Knowns and Unknowns, and Making Transfusion Medicine Better

Recently another arbovirus (arthropod-borne viruses, carried by mosquitoes), Zika virus emerged. The Zika virus was discovered near Entebbe, Uganda, in 1947 by workers investigating monkeys for the presence of the yellow fever virus. It was subsequently identified in humans in 1952. Later outbreaks were noted in Pakistan, Indonesia and Thailand, and as we all know it suddenly appeared in Brazil and other parts of South and Central America and the Caribbean islands last year. In July of this year, 2016, we suddenly heard of locally transmitted, locally acquired Zika in south Florida, leading the U.S. FDA to close donations at blood centers in Dade and Broward counties until such time as a reliable and effective screening test(s) could be utilized. And so once again we are off on the expensive experience of identifying a new emerging disease, transmissible by blood transfusion, for which no test is currently applicable for prevention. Then come test development, test trials, and eventually approval, all of which costs are then paid by test manufacturers, blood testing agencies, and then passed on to hospitals and insurance carriers, a topic much discussed in recent meetings, articles, and editorials. So we now are concerned about several arboviruses: yellow fever, dengue, West Nile virus, chikungunya, Ross River virus (southern hemisphere), and Zika. Undoubtedly there are more coming along.

Two of the many articles in this edition of the journal that should be of great interest are briefly noted below. (See references.)

The authors of the first article, from Australia and Germany where the UVC treatment was developed, looked at the ability of the THERAFLEX-UV-Platelets system to inactivate the 3 arboviruses noted in the title. The other related viruses are thought to react similarly, although studies using this system...
haven't been done. There are literally hundreds of millions of infections worldwide caused annually by these viruses, and all three have been found to be transfusion-transmissible. Using all three viruses, the authors spiked virus into buffy-coat derived platelet concentrates which were then added to the THERAFLEX-UV Platelets system illumination bag and treated with 4 increasing doses of UVC irradiation. At the standard UVC dose, viral inactivation of at least 4.43, 6.34, and 5.13 logs or more was observed for dengue virus, chikungunya and Ross River viruses, respectively. Dose-dependent inactivation was observed with increasing doses of UVC.

Currently we have FDA and/or Council of Europe approved pathogen reduction technology for individual donor platelets and individual and pooled plasma. Phase 2 studies in the U.S. have been completed for red cells and whole blood, and Phase 3 studies may be underway. It would seem to most of us that it is extremely important to complete development of these products and rapidly confirm their effectiveness for new threats as they arise.

Similarly burdensome is the fact our nucleic acid based tests for blood donor screening each require their own platform. We currently have nucleic acid based tests for HBV, HCV, HIV-1 and -2, HTLV I-II, WNV, Chagas’ disease, babesiosis and dengue. The first four of these are required on every donation at every time of the year, and we’re still testing for syphilis, as well, even though there have been no reported cases in several decades and the spirochete is usually cleared by the time the serology turns positive. Staff at the FDA, using technology from 2 private organizations, have evaluated a multiplex detection system for viral, bacterial and protozoan pathogens using a high density microarray platform. This is the sort of work we need from our scientists, be they in academia, government, or blood bank laboratories to move forward in this century to a reasonable, effective and secure way to test the blood we transfuse to our patients without bankrupting the healthcare system.


Using More Red Cells in Joint Replacement Surgery?

There have been many recent articles in the medical literature, some of which we have reviewed in PLUS, that have addressed the utility of patient blood management (PBM) programs as a way to: 1) reduce hospital costs; 2) reduce peri- and post-operative complications, including infections and transfusion reactions; 3) reduce hospital stays; and thus, 4) improve outcomes for patients by limiting blood exposure. A significant part of this effort is the pre-operative assessment of health, including blood counts, and the correction of factors predictive of poor outcomes or complications, such as iron deficiency or chronic disease anemia.

Total joint arthroplasty (TJA) is a well-known and very commonly performed surgical procedure for restoring orthopedic function and relieving pain. Tens of thousands of these procedures, primarily hips and knees, are performed each year in the United States alone. Despite advances in surgical techniques, significant blood loss is still very common, occurring in about 50% of all cases. This perioperative anemia is associated with blood transfusion in about 40% of cases. In addition to the potential for transmission of infection and transfusion reactions, transfusion compromises the outcomes of patients, prolongs the hospital stay and increases the risk of surgical site infections, including mortality.

