UCB: Collecting adequate stem cell doses for stem cell transplantation

Umbilical cord blood (UCB) collection for bone marrow transplantation has been shown to be an effective alternative for providing stem cell transplantation. UCB is rich in stem cells, has more lenient HLA-matching requirements, a lower incidence of graft vs. host disease, a decreased likelihood of infectious disease transmission and is readily attainable, requiring less personnel to carry out. UCB transplantation has been increasing in use. Most interestingly, it can be collected in utero, that is after delivery of the baby, or ex utero, after delivery of the placenta. As with any transplantation of cells designed to reconstitute a normal marrow, the number of stem cells collected is critical to the success of the effort. The variables that have an effect on this success are known and generally measurable.

This study, from St. John Hospital in Detroit, Michigan (see reference), set out to determine the effect of several previously identified variables on the suitability of UCB collections for cryopreservation and transplantation. These included: maternal age, maternal gravidity and parity, presence of diabetes and/or hypertension, gestational age, neonatal sex and race, birthweight, route of delivery, and cord blood collection volume. Also at issue was which of these variables indicate collections with the highest total of nucleated cells (TNC). Their prospectively collected/retrospectively analyzed data set included more than 7,000 cord blood units.

The actual methodology of the in utero collections (and how they differ from ex utero) is detailed in the paper and is of interest, especially if you were not aware of them. Those with a TNC greater than 90 x 10^7 were cryopreserved within 48 hours of collection. Multiple linear regression analyses were used to evaluate each factor. There was a small, but significant, difference between sex of the baby, favoring girls. As expected, the volume of the collection was the most important issue. Other positive predictors included sex (female), birthweight (higher), gestational age (older), and parity (lower).

The authors point out that the cost to facilities of bone marrow stem cell transplantation is much greater than with cord blood collection, and that for those latter procedures, it is less expensive to use the in utero collection method, since specialized staff do not need to be kept in house around the clock. The authors claim they have cut their UCB collection costs by 2/3 since converting to an all in utero collection program. By using these data, the authors believe they can improve donor selection, as well as improve decision making as to which collections are going to be suitable for transplantation.

Looking for bugs in cord blood

The collection and processing of cord blood (CB) has significant potential for contamination. Thus, like platelets, CB standards require screening and monitoring of the final product for bacterial contamination. Studies on platelets have shown that the most effective screening methods use both aerobic and anaerobic bottles, each holding as much as 10 ml of product, the more the better. Practically speaking, though, this amount of product loss severely compromises the final product volume when dealing with CB. To conserve volume, a single pediatric culture bottle has been used, even though up to a 4 ml volume is recommended; in addition, these bottles are not optimal for detecting obligate anaerobic bacteria. The authors undertook this study to evaluate the best bacterial screening method for CB samples collected for transplantation. They compared two different culture systems, BacT/ALERT® and BACTEC™, the media (bottle) type, sample size of the CB collection, and the fraction best used—final product sample, plasma fraction and final product, RBC fraction and final product, and a combination of plasma red cell final product.

CB collections were obtained in a closed system, and then spiked with selected microorganisms at either 1 or 10 CFUs per ml. They used both adult and pediatric incubation bottles for each CB unit, as well as a variety of “fractions” for inoculation. They used 11 organisms for spiking, including 7 common aerobes, 2 anaerobic and 2 fungal (Candida albicans and Aspergillus brasiliensis). A total 94 units of CB were inoculated at doses of 1 and 10 CFUs per ml. For comparison purposes, the analysis also included testing of 34 of the 10 CFUs/ml samples by PCR.

Twenty seven of these last-mentioned 34 were positive by bacterial culture techniques whereas polymerase chain reaction (PCR) detected only 3, suggesting PCR is not an acceptable method for bacterial screening of CB units. Of the 94 spiked units, 81% tested positive for contamination overall; 87% for the 70 CB units spiked at 10 CFUs/ml. In both screening systems (BacT/ALERT and BACTEC), there were equivalent rates of detection of 33% at 1 CFUs/ml and 73% at 10 CFUs/ml. The pediatric screening bottle detected only 15% of the anaerobic bacteria, as compared to the 81% with the larger bottles. The combined fraction method (Method 4, above) showed superior detection at 71%, compared to just 27% for the plasma fraction alone.

