Emerging Pathogens in Transfusion Medicine

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Transmission of infectious agents has long been recognized as an adverse outcome of transfusion, with the earliest concerns directed toward syphilis and viral hepatitis. Testing donors for evidence of syphilis infection was established in the 1940s, but in the absence of effective knowledge about viral hepatitis, the earliest measures relied on questioning of donors about a history of hepatitis: a precaution still in place, despite its currently demonstrable absence of value. The frequency of post-transfusion hepatitis prompted epidemiologic studies in the late 1950s, eventually leading to the elimination of blood collection from prison inmates and discouraging the use of paid donors. The essentially serendipitous discovery of HBsAg and of its relationship to hepatitis B opened up the use of donor testing but also revealed that another viral hepatitis (subsequently termed hepatitis C) was transmissible by transfusion. After a great deal of pioneering work, the causative agent (hepatitis C virus [HCV]) was identified by molecular techniques, antigens were expressed, and a test for antibodies to virus was developed and implemented for blood donors in 1990. Additionally, over the years, it became apparent that malaria could be transmitted by transfusion and deferral policies were established to prevent the collection of blood from individuals potentially exposed to malaria outside the United States. Taken together, these approaches, established for existing, chronic infections, defined the mechanisms for dealing with subsequent transfusion transmitted diseases.

EMERGING INFECTIONS

Before 1980, it was generally thought that the problem of infectious diseases had been solved, at least in the developed world. But the advent of AIDS, the appearance of other novel diseases in human populations, and the expansion of other known infections led to the now well-established concept of emerging infections. These have been defined as those infections whose incidence in humans has increased within the past

2 decades or threatens to increase in the near future. There are many reasons that infections emerge; these have been described elsewhere,[1] but some key factors include ecological disturbances (including climate change), changes in human behaviors, failure of disease and vector control, urbanization, population movement, and genetic change among disease agents. Often, these and other factors work in concert.

Many emerging infection are zoonoses and, although the transition from an animal to a human disease may involve many steps,[2] it may be rapid. Such a transition may be facilitated by genetic change, but this is not always the case. Once established in human populations, outbreaks may prove explosive and worldwide, as exemplified by SARS, which was caused by a previously unrecognized animal coronavirus that apparently first infected humans in Southern China.[3,4] Thereafter, it spread rapidly, apparently in part due to the rapid movement of infected individuals by jet aircraft.

It has become clear that some emerging infections may be transmitted by transfusion—this potential exists for any infectious agent that has an asymptomatic bloodborne phase. It has also become apparent that, although HIV, the first emerging infection to have a significant impact on blood safety, was chronic, parenterally and sexually transmissible, these characteristics did not all apply to subsequent transfusion transmissible emerging agents, such as variant Creutzfeldt-Jakob disease (vCJD), West Nile virus (WNV) and *Babesia*. Thus, although it is important to be prepared for emerging infections that threaten blood safety, it will never be possible to make an accurate determination of the next agent of concern. A framework can be built to establish readiness for such an event, however. One such attempt is a recent effort to catalog and prioritize agents of likely concern.[5]

HIV/AIDS

As discussed previously, HIV/AIDS was the first emerging infection to have a profound and unexpected effect on blood safety. It was first recognized as a syndrome of unusual opportunistic infections and a normally rare malignancy (Kaposi's sarcoma) among gay males, Haitian immigrants, drug abusers, and hemophiliacs. The etiology of the disease was unclear, although a leading hypothesis was that it was caused by an infectious agent. Eventually, a few cases were observed among individuals whose only potential risk factor was prior receipt of a blood transfusion.[6] Eventually, the etiologic agent was determined to be a retrovirus, now known as the human immunodeficiency virus (HIV), codiscovered by Montagnier and Gallo and their collaborators in 1983–1984.[7,8] By March of 1985, tests for antibodies to HIV had been developed and commercialized and their routine use for blood donations had been initiated.

It became apparent that the actual epidemic of HIV infection had started many years previously and that the disease itself had an extended incubation period, perhaps as long as 10 years. As a result, many individuals had unknowingly been infected and at least 12,000 transfusion transmissions had occurred in the United States alone.[9] This occurred in spite of measures that had been taken to defer donors with risk factors, in part because they had been implemented too late. Back-calculation showed that more than 1% of blood donations in San Francisco were probably infectious for AIDS at the beginning of the 1980s and that preventative measures resulted in a major decrease in that risk even before testing was put in place.[10] Because of the social sensitivity of the issues, early measures placed much reliance on education of donor populations and requests for self-deferral of those with risk factors, but within a few years, direct questioning of donors had been introduced. Even at the height of the epidemic, fewer that 2% of all AIDS cases in the United States were attributable to transfusion.