The authors of this study, from Philadelphia, PA, and Tehran, Iran, reviewed data from 2,225,054 TJA cases in the United States, from 1993-2011, and used logistic regression to identify predictors of RBC transfusion and relationships between transfusion and mortality. They noted a study from 2013 that looked at TJA and transfusion from 2005-2008 and noted a trend towards more RBC transfusions. So they embarked on this study to see if there was a pattern of conservation strategies and RBC use. The predictors of transfusion might...
be, and whether or not RBC transfusion was an independent predictor of mortality in TJA. All of their patients had total hip or knee replacement, or revisions of same.

They found that the number of cases of TJA increased in linear fashion every year. The rate of RBC transfusion also increased in all types of TJA, while autologous transfusion decreased, and cell salvage rates remained relatively constant. The highest rate of transfusion was found in hospitals in the Northeast, closely followed by those in the South, the West and then the Midwest, where rates were discernably lower. Large hospitals had lower rates, as did urban academic hospitals. These were significant differences. The graphs in the paper show in linear fashion the clear increase in transfusion of RBCs over the years, especially for total hip revisions.

The authors also found an increased and independent risk of in-hospital mortality in patients undergoing TJA. This is consistent with previous reports of an association between allogeneic transfusion and mortality in cardiac and non-cardiac surgery. The exact connection, they note, are not entirely clear, but one possible explanation is based on demonstrable evidence, is that transfusion leads to tissue hypoxemia, at least initially. Increased RBC aggregability and rigidity, reduced microvascular regulatory abilities of stored RBCs, and the accumulation of potentially harmful microparticles and pro-inflammatory cytokines are contributing factors to such hypoxemia.

As noted in a previous edition of PLUS, it has been shown that restrictive vs liberal transfusion thresholds (< 8g/dl vs 10 g/dl) does not compromise the outcome in patients having surgery for hip fracture. In this current study there were a number of variables that were identified as independent predictors of RBC transfusion, but the greatest effect on blood transfusion were bilateral TJA, blood loss anemia and deficiency anemia (mostly iron-related). Thus the presence of preoperative anemia is the most important predictor of transfusion. In addition, patients having bilateral TJA are much more likely to receive a transfusion of RBCs. Although previously collected (autologous) blood reduces the likelihood of transfusion in many patients, the authors note that it is not cost-effective and raises problems of its own.

Ethnicity and insurance status were, surprisingly, also found to be independent predictors of RBC transfusion. Other studies have shown the same, although exactly what the underlying reasons are isn’t clear. Overall health status may be playing a role, but no studies have detailed this. The authors note that hospitals serving such populations may not have well-organized blood conservation strategies.

That such an increasing transfusion trend was noted over such a long span of time, independent of patient demographics and comorbidities, the authors find worrisome. And, these RBC transfusions are clearly an independent predictor of in-hospital mortality following TJA. They hope the increasing use of tranexamic acid as an effective and safe blood conservation measure will reduce the rate of allogeneic transfusion in these surgical patients. In the meantime, careful and expanded use of PBM programs can be a major help.

What Age of Red Cells for Pediatric Cardiac Surgery?

Traditional standard practice in the blood bank has been to use the oldest units first. In years past, including this decade, physicians have expressed concerns about greater morbidity and mortality that might be related to the age of the red cells transfused in various clinical groups of patients. These clinical groupings have included acute gastrointestinal bleeding, cardiac surgery in adults, major joint replacements and pediatric cardiac surgery patients. It is known that during storage various “storage lesions” occur, including alterations in red cell membrane structure and fragility, and biochemical changes that include decreased levels of 2,3-DPG with impaired oxygen delivery as well as the release of some pro-inflammatory cytokines, an effect altered to some degree by near-universal preparation of leukocyte-depleted red blood cells.