The authors believe that appropriate microbial screening can significantly reduce, but likely not prevent, the release of a contaminated CB unit. PCR is not a reliable tool for this. The use of pediatric-sized incubation bottles is of no help and should be avoided. They also point out the importance of each CB bank validating their own process for site-specific centrifugation speeds and techniques, cryopreservation and incubation conditions. They saw no major differences between the two manufacturer’s bacterial detection systems.

Glucose-6-phosphate-dehydrogenase (G6PD) is a hereditary X-linked disorder of glucose metabolism that primarily affects red blood cells (RBCs). It also primarily affects men, though homozygous women are subject to the same risks given oxidative stress on their RBCs. Its discovery resulted from studies of hemolysis in the 1950s related to the use of primaquine, an antimalarial drug. As RBCs mature in affected individuals, levels of this critical enzyme decrease markedly, and without this enzyme the cells cannot generate enough NADPH and keep glutathione, a critical red cell antioxidant, in a reduced state. Thus, any oxidative stress results in methemoglobin formation from oxidized hemoglobin and in the loss of cell membrane capacity to transport cations appropriately across its membrane. The cells become rigid and are removed by the spleen. Most of the common G6PD-deficient variants show increased turnover of RBCs as they age, but are generally asymptomatic. However, with a large oxidative stress, such as from primaquine, some sulfa drugs, fava beans and acetanilid (an older antipyretic, anti-inflammatory drug), intravascular hemolysis may occur, with Heinz body precipitates of hemoglobin seen in RBCs on the peripheral blood smear.

The authors of this article (see reference) point out that the WHO says this problem is estimated to affect about 400 million people globally. There are at least 200 variants, and of course many other sorts of hereditary hemolytic diseases. The most common variants affect sub-Saharan and Mediterranean males, the prevalence being about 8.5% in the former and 7.9% in North Africa, the Middle East and the Mediterranean. There are lower prevalence rates, by at least half, in the Pacific region and in Europe. Asia and the Americas have a prevalence of about 5.2%. The WHO has recommended that donors with known G6PD deficiency but no history of hemolysis be accepted, but that the blood not be used for intrauterine or neonatal transfusion.

This study involved a review of over 600 articles on the subject, written in English, in an attempt to more clearly identify risk factors in the transfusion of G6PG deficient RBCs. Inclusion criteria required that studies be randomized controlled trials, case controls, case reports or prospective clinical series. Data were extracted following the Preferred Reporting Items for Systematic Reviews using a previously piloted form, which included fields for study design, population under study, sample size, study results, limitations, conclusions and recommendations. Of all these studies, only 13 met the criteria for inclusion! Eight of these studies were among newborns and children, and 5 were looking at adults.

All together, there were 9 of the studies that identified harmful effects in recipients, 7 of which were among neonates and children, and these all recommended screening for G6PD deficiency in units to be transfused. Two of these 9 were studies involving adult patients, so 3 of those 5 studies (60%) involving adults stated that such screening was unnecessary. One study involved a series of 114 patients, ages 5–14, who had G6PD deficiency themselves and were hospitalized for hemolytic anemia and exchange transfusion. There were 114 units of blood transfused, of which 14 contained G6PD-deficient red cells. After 6 hours, hemoglobin levels in all of the patients showed significant increases, 3.0 in the group receiving normal cells and 2.3% in the other group. Another, larger study of 261 transfusions for variously anemic children with aplasia, blood loss, sickle cell disease, thalassemia, ITP, hemophilia and so forth, found that those receiving G6PD-deficient red cells showed evidence of hemolysis, increased bilirubin and an insufficient rise in Hgb values.

Thus, the reported effects of G6PD-deficient transfused blood on neonates and children appear to be much more deleterious than effects reported on adult patients, unless the latter already have the problem. In most cases, the rise
of total serum bilirubin was abnormal in infants transfused with G6PD-deficient blood from 6 hours up to 60 hours after transfusion. All studies on neonates and children, except one, recommended a routine screening for G6PD deficiency for this at-risk subpopulation because their immature hepatic function potentially makes them less able to handle any excess bilirubin load. These authors state that it is difficult to make firm clinical conclusions and recommendations “...given the equivocal results, the lack of standardized evaluation methods to categorize red blood cell units as G6PD deficient (some of which are questionable), and ...the low quality of evidence.”