Shortly after the introduction of testing for HIV antibodies, it was found that nation-wide, approximately 0.038% of donors were seropositive; almost all of them would have been infectious. The majority of seropositive individuals were men with a history of having had sex with other men; this finding led to a tightening of donor questioning strategies.[11] Measures to reduce the risk of HIV transmission by transfusion have continued to be refined and tightened over the years, with increasing focus on: donor questioning; enhanced test sensitivity, including the addition of nucleic acid testing in 1999 (in the United States); and, now, interest in the implementation of pathogen reduction technology. The measures taken to date have proved efficacious: modeling studies suggest that the residual risk of transfusion transmission is on the order of 1 per 1.5 to 2 million component units in the United States, but the actual number of transmissions detected is much lower, with only 4 cases recognized in the United States between 1999 and 2009.

HIV/AIDS is widely recognized as an enormous human tragedy and it continues to be a devastating global epidemic. It undoubtedly had a profound impact on transfusion medicine, but it also materially affected and reoriented global attitudes toward blood safety. Before the advent of AIDS, there was a prevailing attitude that the development of some cases of post-transfusion infection was expected as an inevitable conse-quence of transfusion. This is not to say the issue was ignored, rather, that it was not an overriding priority. In several countries, those responsible for transfusion were subsequently held responsible for failing to prevent transmission of HIV/AIDS by trans-fusion and were actually prosecuted. In addition, many civil cases were brought against hospitals and blood centers on behalf of patients who had been infected. Whether or not these responses were appropriate will continue to be argued, but it is clear that there is now a low tolerance for failing to deal with any transfusion-transmitted infection. This may best be illustrated by the high cost-effectiveness ratio of many of the measures that have been routinely implemented in support of blood safety.

Although HIV/AIDS is now considered to be a globally endemic, rather than an emerging, infection, the virus itself is continuingly evolving. New clades and recombi-nant forms of the virus continue to appear, and there is justifiable concern that emer-gent subtypes may not be readily detectable by current test methods. This occurrence has already been observed, particularly with the type O clade, which emerged in some West African countries.[12,13] Continuing surveillance must be assured, along with monitoring of the capabilities of test kits to detect infection with new strains.

vCJD

Although there have been no cases of transmission of classical CJD by transfusion, the possibility has always been of concern, as exemplified by regulatory requirements around the disease. Also, transfusion transmission of animal-adapted strains has been shown in small animal models. When vCJD first appeared in humans (as a result of exposure to the BSE agent present in the food chain), there was concern that this new, emergent transmissible spongiform encephalopathy (TSE) might prove a risk to transfusion safety. This concern arose from the unknown nature of the infection and its unusual association with lymphoid cells and tissues. As a result, several preventative measures were put in place, well before there was any actual evidence of transfusion transmission. In the United States, the primary intervention was to defer as donors any individuals who had spent time in the United Kingdom at the peak of the BSE epidemic. The deferral was subsequently extended by including Western European countries (albeit with a different residence time) and eventually by deferring individuals receiving a blood transfusion in the United Kingdom. Several other

criteria for deferral were also introduced; all are described on the Food and Drug Administraion Web site (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm). In the United Kingdom, the deferral option was not available, but universal leukodepletion was introduced, locally derived plasma was no longer sent for fractionation, and plasma for transfusion was imported from countries at low risk of BSE.

As a result of careful surveillance, 4 cases of transmission of the vCJD agent by blood transfusion have been identified in England.[14,15] Three of the cases resulted in the development of fatal vCJD in recipients of blood that was collected from donors who subsequently developed vCJD. In a fourth instance, the agent was found in the spleen and 1 lymph node of a similarly exposed but asymptomatic individual who died of unconnected causes. The source of the infection was a donor who had transmitted the disease to 1 of the other 3 cases. All of these cases were attributable to blood components that had not been leukoreduced. More recently, the agent was also identified at autopsy in a hemophilia patient who had received products from plasma pools that included units thought to be at risk of containing the agent (http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859690542?p=1231252394302). The agent has also been shown to be transmissible in a sheep model.[16]

