Ebola Lessons: Déjà Vu All Over Again

By the time this gets into print in 2–3 months there will be no particular news about the Ebola outbreak that originated in West Africa that hasn’t been known for a while. Hopefully, the world will have rallied and stopped the outbreak without too much more loss of life. But, this event needs to serve as a real lesson — again — about preparedness and an awareness that there are still a lot of things that we don’t know, can’t control and which point out our ignorance about the status of infectious diseases in the world, especially in the parts that lack the public health infrastructure that we have in the more developed world. Indeed, the far higher mortality rate from the Ebola outbreak in West African countries can be ascribed to lack of good general medical facilities where they are needed, adequate isolation procedures, careful contact tracing and a heavily co-infected population, including especially malaria. Once again, as was witnessed early in the AIDS years of the 1980’s and ’90’s, the scale of corruption and mismanagement in government, particularly with regard to health infrastructure and public health expenditures has been the biggest single factor in the spread of Ebola. This has been noted by many observers, including Dr. Paul Farmer writing in The London Review of Books (see References): “Weak health systems, not unprecedented virulence or a previously unknown mode of transmission, are to blame for Ebola’s rapid spread.” He continues in detail, recounting that the Dallas Cowboys football stadium consumes more energy in one year than does the entire country of Liberia.

A great deal has been written about Ebola since it was first discovered in 1976 by a team of Belgian public health workers, including Dr. Peter Piot, who went on to spend many years at W.H.O. and is now head of the Liverpool School of Tropical Diseases in England. In an October, 2014, edition of Nature (online), there is an excellent history of the ebolaviruses. There are four strains of ebolaviruses, including Ebola Zaire, the current strain, plus the related filoviruses, Marburg and Reston, named after outbreaks from primates moved from Africa to Germany and Virginia, respectively. Ebola virus disease, or EVD, was originally seen in Central Africa, not West Africa, but the viruses have been found in other parts of the world, including as far away as Australia and the Philippines. Pigs have been found to harbor ebolaviruses, and some wonder if they could become a mixing vessel for them. Human populations in the countries harboring ebolaviruses have grown almost 3-fold since they were discovered, and flight traffic in the region there has increased by 30% since 2005. Thus, the viruses are not coming to us; rather, we are encroaching on their territory, exposing ourselves to viral contact and the capacity to move them around the world.

As with the other types of viral hemorrhagic fevers, the most severe damage in Ebola is caused by the human immune response to the infection. There is a strong release of tumor necrosis factor (TNF) and interleukins (IL-1, IL-8) that lead to sloughing of the infected linings of blood vessels, including in the intestines and other organs, just as occurs in severe cases of bacterial septic shock. Death is thus caused by massive fluid losses, with attendant shock, dehydration and death. Articles from the NEJM (see references) and other sources, including Dr. Farmer, point out that with appropriate isolation...
and massive fluid replacement accompanied with careful monitoring of hematologic parameters and electrolytes, the death rate form EVD might be markedly less, even perhaps as low as 10-15%. In Africa now, oral rehydration attempts occur because of lack of IV fluids, IV catheters, and of course light to see what one is doing. But if their is no electricity, no contact tracing, no careful isolation and protective equipment, not much will change. This Ebola outbreak should be seen as an extremely urgent call to everyone to find ways, to make ways, to get proper health care delivery mechanisms to where they are needed now before they are needed everywhere. Remember SARS? Please do!


What to do about Babesia microti and friends?

What is the most common transfusion-transmitted infectious disease in the United States in the last few years, and why? When a case treated by exchange transfusion was reported at a meeting of the International Society of Blood Transfusion (ISBT) in Montreal in 1980, many hands shot up in the air when the presenter asked for questions. All had questions about the indications for giving platelet concentrates to a patient with high-titer anti-platelet antibodies. Since then, in general, all of us have become more careful in the use of blood components. Nonetheless, from then until 2005, 159 cases of babesiosis have been reported. Half of these were recognized from 2009 to 2005, so the rate of recognized cases would be 1.2 per million units transfused. One assumes the actual rate is higher, and it definitely is in certain parts of the country, since virtually all of these cases came from the northeastern United States, with a significant but lesser contribution from Minnesota and Wisconsin. However, we have no FDA-approved screening test for the disease, and the editorial by Drs. Katz and Sayers (see References) review and illustrate this story, with comments on the several articles on the topic found in the same journal issue.

