There is a much-quoted (but enigmatic) poem, written in 1919 by William Butler Yeats, one of the many great Irish poets of the late 19th and early 20th centuries, that is titled “The Second Coming,” the final lines of which are often spoken to indicate the lurking presence of some great calamity. The first stanza describes a sense of disorder, anarchy, a blood-dimmed tide, the drowning of innocence. Things are out of control, “The falcon cannot hear the falconer...,” and the scene is set for a “Second Coming.” But rather than a familiar and comfortable religious figure, a mysterious and fearsome sphinx-like creature in the desert “begins moving its slow thighs...” and the poem ends with:

“And what rough beast, its hour come round at last, Slouches towards Bethlehem to be born?”

The terrible and mostly unnecessary loss of life in the trenches of World War I may have been part of the thought behind this poem, but the last lines are mostly used to indicate our fear and ignorance about what terrible thing might be next visited upon us. Well, we know what accompanied the end of that war.

The massive influenza pandemic that followed in the last year of the war in 1918, and killed about 6 times more people than the roughly 9 million soldiers lost in that war, may have played a part in his thoughts. After the Asian flu of 1957–58 and the Hong Kong flu of 1968, each of which killed about a million people worldwide, our vigilance for international outbreaks increased. Everyone is carefully watching the developments associated with the highly pathogenic H5N1, avian influenza, which has a very high mortality rate in poultry and about a 60% fatality rate in affected humans, almost all of whom had direct contact with infected animals. There is no, or little, direct human-human transmission of H5N1, but because of the ability of the type A influenza viruses to “drift”—develop small but frequent antigenic changes as they pass through humans—the flu vaccines are made newly each year to reflect the best estimate of next year’s prevailing strain.

In January 1976, a novel influenza strain of swine origin emerged among soldiers at Fort Dix, N.J. One soldier died and an estimated 230 were infected. Because of this, a decision was made to start a national swine flu vaccination program, and to expedite things, the U.S. Congress funded vaccine production and liability indemnification. A vaccine was rapidly (for influenza vaccines) produced and about 46 million Americans vaccinated. However, sustained transmission never occurred outside of Fort Dix, and no pandemic occurred. Several problems in response and planning were identified, though, and led to major revisions in flu research and preparedness, vaccine production, and interagency communications as well as clearer operational responsibilities among various levels of government.

Influenza viruses of similar type may infect a variety of animals, including wild and domestic birds, pigs, seals, horses and others, including people, of course. When an animal cell is co-infected by two different viruses of a given type, mixtures of these gene segments may parent progeny resulting in a sudden “shift,” or genetic re-assortment. Pigs and humans share many flu viruses, and pigs and birds/fowl even more. By such passage through another animal, such as bird flu in pigs, there may be “easier” transmission to humans. When ease of transmission of that variant between humans develops, the possibility for a very widespread outbreak exists. There are 14 subtypes of the hemagglutinin antigen and 9 of the neuraminidase antigen, 2 major antigenic structures on the cell membrane that are the basis for the annual vaccine; thus, a large number of re-assortment possibilities are possible.

The emergence of avian H5N1 in Hong Kong in 1997, then its re-emergence in 2004, also led to wider vigilance and monitoring of influenza among most of the world’s national and international health organizations. But, in the meantime, the world was reminded very forcefully of our global vulnerability to emerging infectious diseases by severe acute respiratory syndrome (SARS) with a cluster of cases of very severe respiratory infection in Guangzho, in southern China. Sporadic cases
had been seen, in retrospect, but in January 2003 an outbreak of nosocomial (hospital-acquired) infections were noted in 2 of that city’s hospitals, including many health care workers. In February, the World Health Organization became aware of it, but detailed information was not released internationally until March, by which time cases had spread to Hong Kong, and from there to Hanoi, Singapore, Toronto and more than 30 other countries around the world—by jet transport, no less. Prior to mid-late March, hospital staff around the world had no idea how it spread and took no special precautions with health care workers. Thus, SARS dramatically illustrated how much our world has grown closer, not smaller. An important and hard-earned lesson. SARS was not due to an influenza virus, but to a coronavirus (SARS CoV) that emerged from animal (wildlife) sources into humans in the fall of 2002.

