transplantation, 212 cases; complications of a transplanted kidney, 172; and hemolytic-uremic syndrome, 130. There was an increase in these cases over time. The authors go on to discuss the questions of coagulation and general laboratory monitoring, calcium supplementation and fluid replacement, as well as to perform a careful analysis of all the data related to TTP, the most common indication found in the study and one in which TPE is considered to be urgent first-line therapy. Compared to other published data in adults, the use of TPE for Category I and II ASFA indications is lower than was anticipated, including for TTP, which may represent an opportunity to improve care and certainly warrants further investigation.

Sometimes it seems there are no real solutions, just new problems. Solve one; create another, so to speak. So it seems to many of us watching progress in medicine over time. Some amazing accomplishments have come our way, and no one would wish them away; however, being the mortals that we are, complications always arise and require further work to neutralize or avoid them. Acute coronary syndrome (ACS) or percutaneous coronary interventions with placement of stents require dual antiplatelet therapy (in itself a fairly recent type of progress) for 4 weeks after bare metal stent implants or for 3–12 months after ACS or a drug-eluting stent (DES) placement. Stopping therapy too soon has a high risk of stent failure/thrombosis. But if urgent surgery is required, perioperative severe bleeding risks increase by about 50% in patients receiving such therapy. The need to provide sufficient platelet function to avoid serious bleeding must be balanced against the risk of coronary thrombosis.

The authors (from Greifswald, Germany) devised a protocol for transient reversal of the antiplatelet therapy using specifically timed platelet transfusion based on the pharmokinetics of aspirin and clopidogrel (ASA and Plavix), the commonly used “pairing” of antiplatelet therapy in their institution. Both drugs have short half-lives, so that platelet administration 12–24 hours after the last drug dose would occur well after the drug and active metabolites had cleared, and would be expected to provide effective platelet function, just as we see in patients with inadequate numbers of platelets or heritable functional defects in platelets. And since ASA inhibits thromboxane formation by platelets—but not the thromboxane receptor—the permanently ASA-inhibited platelets can still be recruited to clot by thromboxane formation from the transfused platelets. The infused platelets similarly are able to recruit the platelets affected by Plavix inhibition of the platelet ADP receptors. Surgery was performed 1–2 hours after platelet transfusion; ASA was resumed 6 hours later and Plavix after 24–48 hours, depending on bleeding status.

The authors ran a pilot study of 14 consecutive patients, 7 men, 7 women, median age 71 years. All patients were on combination anti-platelet therapy, but required urgent intervention for other problems. Emergent procedures included: spine surgery, 5 cases; intracranial neurosurgery, 2; orbital surgery, 1; joint replacement, 4; nephrectomy, 1; and hemicolecotomy, 1. Details of drugs and procedures can be found in the letter. Twelve out of 14 patients had an uneventful course. One patient developed prolonged bleeding after nephrectomy and recovered and another had ACS that was treated with balloon angioplasty. The stent was not involved.

More work to expand the experience will require large prospective studies, but the intervention would seem to be worthy of additional thought and effort. One would hope, however, if early promise is borne out, that this technique would be used sparingly and not create a whole new problem of elective surgical procedures in cardiac patients so treated.

B19 Parvovirus and human parvovirus 4 (PARV4) are two small viruses (parvo = small, in Latin) that are identified in humans, the latter just discovered about 2005, the former reported in 1975. They belong to a family of small viruses affecting a variety of mammals including mice, pigs, cows and mink. They are quite prevalent in humans in North America and Europe, up to 88% seropositivity in some studies, less so in South America, Africa and Asia, although it may simply be not enough data have been accumulated. B19 is now known to be the cause of a childhood exanthem (rash) known as 5th disease, or erythema infectiosum, due to the “slapped cheek” facial appearance in children so affected. In adults, it has been related to rheumatoid arthritis, as well as questions of hepatitis, but has also been found in normal synovial fluid. The virus is erythrotropic, meaning it likes to grow in a red cell rich milieu. It replicates in RBC progenitor cells, has been associated with aplastic crises in sickle cell patients and others with very hyperplastic anemia conditions, and is also associated with chronic anemia in HIV patients.

PARV4 has been found in the plasma, marrow and lymphoid cells of patients with HIV and HCV and in the peripheral blood of IV drug abusers. Both viruses have been found in pooled plasma lots of human donors and subsequently in products made from fractionated plasma for the treatment of hemophilia and von Willebrand’s disease. With so many normal donors, one would think that any active viruses would be neutralized by the antibodies from the large numbers of healthy, previously affected, donors in the pool. And such is generally the case, at least with B19, since although almost 1% of normal donors have B19 DNA in their plasma, about 50% have measurable plasma antibodies. So, transmission has been quite rare, but it has occurred. PARV4 has not been identified with a specific illness, as has B19, but it has been associated with encephalitis and found in the blood of 3 women with hydrops faetalis, a usually fatal condition of severe anemia and subsequent edema in newborn infants.

