Transfusion-transmitted infections: Existing and emerging pathogens

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ABSTRACT

In general, the risk of transfusion-transmitted infections has been greatly reduced today. However, blood-borne bacterial and parasitic infections and emerging infections transmitted through transfusion are an area of increasing concern. Implementation of stringent donor eligibility criteria, improved donor screening and more sophisticated as well as sensitive methods of antibody, antigen and viral genome detection, have virtually eliminated transfusion transmitted infection in developed countries. In developing countries like India, the risk of transfusion-transmitted infections is still considerable. A comprehensive MEDLINE search and review of relevant transfusion medicine literature were carried out and the data extracted and studied with particular reference to emerging pathogens transmitted through blood transfusion and posing a huge threat.

KEY WORDS: Transfusion transmitted infections, Emerging pathogens

Advances in infectious disease testing have continued to improve the safety of blood supply. Besides the established viral, bacterial and parasitic diseases, novel agents have now appeared, and are still emerging. Thus, infectious complications of blood transfusion continue to be an important area of concern in transfusion medicine. In recent years, numerous infectious agents (found worldwide) have been identified as potential threats to blood supply. These newly discovered agents namely transfusion transmitted virus (TTV), SEN-V (SEN virus), Human herpes virus-8 (HHV-8), Hepatitis G Virus (HGV), West Nile Virus and Prions present a unique challenge in assessing the possible risk they may pose to the safety of blood and plasma products, and this makes pathogen inactivation even more important.

Viruses

Hepatitis Viruses

Transfusion related hepatitis is almost exclusively caused by viruses. These viruses include hepatitis viruses A through E (HAV, HBV, HCV, HDV and HEV), Cytomegalovirus (CMV), Epstein Barr virus (EBV) and possibly newly described viruses (such as HGV/GBV (GB virus), TTV and SEN-V). The incidence of HAV varies significantly with age. Highest incidence rates are seen in children in the age group of 5-15 years accounting for 30% of all cases. HAV is rarely acquired by blood transfusion with a transfusion-associated risk of less than 1 per 1,000,000 units of blood transfused.[1] Rarity of parenteral transmission of HAV has been attributed to short duration of viraemia, exclusion of infectious potential blood donors on the basis of history and absence of a chronic carrier state. However, rare transmission via blood products [2] and clotting factors[3] has been reported. Currently, no specific laboratory screening of blood donations for HAV is performed, as there is no chronic carrier state.

In contrast to HAV, HBV is a major source of percutaneously transmitted hepatitis and is associated with a protracted carrier state and chronic liver disease. The risk of HBV transmission by blood transfusion in the USA was estimated by the Retrovirus Epidemiology Donor Study (REDS) as 1:63,000 units transfused.[4] Percentage sero-positivity of HBV in an Indian study was shown to be 1.55% in 1996, which came down to 0.99% in 2002.[5] Sero-prevalence of HBsAg in various other Indian studies has been shown to range between 1.86% to 4%.[6-9] Chronic carriers of HBV (3-5%) are at risk for long term sequelae and may progress to cirrhosis, liver failure and hepatocellular carcinoma. Evaluation of an individual for HBV usually includes testing for serum HBsAg, antibody to HBsAg and IgM anti-HBc (antibody to hepatitis B core antigen). Detection of IgM anti HBc in serum is helpful in the diagnosis of HBV infection during "window period" prior to the appearance of HbsAg. Moreover, it can detect recent HBV infection in rare HBV mutants with altered HBsAg epitopes. Although most blood centers perform screening for HBsAg, there is a convincing argument to augment it with anti-HBc testing.[10]

HCV is transmitted primarily through blood exposure. In contrast to HBV, about 20-40% of HCV cases are acute while majority progress to chronic infection. The long-term significance of subsequent disease due to cirrhosis and hepatocellular carcinoma is greater in HCV infected individuals than in those infected with HBV. An enzyme-linked immunoassay (EIA) is used for screening. Indian studies indicate that seroprevalence

of HCV ranges between 0.4 and 1.09%.[5,8,9,11] The recent risk estimate of HCV is 1:103,000 per donor exposure in the US.[4] This was calculated using second generation HCV test with window period of 82 days. Screening by third generation EIA reduces the window period to 66 days and hence further decreases the risk of transmitting HCV through transfusion to 1:127,000 units transfused.[12] With the implementation of nucleic acid technology-based HCV screening (HCV-NAT) there has been a major decline in the risk of HCV transmission to 1:3,68,000 units transfused in the US. NAT testing for HCV has shown reduction in window period for HCV from 66 to 10-30 days.[12,13] A recent study in US has shown risk of HCV infection with mini pool-NAT screening to be as low as 1 in 2 million.[14] Though NAT can significantly improve the safety of blood supply; its widespread use in developing countries like India is unlikely in the near future due to the expenditure involved.