Some of the problems, of course, relate to the cost-effectiveness of the test and cost considerations are not seen as part of the FDA’s rule-making process. How much are we willing to pay for what is called a quality-adjusted life-year (QALY), a sort of internationally agreed-upon measure of the costs and value of social intervention? A million dollars? The World Health Organization, using a much different data base, of course, sets a threshold of no more than 3 times the annual per-capita gross domestic product (GDP), which in the U.S., unlike much of the world, is about $155,000. How much of the cost can be accepted and passed through to hospitals and payors? And especially for a test that, so far, is not needed in most parts of the country? Who, or which, of our licensed reagent-makers would be willing to expend the resources to develop an effective, quick and (relatively) inexpensive test? And which test?

Moritz and colleagues from the American Red Cross Laborato ries and IMUGEN, a manufacturer, tested a PCR method and an investigational immunofluorescent antibody (IFA) test, using over 13,000 paired samples from a non-endemic, moderately endemic and highly endemic parts of the United States. This IFA was a second-generation test designed to facilitate high-throughput-screening. The prevalence of positivity in these donors from these areas was 0.025%, 0.12% and 0.75%, respectively. One of the problems they discovered was that a positive IFA with detectable babesia-specific IgG antibody persisted in some donors for up to three years afterwards. Possibilities of a PCR-positive window period were also noted.

Adding to this discussion, authors from the American Red Cross and CDC’s Parasitic Disease and Malaria branch published in this same edition of *Transfusion* a longitudinal study of B. microti infection, as demonstrated by an IFA titer of 64 or more, in previously identified seropositive blood donors. (See reference 3). They monitored the subjects for up to 3 years and noted that several of them had been infected for at least 1 year when their last positive specimen was collected. They conclude that seropositive donors can have low-level parasitemia that is

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intermittently detected by parasitic and molecular mechanisms, suggesting that donor-screening algorithms should include both serologic and molecular testing.

Finally, also in this issue (see Reference 4), another group of authors from the Blood Systems Research Institute, U. of California in Berkeley and in San Francisco, and from the Yale School of Public Health, examined costs and consequences of B. microti donor screening of the U.S. blood supply using models for a 4-state, 7-state, 20-state or national implementation plan. They reported their results using the afore-mentioned QALY. Their data found that using both an ELISA and PCR, together, would be effective and would yield results of $5.2M and $6.6M per QALY for the 4 state and 7 state models, respectively. The larger strategies were much less favorable!

As we look at all this, one can’t help wondering where it will all go. Can we ever have a zero-risk blood supply? What about chikungunya, dengue, yellow fever? What about SARS, MERS-Co-V, Ebola, hepatitis X, and whatever else is out there? What can we afford, and who decides? Or, what is a tolerable risk, as our editorial authors ask? Do we test everyone, or just donors from endemic areas? Or just donors who have been outdoors for work or recreation in affected areas? What about travelers, vacationers to such places? In addition to science and medicine, and the changing and emerging epidemiology of new – and old – infectious diseases that may be transmissible by blood transfusion, we must face, accept and plan for the economic realities. Let’s hope that we can find the technology to accomplish this, the will to see it through, and the fortunate grace to not have these efforts subverted by inordinate/inappropriate profit, or decided by Congress. Let’s hope.


Are blood product recalls an assessment of quality?