Infection of birds with H7N2 and H9N2 are well known, for example, but illness has been limited to people with pretty intense exposure to affected poultry. H7N9, however, is a newly recognized variant that surfaced in China in the spring of 2013. Epidemiologic studies are incomplete, but a report on 111 of the first 120 cases was published in June in the NEJM (see references). There had been no prior reports of this in animals or humans, but most of the cases appear to have derived from direct animal contact (poultry); more work is pending.

We now have, in addition to lurking, slouching influenza viruses, coronaviruses to consider, not to mention all the Ebolas, Marburgs, Nipahs, MRSAs, TBs, dengues and other emerging and re-emerging infectious agents. Remember how HIV sneaked upon us? Prepare a “welcome” of some sort for MERS (CoV), the cause of Middle East Respiratory Syndrome! Don’t be misled, though, it is nowhere close to the infectivity of SARS (or HIV or flu) as far as we know, but experience is limited. The first cases in the Middle East appear to have occurred from non-human exposures in the past year, although no animal reservoir has been identified to date (July 2013). These cases occurred in Qatar, Jordan, Saudi Arabia and the United Arab Emirates. Cases have been reported by France, Germany, the United Kingdom (U.K.), Italy and Tunisia, and all of these cases had a direct or indirect link to the Middle East. However, in France, Tunisia and the U.K. there has been limited transmission among close contacts with the sick traveler. The first cases were reported from Jordan in April 2012. The most recent 5 cases, bringing the total to 64, were reported from Saudi Arabia on May 28, 2013. These new cases, unconnected to any previous ones, suggest that the source of the infection, still unknown, remains active in the Middle East and is present throughout a large area. About half of all cases have died.

In a recent article in the New England Journal of Medicine, authors from Saudi Arabia (see references) looked closely at the 23 cases reported to the Saudi health authorities, of which 65% died. Twenty-one of the 23 cases were found to have been contracted through direct contact in a hospital setting. Two hundred of the 217 contacts were health care workers, of whom 2 became ill. Of the 17 family contacts, 5 became ill; the remainder was presumed to have been from patient-patient interactions in dialysis units and the ICU. One patient infected 7 others, for example.

What all of this emphasizes is that we can never be sure what the large-scale risk to the world’s population will be, nor from where it will come. The lesson deals with preparedness and planning, something we all became pretty heavily engaged in during the resurgence of “bird flu” and the 2003 SARS outbreak, which was pretty quickly shut down by such efforts. The 4 pandemic planning pillars—surveillance, vaccine and appropriate drug delivery, emergency response work and communication—provide a solid foundation for pandemic preparedness, and have the added benefit of organizing a community, as well as a national response for any number of problems, including smaller outbreaks and emergencies. These are nicely summarized, with a review of recent outbreak history, in CDC’s Emerging Infectious Disease journal (see reference). An effective response requires material resources; a commitment to planning, then testing and refining of plans; a
Many blood bankers have said for years, going back to the 1980s when directed donations and autologous donations became very popular (for obvious reasons), that the best place to store one’s blood was in the human body. That sentiment has eventually led to a large reduction in patients or surgeons requesting autologous collection. One notable exception to this is total knee replacement/arthroplasty (TKA), where significant postoperative blood loss is common. To avoid allogeneic transfusion, many surgeons adopted the use of preoperative autologous collected blood. Experience with, and improvements in, cell-salvage techniques have made that a popular way to reinfuse the patients’ own blood, rather than depleting the red cell mass preoperatively. Concerns have developed that there may be procoagulant activities in such blood, a real concern, since patients undergoing TKA are already at increased risk for thrombotic complications. This has not been demonstrated in clinical trials to date, although there have been reports of some increased levels of various coagulation factors.

To look more closely at this question, the authors (see below) used thromboelastography (TEG), a method that measures the overall interaction of both the yin and the yang of blood clotting, coagulation and fibrinolysis, and inhibitors of both. They prospectively included 22 patients from whom they collected preoperative venous blood samples. In 11 patients, the postoperative blood was collected into a system that did not wash the blood, prior to mixing it with the preoperative sample. In the other 11, the post-op salvaged blood was collected into a system in which it was washed prior to reinfusion. A TEG profile was obtained on the preoperative sample, and then the same patient’s sample was mixed in a 10:1 dilution with the salvaged blood, washed or unwashed, and the studies repeated. This dilution is a fair representation of a unit of postoperative-salvaged blood given to a patient.