They basically agree with the statement of the WHO that G6PD-deficient donors should not be excluded from donating red blood cells, but that transfusions of such blood may have negative effects on premature neonates or patients who need repeated transfusions; thus, for this group, screening of the units themselves for G6PD deficiency may be appropriate.


Spinning gold out of flax: the platelet problem in a nutshell

Forty to fifty years ago, the use of platelet concentrates for transfusion was not terribly widespread, and they were not readily available outside of major medical centers. Even then the demand outstripped supply, and despite the very large numbers of available platelets (see below) that we currently produce, a shortage of platelets—especially at certain times of the year—continues to be a pretty common occurrence in most blood centers. In this same 40 years (and before), some enormous strides have taken place in our understanding of the production of platelets, how they work, and what goes wrong with them under certain conditions. Two articles from a recent British Journal of Hematology (see references) devoted to the topic are very informative.

The term “thrombopoietin” appeared in the late 1950s, obviously related to the word erythropoietin (EPO) which was first seen in scientific literature in 1906. Not too long after that it was discovered that platelets in the circulation derived from megakaryocytes in the bone marrow, so thrombopoietin (TPO) came into the language. About 20 years ago, the molecule was actually cloned. Since recombinant TPO became available, research has made clear that not only is it strongly related to megakaryocyte/platelet production, it is vital for the maintenance of hematopoietic stem cells. Thus, dysregulation of its production is related to thrombocytosis, thrombocytopenia and aplastic anemia.

The first article from the Stony Brook University on Long Island (one of whose authors, Dr. Kaushansky, played a major role in the cloning of thrombopoietin) reviews how the function and structure of the protein were discovered and provides interesting detail about how it is made and what it looks like. They discuss how it is produced by the liver and regulated in carrying out its work. Under normal circumstances, platelets absorb TPO from the plasma, so that thrombocytosis leads to increased absorption of TPO, lowering counts, whereas in thrombocytopenia the TPO increases, stimulating production of more megakaryocytes and platelets. Genetic disruptions of these control mechanisms, as well as external/extrinsic insults, may result in serious disease, even death.

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TPO drives megakaryocyte differentiation from marrow stem cells, but, in addition, directly increases the size and production capacity of megakaryocyte colonies. There is still much to be learned about the role of TPO in platelet function, but it is clear that low concentrations accelerate the adhesion and “firmness” of platelet adhesion to vonWillebrand Factor (vWF), thus having a likely role in thrombus formation. It seems pretty clear that complex molecular regulatory molecules and systems are required in our circulation to make sure that all the mechanisms governing TPO signaling are carefully controlled.

A few studies in the late 1990s found that patients with thrombocytopenia due to carboplatinum-based chemotherapy had platelet counts that returned to normal more quickly when they were treated with a recombinant human TPO. Similar attempts to use TPO to increase platelet apheresis yields in clinical trials led to the development of antibody production to TPO in some human donors in a small number of cases. That line of work thus has waned. Since then, several smaller amino acid agents that bind to the TPO receptor site on megakaryocytes have been looked at, and seem not to provoke (in studies so far) an antigenic response with antibody formation, especially when bound or fused to a human IgG heavy chain. This drug, called romiplostim, has increased platelet counts in up to 80% of patients with aplastic anemia in clinical trials and has been approved by the FDA for otherwise non-responding patients. Another TPO-simulating drug, eltrombopag, was also approved for such use in 2008, as a second line drug.

Another line of pursuit in the quest for finding tools to deal with the vexing and life-threatening problems of thrombocytopenia is also thoroughly reviewed in this issue of the British journal. The most common causes we see for this condition are related to our use of chemotherapeutic agents for the treatment of various cancers, some of which might be more thoroughly eradicated were it not for the severe, sometimes fatal, declines in platelet counts resulting from therapy. Stem cell technology holds great promise on a number of fronts, and the field of hematology is no exception. The in vitro production of critical cells and cell fragments, such as red cells, granulocytes and platelets, has been a major field of effort in human biology. Currently, the yield of red cells in these efforts has been inadequate to be of clinical use, and the same seems to be true for platelets. Non-hematopoietic stem cells are being looked at in trials for treatment of myocardial ischemia, for example, and cartilage repair. But considering the fact that about 1 trillion (1 x 10^{12}) platelets are in circulation, and that they must all be replaced in 8–10 days, the problem appears daunting from a growth-media culture point of view.

