Out of madness, some good can come

Two professors from Oxford and Southampton, U.K. (see reference) have written a wonderful review about blood transfusion during WWI, and also filled it with fascinating information about the history of medicine and blood transfusion before and during that time. Citrate was first used in human blood transfusion in 1914, before the August outbreak of war. In 1915 it was shown that citrated blood could be stored prior to transfusion, and such transfusions had occurred in the U.S. prior to our declaration of war on Germany in 1917, many years after it began. By the time the war had begun in Europe in 1914, awareness of blood groups and anticoagulants, and improved methods to transfer blood from donor to patient were known, at least in principle. But compatibility testing was not always carried out. However, the application of new knowledge and new techniques took time. The means—and ease—of communications during those times were not at all like we have today.

The first documented transfusion of a wounded soldier occurred in France in September of 1914, and involved a direct method of transfusion. There was no compatibility testing performed, but donor and patient both survived. By the end of 1914, say the authors, 44 transfusions had taken place in France, some of them with citrate anticoagulant. About a year later, blood was transfused using a small cylinder coated with paraffin wax, to avoid coagulation. Others preferred a simpler syringe-cannula technique. In 1917, blood stored in a sodium citrate-glucose solution (1.2 mL per 0.5 L whole blood) was used fairly extensively by a volunteer medical unit from Harvard, and transfusions were given 10–14 days later after cold storage and removal of some of the supernatant. Usually the transfusion was warmed to 100°F, since cold blood was thought to be undesirable. In some instances, the blood was stored longer without problem. The British tested potential donors, usually lightly wounded army personnel, and used only Group O “volunteers” for their supply.

“The Great War”, otherwise known as “The War to End All Wars”, or more accurately World War I (WWI) began just over 100 years ago. It changed the map of Europe, wiping out the Russian Empire, the German Empire, the Austro-Hungarian Empire and the Ottoman Empire, and set the stage for the almost inevitably-resulting WWII. It also led to the death of about 16 million people, almost half of them civilians. As well, it lent strength and impetus to the great influenza epidemic that began in 1918 and went on to claim probably 50 million lives, most of them in lands distant to the conflict. It is hard, then, to think of any good thing resulting from it. But, sadly in a way, wars have always led to sometimes dramatic changes in medicine, particularly surgery and blood transfusion.

WWI was no exception, and essentially was the impetus for and testing grounds of modern blood transfusion science. Remember, leeches and blood-letting were very common procedures for therapy in general, for all sorts of maladies, even well into the 19th century.

In the news

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Cover photo: Ruptured blood vessel with red blood cells leaking out. Visuals Unlimited, Inc.

This issue of PLUS was written by Dr. Robert (Bob) Westphal.
By 1918, many transfusions were being performed closer to the front lines, and the syringe technique was used in many advanced aid or dressing stations. There were, of course, significant numbers of transfusion reactions. An American doctor, in 1917, described a “minimum procedure” to test for agglutination prior to transfusion, basically using a mixture of donor cells and recipient’s plasma. Sometimes in emergencies, with no capability for lab work, a test infusion of 10-15 ml was given to see if an acute reaction occurred. Donors were generally screened for a history of syphilis and malaria, and although there was concern about trench fever being transmitted (infection with *Bartonella quintana*, carried by body lice, affected over a million Allied soldiers), serum hepatitis (HBV) had not yet become prominent. It was the use of pooled plasma for shipment overseas during the Second World War that led to that discovery.

British resuscitation teams or nursing sisters and orderlies were set up to handle the collection and transfusion of blood before and after surgery to allow surgeons to operate “without the distraction of organizing and executing resuscitation”. The British established formal programs for transfusion, and field ambulance staff and regimental medical officers were given formal instruction and provided with the necessary equipment. This also affected troop morale, since blood could be prepared away from the front lines and stored safely, so that even a poorly equipped aid post could serve as a resuscitation center, to some degree. Blood that was to be transfused immediately, within 24 hrs., was stored in only sodium citrate.

Post-war civilian life couldn’t emulate the pace and breadth of changes seen during the war. Some surgeons came away with a great appreciation for the life-saving capacities of blood transfusion, but there was no infrastructure in place in civilian life to provide it on any sort of scale but that of a large, local hospital. However, in 1921 a London Red Cross officer received a request from a London hospital to find a blood donor and found one in a fellow Red Cross worker. He went on to establish a small, but voluntary, blood bank with 400 donors in London.