Patient demographics and Hgb levels were similar between the two groups, and there were no differences in preoperative TEG coagulation variables. The addition of salvaged blood to the preoperative sample resulted in significantly decreased clot strength as well as a decrease in time to initial clot formation. These changes were more pronounced in the unwashed group, suggesting that washing removed some of the elements that are responsible for these changes. Based on these data, the authors conclude that the reinfusion of salvaged blood leads to impairment of the clotting mechanism as measured by the TEG, and that washing the salvaged blood prior to reinfusion reduces this effect. Since the comparable costs of the salvage reinfusion systems are about $100 unwashed vs. $400 washed, one might conclude that the choice is simple, especially given that hindering the coagulation process to some degree may help reduce thrombotic complications after surgery in these patients. In cardiac surgery, it’s a different story, since significant postoperative blood loss is a much bigger problem than deep vein thrombosis.

Almost 10 years ago, Dr. Glenn Ramsey from the Feinberg School of Medicine at Northwestern University wrote a review concerning blood component recalls and market withdrawals, using information gathered from the Food and Drug Administration (FDA’s) Biologic Product Deviations (BPDs), published regularly. He recommended standard operating procedures, summarized requirements and provided guidelines for notifying physicians about possible retrospective problems in such cases. New issues and new problems have evolved, and the FDA has revised a number of guidelines on post-donation problems. Currently, about 1/250 components is involved in withdrawals or quarantines, not counting plasma for further manufacture, with about 1/5,800 products actually being formally recalled.

Recalls published in 2011 totaled 4,743 blood components involved in 1,072 recalls (4.4 units/recall). Whole blood-derived platelets were counted as individual units, not pools; therefore, other units in the pool are “recalled” but not counted separately. Note that these are actual recalls, which are removal or correction of a marketed product considered to be in violation of FDA regulations. Market withdrawals are removal or correction of a distributed product that involves a minor violation not subject to FDA legal action, or involves no actual violation. Between 2008 and 2010, Northwestern Memorial Hospital in Chicago received 146,200 blood components and received from their blood supplier 326 notices about 671 components, a rate of 1/218, a little less than the national average. Some of these notices were for investigational quarantines that were lifted, following donor-center investigations; these may not become reportable BPDs in the FDA statistics, but they clearly add to the total management workload of the transfusion service.

The total number of BPDs filed by blood collectors in 2011 was 37 times greater than the actual number of potential recalls, 24,754 vs. 681. 18,111 of these BPDs were from post-donation information provided by the donor, or in a few cases, a close family member. 6,483 of them were due to “malaria travel” and 3,093 “vCJD travel.” Many of these malarial travel risk donors who visit some resort areas in Mexico are extremely unlikely to contract malaria, and the FDA has recently amended its malaria risk guidelines, although not all collectors have updated their operating procedures. There is a good

Continues on next page

To view previous issues of PLUS, go to redcrossblood.org/hospitals/plus-quarterly
discussion that includes bacterial contamination of platelets and emerging infectious disease agents, most notable for blood bankers being babesiosis, dengue and its fellow flavivirus West Nile Virus. The need for long-term deferral in donors taking retinoids seems pretty skimpily documented, as many of us have thought. There is an extensive table suggesting follow-up actions for recipients of blood components that are discovered after transfusion to have been in non-conformance, with links to appropriate FDA documents and procedures. There is also a table with currently accepted North American window periods for seroconversion of a recipient possibly exposed to HIV, HCV, HBV and HTLV.

Since 2004, both BPDs and recalls have seen very significant declines, and incidents directly concerned with infectious diseases dramatically so. However, concerns among some centers related to rigid compliance and control requirements sometimes force people to assume the worst and start a withdrawal or recall before all the facts are clear. These notices are disruptive to all concerned. The hospital blood bank has to quarantine the unit, if available, and if transfused, wait expectantly for more information. If—as often happens—investigation clears the unit, the hospital may have seen the product outdated. The paperwork involved is time-consuming, administratively. If the unit has been transfused, then a decision has to be made about notifying the patient’s physician, who then has to decide about informing the recipient, depending on the issue.