Since HDV cannot be expressed in the absence of HBV and requires HBV for its replication, the chance that a blood donor screened and found to be negative for HBsAg and anti-HBc could harbor HDV is exceedingly small. No additional screening of blood products for HDV is thus employed.

Hepatitis associated with CMV or EBV is mild in the absence of severe immunosuppression. Due to rarity of such cases, routine screening measures are not undertaken for CMV or EBV.[15] GBV-C, formerly called HGV is a recently discovered virus distantly related to HCV (flavivirus). Clinical data derived from studies of HGV have established its transmission by blood through donor recipient linkages and by the recovery of virus in the recipient that was not present prior to transfusion. HGV is present in 1-2% of donor population. Detection depends on PCR technology. As yet a causal relationship has not been established between GBV-C infection and hepatitis or any other disease manifestation.[16]

TTV is another newly identified pathogen, which appears to be similar to GBV-C with respect to prevalence and transmissibility, but there is lack of information about it causing any significant clinical disease. Similarly SEN-V has also been strongly associated with transfusion but no significant disease association has been established. SEN-V is distantly related to TTV and is a member of a family of small, circular DNA viruses called Circoviridae. Screening for GBV-C, TTV and SEN-V is not currently recommended, as disease associations have not been yet established.[16]

Human Immunodeficiency Viruses

The transmission of human immunodeficiency virus (HIV) through blood transfusion and the consequent emergence of transfusion associated acquired immune deficiency syndrome (AIDS) epidemic have arguably transformed the field of transfusion medicine over past several decades. HIV-1 and HIV-2 are the etiologic agents. The rate of confirmed positive infections detected amongst blood donors declined markedly due to notification and deferral of repeat donations from individuals, who had tested positive[17] and with implementation of better strategies (donor informational documents and donor questionnaires) to exclude "at risk donors".[18,19] HIV has a high genetic diversity which enables the virus to evolve under in-vivo selective pressures leading to rapid development of immunological escape mutants and drug resistant mutants.[20,21] Besides, HIV has several subtypes and existing HIV-1 ELISA tests cannot detect all antibody responses against certain group O or N.[22,23] Similarly, HIV-2 has six subtypes and each subtype has different geographic distribution.[24] The HIV seroprevalence in Indian scenario has been reported between 0.2. to 1%.[5,25-27] The risk of acquiring HIV from a window period donor based on testing for HIV antibody has been reported to be 1 in 4,93,000 units transfused in the US. It has been estimated that HIV-NAT has reduced the window period from 16 days to 10 days and the residual risk following NAT implementation has diminished to 1/9,86,000 units.[4]

A recent study in US has shown risk of HIV-I with mini pool NAT screened blood to be approximately one in 2 million.[14]

The importance of HIV subtypes for transfusion safety is related to the capacity of screening assays to detect antibodies to the array of subtypes present in the donor population. The availability of sensitive and specific tests targeting viral antigens or nucleic acids has led to the consideration of these assays in donor screening to detect HIV infected persons earlier than with current antibody assays. Sensitive techniques for the detection of HIV nucleic acids such as polymerase chain reaction (PCR) are now under consideration as donor screening assays. Enormous costs involved limits the feasibility of employing these techniques.

Human T-cell Lymphotropic viruses

Human T-cell Lymphotropic virus type I (HTLV-I) was the first human retrovirus isolated and the first to be causally associated with a malignant disease of humans, the adult T-cell leukemia.[28] It is also associated with myelopathy and tropical spastic paralysis. HTLV-II, which was described later, is known to show 60% homology of genetic sequences to those of HTLV-I.[28] The current incidence of HTLV infection in the United States is 1 in 6250 individuals being seropositive per year half of these being infected with HTLV-I and the rest half with HTLV-II.[29]

HTLV-I infection shows geographic clustering with high endemicity in Japan, sub-Saharan Africa and Central and South America. HTLV-II shows clustering in Native American population donors. In these areas, the donors are screened using EIA screening tests.[16] The transmission rate of HTLV-I or HTLV-II in a recipient of an infective blood unit is between 20 and 60%. The risk of transmission of HTLV from a screened blood unit is low (1 in 6,40,000).[4] Contact with infected viable lymphocytes can cause infection, as both the viruses are cell-associated. Implicated blood components for HTLV transmission are whole blood, packed red cells and platelets. As refrigeration of blood product over 10 days results in degradation of lymphocytes and in decrease in load of infectious viruses, plasma and plasma derivatives do not transmit the virus.[30-32] The association of infectivity with fresh cellular components raises the possibility that transmission of HTLV by

transfusion requires viable T- lymphocytes and that their removal from blood donations may clear the potentially infectious cells.