The authors note that military needs clearly stimulated the science and practice of blood transfusion, from donor selection to indications for surgical blood use. Military logistics improved the recruitment of donors, but since the “lightly wounded” soldiers used for blood donation were given extra leave privileges, and some other preferential treatment, they weren’t exactly volunteers. Nonetheless, the idea of an organized, reliable group of volunteers who are standing ready to donate was a direct—and terribly important—outcome of the war.

Something to look forward to is that these same authors will be looking at the development of more sophisticated products and services during another World War.

Two large international studies related to the age of transfused blood in cardiac surgery and in critically ill ICU patients were recently published back to back in the New England Journal of Medicine. (See references.) It really is amazing that so many institutions can be organized so thoroughly in order to maximize the information gained from critically defined clinical trials. The amount and the quality of preparation time in them is what provides for their tremendous believability and power.

The first study (reference 1) was directed from the University of Montreal and included colleague participants from several other Canadian centers, from England and Scotland, from France and from the Netherlands. The question being asked was whether or not “fresh blood” improves outcomes when given to critically ill ICU patients by enhancing oxygen carrying capacity. Also explored was whether “fresh blood” minimized risks of toxic effects from cellular aging changes and the accumulation of various bioactive materials that occur during prolonged red cell storage. Over a 5 year period, at 64 tertiary care centers in Canada and Europe, 1211 patients were assigned to receive red cells stored for less than 8 days while 1219 were assigned to receive “standard issued” red cells, which meant the oldest available appropriate units in the hospitals’ blood banks. This was a blinded randomized trial, with an opaque sticker pasted over the red cell label parts for collection and expiration dates. A number of the previous retrospective observational studies, involving over 400,000 patients, and a few randomized controlled trials with much smaller numbers found higher rates of death in the “old blood” recipients. All patients in this study were 18 years or older, and the groups were statistically similar in all respects, including brain damage, organ dysfunction scores, APACHE (Acute Physiology and Chronic Health Evaluation) scores, ICU days, age, male sex and coexisting illness.

Hemoglobin levels before randomization and transfusion were nearly identical, as were the number of units of red cells transfused per patient in each group. All patients who received at least one unit of red cells were included in the transfusion groups. Storage times in days per group were 6.1 +/- 4.9 fresh and 22 +/- 8.4 standard. Some in the fresh group received an older unit, due to hospital availability, but only 4.6% of them received more than 2 units older than 7 days. After 90 days, 37% of patients in the fresh blood group and 35.3% in the standard group had died. Thus, the study did not show any benefit that could be attributed to the transfusion of fresh red cells. Not only were the primary outcomes similar (death at 90 days), the results of all sub-group analyses were also similar. It should be noted that all red cells were leukocyte-depleted.

In a related article (see reference 2), members of the RECESS study group (Red-Cell Storage Duration Study) reported on the effects of the duration of storage of red cells used in cardiac surgery patients. The group, composed of investigators from about 35 U.S. hospitals, carefully matched the two comparative groups. All units were leukocyte depleted, and patients were entered over a period of 4 years. Patients 12 y/o or more who were undergoing complex cardiac surgery, expectant of median sternotomy and likely to receive red cells, were assigned to receive blood 10 days old or less, or red cells 21 days or more old. The primary outcome was the change in the multiple organ dysfunction score (MODS), the range of which is 0 to 24, comparing the preoperative score to the highest one through post-op day 7 or the time of death or discharge.

In the short-term storage group the median storage time was 7 days (538 patients), and in the long-term group (560 patients) it was 28 days. The mean change in the MODS scores was 8.5 points in the shorter term group vs 8.7 points in the longer (p= 0.44). Mortality at 7 days was 2.8% short-term and 2.0% in the longer, also not significant. Similarly not significant were the differences in 28 day mortality, 4.4% and 5.3%.

It’s all in the planning
Ninety-six per cent (96%) of the patients in each group had cardiopulmonary bypass during the procedure(s). The number and types of procedure were similar between the two groups, with the majority of patients having a CABG, a valve repair or replacement, or both. The duration of cardiopulmonary bypass was 141 minutes in the short-term group and 139 in the longer. The median ages were similar at 73 and 72, as were the baseline MODS, 0.7 and 0.6.