At the time of this writing, the small epidemic of vCJD seems to be declining, although there is some concern that there may be future waves of disease among individuals with a genotype that differs from the one seen in almost all clinical cases of vCJD to date. Further, management of the food chain has reduced or eliminated the risk of food-borne exposure to BSE. In these circumstances, the need for further interventions may be arguable. This would be the case in the United States, where there do not yet seem to be any cases of locally acquired vCJD. Nevertheless, 2 companies have developed and CE-marked affinity based systems for removal of TSE prions from red cell concentrates.[17,18] One of them has been evaluated in the United Kingdom and Ireland.

WNV

In 1999, a small outbreak of West Nile virus infection occurred in Queens, New York. This was the first reported occurrence of this flavivirus in the Western Hemisphere. It is not known how the virus was introduced into the United States, although it undoubtedly involved rapid intercontinental transportation. Perhaps unexpectedly, the virus rapidly spread across the continent, infecting hundreds of thousands of individuals.[19] Although the resulting infections were acute, modeling studies suggested that transfusion transmission of WNV was possible and shortly after the first such study was published in 2002,[20] 23 transfusion transmissions were reported.[21] As a result of an exemplary cooperation between manufacturers, transfusion medicine specialists, public health authorities, and regulators, tests for WNV RNA were developed, commercialized and implemented within less than 1 year. The strategy has been successful, although it is not possible to prevent all infections solely by the use of pooled testing: conversion to single donation testing is necessary in times and places with high incidence rates for infection. Careful implementation of this strategy has been shown to eliminate residual infections, at least in 1 large blood system.

The emergence of WNV in the United States and the finding that it was transmissible by transfusion did challenge preconceived notions. First, that the most likely new concern to blood safety would come from an agent with epidemiologic characteristics similar to those of HBV and HIV, and second, that acute infections would offer only minimal risk of transfusion transmission. It also illustrated the fact that a test for nucleic

acids is relatively easy to develop and implement in a short time -frame.[22] It also led to the recognition that other arboviruses might behave in the same way as WNV, by causing unexpected large outbreaks, consequently compromising blood safety. As discussed later, there have been recent examples illustrating this concern, involving dengue and chikunguya viruses.

Chagas Disease

In contrast to WNV, *T cruzi*, the parasitic agent of Chagas disease, entered the US population as a result of gradual immigration. The majority of infected individuals identified in the United States were born in Latin American countries in which the parasite is endemic. Infection usually occurs early in life and is essentially lifelong, with the potential for late clinical outcomes, cardiac or digestive.Parasite and competent insect vectors, however, do exist naturally in most of the southern US states, even though transmission to humans is uncommon in the United States.

T cruzi has long been recognized as transmissible by transfusion, and in most Latin American countries, donor testing for antibodies to the parasite is routine.[23,24] There have been 7 documented cases of transmission in the United States and Canada, and in all cases where the origins of the infection could be determined, it derived from platelets donated by an individual who had been born, or was a resident in, South America. Extended research studies showed that a significant proportion of blood donors, particularly in California and Florida, were infected with *T cruzi*.[25] A test for antibodies to *T cruzi* was licensed in the United States in late 2006 and was implemented at the beginning of 2007. Nationwide, the donor prevalence rate was found to be approximately 1:30,000.[26] Some of the seropositive donors did not have geographic risk factors and seemed to have been infected in the United States. Lookback studies on prior recipients of blood from seropositive donors, however, revealed only 2 infections from a total of 241 recipients examined (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm155529. htm). This was 1 of the factors that led to a reevaluation of the value of testing and consideration of selective testing strategies. Such strategies were discussed at a meeting of the FDA's Blood Products Advisory Committee. The Committee endorsed the concept of selective testing, specifically on the basis of testing each donor once and accepting seronegative donors without need for any futher testing. The Committtee did, however, express concern abut the possibility of incident (new) infections among donors and recommended that selective testing be considered only if a continuing study of incidence of *T cruzi* infection among donors was to be conducted. One major blood supplier in the United States implemented selective (1-time) testing in August 2009 and several other smaller establishments used a variety of alternate approaches to selective testing.