In the United States, there are over 2,000,000 platelet apheresis units and pooled platelet concentrate transfusions a year, all from volunteer donors. The demand for platelets continues to grow, an increase in 2008–2011 of nearly 12%. This is in marked contrast to red cell use, which has declined by almost that same amount in the past 3 years. Our aging population and the increased application of bone marrow transplantation for hematologic malignancies or bone marrow “rescue” from treatment of non-hematologic malignancies increases annually, it seems. Current platelet shelf life is limited to 5 days, and the 24–36 hours of testing and processing consumes a significant part of that time. Several labs have had success in growing platelets in the laboratory using umbilical cord, embryonic and induced pluripotent stem cells; however, none of these methods have yields, at least currently, to be of clinical use. There are many rate-limiting steps, including inducement of megakaryocyte polyploidy to improve yields, actual release of platelets from the mature megakaryocyte, and the very complicated business of developing the many aspects of various platelet functions in an ex vivo environment.

The authors of this review, from the New York Blood Center’s Kimball Research Institute, point out that the greatest primary need is how to generate the enormous number of stem cells to produce megakaryocytes. Other considerations have been mentioned (above); paramount among them would be the manufacturing problem of timing production to need, particularly if a patient has Class I HLA antibodies after many transfusions. Will the megakaryocytes mature? Current knowledge is closing in on that problem. Remaining questions thus include how such platelets would survive in the circulation, and whether they would work. They feel that these questions are progressing towards solutions. We shall see, and we all certainly hope so.


It’s never too late to improve quality of life and health in hemophilia patients

Those of you familiar with hemophilia patients and their treatment over the past many years are all too familiar with the pain and immobility suffered by so many of them for so long. A former Red Cross regional medical director, himself a hemophiliac from years before cryoprecipitate was developed, informed many of his colleagues in great detail. He subsequently died of AIDS, along with many thousand others, before improved—vastly improved—treatment measures came into being.

Currently, at least in most moderately developed societies, very good therapy and very effective prophylaxis are available. Going back to the 1990s, after development of safer Factor VIII and IX concentrates, two types of preventive regimens were developed. Primary prophylaxis, which is regular ongoing therapy starting before the age of 2 and before the appearance of joint damage; and secondary prophylaxis, begun after joint damage has been noted. Preceding these, and also continuing afterward, was demand treatment, or DT, given to treat at the first signs of hemarthrosis, which was in wide use even before safe concentrates were available. Obviously, prophylaxis of either type is more expensive, almost 4 times so. However, bleeding episodes in demand therapy occurred 15 times in 6 months in one study, compared to an average of almost zero in secondary prophylaxis. When/where it is affordable, there’s no doubt that prophylaxis is far better than demand therapy.

The authors (see reference) from Valencia, Spain, undertook a prospective study of men 21 years old or more who already had joint damage to determine whether they could improve their quality of life and musculoskeletal function by a program of prophylactic therapy, using standardized tools and tables to obtain careful measurements. Retrospectively, there were suggestions that this was so. These men had been on a schedule of demand therapy, and were regularly followed by this same group of authors. The planned prophylaxis consisted of twice-weekly infusions of an appropriate dose of Factor VIII, as they were all patients with hemophilia A.

They found after one year that quality of life improved in these patients and musculoskeletal assessment remained stable or improved, when compared to their previous therapy. The treatment required only a small increase in Factor VIII consumption, managed by measurement of trough Factor levels and spontaneous bleeding, and adjustments for these factors. The number of bleeding episodes, absenteeism from work and joint pain all improved with this intervention of secondary prophylaxis. Patients with primary prophylaxis, of course, had been excluded from the study.