The authors concluded that the duration of red cell storage was not associated with any significant difference in changes in the MODS, and that red cells stored for 10 days or less were not superior to those stored 21 days or more in patients undergoing complex cardiac surgery. The real lesson in both of these studies is that large-scale, carefully controlled, prospective, randomized studies, blinded if possible, are the best way to gather evidence for making rational therapeutic decisions. The amount of discipline and planning involved is enormous, but absolutely integral to the success of such efforts.


Towards a better blood preservative?

For the last 75 years, a large amount of effort has been expended on the biochemistry of anticoagulants and preservatives for use in blood collection and storage. Initially, the target was improved survival of RBCs, so that whole blood could be collected and stored in an ACD (acid citrate dextrose) solution for up to 21 days before transfusion. This not only had the effect of making blood supplies last longer, it allowed for its shipment from one place to another, and especially to the battlefields of the times from a distant—and safer—supply source. The development of CPD (citrate phosphate dextrose) as a primary anticoagulant and preservative was greatly enhanced by the addition of additive solutions (AS) containing adenine, such as AS1, AS2, and so forth, with varying amounts of other things to better control pH, inhibit red cell membrane destruction, and allow for early separation and preservation of plasma coagulation factors. Current maximum RBC storage time in the U.S. is 42 days.

There are other important considerations, however, in a modern blood center, related to logistics and expense. The need to return whole blood units back to a processing lab from sometimes far-ranging mobile operations is expensive, involving second and third shift staffing for laboratory and transport work. European workers, motivated by CE directives to be self-sufficient for plasma and not rely on paid donor plasma supplies, developed a process to hold whole blood overnight at room temperature and thus more efficiently utilize the platelets and plasma from such units while maintaining adequate red cell survival. Key to this practice has been the use of AS-7, an additive solution developed by Dr. Tibi Greenwalt and others. (Dr. Greenwalt was the founding editor of Transfusion in 1961.) A St. Paul, Minnesota, company has spent considerable effort working with a separation system using AS-7 such that it controls metabolic energetics so as to stabilize pH changes early in the storage period at room temperature, making feasible a room temperature overnight hold before component separation. Current requirements in the U.S. are such that manufacturing enough frozen plasma for transfusion, both fresh-frozen plasma (-18°C within 8 hrs.) and FP24, plasma frozen at the same temperature within 24 hours after collection, stress the system and reduce the amounts of plasma that can be frozen. Add to this special plasma needs male (to reduce the risk of TRALI), and specific types (AB, A) and one can see that the room temperature overnight hold (ONH) approach has a great deal to offer.

Medical staff from the Dartmouth Medical School, Hoxworth Blood Center, Norfolk, Virginia Red Cross, Univ. of Washington, and Hemerus Medical LLC in St. Paul, Minnesota, recently published a series of 3 articles in Transfusion looking at the bioequivalence of plasma prepared after ONH using AS-7. They compared “standard” vs. ONH plasma for bioequivalence; the storage and in vivo recovery of red cells at 42 days prepared after ONH in AS-7; and, the effect of ONH and AS-7 on red cell recovery after 6 weeks and after 8 weeks of storage.

Continues on next page
The test plasma was collected in a new test system (including AS-7) and compared with the control in standard CPD and AS-1. Both were leuko-reduced after the hold period and prior to plasma separation. The bioequivalence of plasma held overnight at room temperature then leuko-reduced and frozen between 20 and 24 hrs. was demonstrated by protein assays of the product compared with the standard product tested at 3, 6 and 12 months of frozen storage. Total protein, albumin and IgG levels were basically identical, as were fibrinogen levels, PT, aPTT, Protein C, Protein S, VWF-RCo, ADAMTS13 and Factors V, VII, IX, X, XI and XII. Factor VIII was reduced slightly, between 10-12% in the ONH plasma, as would be expected, but were adequate for normal coagulation function at each timed interval.

Similarly, overnight room temperature hold of whole blood followed by 42 days of storage in the AS-7 solution met current FDA requirements. ATP levels in the test cells were not different from similar red cells prepared at 8 hrs. ATP levels were higher in the test cells at 42 days than in the controls and still met current requirements at 56 days. In vivo recoveries of the ONH cells at 42 days were normal, but 7 of 28 ONH cells transfused at 56 days had less than the required 75% in vivo survival.