Assays for high titers of B19 DNA are performed in pooled plasma by the derivative manufacturers, and such lots diverted from production if they contain more than 104 iu/ml, since infection at levels below that seem not to occur. This is perhaps due to the neutralizing effect of normal donors. Solvent detergent preparation has little effect on inactivating the virus, as the virus does not have a lipid membrane (nor does hepatitis A). So the infectivity of any such product will be directly related to the level of B19 antibodies in the final preparation, as well as to the immune status of the recipient.

PARV4 antibodies have been reported to occur in more than 40% of a cohort of hemophilia patients born between 1972 and 1982 and who were treated with S/D or with heat-treated coagulation factors. Of those who seroconverted during the study, incidence 1.7% per year, the most common clinical presentations with conversion were rashes and exacerbation of hepatitis (mostly HCV). (See reference to Sharp, below). It is also important to note that 78% of the seroconverters to PARV4 were HIV positive, likely adding to their susceptibility.

Given the known infectivity and high prevalence of B19, and now the clear demonstration of a new and infective virus, PARV4, there is an urgent concern to establish clear disease associations and look at methods to deal with the problem of parvoviruses. Standard techniques of fractionation and pathogen-reduction technology are not going to adequately mitigate the problem. There are no cell lines, at least yet, in which the culture and amplification of PARV4 could occur, thus facilitating research into patterns of nullification or modification. Blood bankers hope, of course, that they will not have to add yet another routine screening test for the blood supply. Readers who follow developments around the world concerning emerging and re-emerging diseases know now, and forever, things are “still coming ashore.” Clap your hands! Then slap their cheeks!

“Like a duck out of water...” carries the implication that the object in question, usually a person, is not able to function effectively in the milieu in which one finds oneself. Thus, it has been with platelets, for despite the fact that we have found ways to improve the storage, preservation and function of red blood cells in bags after blood collection, the same has not been true of platelets. Compared to a sturdy, basically bi-functional red cell, with a life span of months in vivo and weeks in vitro, platelets have many complex functions, many as yet poorly described, with very short lives (hours to days); and, they are functionally fussy to a fault. We have traditionally stored platelets in solutions basically derived from whole blood collection solutions, and (to continue our titular analogy) “what’s good for the goose isn’t necessarily good for the gander.”

The plastic enclosures for platelets were made more permeable to gas exchange and stored at warmer temperatures, allowing an extension of shelf life to 5 from 3 days. Leukocyte-reduction and different container systems have become standard in the U.S., while in Europe whole blood-derived platelets are prepared primarily from buffy coats, with pre-storage pooling, leukoreduction and storage in additive solutions. In North America, but less and less in Canada, platelets from whole blood and plateletpheresis are still generally stored in anticoagulated plasma. An excellent review of these developments was presented at the 32nd annual meeting of the American Society for Apheresis in 2011 and published in 2012 (see reference below) by Drs. Hiba Alhumaidan and Joseph Sweeney from The Miriam Hospital, Providence, R.I.

The authors review the advantages of platelet additive solutions (PAS) to patients and to the manufacturing process, such as longer shelf life, reduced volume and allergic reactions, and the manipulation of the in vitro milieu to mitigate bacterial growth and the harmful effects of pathogen-reduction technology. They also provide a table depicting the approximate formulations of 6 primary PAS solutions used in various products, in terms of the anticoagulants, buffers, nutrients and preservatives involved. In addition to reduction of allergic reactions and the increase in plasma made available for fractionation, it is clear that the use of PAS coupled with pathogen-reduction technology provides hemostatic efficacy on a par with standard storage.

They also note another advantage, which is the subject of a second paper published in Transfusion in October, 2012; namely, risk mitigation for ABO-incompatible plasma in platelet transfusions. This report (see reference below) is from Stanford University Hospital in San Francisco, and is part of Transfusion’s ongoing “how-to” series titled “How do I...?”

The realities of inventory limit the ability of a transfusion service to provide only ABO plasma-compatible units for platelets. Thus, if Group O platelet units must be used to treat (as a single donor pack or part of a group of platelets) a non-O patient and have significant anti-A or anti-B activity, hemolysis may occur. Some hospitals have policies that limit the volume of incompatible plasma based on weight, and/or they perform anti-A and B titers, which are notoriously poorly predictive and time consuming. Washing platelets—reducing volume and re-suspending in saline—is also costly and time consuming, and may lead to both loss of platelets and loss of “normal” platelet function. The authors review in some detail how to evaluate these problems, how to reduce plasma volume and how to monitor quality indicators so as to evaluate and adapt transfusion policies. They illuminate this with a detailed case report of a severe hemolytic reaction in a platelet recipient.