In addition to platelets, platelet concentrates contain significant amounts of von Willebrand Factor (vWF) and other coagulation factors at their normal plasma concentration. Although it is known that these factors retain some activity in room temperature plasma, no one has ever looked at them in platelet concentrates stored at room temperature. The question is whether or not they are preserved to a useful degree. Because of the increasing risk of bacterial contamination in room temperature-stored platelets, they are only licensed for 5 days in the U.S. and 4 days in Germany, where the authors of this paper (see reference) work. Platelets are known to contain alpha granules with hemostatically active proteins. Platelet factor XI, a subunit of Factor XIII, and platelet vWF are synthesized in the megakaryocyte. Factors V, VIII and fibrinogen (I) are actively taken up from plasma by platelet endocytosis, and small amounts of Protein S are also found there. To answer whether the concentration of platelets at levels 3–10 times normal plasma levels might have some effect on these various factors led to this investigation.

Twenty-one apheresis platelet concentrates (PCs) used in this study were compared over 7 days to the plasma collected on Day zero. The PCs were collected using a standard approved method on 2 types of apheresis machines, and samples from all 21 units were pooled on the day of testing. Tables and figures in the article summarize the averaged findings for the 18 coagulation factor and inhibitor proteins, including Proteins C, S and vWF. In most of the samples, the PT had declined by Day 4, but the aPTT was only slightly prolonged and remained within the normal range for the 7 days of the study. Factors II, IX and X decreased by less than 10%, and Factor V decreased steadily over time, but Factor VIII showed a flattened decay curve after the initial drop at 4 days. The level of fibrinogen remained steady, with a slight trend to increase. The vWF:Ag increased during storage but the ristocetin cofactor level (vWF:RCo) had a slower increase such that the ratio decreased slightly over time. The proportion of high molecular weight multimers to low molecular weight multimers dropped during storage.

Thus, the levels of procoagulants in the plasma of platelet concentrates remained within the normal range for 5 days. Even after 7 days, the hemostatic potential of the plasma in the concentrates was basically preserved. Factor XII activity actually increased leading one to ask if this factor is released by platelets themselves into the plasma. That particular question has not been explored, according to the authors.

Thus, a new question develops. As we rush to find appropriate additive solutions for platelet concentrates to reduce the rate of various reactions, will we be losing significant procoagulant activity that might be needed for hemostasis in certain conditions, such as massive transfusion? These studies are yet to be done, prompting one to invoke an old—and apocryphal—adage that, “There are no final solutions, only new problems.”

Eighty percent of the world needs safer blood!

As we have previously noted in PLUS, those of us reading this generally are fortunate enough to live in countries with well-developed national blood programs and with a shared sense of responsibility in our citizenry that supports voluntary, non-remunerated donations. Such was not true for some of us 70–80 years ago, and such is not true currently for a huge percentage of the world’s population. The availability and safety of blood for transfusion varies widely. Current estimates, quoted by the authors below, are that 75–90 million units of blood are collected annually worldwide. (This compares with the figures of 70–80 million units reported almost 20 years ago.) Donations per 1,000 people per year range from around 40 in industrialized countries to 10 in middle-income countries to 3 in low-income countries. The rate in most “developing” countries (Aren’t we all still developing?) is generally less than 1%. Basically, 80% of the world has access to only about 20% of the supply of safe blood.

As noted in a previous issue of PLUS (“Lest we forget...,” Fall 2012), pregnant women and children with malaria who need blood services but have none available have a mortality rate of 34%. In addition to the lack of blood, some populations live in an area where there is great potential for disease transmission because the blood that is available is not safe and has not been tested. There are places in the world where someone can sell a pint of blood for a few dollars and then walk around to the other side of the marketplace and pay a few dollars to get a “blood tonic” (usually a small volume of blood in a syringe of saline injected IM) or a blood transfusion (usually whole blood that has not been tested at all except perhaps for group and type). At a blood center in Central America some 20 years ago, one observer inquired about a large, windowless van that pulled up early one morning at the back delivery entrance and discharged a large group of dirty-clothed, disheveled men. An inquiry led to being told that they had been picked up on the city streets over the last night for a variety of offenses, but would be released by the police if they donated blood. Which meant, of course, they had to be accepted as donors. Which also likely meant that they never disclosed information about their personal, sexual or medical history.