Babesia

Babesia is a malaria-like, intraerythrocytic protozoan parasite that is transmitted by ticks. In the United States, the predominant species is *B microti*, which is transmitted by Ixodid ticks, particularly *I scapularis.* There are particular foci of infection in the coastal areas of New England and in the upper Midwest. The parasite may be regarded as emerging, as it seems that its range is expanding and that opportunities for human infection are also increasing.[27] Other species of *Babesia* have been identified in Missouri, California, and Washington. The parasite is readily transmitted from infected donors by transfusion and more than 70 such cases have been documented in the United States: some have been fatal.[28,29] The risk of infection is high in areas of

greatest endemicity, perhaps exceeding 1:1000 in parts of Connecticut. Some donors may be infected and infectious for periods of 6 months or more.

Effective interventions against transfusion transmitted babesiosis do not currently exist. A licensed test is not available nor is an appropriate donor questioning strategy. Some blood establishments avoid collections from areas of high endemicity during the tick season, but given the potentially prolonged period of infectivity, such a strategy is not fully effective. Furthermore, donors and their blood may travel and several transfusion transmissions have occurred in areas that are not endemic for Babesia. There is increasing concern about Babesia and blood transfusion in the United States, as illustrated by an FDA-sponsored workshop held September 12, 2008 (http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/TranscriptsMinutes/default.htm), but the future path is currently unclear. It seems most likely that some geographically limited testing will eventually be implemented for blood donations.

EMERGING INFECTIONS OF POTENTIAL CONCERN FOR THE FUTURE

As discussed previously, it is not possible to predict which infections will emerge, or, once emerged, the extent to which they will compromise blood safety. Consequently, any discussion of specific agents must be regarded as speculative. Furthermore, outcomes may be geographically variable. For example, the pattern of emergence and human disease seen in the WNV outbreak is different from that seen in southern Europe. Further, although the virus is now present in the Caribbean and Central and South America, it does not seem to have the same impact on human health in those parts of the world as it has in North America.

Arboviruses

Until WNV emerged in the United States, arboviruses had not been seriously considered in the context of blood safety. Two of them, dengue (DENV) and chikungunya virus (CHIKV), have now attracted considerable attention, however. Although one is flavivirus and the other an alphavirus, they share common transmission patterns (human-mosquito-human) and vectors (Aedes aegypti and A albopictus). Both viruses cause large outbreaks of infection and disease and one of them has been shown to be transmissible by transfusion. It should also be noted that another flavivirus , St Louis encephalitis virus is endemic to the United States and has, in the past, been responsible for sporadic, but large outbreaks. Thus, it is reasonable to consider this agent to be a potential future threat: continuing surveillance is appropriate.

More specifically, 2 clusters of transfusion transmitted DENV have been reported, 1 from Hong Kong and 1 from Singapore.[30,31] A third transmission has been discussed but not yet published. Investigation of blood donor samples from Honduras, Brazil, and Puerto Rico has revealed significant frequencies of viremia during DENV outbreaks[32,33]; in 1 of these studies, not only have high titers of virus been demonstrated but also the viruses have been shown to be infectious in laboratory systems.[33] To date, there has been no standardized response by blood organizations to the issue of transfusion-transmissible DENV. Perhaps the most comprehensive reaction has been that of the Australian Red Cross Blood Services, which has routinely stopped collection of blood components for transfusion in parts of Northern Queensland during dengue outbreaks. If an intervention is judged necessary, it would be appropriate to consider the use of a test for DENV RNA: a measure comparable to that used for WNV. Such a test is not commercially available (at least as of early 2010), but a test for a viral NS1 antigen is available[34]; it would be expected to identify high-titer viremic donations.

CHIKV is normally endemic in East Africa, but over the past few years, has been responsible for several explosive epidemics, most notably (but not exclusively) in the Indian Ocean islands.[35] A factor that seemed to contribute was a viral mutation resulting in preferential transmission of the virus by the widely distributed *A albopictus* mosquito.[36] The outbreak in la Réunion has been particularly well described. Hundreds of thousands of residents, representing more than 40% of the population were infected. The island is an overseas department of France, and authorities took extensive steps to protect the safety of the blood supply. Tests for CHIKV nucleic acids were implemented (finding 2 in 500 donations to be viremic); red cell collections were discontinued on the island (needed red cells were provided directly from France); and pathogen reduction technology was implemented for platelet concentrates, which were collected locally.[37] Another small but unexpected outbreak occurred in Italy, as a result of an infected traveler.[38] This event also led to regional prohibition of blood collection for the duration of the outbreak.