The move towards quality assurance, QA, and quality control, or QC, really gained momentum in the 1990s with publications by respected blood bankers and federal regulators, including one of the authors of this paper. (See Reference.) The idea developed was that blood is a drug, and that as such it should be regulated in much the same way as standard pharmaceuticals, with strict quality control over reagents, testing, processing, product definitions, batch control, labeling, enforcement reports and other items. Any deviation from such “good manufacturing processes” that potentially or actually might affect the safety, purity or potency of the product must be reported, and some such deviations may lead to blood product recalls.

The FDA classifies recalls as follows: Class I – use of or exposure to the product is not likely to cause adverse health consequences. Using data from the FDA’s publicly available web site, the authors reviewed the blood product recalls for the year 2010 and summarized it for this paper. The reasons for and frequency of the recalls were broken down into the 10 principal activities of blood centers. The data were then summarized for the 19 separate FDA districts and also by the size of the blood center(s) involved.

There were no Class I recalls, a good thing, and 21% were of Class III, those not likely to have a health effect. The majority, then, were Class II, likely to have a health effect but generally temporary or remote. Generally, the smaller the blood center the greater the number of recalls. Nearly three-fourths of the recalls were in the area of donation and donor qualification and almost 15% in product QC. Although these requirements may contribute to overall blood safety, it should be pointed out that some of our blood donors forget, or fib about, important aspects of their personal medical or sexual history, leading some of us to wonder if there is a better way to assess safety.

As Lyme disease worked its way northward from its initial discovery in the early 1980’s in Lyme, CT, it spread pretty rapidly into suburban New York City areas where large and explosive populations of white-tailed deer in the last third of the 20th century served as wide-ranging intermediate hosts. The primary host, the white-footed mouse, or deer mouse, is also widespread throughout the territory. The black deer tick, *Ixodes scapularis*, serves as a primary vector between these animals and other mammals, including dogs and humans. The ticks have also been found in woodland birds, opossums and other wild creatures. These ticks, which can also harbor and transmit babesiosis, have at least one other organism they carry around and have taken it right up the Hudson River Valley to upstate New York; this is human granulocytic anaplasmosis (HGA), caused by *Anaplasma phagocytophilum*, identified as a cause of illness in both pets and people. (The disease was formerly known as human granulocytic ehrlichiosis.) These ticks, then, are widespread and heavily-infested reservoirs of infection for humans in the northeastern United States. Another tick-borne fever, Powassan encephalitis, named after Powassan, Ontario, where the first victim died of encephalitis, has been reported from Minnesota. Formerly, it was seen only in New England and New York, but to a much lesser degree than the tick-borne topics under discussion here.

HGA is a rickettsial-like intracellular organism that infects neutrophils preferentially, and can be seen in infected mammals (including people) as inclusion bodies and vacuoles in granulocytes. The symptoms are flu-like and non-specific, and often asymptomatic except in elderly or immunocompromised people. Infection is associated with leukopenia, thrombocytopenia and elevated liver transaminases. The authors of this report (see Reference) attribute the eighth case of HGA to transfusion of a blood component, in this case a leukocyte-reduced platelet transfusion. A related illness, also carried by ticks of several varieties, affects monocytes preferentially, and is known as human monocytphilic ehrlichiosis.

The infected patient had suffered multiple gunshot wounds in a large city in New England and received 25 units of various blood components, including red cells, fresh frozen plasma (FFP) and platelets, prior to his death not long thereafter from trauma. A day or so after receiving most of the blood, granulocytic inclusions were noted on his peripheral smear and the hospital ordered tests for tick-borne diseases. The hospital was located in a major endemic area for the tick-borne diseases noted above. He was diagnosed with Anaplasma cytphilum, HGA. All 25 donors of the transfused blood components were reviewed and interviewed and 13 were excluded, including 9 donors of FFP, which is considered acellular. Eleven of the 12 remaining donors were excluded based on laboratory tests; however, an apheresis platelet donor, whose product was transfused on hospital day 5, was found to be positive for the organism. The patient himself had been unable to provide a medical or travel history. The positive donor was from Albany County, New York, an area heavily infested with the black-footed deer ticks, *Ixodes scapularis*. The vast majority of ticks in the county are found to be positive each year when samples of ticks collected in the field by public health workers dragging large nets are tested for Lyme disease.