The authors discuss, from personal experience as well as a long career in transfusion medicine, the elements that are needed to develop and support a reliable and safe national (or regional) blood transfusion system. When the World Health Organization (WHO) and the International Federation of Red Cross and Red Crescent Societies developed the Global Blood Safety Initiative (GBSI) in the late 1980s and early 1990s, their efforts were nicely summarized on a poster, developed by a Finnish artist and finalized by the group, that depicted the world encased in a blood drop and said in several languages that safe blood meant voluntary donations, quality testing, and transfusion only when needed. Subsequent iterations of these principles have gotten more specific, as illustrated by a WHO flyer of 2006 which states what safe blood means and can be found at who.int/bloodsafety/en/Blood_Transfusion_Safety.pdf?ua=1.

The authors of this paper (see below) thoughtfully review and expand in constructive detail just what this means in practical terms, breaking down all the above into 11 useful topics, including developing assessment tools, monitoring and evaluation with feedback to improve practice, and developing hospital transfusion practices to maximize patient safety and promote more effective utilization.

In the same issue are a handful of articles reporting on the current status of blood transfusion in several developing countries around the world. One of these reports is from Nicaragua, which poses a significant contrast to practices there 20 years ago. The article was prepared by authors from the Nicaraguan Red Cross, the National Health Ministry and the Pan American Health Organization based in Washington, D.C. The program began using the three primary measures of safe blood denoted above and developed and expanded them

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as needed to deal with their difficult situation. Nicaragua, like other Central American countries, has serious logistic problems related to population centers, geography, natural disasters, and not a lot of local financial resources, thus having to depend for some of these things on outside donors. Education of administrative personnel, hospital personnel, medical and technical personnel and, most importantly, the public was undertaken in a many-leveled effort, detailed at length by the authors.

Their efforts to date have led to development of a blood supply that is 100% voluntary and non-remunerated, and an increase in donation rates from 10.7 per 1,000 population to 12.6 per 1,000. This may not seem like much to most of you, but if you have had any experience in such countries you will recognize the degree of this achievement. These figures are now 3 years old, and a brief update on them would be of interest. If you are interested in helping, read these articles and make some contacts with appropriate organizations.

Make a difference. We are not what we say, we are what we do.


No questions asked...

About 35–40 years ago, faced with staff and donors who disliked the tedium of repeatedly asking donors the same 10 or 12 questions about their health history, one American blood collection agency looked wistfully at the donor registration form from another country. There were then three questions: are you in good health; have you ever had hepatitis; and, are you taking any medicines? Those days are long gone, and we now ask donors more than several dozen questions about their personal health, medical and sexual history. From those “baseline” questions, a series of complicated response trees breaks off that (in one instance) fill well over 200 pages of 1 to several items per page detailing what to do with the answers. Of course, mistakes are made, blood gets wasted, donors get angry, many never return and the myriads of people—including the FDA in the United States—who police adherence to these responses add a very substantial cost to our blood supply. The oversight, staffing and enforcement of these efforts (internal and external), in addition, is onerous and time consuming. No one has ever asked whether these efforts work, are cost effective, or even what the cost is. This study from the Netherlands brings to the fore that the cost effectiveness of the donor health questionnaire (DHQ) has never been quantified, or questioned, with regard to its effectiveness in preventing transfusion-transmitted infectious disease (TTIs). They did so using a tool called the incremental cost effectiveness ratio (ICER).

The Dutch recruitment and collection system is more efficient than most of ours in the U.S. They have analyzed their costs by “New donors” and “Regular donors,” the former representing about 5% of the total donors, over a 3-year period. (Whether “repeat donors,” as we call them here, are the same as their “regular donors” is uncertain from this article.) New donors attend a session where about 15 minutes is spent on the questionnaire, and a sample of blood is taken for testing only, not donation. Regular donors require only a brief time to register and sign in; new donors average 15 minutes just to complete the questionnaire. The incidence of TTIs in the country is lower than that of the U.S. Calculations included the number of donors from both groups in the “window phase” of infection, the time between infection occurrence and measurable evidence of it in the donor. New donors had a TTI risk of 5.5% and regular donors 0.6%.