In 2004, Dr. Ramsey suggested six actions hospitals should take for managing such notifications: 1) develop a standard SOP for directors and lab staff; 2) act immediately to quarantine, return or discard such products; 3) determine medical implications of any transfused product; 4) keep careful records of all documents involved; 5) consider involving the transfusion committee; and, 6) consult ID staff, ethics committee, PR, risk management, or the legal office, as needed.

In addition, he offers five suggestions for quality improvement and prevention: 1) improve data availability and analysis, perhaps creating an interactive database; 2) improve donor screening; there are too many false-negative deferrals; 3) improve notification processes; 4) improve knowledge about outcomes and consequences, since we don’t have much information on anything except HIV/HCV look-backs; and, 5) use outcomes knowledge from recipients to better inform the donor-screening process, completing the quality-improvement loop from donors to recipients and back.

All in all, a very useful and timely review, and one very much worthy of your time.

Platelet size and volume: what can they tell us?

Really, it hasn’t been that long since Giulio Bizzozero, an Italian pathologist, discovered platelets in 1882. He found them (using a microscope) in the blood of living animals and in blood carefully removed from them. He also described their adhesive properties and their aggregation. Today we know that platelets, with support from the plasma coagulation cascade and the formation of fibrin, of course, are what keep us from running over into the outside world whenever we have an injury. Platelets continue to be thoroughly studied as to their function and dysfunction.

It is possible to measure production of new platelets from a patient’s bone marrow by examining them for RNA, in a manner somewhat analogous to staining for RNA in reticulocytes, “brand new” red cells. Such RNA degrades pretty rapidly after release into the circulation. This can be useful in caring for patients with marrow failure and in those receiving high-dose chemotherapy. Platelet recovery lags behind neutrophil recovery. A recently developed blood cell analyzer (see reference) allows for measurement of the immature platelet fraction (IPF) as a percentage of the total platelet number. The % IPF times the platelet count has been used to calculate the absolute immature platelet number (AIPN), which helps to separate immune destruction from lack of platelet production without requiring bone marrow aspiration or biopsy. Transfused platelets do not demonstrate the staining, and so after transfusion, the IPF decreases significantly the day after platelet transfusion due to the increase in platelets, returning to pre-transfusion levels the next day. This can be used as a tool to predict marrow recovery and platelet transfusion requirements.

In another recent article of interest to platelet students, workers in several university hospitals in Italy evaluated the use of mean platelet diameter (MPD) and mean platelet volume (MPV) to differentiate between cases of immune thrombocytopenias (ITP) and inherited thrombocytopenias (IT), such as Bernard-Soulier disease, since both are associated with “large” platelets. Splenectomy has been performed, mistakenly, on some of the latter patients. The study group evaluated these two variables in 130 subjects with proven ITP and 113 with IT in six separate centers. They used the existing instrumentation in each hospital to measure the MPV and evaluated the MPD in the cases at a single, central location with image analysis of the peripheral blood smear. The accuracy of the assessed MPV was deemed to be inadequate, but MPV was found to be reliably higher in IT than in ITP. However, there were many problems with reproducibility and variability of the instruments involved, making it hard to recommend this measurement of MPV for the average hospital laboratory.


Sinking the iron hypothesis

For years, many of us have believed that people, especially men, who were regular blood donors, often enough to somewhat deplete their iron stores, were less likely to suffer from myocardial infarction and other ischemic cardiac disease. It sounded good to a lot of us, since we all knew that iron in the Fe++ ferrous state has some oxidative effects that could damage cells. After all, look at the complex way in which it exists in the body. It is best absorbed from food in the Fe++ state, which relies strongly on stomach acid to reduce it from the Fe+++, or ferric state. Some doses of acid reducers can, in some people, render food iron to be less absorbable. Most of it is absorbed in the proximal duodenum via very specific receptors, from whence it is carried via transferrin to all the cells in the body. It is stored as ferritin, a very large molecule, and both ferritin and transferrin have it wrapped up in a big molecule so as to protect tissues from oxidative damage. In the form of hemoglobin, Fe++ is also wrapped up in a big protein molecule, globin, and is nestled in a complex protoporphyrin ring within the globin’s chain of amino acids. Many studies in the 1980s and 1990s offered evidence that high stored iron levels were positively associated with increased ischemic heart disease in certain populations. Boy, what a recruiting tool: donate blood, live longer!