In the Stanford laboratory, they decided to simply make maximal use of plasma reduction for all group O platelets that were destined for non-group O patients. This change in managing their platelet inventory resulted in a 4-fold increase in plasma reduction procedures, with a concomitant increase in both personnel and equipment costs. But the alternative, transfusing all patients with ABO-compatible platelets, would cause a shortage of ABO-matched inventory and an increase in the outdate rate for group O platelets. The authors note that wide use of PAS, as occurs in Europe, would relieve this problem; however, as the Rhode Island authors point out, U.S. physicians will need to be educated about the product and current regulatory hurdles will need to be overcome.

The authors, like the rest of us, have noted the increasing number of reports of transfusion-transmitted babesiosis and as well were aware of reports from 2010 and 2011 of record numbers of cases of babesiosis in Minnesota and Wisconsin, upper midwestern states known to have endemic babesiosis. More than 160 cases of transfusion-transmitted babesiosis have been reported between 1979 and 2009, and Red Cross centers in the northeast, another endemic area, have been screening donors from selected regions in the past year. The authors, from the North Central Region of the American Red Cross Blood Services and the University of Minnesota, screened allogeneic blood donors from various geographic areas of Minnesota during the peak tick season (spring to fall) from October 2010 to October 2011. (The host ticks are inactive in the winter in Minnesota...so are a lot of other creatures!)

They screened for *Babesia microti* antibodies with an immunofluorescent assay (IFA); all positive IFA samples were examined for Babesia DNA through real time PCR. The donors were from 32 counties, and were collected at 51 blood drives in those counties. A total of 2,150 donations were tested and IFA found 42 positives (2%) at titers of 64 or greater; 38% of the donations were 64, 36% were 128, and others ranged as high as 1,024. Positive samples collected during August and October, the 2 months with the highest numbers of positive donors, reported most of the highest titers, including the 2 of 1,024. One of these was the only positive PCR sample, collected in October. In the Northeast, October and November are the peak months for tick nymph “questing,” searching for new hosts by the youngest ticks, and likely would show temporal results similar to this.

Of the 42 positive donors, 32 agreed to answer questions related to tick exposure. Thirty-seven percent of the donors had found ticks on their body, often more than 1, and 6 (19%) had had flu-like symptoms around the time of their last donation. All of the donors (97%) affirmed that they spent time outdoors, many engaged in farm work or in wooded areas. Trace-back for 1 year was performed on products donated by seropositive donors. A total of 11 recipients from 11 different seropositive donors were tested for antibodies and all were negative.

For more than 11 years, the Red Cross has been conducting Babesia seroprevalence studies in New England and has described a rate of 1.1% among Connecticut blood donors. That sampling has been expanded. This article is the first to describe seroprevalence in Minnesota, and it is very likely we will be hearing more from both regions of the country.


*Babesia: It’s not just a Yankee, for sure!*
Dr. Merlyn Sayers, of the Carter Blood Center and University of Texas in Dallas, is a widely respected "elder statesman" in blood banking circles in the U.S. and elsewhere. As such, it seems very appropriate to review his commentary in a recent issue of Transfusion concerning the aging of the donor base (see reference below). Despite the recent decreases in red cell demand, thought to be a result of a decline in surgical treatments due to current economic difficulties, trend lines are indicative of a coming problem if all things stay pretty much the same. Of course, they never do, but sometimes they get worse.

A predicted surplus of RBCs in 2009 became a reality as the economic downturn developed teeth. In 2011, RBC distributions to hospitals had fallen 4–6% since 2008, and the American Hospital Association reported a 6% decrease in elective surgery, compared to projected levels. Part of the roughly 20% greater collections of red cells between 2006 and 2008 was due to a significant increase in double red cell apheresis procedures, adding to the new surplus. In addition, those people who had labored for some time to reduce unnecessary transfusions and stabilize conservative criteria for transfusions felt some credit was due them for improvements in clinical practice.

But the authors point out that this is no time for complacency, and then go on to argue their main point, that the aging of the donor base and the lack of younger donor replacements is a real issue. Hospital and blood utilization is expected to rebound as we see improvements in growth, jobs and spending. Add to that the fact that there are now approximately 35–40 million people who now have some modicum of health care expense coverage who did not, previously. The longer term consideration, the main point of their paper, is the anticipated changes in the proportions of older Americans, many of whom will be moving from providers of blood products to consumers of same.