Finally, in a study using autologous collection/transfusion, the authors looked at the red cell cold-storage lesion and compared data from AS-7 units stored for up to 56 days with AS-1 collected units at 42 days. The samples were analyzed for pH, free Hgb, ATP levels, 2-3-DPG, extracellular potassium and lactate, packed cell volume and MCHC. In addition, microvesicle shedding from the red cell membranes and resulting damage and morphologic changes were monitored. In sum, all measurements favored the AS-7 stored RBCs. The pH initially of AS-7 units was significantly lower than AS-1 units, but during storage it maintains a pH that is higher than AS-1, which also favors an increase in ATP levels and membrane integrity. In this study, RBCs stored with AS-7 for 56 days met current FDA requirements for 24 hrs. survival recoveries.

If the use of AS-7 and an overnight hold at room temperature meets with approval from the FDA, we will likely see benefits in terms of logistic and labor costs and improved availability of frozen plasma as a source of soluble coagulation factors. Longer red cell shelf-life might be of special interest for military and other special need programs, but the improved red cell preservation and performance at 42 days, the current accepted shelf life, would also be a valuable contribution.

**Dumont LJ, Cancelas JA, Maes LA, Rugg N, et al.** The bioequivalence of frozen plasma prepared from whole blood held overnight at room temperature compared to fresh-frozen plasma prepared within 8 hours of collection. *Transfusion* 2015; 55:476-484.


To those who are aware of the many serious, potentially fatal, reactions that may occur after blood transfusion, a diagnosis of a febrile, non-hemolytic transfusion reaction (FNHTR) may seem like a benign event. After all, with TRALI, TACO, hemolysis, post-transfusion purpura (PTP), and other uncommon but potentially fatal events as possible reactions, a little fever may seem pretty benign. We used to say that FNHTR were mostly related to WBC-containing transfusions, and that they occurred at a rate of about 1%; and, it’s true that leukocyte reduction of red cells within 24 hrs. of collection has reduced this rate.

However, to those patients affected by it, a FNHTR is not at all benign. There is fever, sometimes chills and rigors, often accompanied by an overall feeling of confusion and anxiety, and many hours may slip by until relief occurs. Add to that the fact that fever may be the first sign of an even more serious reaction, such as that of bacterial contamination, and the need to work up the cause by drawing blood samples, perhaps administering antihistamines or antipyretics, and one can see there is a toll on nursing and laboratory staff as well as the patient. Thus, it is not a benign event, and may prolong the hospital stay, as well.

Recently, a group of researchers from the FDA’s Center for Biologics Research and Evaluation (CBER), the Centers for Medicaid and Medicare Services (CMS), and Acumen, LLC, a provider of analytic services to government agencies looked at occurrence rates of FNHTRs and risk factors among elderly U.S. inpatients receiving transfusion (see reference). They examined a large Medicare database, 4,336,338 inpatient stays over the years 2011–2012 and categorized them by age, gender, race, blood components and number of units transfused. Risk factors were assessed using multivariate log regression analyses looking retrospectively at this population. The occurrence of a FNHTR was determined by ICD-9-CM diagnosis codes.

Among this large population of “elderly” (patients over the age of 65), 2517 had a diagnosis of FNHTR, a rate of 58 per 100,000 hospital stays; overall, 0.0006%, quite a decrease from a few decades ago. The study did not differentiate for non-leukocyte-reduced red cell transfusions, but it can be assumed that the large majority of red cells were so modified.

FNHTR rates were substantially higher for RBCs-and platelets-containing units, as opposed to plasma only. There were significantly higher odds of a reaction occurring with more units transfused, for women vs men, with a prior transfusion within a year, and with a history of lymphoma, leukemia, and some other conditions including metastatic cancers, chemotherapy, and bone marrow failure. Older patients (>79 years) had fewer such reactions, as did those patients with a higher Charlson Comorbidity Index score.

As the study was a retroactive one, based on Medicare claims data, it was not possible to evaluate some possibly contributing factors—such as methods and reliability of component storage, donor antibodies to leukocytes, demographic characteristics of donors—and equally difficult to establish in all cases the temporality of contributing conditions as risk factors. In addition, perhaps a population study of recipients of leukocyte-reduced only red cells might add information. As well, the role of the patient’s underlying immunity status would further illuminate the effort.