This is a very brief summary of a very sophisticated article, but based on costs and calculations of both sensitivity and specificity data, that are explained in great detail in the tables and figures of the article, the authors conclude that the ICER for quality adjusted life-years (QALYs) far exceeds the recommended WHO guidelines of $100,000/QALY gained. The ICER for the donor questionnaire in preventing TTIs approached 700,000 Euros for the blood centers alone, nearly $1,000,000! It’s true that the relative risks of TTI in the Netherlands are exceeded by those in our country, but they do not ask their regular, repeat donors the same battery of questions that we do every time they appear. Coupled with the article on RBDM, there is surely something to learn here, for both regulators and regulated!

And some, such as the authors of this paper, might add: and also the war against irrational and outrageously expensive health care. The March 2014 issue of Transfusion came in two parts, the second of which is largely devoted to issues surrounding donors, including iron deficiency, donor recruitment, donor-related infection risks and the adverse impact of donation. The authors of the article below (see reference) identified seven articles in the issue that look at how we might approach various aspects of transfusion safety with very little regard for cost. They also point out that costs are getting out of hand, and the only tool we have available to date to reduce them seems to be simply to reduce the amount of blood transfused, especially via our “patient blood management” programs. Most decisions, notably since the awful tragedies of HIV and HCV 30 and 25 years ago, have been in favor of a “zero-risk blood supply,” which led some wags at the time to publicly wonder if we could find “zero-risk lives” that would benefit. Once bitten, twice shy; twice burned, thrice learned?

The article points out that United States health care costs are now at 17.4% of our gross national product, and still headed up. This is almost twice as much as any other developed country, almost all of whom far out perform us with regard to measurable outcomes such as longevity, teenage pregnancy, infant mortality and many other metrics. And even though we have decreased red cell utilization significantly to about 40 units/1,000 population, current trends in the Netherlands, Canada and Australia are approaching 30/1,000, with most of Europe close approaching. The authors state: “Professional standard setting organizations in the United States and elsewhere issue standards that focus on product safety without a comprehensive or transparent consideration of cost utility...,” which leads to a variety of problems, both with regard to cost as well as to more global issues of patient safety that may have a higher impact. They also point out that in this climate some patient-safety initiatives cost more than 10 times the generally accepted threshold of up to $100,000 per quality-adjusted life-year used to assess other types of medical interventions. Part of the problem is felt to be that governmental blood industry regulators consider only safety data, not cost considerations.

Enter RBDM—risk-based decision-making. Is there a role for thoughtful analysis of risk and careful calculations of how much mitigating that risk will cost? A great deal of such thinking is at work in other areas of medicine, agriculture, manufacturing, education and government. Why not in the arena of transfusion medicine and patient safety? Our current blood safety decision-making process is very complex and difficult to understand, does not deal proportionately with proportionate risks and leads to dissatisfaction on the part of everyone, including patients, funders/payors and regulators. In October of 2010, an independent panel of professionals from several countries with credentials in health care and the risk industry stated: “… zero risk is an unattainable goal.”

The authors all are serving as members of a RBDM project that hopes to develop a framework for decision-making based on framework development, health outcomes economics, best practices for decision-making, and a Web portal to serve as a resource for RBDM tools. This certainly seems to be a worthy undertaking.

We regret to report the passing of George Garratty, Ph.D., FRCPath. Dr. Garratty was scientific director at the American Red Cross Southern California region and recognized worldwide for his deep knowledge and contributions to the understanding of immune hemolytic anemia. Dr. Garratty published more than 300 scientific papers and edited numerous text books. He was a founder of PLUS and one of its editors for more than seven years. He is greatly missed.

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Publications Corner

Recent publications by American Red Cross scientists and physicians:


**The international experience of bacterial screen testing of platelet components with an automated microbial detection system: a need for consensus testing and reporting guidelines.** Benjamin RJ, McDonald CP; for the ISBT Transfusion Transmitted Infectious Disease Bacterial Workgroup. *Transfus Med Rev.* 2014 Feb. 5. doi: 10.1016/j.tmrv.2014.01.001. [Epub ahead of print]


**Probable transfusion-transmission of Anaplasma phagocytophilum by leukoreduced platelets.** Townsend RL, Moritz ED, Fialkow LB, Berardi V, Stramer SL. *Transfusion* 2014 Apr. 17. doi: 0.1111/trf.12675. [Epub ahead of print]


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