Physicians at the Kobe University Hospital in Japan decided to look at a large group of pediatric cardiac surgical patients who were operated upon for congenital heart disease, and looked at the relationship between the occurrence of serious adverse events and the storage time of transfused red cells. (See reference.) They included pediatric patients admitted to the pediatric ICU after congenital cardiac surgery who received red blood cells during or on the day of surgery between January 1, 2009 and December 31, 2011. In their hospital, the red cells are transfused chronologically beginning with the oldest units first. Contrary to most published studies in adult patients, in Japan the expiration date of red cells is 3 weeks. The primary outcome was the occurrence of at least one of three serious adverse events (SAEs), death, cardiac arrest, or a requirement for extracorporeal membrane oxygenation (ECMO).

Of the total of 747 patients who underwent cardiac surgery, 230 did not require any transfusion and were excluded from the study. A total of 517 patients required transfusion on the day of surgery, with a mean age of 6 months. There were 22 patients with at least one SAE (4.3%): 9 patients died in the ICU, 9 experience cardiac arrest, and 10 required post-operative ACMO. Sixteen patients had one SAE, the remainder 2 or 3. The 495 patients with no SAEs were significantly older and thus heavier than those with SAEs.

In this retrospective observational study, the storage duration of the transfused red blood cells was not associated with the incidence of post-operative SAEs, and nor was the 28 day ICU-free survival following pediatric surgery. These results are at odds with some of the previous studies in children. More recent studies, generally blinded, controlled and randomized, in adult patients have not shown a relationship between age of the stored blood and adverse events, including ICU patients, and cardiac surgery patients. Such studies have not yet been done in pediatric cardiac patients. This article from Japan suggests that no differences will be found.

Cures and Prevention: What for Sickle Cell Disease?

In recent issues of PLUS we have noted the significance of chronic transfusion therapy in stroke prevention in children with sickle cell disease (SCD) who have had a stroke, which is a not uncommon occurrence in such patients. There has been a dramatic improvement in morbidity and mortality in children, including from stroke, resulting from the clinical research of the last 2 decades. Chronic blood transfusion has become an accepted standard of care. As the writers of the editorial note (see references), SCD which was once a fatal pediatric condition has now transitioned to an adult disease characterized by progressive ischemic organ failure punctuated by acute, life-threatening events. Reductions in central nervous system injury in children is largely the result of development and implementation of such therapy; however, the number of strokes in adult patients with SCD appears to be increasing, and has been noted in several studies.

The authors of the current study from Philadelphia, one of whom is now at Yale, report on the outcome of 22 patients with SCD who were transitioned to the adult program from their pediatric one utilizing chronic transfusion therapy. These patients were transitioned from their chronic transfusion program into the regular adult SCD program; they were not selectively chosen. They were kept on chronic transfusion treatment, the aim of which was to keep Hgb S levels below 30% and hemoglobin levels generally at not more than 10 g/dl. (Blood viscosity tends to increase more after transfusions much above that level.)

Eight of the 22 patients thus transitioned, however, refused to be maintained on chronic transfusion, “standard” or exchange transfusion, or were non-compliant and failed to show up for their appointments. All of these non-compliant patients died within 5 years of transition, at an average of 3 years post-transition. Chronic transfusion patients received an average of 51 units of red cells/year, and the non-compliant ones an average of 28. Interestingly, the chronic transfusion group had an average serum ferritin level (a measurement of iron stores) of 1438 ng/ml, considerably lower than that of the non-compliant group who died, 2905 ng/ml. This is likely due to the presence of increased frequency of exchange red cell transfusions in the compliant group. Fetal hemoglobin levels were also higher in the active patients, presumably due to the longer duration of treatment with hydroxyurea, which promotes Hgb F production. Hgb F is known to have a protective effect in SCD.

There are more details and tables in the publication, but basically all other measures except compliance and subsequent lack of transfusion therapy were the same. None of the compliant patients died, whereas all of the non-compliant ones did, as noted. The rate of hospitalization for acute events, and thus total costs over the period, were higher in the non-compliant group. Most of the deaths occurred in the setting of an acute pulmonary event or in a sudden association with vasoconstrictive events. SCD is not just a hemoglobinopathy; there are chronic inflammatory and vasoconstrictive elements at work, as well, related of course to the presence of Hgb S and red blood cell malformation and hemolysis. Exchange transfusion removes these and other pro-inflammatory molecules, as well as Hgb S-containing red cells, and thus appears to be a better alternative than simple chronic transfusion, as suggested in this and other studies.

An ounce of prevention is worth more than a pound of cure—especially when there is no currently available cure.