Febrile, non-hemolytic transfusion reactions in the elderly
Cardiovascular cohort *redux*

As demonstrated again with this issue of PLUS, discussions about the age of blood at the time of transfusion and the subsequent morbidity and mortality rates of seriously ill recipients continue. As noted in this issue’s article titled “It’s all in the planning”, there are clearly some ways of doing a study that are better than others. Observational studies on this topic over the past several years have shown conflicting results related to this topic of “old blood” vs. “ fresher blood”. The authors of this paper (see reference) reported in 2010 that there was an association between the exposure to older blood and in-hospital mortality among transfused cardiac patients. The period of time covered was from 2002-2006. The authors have now expanded their analysis to include patients from 2002 to 2011, with the aim being to reaffirm with larger numbers their conclusion between exposure to older blood and in-hospital mortality. The study comes from McMaster University, the Canadian Blood Services, and the University of Waterloo, all in Ontario, Canada.

Patients included were adults admitted to one of the 3 acute care sites of Hamilton Health Sciences between 2002-2011 who received at least 1 unit of red blood cells and a primary cardiovascular diagnosis at admission or as a post-admission comorbidity. Only first admission data were included in the analysis. Some potential confounding factors were minimized by use of time-dependent stratification, which aims to assess the effect of exposure variables in similar groups when the confounding factors can change over time. Others, such as age, creatinine levels, recipient sex, ABO groups, etc., were controlled for by stratification or regression. Age of blood was categorized in weeks, ≤ 2, 2-3, 3-4, 4-5, and 5-6.

The authors present a table defining and comparing the variables included in the original study and the later study. There were 46,868 hospitalizations for the cardiovascular cohort, and red cells were transfused during 21.7% of these hospitalizations. Second or subsequent admissions were excluded. The crude rate of hospital death, which was the end-point, was 11.3% overall. The original study included 5075 patients, the second study 4594 for a total of 9669 patients evaluated using the same criteria. Overall, almost 42,000 red cell units were transfused, the median number of units transfused for the group was 3 per patient and was similar in both of the studies. In their exploratory analysis of the data, the authors noted a mortality difference when blood age was used as a continuous variable, but did not see this when using the age of the blood in weeks. In addition, when the calendar year (time) was included as a stratification variable, no differences were found, suggesting that this method accounted for medical and operational factors that could have changed over the study period. Thus, the year of admission was an important variable to control for.

By analyzing a larger cohort of data, the authors did not find an association between age of transfused blood and in-hospital mortality, in contrast to the original publication. They postulate this could have been due to a false-positive error, or that year of admission was a confounder that they had not considered. They plan to investigate if differences in blood processing over the time period might account for the differences seen.


American Red Cross
Lumpers, splitters and thrombotic disease

Traditionally, at least according to Wikipedia, “lumpers” and “splitters” are opposing factions in any discipline which has to categorize things, to place individual examples into rigorously defined categories. Some of us are lumpers out of laziness, who sometimes think splitters are just being perversely picky. So for lumpers, a recent review article related to some very complex and poorly understood thrombotic disorders is both welcome and interesting (see reference).

First, if you didn’t know, ADAMTS13 stands for “A Disentegrin And Metalloprotease with a Thrombospondin type 1 motif, member 13”. A metalloprotease is an enzyme that cleaves specific proteins and contains a metal ion, usually zinc. And then there are metalloprotease inhibitors, of course, basically metal-chelating compounds that decrease their activity, another example of the Yin and Yang of biological activities. ADAMTS13 has the important job of cleaving large multimers of von Willebrand Factor (VWF). These ultra-large multimers are called UL-VWF and are closely linked with the development of thrombotic thrombocytopenic purpura, TTP. Newly secreted (from the endothelial cell wall) UL-VWF have a very high tendency to bind with platelets and must be enzymatically degraded into smaller, “standard”, VWF molecules, by ADAMTS13.

TTP is the prototypical thrombotic microangiopathy, and it develops due to abnormal persistence of UL-VWF molecules which result from autoantibodies directed at the protease ADAMTS13. In congenital TTP, there are mutations that lead to lack of this metalloprotease. The UL-VWF multimers are easily seen in thrombi, as they are at least 1 mm in length, and have a very high molecular weight. If they are deposited with platelets to form an occlusion of very small blood vessels, red cells forced through the mesh can become fragmented, leading to schistocyte formation and the presence of plasma-free Hgb. Similar things happen with sepsis in that the inverse relationship between high VWF levels and low ADAMTS13 is associated with the extent of inflammation and degree of organ failure.