With the use of combination of viral lysates from HTLV-I and II viruses, there is sensitive detection of both anti-HTLV-I and anti-HTLV-II. Such combination HTLV-I/II EIA test is being used in United States for HTLV screening as the originally licensed anti HTLV-I EIA can miss upto 50% of HTLV-II infections.[33] HTLV-I and II infections have not been reported in the Indian subcontinent.

Cytomegalovirus (CMV/HHV-5)

Transfusion transmitted cytomegalovirus infection (TT-CMV) has been documented as a cause of significant morbidity and mortality in immunocompromised as well as immunocompetent recipients. The prevalence of anti-CMV ranges from 40% to 90% in the general population[34,35] (Western figures). Although approximately 50% of blood donors can be expected to be CMV seropositive, it has been estimated that currently less than 1% of seropositive cellular blood components are able to transmit the virus.[15] Post-transfusion hepatitis may rarely be due to CMV infection. Post-transfusion CMV infection is of concern in certain categories of immunocompromised individuals such as neonates, pregnant women, recipients of bone marrow and other organ transplants and individuals with immuno-deficiency diseases. It is generally of no clinical consequence in immunocompetent recipients. CMV is carried in leukocytes and the pathogenesis of CMV related infections is based on the tropism of the virus for peripheral blood monocytes, which harbor, transmit and produce infectious CMV virions after infusion into seronegative (susceptible) transfusion recipients.[36] Although the precise leucocyte population that harbors the virus has not been defined, leucocyte removal with high efficiency filters can significantly reduce, if not prevent, post-transfusion CMV infections in premature neonates and transplant recipients.[16] In comparison to unscreened blood, the use of seronegative units can reduce the incidence of TT-CMV from 13–37% to 2.5% in at-risk individuals.[37] The demonstration of CMV DNA in the peripheral blood monocytes of some seronegative donors,[38] implies past infection, and indicates that serology alone has limitations in detecting all CMV infected blood donors. Monocytes harbor latent CMV but differentiation of monocytes into macrophages in the transfusion recipient leads to reactivation of CMV suggesting that TT-CMV can occur in recipients of seronegative units also, although at a lower rate. The need for CMV antibody screening in Indian blood donors needs to be evaluated.

Epstein Barr Virus

The majority of healthy blood donors are infected with EBV. In spite of so many healthy individuals being infected, transfusion associated mononucleosis is a rare complication of transfusion therapy. This is because most adults who receive transfusions have antibodies to EBV. Hence, serologic screening for this virus is not considered worthwhile.

Human Herpes Viruses (HHV) 6 and 8

With ubiquity of HHV-6 antibodies and absence of disease associations after transfusion, no recommendations have been made for protection of seronegative blood recipients from transmission by blood components.[39] HHV-8 (Kaposi's sarcoma associated herpes virus) has been found in apparently healthy blood donors but transfusion transmission of HHV-8 has not been demonstrated.[40,41]

Parvovirus B19

B19 Parvovirus was discovered by chance during the screening of blood samples for hepatitis B surface antigen. About 30 to 60% of blood donors have antibodies to parvovirus B19. This is indicative of immunity rather than chronic persistent infection.[42] The virus has been found regularly in clotting factor concentrates and has been transmitted to persons with hemophilia. Rare transmission through cellular blood components and plasma, but not intravenous immunoglobulin and albumin, has been reported.[43] Parvovirus B19 can infect and lyse red cell progenitors in the bone marrow.[44] This may result in sudden and severe anemia in patients with underlying chronic hemolytic disorders. Patients with cellular immunodeficiency, including those infected with HIV, are at risk for chronic viraemia and associated hypoplastic anemia. However, parvovirus B19 screening of whole blood donations has not been a high priority because of the benign and/ or transient nature of most parvovirus diseases, the availability of effective treatment for chronic haematologic sequelae and the extreme rarity of reports of parvovirus B19 transmission by individual components.