This reported case of probable transfusion-transmission is the first to implicate leukocyte-reduced apheresis platelets as a transmission vehicle for HGA. It also represents a nice case of good detective work by the involved staff. How widespread a concern this might be is hard to estimate, since so many healthy adults can harbor it for unknown periods in their blood without any symptoms whatsoever. Is screening for the organism, by blood smear exam, or serologic testing, something we should be looking towards? Not right now, say the authors, since much more needs to be known about the illness, its manifestations and its prevalence. But, stay tuned! Between inexorable climate change and the displacement of animals by people encroaching on their natural habitat, encounters between blood donors and potentially transmissible agents will likely increase all over our world, which is not exactly shrinking but is getting closer and closer.

And they’re still coming ashore!

Attention has focused recently on another flavivirus, Chikungunya virus (CHIKV), carried by the same Aedes mosquitoes that carry dengue, yellow fever and other arboviruses, A. aegypti and A. albopictus. This virus is named in an East African language because of the very crippling arthralgias associated with infection. It was responsible for large outbreaks of mosquito-borne outbreaks in Africa, the Indian Ocean, other parts of south Asia and the western Pacific islands. In December of 2013, the French National Reference Center for Arboviruses confirmed local transmission on the Caribbean island of St. Martin. It has now spread throughout the Caribbean and South and Central America, in a distribution consistent with the known distribution of the Aedes species noted above. The authors of this editorial (see References) provide a helpful review of the history of CHIKV in our recent times.

It’s also interesting to note two things about these mosquitoes in the continental United States. First, 60 years ago the upper northern range of A. aegypti was delimited by the Tropic of Cancer, 15 degrees north latitude, a line running roughly from Jacksonville, FL through New Orleans, Houston and parts of northern Mexico. Currently, A. aegypti can be found from tidewater areas of Virginia and Carolina across much of the deeper South, into Arkansas and eastern Texas. Second, A. albopictus, the “tiger mosquito” imported in the last century from Asian ports to the U.S. in stagnant water on ship’s decks and in tires made made in eastern Asia, has a much wider range, being able to winter over at latitudes as far north as 40 degrees, the border between Pennsylvania and New York State. There have been small dengue outbreaks in Florida and Texas recently, but they were pretty limited, perhaps due to the widespread use of air conditioning that markedly decreases contact with the indoor-biting A. aegypti. A. albopictus, on the other hand, can tolerate cooler temperatures, feeding outdoors as well, and was the vector identified in a recent outbreak of over 300 cases of CHIKV in northern Italy.

Despite its rapid spread around the world, from eastern Africa across the Pacific to the Americas, a spread engendered by human and freight/shipping/cargo traffic, do we need to worry about transmission from blood transfusion? The authors from Thailand (see References) developed a model to evaluate this question, using epidemiologic and serologic data from the documented 2009 epidemic in Songkla Province in southern Thailand. The model was based on the facts that CHIKV has a high attack rate (especially in a ‘naive’ population), a rapid rate of replication, high levels of viremia and a significant number of asymptomatic infections. In the large outbreak on the Pacific island of Reunion in 2006, the CHIKV genome was identified in platelet units, the only product collected during the outbreak.

The authors used three modeling assumptions in their study. They assumed that symptomatic cases would self-defer due to illness or be excluded by screening; however, this would not exclude asymptomatic donors. Second, they assumed that any viremic but asymptomatic donors (who have already been shown to have high viremic loads) would infect any recipient due to the low level of herd immunity in the outbreak. Third, they assumed that the prevalence of mosquito exposure and infection risk was the same in the donor population as the population at large. The assumptions on prevalence of infection and the duration of viremia in pre-symptomatic and asymptomatic donors were based on prior studies carried out during the actual outbreak. [During the actual epidemic, pre-donation screening with regard to CHIKV symptoms (fever, arthralgias and rash) was applied. Post-donation callback for symptom follow-up was instituted and all non-platelet products were held for 7 days post-donation to confirm donor status before distribution. Units from symptomatic donors were discarded.]