In Disseminated Intravascular Coagulation (DIC), the deposits in the microcirculation are of fibrin, with fibrin-rich microthrombi rather than platelets. Plasma coagulation factors are markedly decreased due to consumption, and ADAMTS13 levels are decreased in relationship to the severity of the precipitating sepsis and organ damage. Sepsis is more likely to reduce the levels, as opposed to other less-common causes of DIC, and early renal failure is considerably more likely in the presence of DIC. A low activity level of ADAMTS13 strongly correlates with the severity of the coagulopathy and patient mortality and is generally a predictor of poor survival.

In severe falciparum malaria there is also a thrombotic microangiopathy, since the red cells infected by the parasite obstruct small blood vessels. The parasites induce tissue factor expression from the endothelial cells with activation of the complement cascade, impairment of coagulation inhibitors and dysfunctional fibrinolysis. However, even before clinical symptoms develop in falciparum infection there is a significant drop in the platelet count that worsens as the illness becomes progressively more severe. The microvascular occlusion damages the endothelium, leading to release of the UL-VWF molecules that are stored there, further leading to platelet consumption. This is accompanied by a persistently reduced level of ADAMTS13. There has, as yet, been no study demonstrating a direct relationship between ADAMTS13 and the outcome of the malaria.

Replacement of ADAMTS13 by plasma exchange or plasma infusion in TTP has been demonstrated; however, it is not known if such therapy will improve or prevent organ failure related to sepsis/DIC. We lumpers would like to think so.

Success—and failure—with monoclonal antibodies for hyperhemolysis

Case reports are published for a number of reasons, often because the condition or treatment discussed is new, or unusual, or both. Such is the case with the development of hyperhemolysis syndromes and of their treatment with functionally specific monoclonal antibodies. Immune hemolytic anemia, which has a very low incidence in the general population, occurs in 3-6% of patients receiving an allogeneic hematopoietic stem cell transplant (HSCT). It may occur 2 months to 2 years after transplantation and has a reported mortality rate greater than 50%. Options to treat immune hemolysis in HSCT include steroids, red cell transfusion, IVIG, splenectomy, plasma exchange, donor lymphocyte infusion, rituxumab and other agents such as cyclosporine. Rituxumab is a monoclonal antibody against the surface membrane protein CD20 and is used in the treatment of rheumatoid arthritis and some B-cell lymphomas.

This report from Atlanta, Georgia, describes a case of severe immune hemolysis in a 57 y/o man, blood group O, following a HSCT for acute myeloid leukemia developed after treatment for myelodysplastic syndrome. The donor’s blood group was A. He remained RBC transfusion-dependent with ongoing hemolysis after achieving granulocyte and platelet engraftment in the third week post-transplant. Host-type plasma cells persisted in his bone marrow with elevated anti-A, IgG and IgM levels. Four months later, he received IV methylprednisolone but his red cells didn’t respond and the anti-A antibodies persisted. He was given rituximab weekly times 4, still requiring transfusions every 10 days. CD19+ cells disappeared from his marrow, but anti-A antibodies persisted.

As a third line of therapy, he was given weekly injections of bortezomib, a proteasome inhibitor used in the treatment of refractory multiple myeloma and mantle cell lymphoma. The drug binds the catalytic site of the 26S proteasome in plasma cells, which regulates protein expression. After 4 doses, the patient’s anti-A levels decreased and disappeared, and now after almost a year of treatment the patient’s reticulocyte count and Hgb levels increased with resolution of his transfusion-dependent hemolysis.

Another, older cause of hyperhemolysis, now becoming rarer, is an acute hemolytic reaction to an ABO-incompatible red cell transfusion. In such cases of major incompatibility, the iso-agglutinin attachment to RBC membranes activates the complement system and subsequent formation of C3a and C5a occurs, along with lysis of the red cell membranes and the release of both free Hgb and red cell membrane particles into the circulation. This results in fever, chills, hypotension and acute renal failure. In this reported case (see references), the patient (group B) was transfused with a Group A unit of red cells, and within an hour was given eculizumab, a monoclonal antibody that binds C5 and blocks its cleavage. The patient had no renal failure, no DIC, and the transfused Group A cells survived until 75 days after transfusion.