The percentage of elderly, those 65 years and older, was 12.6% in 2000 and is expected to be 20% in 2030, an increase of 30 million people. The statistics are similar for Europe. The 40 million people ≥65 y/o in 2010 will increase to almost 90 million by 2050; however, at the other end of the age range, the 18–24 year olds, will only increase from about 31 million to 40 million over that same period of time. In addition, the authors supply graphs delineating the data from their blood center (which serves over 200 hospitals) clearly showing a shift to the right in the age distribution of whole blood donors between 2002 and 2011. This shift was even more pronounced when they looked at platelet apheresis collections.

Their experience raises the questions of: 1. Why is blood donation (outside the high school setting) increasingly less appealing to young donors; and, 2. What can be done to deal with this progressive decline in true civic engagement? Add to these concerns the fact that the U.S. regulators are now trying to determine how to deal with the loss of iron in frequent donors and donors of child-bearing age, and raising Hgb cutoff levels is one possible alternative. Cost containment efforts and stricter compliance with agreed-upon transfusion guidelines in hospitals may ameliorate the situation (see other articles in this edition of PLUS), as might carefully devised iron supplementation programs. Much remains to be examined, such as the disincentives of intrusive donor questions, and the complications of qualifying to donate, based on travel and other (apparently to the donor) unrelated information. Readers are urged to examine and discuss this paper in their own blood centers and hospitals.

TTP and Tennessee

Once in a while something jumps right out and reminds us that things we take for granted and seldom notice—such as our state and county public health systems—are an important part of our society and health care community. Such was the case when skimming over the CDC’s Morbidity and Mortality Weekly Report (MMWR) in early January this year. Last year, a nephrologist in Tennessee reported to the state health department (TDH) three cases of TTP, which has an annual incidence of about 1:100,000 population. Known TTP risk factors include Shiga-toxin producing *E. coli* infections and intravenous drug use. All 3 patients were IV drug-users from rural northeast Tennessee. TDH did a case-control study which found a total of 15 recent cases, and concluded they were all caused by dissolving and injecting tablets of Opana ER. The control group of 28, roughly half men, half women, was recruited from patients in a methadone clinic with a recent history of injection drug abuse.

Opana ER is a recently reformulated extended release form of oxymorphone, an opioid pain reliever that is intended for oral administration. Fourteen of the 15 patients reported dissolving and injecting this drug intravenously. Indeed, 7 of the 15 were also treated for sepsis and 12 of the 15 reported chronic hepatitis C infection or demonstrated positive test results for the HCV antibody. Thirteen of the 15 were women, none were pregnant. Patients ranged in age from 22–49. Twelve patients were treated with plasmapheresis and, as noted above, 7 were treated for sepsis. There were no deaths. In 8/15 patients, activity levels for the von Willebrand factor-cleaving protease (ADAMTS13) were available. Among patients with concomitant infection, the level was 64% (42–100%); in those without infection it averaged 90% (84–131%). The median admission platelet count in patients with infection was 20,000/ul (9,000–40,000) and 26,000/ul (9,000–49,000).

It is known that HCV and systemic infections are often associated with IV drug abuse as well as with thrombocytopenia, hemolytic anemia and relative deficiency of ADAMTS13. In previous reports, it hasn’t been clear if the TTP was due to infection or the non-infectious exposure of IV drugs. In this case-control study, the injection of reformulated Opana ER was strongly associated with illness in the case-patients, odds ratio (OR) of 35.0; CI 3.9–312. The reformulation involved including 2 other inactive ingredients, polyethylene oxide and polyethylene glycol. OxyContin, another ER opioid analgesic has also been reformulated in 2010 to deter abuse; the added components weren’t given in the article, but it did say that no cases of TTP-like illness following injection of reformulated OxyContin have been reported.

Thus, it isn’t clear exactly what in the formulation, in addition to sepsis, triggered the TTP in these cases, but the association is very clear and unmistakable. It is clear that IV drug abuse is a clear cause of TTP and should be kept in mind when caring for such patients. The other thing that’s clear is that an alert and informed physician (but it could have been any health care professional) and dedicated public health departments can—and do—play an important role in our nation’s health.

Reimbursement Resources

Reimbursement by the Centers for Medicare and Medicaid Services for blood-related products and services can be complex. The American Red Cross provides updates and other information concerning this topic to our valued hospital partners. Please visit redcrossblood.org/reimbursement to explore these resources.

Publications Corner

Recent publications by American Red Cross scientists and physicians:


**Wagner SJ and Seetharaman S, Kurtz J.** A rest period does not affect *in vitro* storage properties in apheresis platelets collected from the buffy coat layer. *Transfusion* 2012; 52:2427-31.


Remember these Websites

*Immunohematology Journal*
redcross.org/immunohematology

Reimbursement
redcrossblood.org/reimbursement

SUCCESS
success.redcross.org

PLUS
Winter 2013, Volume Seven, Issue Two