The mean risk of viremic donation in this study was found to be 38.2 per 100,000 donations; the maximal risk of 52.3 per 100,000 if a longer period of viremia in asymptomatic donors was assumed (18.5 days vs. 9.5 days). A shorter viremic donation 1.5 asymptomatic days and a total of 7.5 days of viremia was used in models of the Reunion outbreak of 2009. Of course, as with West Nile virus and others, the duration of viremia will vary depending on the sensitivity of the assay. The Thai model predicted that 11 to 15 of the 26,722 donations during the outbreak would have led to CHIKV infection in a recipient. These would have been discarded, based on the actual mitigation steps listed in the preceding paragraph.

The editorial authors, from the CDC and the FDA, listed 5 mitigation strategies that might be used to reduce CHIKV (and likely other risks) in the Americas, pointing to the settings in which they might be used and commenting on their shortcomings. This is a very useful table when considering what steps...
we might invoke in such circumstances. Enhanced pre-donation screening, better post-donation follow-up of/ by donors, donor deferral from affected areas, cessation of collections in affected areas, photochemical inactivation, and NAT testing specific for the agent: all have limitations in effectiveness when put into actual practice and some are very disruptive and expensive. They point out that CHIKV might be the latest, but will certainly not be the last, emerging pathogen liable to affect blood safety. Until we have effective and practical methods for pathogen inactivation applicable in a wide range of settings and requirements, we have to rely on less satisfactory options, which they outline in their table.


Not ashore...yet

For three years, 2007 to 2009, the Netherlands experienced large numbers of outbreaks of Q fever, a systemic disease carried primarily in goats, sheep, cattle and other animals, in whom it causes large-scale herd abortions. The organism is Coxiella burnetii, which brings to mind for some a name for an Italian race car driver. In the Netherlands, waves of abortions in dairy goats, and to a lesser extent non-dairy sheep, were responsible for more than 3500 cases of Q fever in humans, who may become infected through aerosolized dust from herd areas, or from ingestion of meat or dairy products from affected animals. Since then authorities have noted an increased number of chronic Q fever cases being reported from hospitals in the outbreak areas. Most of them had not had, or at least recognized, the acute illness. Most of the chronic cases involve people with diseased or artificial heart valves, or vascular grafts or aneurysms, or people who were immunologically incompetent or pregnant, but - as in this case - it also may be seen in healthy patients who had no history of the illness. The agent causing Q fever is also classified as a bioweapons agent and has been known to have been militarized by some, i.e., prepared in lyophilized powder form for widespread dissemination as a battlefield aerosol. Occasional cases are seen worldwide, from natural causes.

Because of the severe nature of the outbreak and the appearance of chronic carriers, the authors of this study (see Reference) wished to see if it might be infectious for transfusion recipients. Four years after the initial outbreak, samples were collected from about 2,500 blood donors at two sites located in the center of the area of the highest Q fever incidence. They represented 58% of the registered donors at those sites. Samples were screened using an ELISA method, and borderline or positive samples were tested with an immune fluorescent antibody (IFA) test for the presence of the Q fever antigen. A titer of 1,024 or greater to the Phase I antigen using ELISA (there are 2 phases) for the organism is considered positive. Positive tests were then confirmed using the Phase II IFA, considered to be a more sensitive and equally specific test.