1. McLaughlin JF, Ballas SK. High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program. Transfusion 2016; 56:1014-1021.

“There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy.”

This quote from Shakespeare’s “Hamlet” is a good reminder that there is a great deal in our world that we don’t know, some of which are things that are really new. We can’t always tell the difference.

Hemophilia A, an X-linked recessive coagulation disorder has been with us for a very long time, occurring in about 1 out of 5,000 live male births. Around 40% of cases occur in the absence of any family history, reflecting the high rate of spontaneous germ line mutations in the factor VIII gene. Since the disastrous years (1980s) of contamination of the plasma supply by the human immunodeficiency virus (HIV), therapy has transitioned to the use of human recombinant DNA-manufactured Factor VIII concentrates, as well as the use of virally-inactivated plasma-derived products. Safe and effective, these drugs are not cheap, but virtually all hemophilia A patients in the more developed countries have them available.

Prophylactic programs have been developed to retard or prevent the severe hemarthroses and other calamitous bleeding events affecting our patients. Approximately half of them have severe hemophilia, a factor VIII level of less than 1%, which is one international unit per deciliter (1IU/dl). Moderate levels, 1-5 IU/dl, have less frequent bleeding, and those with mild hemophilia, 6-40 IU/dl, bleed primarily under severe stress, such as surgery or severe trauma. Prophylactic programs of raising levels of VIII in severely affected patients have become popular and useful over the past decades, being comprised of every-other-day, or three times weekly, administration of factor VIII, anti-hemophilic factor (AHF).

But it has been said that there are no such things as solutions, only new problems. And so it has been with AHF prophylaxis in severe and some moderate cases, with the development of antibodies to AHF about 30% of the time. Some can be overcome with increased doses, but this is expensive and not always feasible. Consider also the problem of venous access and the difficulties experienced in regularly injecting small children. The use of activated factor VIIa or activated prothrombin complex concentrates provides imperfect control of bleeding, and is pretty expensive for episodes that are non-life threatening. Similarly, the induction of immune tolerance with AHF concentrates is very intensive and not helpful for those with the higher antibody titers. These latter options are not available in much of today’s world.

Hemophilia experts in Milan, Italy, (see reference 1) just published a large randomized study comparing the rates of development of AHF antibodies in patients treated solely with recombinant AHF vs those treated with plasma-derived AHF. The study was carried out in 14 countries, quite an organizational feat. It is known that plasma-derived product also contains significant levels of von Willebrand Factor (vWF), an important cofactor for normal hemostasis, especially due to its relationship to platelet stickiness and aggregation. The development of AHF antibodies was found in 23% of those boys treated with plasma-derived product vs 37% of those treated with recombinant DNA products. A variety of FDA- and European Medicines Agency-approved products were used, one of each type per country.

Now coming onto the stage—the use of monoclonal antibodies (how about that, Horatio!) Physicians at one of the Japanese hemophilia treatment centers responded to the need for a more effective and less burdensome treatment for patients with hemophilia A (see reference 2). Their tool for this was emicizumab, a humanized bispecific antibody that binds to and bridges activated factor IX and factor X, thus mimicking the effect of factor VIII in the coagulation cascade. This is
The thalassemias are a group of inherited abnormalities of globin chains, which form with heme molecules to make hemoglobin (Hgb). Although there are other mutations, the primary globin chains in humans are alpha, beta, delta and gamma. After the first few months of life, Hgb A1 comprises 95-98% of the total, Hgb A2 1.5-3.5%, and Hgb F <2%, this latter decreasing rapidly after birth. Hgb A1 is composed of a heme molecule and 2 pairs each of beta and alpha chains. Hgb A2 has heme, 2 beta and 2 delta chains; Hgb F is heme plus 2 alpha and 2 gamma chains. Hgb F has a higher affinity for oxygen and is higher during the fetal stage of human life, and is called fetal Hgb. Methods to increase Hgb F levels in patients with sickle cell disease are helpful in decreasing somewhat the amount of sickling that takes place.

How Can We Manage Long-Term Care of Beta Thalassemia?