Over many years, other reports failed to find such a positive effect, while some did. The major analytical concern was that healthy people are more likely to be blood donors, so that the “protective” group was self-selective. To get around this confounding bias, authors from Hema-Quebec and other health/medical institutions in Quebec City hit upon a way to obtain a legitimate control group by using the several thousand donors who had been permanently disqualified as a result of a false positive test for transmissible infectious disease (TD). They included all whole blood donors presenting to the blood service in Quebec between June 1990 and March 2007, including those who had a reactive screening test for TD, but excluding all autologous donors and all donors with a confirmed positive test. For each falsely reactive donor, they identified up to 4 donors who remained eligible; the groups were then matched for age, sex, number of donations, date of donation and region of residence (Montreal, Quebec City or Other). All donors had to be alive at least 2 years after donation, and traceable through the health insurance registry; deaths unrelated to coronary heart disease were not included.

They identified 13,753 permanently disqualified donors with a false reactive screening test and matched them with 54,957 donors who remained eligible. Their statistical analyses demonstrated that the various cohort comparisons were comparable and evaluable. As expected, increasing age affected rates in both groups, as did male sex. Interestingly, donors who remained eligible donated at a rate of 0.36 donations/year, and 1/3 of them never donated again. They also did another analysis comparing donors who had donated at least 4 times in the 2 years prior to the study with the controls. In none of the comparisons could even a discernible difference in CHD be seen. There are many interesting findings in the results, as well as in the discussion section of the paper, and readers are encouraged to look at it. Whether or not the “healthier-by-nature” effect explains the differences noted in other studies of “super-donors” compared to those who donate less frequently still remains a question in some people’s minds; these authors think better health leads to more frequent donation, not the opposite.

Apples, okay, but don’t pick your own donors...

Those of us who worked in blood banks/blood centers in the 1980s remember what a difficult and sometimes discouraging job it was. The great—and justifiable—alarm about HIV from blood transfusion drove many people who needed surgery to postpone it, risk having no blood, or to have family members or close friends provide it. Often the impetus came from family members themselves, sometimes motivated by another family member, or sometimes just wanting to exert control over the process, no matter what. Many people argued that asking a relative to provide blood might lead them to donate even if they knew they shouldn’t. In some cases it was clear that, to a greater extent than among other donors, friends and family members would be prone to forget—or even lie about—some aspects of their personal social, medical and sexual history. The appearance of a reliable HIV test in 1985 eased these concerns somewhat, but after Rock Hudson announced in May of that year that he was suffering from AIDS, the mania returned.

Over time, mania recedes, affected by new facts, the spread of common sense and evidence to support a calmer approach. Autologous donations had also become very popular, despite warnings by some that the very best and safest place to store human blood was in the human body. Things have calmed considerably in the last 30 years, but some insistence on picking one’s own blood donors persists. Investigators at the headquarters of the American Red Cross Blood Services, with a large data set to examine, did so to look at infectious disease (ID) markers in voluntary vs. directed donations over the period 2005–2010. Between 1995–2010, directed donations decreased from 1.6% to 0.12%. This represents a decrease of about 92%. During the study period of 2005 to 2010, there were 38,984,782 volunteer and 69,869 directed donations. In voluntary donations, rates of positivity for HIV, HCV, HBV and HTLV were 2.9, 32.2, 12.4 and 2.5 per 100,000 donations, respectively. For directed donations, the rates, in the same order, respectively, were 7.2, 93.0, 40.1 and 18.6. All crude odds ratios, except for HIV, were statistically significant at p<0.0001. The HIV p value approaches significance at p<0.056. The directed donors were significantly more likely to be first-time donors.

These unadjusted rates confirm what we have all known or suspected from smaller sample studies. Crude rates for ID markers are much higher in directed donors. This is explained in part, at least, by having more first-time donors in the directed-donor group. It was possible, with this very large sample, to adjust for the fact of first-time donation status and for demographics and to then analyze both data sets. As expected, rates remain generally higher for all first-time donors, but a statistically significant difference was still the higher rate of HCV positivity in the directed donors, even adjusted for first-time vs. repeat status. So, if you’re really picky, stick with the volunteer donor.