Of the original 2490 donors, 110 (4.4%) tested positive for Phase II antibodies by IFA, felt to be the superior test. About 400 of these donors had been tested in a previous study in 2009-2010 and the seroprevalence then was higher, at 12.2%, suggesting a fairly rapid waning of the antibody titers in these healthy individuals. Using ELISA alone, none of the originally positive donors had detectable antibody; the more sensitive IFA also showed a large decline in titers, but only 3 of the 23 serial donor samples turned totally negative, which the supports the claim of increased sensitivity for the IFA assay.

The authors believe these findings support the decision by health authorities in the European Union to allow re-entry of donors two years after resolution of infection. There remains, however, a CDC public health note from 1977 (see Reference 13 of the article) that apparently reported Q fever transmitted by blood transfusion, and a case from an organ transplant. Nonetheless, given the more modern experience, it seems fair to say that – for now, at least – Q fever is not coming ashore.

Weak evidence for transmission of vCJD from blood transfusion

Variant Creutzfeldt-Jakob Disease (vCJD) appeared in 1996 as a zoonotic infection spread to humans who had ingested bovine spongiform encephalopathy-infected beef products, especially those products containing tissues from the animal’s central nervous system (CNS). vCJD has been diagnosed in 177 people in the United Kingdom, and some in France and Saudi Arabia – all with a link to British beef. Retrospective studies of lymphoreticular material obtained at autopsy from random sample of the general population have suggested that 237 people per million general population to 1 in 2,000 may be “carriers” of prion proteins, thus defined. An ongoing British study has identified three clinical cases of vCJD and one individual dying of intercurrent illness who were infected by non-leukocyte-depleted blood derived from asymptomatic donors who later developed the condition. The subclinical case was an MV heterozygote at codon 129, providing the first indication that individuals with PRNP (the gene in which a mutation occurs that causes CJD) genotypes other than methionine homozygous (MM) could be infected by the vCJD agent.

What about the rest of the 177 people? Did they receive blood from an asymptomatic vCJD carrier? There have been seven cases of vCJD who received a blood transfusion, in which none of the linked donors is known to have developed vCJD. In this paper, the authors compared variant Creutzfeldt-Jakob disease (vCJD) cases definitely linked to blood transfusion, those with a history of blood transfusion in which no donor has developed vCJD, and primary cases with no history of blood transfusion. The ongoing study identified 15 cases reported to have received a blood transfusion. Transfusion records were found for just 10 cases; the others occurred before 1980. The aim was to determine whether there were any differences in the demographics or clinical phenotype in these groups that might suggest that there may be additional unrecognized cases of transfusion transmission of vCJD by donors who had not yet developed clinical disease.

They concluded that it is possible that one or more of the vCJD cases that received a blood transfusion derived from donors not known to have developed vCJD were in fact infected by the blood transfusion. However, the evidence for this is very weak and the epidemiological evidence from observed cases of vCJD clearly excludes a large number of unrecognized transfusion-transmitted cases as the great majority of cases have no history of prior blood transfusion.

Another decrease in the need for blood

It is in the nature of man, when faced with formidable odds in a difficult situation, to use every available tool to try to save a life; it is very hard, in such circumstances, to ascribe success to any particular treatment over others. When faced with septic shock, the use of resuscitative fluids and antibiotics are clearly indicated and proven. The need for blood component transfusion has been unclear. Red cell or whole blood transfusion has been associated with increased mortality in some subgroups of critically ill patients in randomized trials as well as cohort studies, but there have also been reports of improved survival, including among patients with septic shock. The use of non-leukocyte-reduced blood has added to the confusion in some studies.

A large study of about 1,000 patients in roughly 20 institutions in Denmark, Sweden, Norway, Finland and a hospital in Australia representing 2 large clinical trials groups was published in October, 2014 in the New England Journal of Medicine (see Reference), representing the work of about 40 authors. Criteria for patient selection and data collection were agreed upon and patients were stratified according to study site and the presence or absence of active hematologic cancer. Those with septic shock were randomized to either a low (7g/dl of Hgb) or high (9 g/dl of Hgb) threshold for transfusion of – on average – 1 unit of leukoreduced RBCs while in the ICU. The study was not completely blinded; the primary outcome measure was death by 90 days after randomization. Patients with severe burns, blood transfusion before randomization, acute coronary syndrome were excluded, as were a handful with other reasons. 1,005 patients were randomized into two final groups of 503 to the lower threshold and 497 to the higher one.