Given this background, it is reasonable to speculate on the possible implications to other parts of the world, such as North America. As discussed previously, dengue is already endemic in Puerto Rico and is subject to annual outbreaks. There have also been outbreaks in Hawaii and a high seroprevalence rate has been found in residents of Brownsville, Texas, with much higher rates across the Mexican border. In late 2009, there was an outbreak of locally transmitted dengue in Key West (http://www.doh. state.fl.us/Environment/medicine/arboviral/Dengue_FloridaKeys.html). Certainly, *A aegypti* (the preferred vector for DENV) is present in parts of the Southern United States; thus, conditions exist for some spread of the virus on the mainland. It is not, however, clear that sustained transmission could occur. The issue for chikungunya may be a little more complex, as *A albopictus* is much more widespread and chikungunya cases among travelers returning to the United States are not uncommon.[39] There are many other arboviruses, but there is really no clear basis for making any predictions about their future spread.

TSEs

Experience with vCJD has been salutary. To date, there is no evidence that (despite animal model studies) classic CJD has been transmitted by transfusion. Lookback studies on recipients of blood from donors who subsequently developed CJD have been uniformly negative and show that, if such transmission is possible, it would be much less frequent than for vCJD.[40] Chronic wasting disease (CWD), an affliction of cervids in the United States, seems to be emerging. Given that it sems transmissible between animals by the oral route, it is reasonable to question whether or not it could become a human pathogen in a fashion analogous to BSE.[41] Despite some apparent clusters of CJD in younger individuals with a history of hunting,[42] there has been no evidence to date to support such a species jump for the CWD agent.

Retroviruses

As discussed previously, there is little doubt that the emergence of HIV/AIDS as a transfusion transmissible disease has materially altered perceptions about blood safety. In a more particular sense, it has also focused concern on retroviruses themselves. Two examples are relevant. The first is simian foamy virus, which has been shown to be transmissible to humans, generally as a result of close contact with monkeys in a professional or recreational (travel) setting.[43,44] To date, there has been no evidence whatever that such human infection has any clinical outcomes. Regulatory agencies, however, have questioned whether or not there might be risk of emergence of a pathogenic mutant of SFV in association with species jump.

When linked with concern about the potential for transfusion transmission of the virus (which has been demonstrated in macaques but not in humans),[45–48] this has led regulators to ask whether or not some intervention is warranted. Although such a proposal was not supported by the BPAC in the United States, Canadian regulators have imposed deferral from blood donation on individuals employed as monkey handlers.[49]

There has been renewed interest in the xenotropic murine leukemia-like retrovirus (XMRV) as a result of a high-profile article describing a potential association of this virus with chronic fatigue syndrome.[50] The article also suggested that evidence of XMRV infection could be found in 3.7% of normal controls and that the virus from the clinical cases was infectious in vitro. The authors of the publication expressed concern that the virus might be transmissible by transfusion[50]; a point also raised in an accompanying editorial. To date, however, there are no specific data to support this contention nor is there any current evidence that XMRV is the causative agent of any disease although it had previously been found in association with selected cases of prostate cancer. Studies will be planned to determine whether or not the virus is transmitted by transfusion.

PATHOGEN REDUCTION

Several interventions might be used to eliminate or reduce the risk of transfusion transmission of an emerging infection. They include measures based on management of donations in affected areas, donor medical, travel or risk history, implementation of tests, or product manipulation. None of these approaches is 100% effective, and all suffer from some disadvantages, such as poor sensitivity or specificity, lengthy development process, high direct or indirect costs, and so forth. Conceptually, it would be desirable to have a generic method that would be proactive instead of reactive. Many believe that pathogen inactivation represents such a solution. Several treatment methods are available for plasma for transfusion and for platelet concentrates but no method for red cell concentrates has yet been brought to market.[5] The approaches have been put into practice at least in part, in several European countries. Although the methods have been shown to effectively inactivate significant titers of a variety of pathogens and model organisms in laboratory studies, their potential for elimination of as yet unknown emerging infections is necessarily unknown. Also, the absence of methods that can inactivate all blood components is a disadvantage. It is also apparent that currently available methods do have some negative impact upon treated products. No method is currently available for use in the United States and the regulatory barrier appears to be high. Available methods, their properties and advantages and disadvantages are described in several reviews and other publications.[5,51,52]

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