It is a generally recognized phenomena that—at least in the biological sciences—there are often trades to be made between having an assay or analysis that is broad in scope, or sensitivity, and having one that is very specific, albeit perhaps somewhat limited in scope. This is certainly the case for a lot of assays in which we are looking for alloantibodies prior to transfusing red cells from one person to another. Techniques used in the clinical laboratory have gone through major changes, and today include reaction-enhancing reagents such as low-ionic-strength saline (LISS), polyethylene glycol (PEG), and the use of solid-phase assays and gel microtubes. Gel and solid-phase assays provide straightforward platforms for automation and standardization, according to our authors (Ref.1), and are in use in almost 2/3 of labs in North America. But tests for red cell antibodies that increase sensitivity detect many “unwanted” antibodies that seem to be of no importance, although they increase the amount of work expended. At the authors’ institution, these are called, and reported as, “antibodies of undetermined specificity,” or AUS, after antibodies to FDA-specified red cell antigens have been ruled out.

They collected data over a 30-month study period from July 2009 through December 2011, and found a total of 8,121 antibodies in 6,058 patients. 1,422 (18%) of these were reported as AUS, and this was the single most reported event, followed by anti-E (18%) and anti-K (14%). (See article for table of antibodies noted.) In the first 3 months of 2012, they further investigated the AUS found in 174 individual patients. Most AUS (78%) reacted with 2 cells or less in gel and 98% of the reactions were 1+ or weaker. Forty-five of the patients who
presented with an AUS for the first time were subsequently re-evaluated. In 31 cases, the AUS presence persisted for 2–60 days. AUS disappeared in 14 cases; however, 7 of these developed a total of 10 “new” antibodies from 3–21 days after original antibody testing. There were 3 anti-E, 1 anti-D, 1 anti-C, two anti-Jkb, 1 each of anti-Lea, anti-s, and a warm autoantibody. The authors provide a useful time-line graph for 6 of the patients, showing a serologic profile of the alloantibodies possibly developed from the initial AUS reaction, 3 of whom had not been transfused in a month or more before antibody detection.

The authors of the accompanying editorial (see below) emphasize the importance of these findings and raise several questions for consideration:

- Should transfusion services reconsider the use of gel-based platforms due to lack of specificity?

- Can alternative Ab screening modalities offer the sensitivity of gel and solid phase analysis with improved specificity?

- What can be done to determine if an AUS represents a low-titer alloantibody?

- What, then, are reasonable approaches to transfusion in such patients?

As well, they offer some useful thoughts. Echoing the article’s authors, they also recommend that patients with AUS have an AHG-phase crossmatch. Such “extra mile” measures are warranted, especially in patients with many transfusions in the past, such as those with hemoglobinopathies. Some hospitals have reported development/use of local or regional alloantibody registries. In today’s itinerant world, perhaps a national centralized database is in order. At the least, a patient or family interview to determine past pregnancies or transfusions would be useful. In addition to evaluating such affected patients for the presence of low-incidence antigens, obtaining a new sample several days later may be helpful, especially if a significant antibody is “smelled,” or suspected. Since warm or cold autoantibodies are common agglutinins in gel, a more thorough evaluation for their presence should be undertaken; certainly performing enhanced tube-testing on such samples might help to support the assumption that an AUS reaction is not significant.

Of course, in urgent transfusion situations, all of this would not be done until after the original transfusion(s), but would help alleviate further problems. In neither article are costs mentioned, an issue which our hospital budget folks and payers will always raise; however, although the time costs are not irrelevant, tubes and reagents for such cases are pretty cheap. But, a severe transfusion reaction is not cheap at all, as we all know.


Visit the American Red Cross at the AABB annual meeting in Denver

Please stop by the Red Cross exhibit, #907, at this year’s AABB annual meeting in Denver, CO, in October. Red Cross physicians and blood banking experts will be staffing the booth, so please bring your questions. We hope to see you there!

Publications Corner

Recent publications by American Red Cross scientists and physicians:


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*Immunohematology Journal*  
redcross.org/immunohematology

Reimbursement  
redcrossblood.org/reimbursement

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Fall 2013, Volume Seven, Issue Four