A large amount of data concerning the use of life support measures, adverse transfusion reactions, ischemic cerebral and cardiac events and ischemic bowel or limb events, etc. exist. Readers should review the article for these other useful pieces of information. In the lower threshold group there were 502 evaluable patients, and 496 in the higher threshold group. The first group received 1,545 units of leukoreduced RBCs, the higher group received 3,088 (p<0.001). 36% of those in the lower threshold group received no transfusions, compared with 1.2% in the higher group. At 90 days after randomization, 216 patients (43%) in the lower group and 223 (45%) in the higher had died (relative risk 0.94; 95% confidence interval 0.78 - 1.09; p=0.44). Analyses of specific subgroups of these patients, based on age, heart disease, hematologic cancer, source of sepsis, as well as other treatment variables showed that the two groups were statistically similar.

Although the trial had some limitations, it in fact was blinded to the extent that group assignment at randomization was concealed, and the assessors of mortality and the statistician were ‘blinded’ during the analysis. The authors conclude that patients with septic shock who underwent transfusion of leukocyte-reduced red blood cells at a Hgb threshold of 7g/dl, as compared to those with a threshold of 9g/dl, received fewer transfusions and had a similar mortality at 90 days. In addition, the number of days of life support, number of ischemic events and number of days alive outside of the hospital were also similar. Sometimes less is best.


Winter 2015 | PLUS 9
Can it be that less blood is best for some and more is better for others? One cannot generalize, of course, across the whole spectrum of human disease conditions. There are reasons for both statements, but not everyone agrees, even when considering just one clinical condition, since there are always qualifying factors. Blood transfusion can have many unwanted effects, in addition to the desired one of, say, increasing the oxygen carrying capacity of the blood.

A case in point is sickle cell disease (SSD) and its attendant severe hypoxic and vaso-occlusive effects. The infusion of donor red cells does improve O2 delivery in the short term; however, it also leads to allo-immunization and to iron storage disease, over time, making transfusion a potentially life-shortening, as well as life-prolonging, intervention. Ah, to find the right balance!

Authors from several well-known institutions involved in the care of patients with SSD have published a multi-center clinical trial involving the preventive role of red cell transfusions in children with SSD and cerebral infarcts. Silent cerebral infarcts are the most common neurologic injury in such children, and have only been recognized as such fairly recently. They are known to be associated with clinical stroke. The authors compared children from such a group who received regular transfusions to others in that group who received standard care. Standard care patients received no blood and no hydroxyurea therapy for silent cerebral infarcts. The transfusion group received a transfusion approximately monthly to maintain a Hgb level > 9g/dl. and a target Hgb S concentration of 30% or less of total Hgb. Ferritin levels were monitored before each transfusion and chelation therapy was initiated for participants who had ferritins >1500 ng/ml for 2 or more consecutive months.

Assigned to the transfusion group were 99 participants and 97 children were assigned to the observation group. The mean age of the participants was 10 years, and all were followed for a period of 3 years. In the transfusion group 6 of 99 (6%) had an end-point, 1 with stroke and 5 with a new or enlarged silent cerebral infarct. In the observation group there were 14 events, 7 with stroke and 7 with a new or enlarged silent infarct. The incidence of such a defined end-point was 2.0 and 4.8 events, respectively, per 100 years of risk, a rate ratio of 0.41%. There were concomitant and significant reductions in other risks, as well, in the transfused group, including acute chest syndrome, vaso-occlusive pain, priapism, serum ferritin levels, and symptomatic avascular necrosis of the hip.