The thalassemias are a group of inherited abnormalities of globin chains, which form with heme molecules to make hemoglobin (Hgb). Although there are other mutations, the primary globin chains in humans are alpha, beta, delta and gamma. After the first few months of life, Hgb A1 comprises 95-98% of the total, Hgb A2 1.5-3.5%, and Hgb F <2%, this latter decreasing rapidly after birth. Hgb A1 is composed of a heme molecule and 2 pairs each of beta and alpha chains. Hgb A2 has heme, 2 beta and 2 delta chains; Hgb F is heme plus 2 alpha and 2 gamma chains. Hgb F has a higher affinity for oxygen and is higher during the fetal stage of human life, and is called fetal Hgb. Methods to increase Hgb F levels in patients with sickle cell disease are helpful in decreasing somewhat the amount of sickling that takes place.

There are, literally, dozens of variants of thalassemia based on the types of globin chains being produced. The type most common to us, and far more common than any others (except alpha thalassemia in some areas, such as Southeast Asia), is beta thalassemia, originally described by Cooley in the 1920s and called Cooley’s anemia. Geographically, these beta gene mutations were most common in Mediterranean countries (southern Europe, North Africa, much of the Middle East) and extending across south Asia to the Indian subcontinent.

Eighteen Japanese patients with severe hemophilia A, with or without factor VIII inhibitors, were divided into 3 groups and were given the emicizumab subcutaneously weekly for 12 weeks. The groups were given 0.3, 1.0, and 3.0 mg per kilogram body weight, respectively cohorts 1, 2 and 3, with 6 patients in each group. The age and weights of patients were similar in each group, and each group contained 3-4 patients with inhibitor antibodies. The drug had no serious side effects and no significant coagulation abnormalities. Concentrations of the drug in patient plasma increased in a dose-dependent manner. Importantly, no antibodies to emicizumab developed in any of the patients. Graphs of cohort blood levels and coagulation tests are nicely presented in the body of the article.

Activated partial thromboplastin times (aPTT) remained short throughout the study, and the annualized bleeding rates decreased markedly. Three patients with factor VIII inhibitors and 2 patients without inhibitors had bleeding episodes that responded to traditional treatment. There were no thrombotic episodes in any of the study groups, nor were there other serious adverse events. The higher dose cohort, number 3, had more adverse events, such as rash or itching at the injection site. This short-term study will be followed by more complete and longer studies; however, this is clearly one of the more exciting and positive things to happen in a long time for patients with hemophilia, and offers a new pathway for further exploration in the treatment of hereditary bleeding disorders.


as well as in the tropical belt of sub-Saharan Africa. There is evidence that the milder forms provided some resistance to malarial infection. In beta thalassemia, we see variations of expression, leading us to call the variants beta thalassemia major, minor and intermedia. Some of the latter also produce severe symptoms. In beta thalassemia major (BTM), there is overproduction of alpha globin chains, and these cause damage to erythrocytes and red cell precursors in the marrow. This leads to profound anemia which affects infants from birth.

This profound anemia leads to marked expansion of ineffective bone marrow, with severe effects on bone formation, growth and development. The major cause of morbidity and mortality is the effect of extensive iron deposition, in the endocrine organs, liver and heart. This is made worse, of course, by the need for extensive and life-long reliance on blood transfusions. The alpha thalassemias are different, in that beta globin chains in excess form beta 4 molecules, or Hgb H, which precipitate in red cells causing hemolysis.

All of which brings us to our article on healthcare costs and BTM in the United Kingdom (UK). The UK’s National Health Service has an amazing amount of data for the country, which includes data from England, Wales, Northern Ireland and Scotland. There are more than 700 individuals with BTM in the UK, and their diagnosis leads to a life-long disease management program. A small minority of BTM patients fulfill certain requirements and are eligible for bone marrow transplant, after which long-term care is usually not needed. The current guidelines in the UK call for maintenance of Hgb levels from 9.5 to 10 g/dl, which of course leads to fatal iron overload unless rigorous iron chelation therapy is instituted. This has a substantial impact on the adherence level to therapy and the development of complications including hypothyroid and parathyroid conditions, hypogonadism, enlarged spleen liver infiltration, diabetes, and cardiac complications—all from iron overload in target organs.