West Nile Virus

The West Nile virus infects humans only incidentally when a human host contacts an infected mosquito. The virus is very similar to HCV. It is a Flavivirus and has a 5-10-day period of high titer viraemia. The presence of West Nile virus RNA confirms infectivity but does not necessarily indicate the development of disease. In 1999 through 2003, West Nile virus spread in the US and was found to be transmitted by the transfusion of blood components. The mean risk of transmission via transfusion ranged from 1.46 to 12.33 per 10,000 donations during the 2002 epidemic. Now blood donations in the US are screened for the presence of West Nile virus genomes by PCR.[45]

Prions

Transmissible Spongiform Encephalopathies

The transmissible spongiform encephalopathies (TSEs) are degenerative brain disorders caused by agents often called prions, postulated to be infectious proteins. Two such TSEs, Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jacob disease (vCJD) are of interest in transfusion medicine. CJD is a degenerative brain disorder that is rapidly fatal once symptoms of progressive dementia and motor disturbances develop. So far, transmission of CJD through blood transfusion has not been reported. Iatrogenic CJD has been transmitted by administration of growth hormone and gonadotropic hormone derived from pooled human pituitary tissue and through allografts of duramater.[46] Such individuals at increased risk for CJD are excluded from donating blood.

Bacteria

Bacterial Contamination

Bacterial contamination, one of the earliest recognized complications of stored blood, remains an important cause of transfusion-related mortality and morbidity. Bacteria are believed to originate with the donor, either from the venipuncture site or from unsuspected bacteraemia. Bacterial multiplication is more likely in components stored at room temperature than in refrigerated components, especially when the room temperature storage is in gas permeable containers.[47]

RBCs are primarily infected with psychrophilic gram-negative organisms such as Yersinia enterocolitica and Serratia liquifaciens. Other pathogens such as Staphylococcus, Klebsiella, Enterobacter, E coli, Streptococcus, Bacillus and Pseudomonas are also known to infect erythrocytes. Usually, platelet transfusion-associated sepsis is not as catastrophic as sepsis associated with transfusion of packed cells. The former occurs several hours (or longer) after transfusion making it more difficult to diagnose and link it to the transfusion received.

Discarding the first aliquot of donor blood removed has been proposed as a measure to reduce bacterial contamination of blood components based on association of skin bacteria that enter at time of phlebotomy.[48] Various approaches to detect bacterial contamination besides visual inspection before release of the component are Gram's stain and culture, endotoxin assays and detection of bacterial nucleic acids by amplification techniques.[48,49]

Syphilis

Transfusion transmitted syphilis is not a major hazard of modern blood transfusion therapy. *Treponema pallidum*, the infectious agent causing syphilis survives at the most for 5 days in blood stored at 4°C.[50] Only rare cases of transfusion transmitted syphilis have been documented. The rapid plasma reagin (RPR) test is commonly used for screening the blood product for syphilis. Blood donations from individuals who have had or been treated for syphilis should be deferred for at least 12 months after successful completion of treatment. As per the AABB standards, blood donations from any person with a positive serological test result for syphilis should be deferred for 12 months.[51] It is not the transmission of syphilis that is worrisome. Being a sexually transmitted disease, its presence points towards donor's indulgence in "high risk" behavior and consequent higher risk of exposure to infections like HIV and hepatitis. It should however, be remembered that the RPR test used for screening is not specific. In healthy blood donor population, a large portion of positive tests may represent a biological false positive reaction. Although, elimination of screening test for syphilis from the panel has been advocated for the reasons stated above; [52] FDA regulations mandates its performance.

Parasites

Malaria

Although rare, malaria is probably the most commonly recognized parasitic complication of transfusion. Malarial parasites survive for at least a week in components stored at room temperature or at 4°C.[53] Asymptomatic carriers are generally the source of transfusion-transmitted malaria. Screening for malarial parasites is routinely done by examination of peripheral blood films. Thick and thin smears detect parasitaemia of more than 300-500/μL whereas parasitaemia of as low as 10/μL can give rise to transfusion-transmitted malaria.[54] Smear method fails to detect majority of samples, which may be positive by a monoclonal antibody based detection test.[55] Hence, only smear examination is inadequate and more sensitive tests for detection of malarial parasite need to be introduced to prevent transfusion-transmitted malaria. Both molecular and immunologic detection methods are available, but are not widely employed. Since healthy blood donors are selected for blood donation, density of parasites is usually very less, if present and hence may be missed. Thus, in endemic ar eas, it is recommended that chemoprophylaxis should be given to all recipients. In non-endemic areas, screening donors by travel history can exclude the asymptomatic carriers.

Babesiosis

As with malaria, asymptomatic individuals infected with Babesiosis may present as prospective blood donors. Babesiosis has been transmitted following the transfusion of infected packed red cells, frozen-thawed-deglycerolized red blood cells[56] and platelet concentrates.[57] The parasite can survive at 4°C in a unit of RBCs for up to 35 days. No test is currently available for mass screening to detect asymptomatic carriers of Babesia species.