As a final report, a case of hyperhemolysis in a patient without a hemoglobinopathy is presented, a case in which eculizumab had no effect (see references). Hyperhemolysis, though rare, has been noted in patients with a hemoglobinopathy who develop a delayed hemolytic transfusion reaction (DHTTR), since so many patients develop multiple antibodies over time. The patient presented here developed an antibody to an unknown, high frequency red cell antigen, demonstrated hyperhemolysis (Hct dropped to 10% with no bleeding) and pretreatment with eculizumab had no effect. She gradually improved with steroids and erythropoietin.

Much remains to be learned about these antibodies and their use.


Planning for disasters…for YOUR blood center

National, as well as international, governmental agencies, and specifically the World Health Organization (WHO), have for years urged national governments to consolidate their blood services into one organization with strong direction and oversight, if not outright control. This effort has been going on for many years. In addition, there has been a falling demand for red cells as physicians have learned to transfuse less than in the past, with a resulting decrease in collections and further pressures to merge and streamline functions, facilities, and organizations related to blood collection, testing, processing and distribution. There is also a much greater role for information technology in these processes, often leading to a single control system for a nation’s entire blood supply. Authors from Britain and Australia recently collaborated to share information concerning the management of potentially catastrophic events affecting their business continuity (and thus public health safety) in a national blood service.

Australian Red Cross Blood Services (ARCBS) spent some considerable effort developing an emergency and business continuity framework, the objectives of which are to limit disruption of services to customers, patients and donors, thus ensuring timely resumption of operations. Similarly, the British National Health Service Blood and Transplant unit (NHSBT) has done the same, as have just about all the major national blood services and their composite parts. Both of these recently (2012) experienced challenges of a potentially catastrophic nature to key assets, and together have written a report describing the problems of business continuity in disasters.

The NHSBT is the sole supplier of blood components and diagnostic services to hospitals in England, Northern Ireland and Wales, and retrieves and allocates organs for the entire UK. At the time of the incident, the blood center in Filton, located just north of Bristol in the southwest of England, was responsible for about half of the country’s component production and currently tests about 65% of the country’s donations. It also houses special services, including the cord blood bank, the bone marrow registry and the blood group reference laboratory. Following a heavy rainstorm, the building flooded, to a depth of 20 cm. in the main manufacturing area. All power, data supply and telephone services were lost, including all refrigeration, environmental monitoring, air handling and building management systems. Local and national emergency teams were activated. A senior fire officer declared the building should be evacuated, and so all 12,000 blood products on site were transferred to other blood centers within 6 hours of the event, and collections were re-routed to other sites. In addition, their communications plan was activated to alert all customers involved, with the result of these actions being that the NHSBT filled every hospital order that day without any modifications or delays.

Specific and interesting details on procedural modifications are presented in the paper. The facility, in modified form, was back to regular work in the manufacturing and testing areas, including component production, by Day 7. As a result of the careful monitoring of the recovery effort, several lessons were learned, and are detailed in the paper.

In the case of the ARCBS, there are 4 main processing and testing sites across the country and it is the sole supplier of blood services to the country. At 4:00 am one morning, the network switches in the National Blood Management System (NBMS) production data center failed in several ways. Manual contingency procedures were undertaken, since the NBMS application was totally unusable, and regional emergency management committees took over local operations, as specified in the national business continuity plan. Manual control systems ensured that the quality of the blood supply was not affected. ARCBS performed an interesting root cause analysis, which the paper reviews in detail. Lessons learned are presented, and this article deserves a thorough viewing by all who are involved in large regional or national blood centers.

The American Red Cross exists to provide compassionate care to those in need. As a non-profit humanitarian organization, the mission of the Red Cross is to prevent and alleviate suffering in the face of emergencies at home and around the world by mobilizing the power of volunteers and the generosity of donors. It accomplishes this mission through the commitment of our staff in local Chapters located throughout the country, numerous local Blood Service Regions, testing and manufacturing sites, Divisional leadership teams, and the National & Biomedical Headquarters, which are based in Washington D.C. The American Red Cross operates five key services areas: Biomedical Services, Disaster Relief, Health and Safety Services, Military family support and International Services.

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