Based on all this available data, the authors set about designing a model of care, based on the 50 year history of care administration that could be used to estimate the incidence-based health economic impact that BTM has and will have in terms of the number of quality-adjusted life years (QALYs). (In the U.S., a cost effective procedure is accepted to cost between $50-100,000 per QALY.) Based on careful review of all the available data, the authors assigned costs based on calculating all interventions in 2013-2014 terms. They were able to assign typical ages of onset for the various complications, such as diabetes, hypothyroidism and cardiac complications and created a model composed of all these costs, visits to doctors, medicines, transfusions, chelation therapy, and so on.

The study found an expected probability of survival of BTM patients to 50 years of age to be 0.63. Of those patients who survive, 33% are expected to have no further complications and the other 67% to have at least one (more) major complication. The total healthcare expenditure attributable to managing a patient with BTM without bone marrow transplant was estimated to be $720,000 at 2013-2014 prices over fifty years. The principal cost drivers were blood transfusions and intravenous iron chelation treatment.

Based on all of this, the authors conclude that the costs of managing BTM in the U.K. could potentially be reduced by up to 37% if 1 in 2 patients had a bone marrow transplant and ensuing improvements in health. This would also increase the quality of life of such patients who are transplanted. These figures cannot be directly extrapolated to countries such as the U.S., since the billed costs for most of the items and procedures are generally higher. It also points out that we should not be too reluctant to assign patients into marrow transplant programs, since the initial heavy outlay of money is more than made up for over the ensuing years.

Oxidative Stress in Stored Red Blood Cells

When blood for transfusion is removed from its normal “home”, the human circulation, it has not only lost its protective environment, it has lost all the nutrient mechanisms that keep it alive and working. No matter what anticoagulants and functional preservatives we put them in, the red cells start to lose their structural and functional integrity. They just don’t work like they used to do! One of the functional properties, the maintenance of hemoglobin in the reduced ferrous state is lost, and as the hemoglobin is oxidized faster than its systems can reduce it, hemoglobin loses its capacity to carry oxygen. The authors of this paper (see reference) wanted to determine if this increase in oxidative stress during red cell storage is associated with impaired cell membrane deformability that would affect the circulatory (rheologic) properties of these cells.

The studies were done in 34 patients who had multilevel spinal fusion surgery. They were divided into groups depending on the amount of blood they received on days 1-3. Nine patients received no stored blood; 7 patients received 1-3 units of stored blood; and, 17 patients received 4 units or more. One patient who got 22 units was omitted from the study. Cell salvage was used and the 3 groups respectively received 70+-108 ml, 54 +/-67 ml, and 151 +/-169 ml of salvaged red cells. Red cell deformability and red cell aggregation were assessed by standard measurement, and levels of fluorescent hemoglobin degradation products and methemoglobin were obtained.

Analyses were performed on samples drawn directly from the storage blood bags just before transfusion and compared to fresh preoperative patient blood. The red cells were stored for 28 +/- 8 days and had significantly higher hemoglobin degradation products and methemoglobin levels (p< 0.001) compared to the fresh patient samples. Both of these (degradation products and methemoglobin) increased with increased storage duration.

Oxidative stress was significantly increased, but cell deformability was not significantly different between the fresh samples and stored samples, although deformability did decrease somewhat with age of the blood. Salvaged cells had less deformability, but also had less degradation of the hemoglobin molecule. Additional studies showed that only in the moderately transfused group (4 units or more) were the hemoglobin degradation product levels higher for 2-3 days, but not significantly so. Thus the studies showed that there is indeed an increase in oxidative stress on red cells and hemoglobin in stored blood, but there is no direct correlation with membrane deformability, and thus no major rheologic effect of this stress on red cell membranes. Changes in red cell deformability in stored blood appear to be more likely due to other factors.

The first case of transfusion-transmitted babesiosis (TTB) was reported from Boston in 1979 and presented at a meeting in Montreal the following year. The cause was transfusion of an infected platelet concentrate to a patient with immune thrombocytopenia. Such occurrences have become much more common as populations of *Ixodes dammini*, commonly known as deer ticks, or black-legged ticks, have exploded into every northeastern and some mid-Atlantic states. They are also found in the upper Midwest, and another variety of Babesia has been found in ticks on the west coast. The authors of this article (see reference) note that it has become the most common cause of transfusion-transmitted infection. This is the same tick that carries Lyme disease, *Borrelia burgdoferi*, and human granulocytic anaplasmosis.