Trypanosomal infection

Only a few cases of transfusion-transmitted *T. cruzi* infection have been diagnosed. The parasite is viable for at least 21 days in the whole blood and RBC units that have been stored at 4°C.

Leishmaniasis

Transfusion transmission of Leishmania species is a rare risk in countries where such organisms are endemic.

Toxoplasmosis

Toxoplasma gondii is a WBC-associated parasite that can survive for several weeks in stored whole blood. Toxoplasmosis is caused by the ubiquitous parasite toxoplasma gondii and infection has been reported as a rare transfusion complication in immunocompromised patients.[58] Given the high risk of symptomatic transfusion-transmitted toxoplasmosis, the option of using leucocyte-reduced blood may be considered while providing packed cell or platelet transfusions to the immunocompromised individuals.[59]

Microfilariasis

Filarial infections are usually transmitted by vectors but if blood from a microfilaremic individual is transfused, the transfused microfilaria may persist in the recipient's circulation for more than 2 years.[60] Transfusion-acquired microfilaremia is self-limited because transfused microfilariae do not develop into adult filarial worms. Routine testing of donor blood is, therefore,

not warranted.

Strategies of Risk Reduction [Table 1]

With the introduction of better technologies of donor screening and viral inactivation procedures, the risk of transmission of infections through blood and its products is declining. Voluntary non-remunerated blood donation is the source of safest blood supply to the transfusion services. Building up of a strong voluntary donor base combined with creating awareness to gradually abolish the replacement donations should be one major step in ensuring safety of blood and its products. Studies in India and worldwide have reported a higher seroprevalence of transfusion transmitted diseases in replacement donors as compared to voluntary blood donors. Hence, stress should be laid on recruiting voluntary non-remunerated repeat donors.

NAT is a very expensive screening method. In order to make screening of blood by NAT a feasible option, donor samples are tested in pools. NAT requires a good infrastructure expensive equipment as well as trained technical staff. In the present scenario NAT is not feasible in a developing country like India. The cost is prohibitive and there are much more pressing health concerns. In future when this technology becomes cheaper and more accessible, it will be possible to implement this screening method in developing countries.

Viral inactivation steps, which were originally developed for purified plasma protein fraction, have now also been applied to plasma intended for transfusion. Solvent detergent treatment and psoralen (S 59) activated by ultraviolet A light are available for pathogen inactivation in platelets and plasma. An organic chemical (S 303) and a nucleic acid targeting compound have undergone initial evaluation for pathogen inactivation of red cells. These methods can inactivate bacteria, viruses and parasites including intracellular forms.[61,62]

With the rigorous application of viral inactivation steps, clotting factor concentrates have now become quite safe. However, such procedures though effective against lipid enveloped viruses are ineffective against non-enveloped agents such as HAV and parvovirus B19. Certain drawbacks also exist such as reduction of yield and biological effectiveness of the product and induction of factor VIII inhibitors in haemophiliacs. Factor VIII concentrates produced by recombinant DNA technology can be used in previously untreated patients with haemophilia. Such products are free of human derived proteins, HIV, hepatitis viruses and other agents.[63]

Haemovigilance systems would help determine trends of transfusion-transmitted infections and the need to implement screening for the newer infections.

Conclusion

Over the years, there has been a substantial decline in the incidence of transfusion-transmitted infections due to improvement in donor screening, testing and viral inactivation of blood products, particularly in developed nations. However, in developing nations, blood safety continues to be a major problem due to the high prevalence of infections markers among blood donors compounded with the problem of limited resources that preclude the use of sophisticated, sensitive but expensive technologies for screening of blood products. The last two decades have also witnessed surfacing of new and re-emerging infections. Hence, despite stringent donor eligibility criteria, improved donor screening and introduction of sophisticated technology, transfusion-transmitted infection continues as a challenge for transfusion experts.

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Table 1: Strategies for reducing risk of transfusion-transmitted infections

Careful donor selection	Reduction of product contamination	Improvement in blood component processing and storage	Improvement in pretransfusion blood testing	Reduction in recipient exposure	Pathogen inactivation
Repeat voluntary blood donors and improvement in eligibility criteria	Improvement in venipuncture site disinfection	Optimising storage temperature	Sensitive and specific serological testing	Optimizing transfusion indications	Methylene blue-photo inactivation
Education, counselling and retention of voluntary donors	Removal of first aliquot of donor blood	Universal leukocyte reduction	NAT test on mini pools	Reducing transfusion triggers	Psoralen + Ultraviolet A light
Confidential donor unit selection and telephonic call back		Limit the storage time	Visual inspection of components before use	Increased use of single donor products	Solvent detergent treatment

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