Not all of the participants assigned to the transfusion group received that full treatment, as 15% declined transfusion after enrollment or crossed over to the observation group. In his editorial Dr. Steinberg from Boston University, pointed out other items that do temper this information. About 35% of children with SSD have cerebral vascular disease, including infarction and stroke, and in this study the relative risk reduction was 56% in the transfused group, but no differences in cognitive ability were noted. The study lasted but 3 years. Should such interventions start earlier? What about treatment of adults? Can such a treatment protocol be carried out outside the academic setting? Can the inevitable iron overload be managed successfully? Cost-effectively? And intravenous access? Iron overload? Since vascular occurrences increase with age, how likely is it that “short-term” transfusion therapy will protect the aging brain?

Other approaches to maintaining helpful levels of fetal hemoglobin are needed. Hydroxyurea is used in adults towards this end, but its long-term effects in children are not known. The long-term RBC- endothelial interactions with concomitant inflammation need to be addressed in other ways, as yet unknown.


Regular transfusions in sickle cell disease
Blood thrown in the sewer?

Those of us who work in labs have been aware of the relatively large volumes of blood collected. Two correspondents in the Forum section of the Journal of Thrombosis and Hemostasis have noticed this as well, and done some calculations, made some comparisons, and are entreating us all to do something about the excessive amounts of whole blood collected from patients for laboratory tests. (See References.) Relatively large volumes are harvested, even when only plasma or cells might be needed for analysis, and modern instrumentation just doesn’t need, or use, large volumes of several ml for each analysis. Dr. Levi quotes from a pair of recent studies, one from the U.S., one from Europe, that for every 50 ml of blood collected during hospitalization the risk of hospital-acquired anemia increases by 20%, and that iatrogenic anemia is associated with an adverse outcome in the cardiac unit. A uniform collection system, he says, to collect just cells, or just plasma as needed, would cut in half the amount of wasted blood.

He further calculates (extrapolating from experience in the Netherlands) that half a million liters of patients’ blood is thrown into waste containers in a year. This is 4 times the amount of blood transfused there, he states. He extrapolates that to all of the western world and concludes that 25 million liters is discarded each year, which would be roughly 50 million units of whole blood. The addition of the components from those 50 million units would benefit untold numbers of patients, were it to be widely available, of course.

But, from another point of view, that of elderly patients, children, those with critical injuries or illnesses, hematology or oncology patients, these losses have great significance. The new, and future, methods of lab analysis just don’t need, or use, such large volumes. Some are working on novel methods such as single chips that can perform multiple analyses on simple drops of the precious stuff. Time for nanochemistry! Where are our laboratory entrepreneurs?


A long time colleague steps down

On October 31st Dr Roger Dodd retired from his position of Vice President of American Red Cross Research and Development and director of the Holland Laboratory.

Roger Dodd was born in England and obtained his Bachelor of Science degree in biochemistry at the University of Sheffield in 1964. He worked as a Scientific Officer in the Ministry of Defense (UK) for about six years and in 1970 left for the United States to join the American Red Cross, where he worked for the past 41 years. He rapidly developed his research expertise in transfusion-transmitted infections.

In 1978, he obtained his PhD in Microbiology at the George Washington University. Dr. Dodd has more than 175 publications and has edited three books on transfusion transmitted infections. He has been an Advisor to WHO and he serves on the Editorial Boards of Transfusion, Transfusion Medicine, and Transfusion Medicine Reviews and is a Past President of the AABB. He was elected to the position of Vice President on the ISBT Board in 2010. He served as Chair of the Global Collaboration on Blood Safety. He has received the Morten Grove-Rasmussen and Emily Cooley Memorial Awards from the AABB, a Tiffany Award from the American Red Cross, and the John Snow award from the American Public Health Association.

Dr. Dodd will be sorely missed not only by our organization, but the industry as a whole. Dr. Dodd looks forward to spending more time fly fishing, cooking, traveling, reading and continuing to follow his scientific interests.

Publications Corner

Recent publications by American Red Cross scientists and physicians:


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