The incubation period following tick bite is usually 1-6 weeks; however, transfusion transmission of 2 months or even longer have been reported. Since many babesia infections in healthy people go unrecognized, or result in a few days of flu-like symptoms, healthy-seeming donors can be a source. Older or immunocompromised or splenectomized patients may have severe hemolytic anemia, with organ failure, disseminated intravascular coagulation, acute respiratory distress syndrome, and even death. Patients with a functioning spleen often have a self-limiting disease but can become chronic carriers for months, wherein lies the problem for blood transfusion.

The authors carried out an extensive review of the literature by accessing PubMed, AABB annual meeting abstracts, and 7 volumes of the FDA’s fatalities report from blood transfusion. The goals were to identify patient population characteristics, factors related to the transfusion that might play a role, and based on the outcomes of this provide recommendations for the potential role of *B. microti* test-negative blood products. They report that there were 256 transfusion cases where the donor tested positive for *B. microti*, 165 of which resulted in TTB and had a positive test for babesiosis. Sixty recipients did not develop disease or become test positive; test results were not known for 31 recipients. (Sum equals 256.) The FDA reported 4 TTB deaths from 2010-2013, but no corresponding cases could be found in the literature. Thus, the total number of deaths reported in the 165 cases was 32.

In one remarkable case from 2009, a trauma patient who had received multiple blood products, including one from a *Babesia* seropositive donor died and had both his kidneys donated. Both kidney recipients developed post-transplant babesiosis. Both kidney recipient pre-transplant samples had tested negative for Babesia. Only the kidney donor was counted as a transfusion-acquired case.

The nature of the underlying disease was not categorized in about half the cases, the rest scattered from hematologic to gastrointestinal, neonatal, and cardiac. The presence or absence of a spleen was not noted either in about half the cases. One third of the TTB patients developed serious disease, including death in 20% overall. There was a trend towards more severe disease in older patients. However, many of the older patients had no symptoms or were easily managed with standard antibiotic therapy. 81% of the implicated transfusions were of red cells, 4% from platelets, and 15% not specified. As is commonly recognized, not all medical records contain all the information that later evaluators are seeking. The age of the red cells was not a factor, and one case was from a 110 day old frozen, deglycerolized unit.

Babesia was a key factor in 25 of the 32 deaths, but there was no relationship to the underlying condition(s) of the patient. The current hot issue for transfusion medicine revolves around the question of testing of donated blood for *B. microti*. Despite the fact that TTB is now the most common disease transmitted from blood transfusion, there is not general agreement on whether to require the test, exactly what test is best (serology can remain positive for long periods after the organism is cleared), should testing be limited only to affected endemic areas, should testing only be done when a “significant” number of ticks are out and about, and related issues. Blood testing agencies and the hospitals who pay their bills are loathe to add yet another cost to the already high costs of blood products. We are all waiting for a magic blood additive that would inactivate all infective organisms in our blood supply once and for all, and get away from our current paradigm of “new disease, mysteries, blood transfusion can transmit it, let’s develop some tests, which one is best, cheapest, etc.” It’s a tough biological world, and they are still coming ashore!

Zika Virus

Zika is a virus spread by Aedes species mosquitoes (Ae. aegypti). Transmission of the virus is possible by a pregnant woman to her fetus: this can result in birth defects. At this time, there is no treatment or vaccine for Zika virus. The Red Cross is participating in the Hologic investigational new drug (IND) study, recently allowed by the FDA. Under the IND, the Red Cross began blood donor nucleic acid testing (NAT) for Zika virus in areas that are believed to be at greatest risk of local Zika virus mosquito transmission where our collections occur. In light of recent FDA guidance we are transitioning to testing nationwide. Transfusion specialists are encouraged to visit the CDC and FDA websites frequently for updates on this fast-evolving situation.

Publications Corner

Recent publications by American Red Cross scientists and physicians:

Cost-effectiveness of a Babesia microti blood donation intervention based on real-time prospective screening in endemic areas of the United States. Bish EK, Moritz ED, El-Amine H, Bish DR, Stramer SL. Transfusion. 2016 Mar;56(3):775-7

Consider the source: the importance of including all transfused products and exposures in red blood cell alloimmunization research. Brunker PA. Transfusion. 2016 56(2):290-3


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