



Overview on Blood Transfusion-Transmitted Diseases

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 04 Nov 2023	<p>As it is important for the Blood transfusion to be extremely safe, some measures have to be taken long safeguarded the blood supply from the major transfusion transmissible diseases (TTIs). The risk of transfusion-transmitted infection (TTI) rises with the number of donors exposed, and the effects of TTI are frequently more severe in immune compromised people. TTIs (hepatitis B virus [HBV], HIV, and hepatitis C virus [HCV]) are examples of typical transfusion-transmitted infectious agents. As a result of the gradual application of nucleic acid-amplification technology (NAT) screening for HIV, HCV, and HBV, the residual risk of infected window-period donations has been minimized. Nonetheless, infections emerge far more frequently than is commonly acknowledged, needing ongoing surveillance and individual assessment of transfusion-associated risk. Although there is a constant need to monitor present dangers owing to established TTI, the ongoing issues in blood safety are mostly related to surveillance for developing agents, as well as the creation of quick reaction systems when such agents are detected.</p>
CC License CC-BY-NC-SA 4.0	<p>Keywords: Blood transfusion, transfusion transmitted infections, transfusion transmitted viral diseases, bacteria, parasite, safety, prevention.</p>

1. Introduction

Blood is the source of life. Millions of lives are saved each year globally via the use of transfusions of blood and blood components, which also lower morbidity. It is generally recognized that receiving blood transfusions can result in a wide range of problems, some of which are minor while others could be fatal, necessitating careful pre-transfusion testing and screening. An improper blood transfusion, on the other hand, is extremely expensive from both a human and economic standpoint. Morbidity and death caused by contaminated blood transfusions have far-reaching effects not just for the recipients, but also for their families, communities, and society as a whole. Transfusions may contribute to an ever-growing reservoir of illness in the population since an infection might spread while a person is still asymptomatic [1].

Infectious agent transmission is one of the negative outcomes of allo-genic blood transfusion (BT). Although the danger of transfusion-transmitted diseases (TTDs) has decreased dramatically over the last decade, it still remains [2]. Transfusion-transmitted infections (TTI) are a major source of worry for patients' safety. Since the scientific study of blood transfusion began in the early 1940s, several

transfusion-related issues have come to the attention of the scientific community. These include TTI, allo-immunization to different blood components, problems with maintaining the cold chain, platelet refractoriness, transfusion (iron) overload, transfusion-associated graft versus host diseases (GvHD), immune-modulatory effects, etc. TTI, however, wasn't discovered until the blood transfusion procedure in the late 1940s. Blood bank staff members exclusively focused on a few blood-borne illnesses, notably syphilis and serum hepatitis, until the early 1970s. The scientific community, however, was well known that there would be a variety of agents. Over the last 40 years, scientists have discovered that several viral, bacterial, and parasitic infectious pathogens are implicated as barriers to patient blood safety. Some illnesses have even been proven to be transferred via transfusion. In patients, viral infections have a significant role in transfusion-related mortality and morbidity. A variety of viruses, parasites, and bacteria can be transferred by blood transfusions. Human immunodeficiency virus (HIV-I/II), hepatitis B and C viruses, syphilis infection by spirochetes, and transfusion-associated malaria infection are all examples of major transfusion-transmitted viruses. There is a danger of 1-2 patients per 1000 obtaining tainted blood with viral, bacterial, or parasite organisms. However, if blood transfusion is not performed or completed, patients face a 50% chance of significant morbidity and fatality. The majority of the difficulties are caused by the presence of asymptomatic carriers in society, as well as blood donations during the infection window [3].

The transition has enabled attention to be directed towards previously overlooked transfusion-associated infectious concerns, while also creating pathogen reduction technologies to deal with infectious risk proactively [2]. Blood safety at any cost carries its own risks, affecting sustainability and the ability to deal with difficulties as they emerge [4]. TTIs are a gauge of related dysfunction that, despite its extensive influence on public health, has received little long-term investment or public attention [5]. This is not a unique issue; rather, it fits within the umbrella of pathology and laboratory services in general [6]. Blood transfusion demand is strong, necessitating continuous dependence on suboptimal practices (e.g., replacement and compensated donation, fast testing, and so on) [7]. Furthermore, there is a paucity of post-transfusion monitoring, which might assist inspire change by demonstrating transmission and clinical sequelae [8]. The following is a summary of blood transfusion-related infections. A description of the main TTIs is used to highlight some of the key takeaways and how developments have shaped modern practice.

Epidemiology of transfusion transmitted diseases

The hepatitis B virus is thought to infect 240 million people on a long-term basis. Out of these instances, liver cancer and cirrhosis account for more than 680,000 annual fatalities from hepatitis B. Around 150 million people worldwide are infected with chronic hepatitis C, and each year, the liver disease claims nearly 700,000 of them. Hepatitis B and C are widespread across the world, particularly in people with HIV, hemodialysis patients, and those with coagulation abnormalities [9].

As of 2016, the global estimated number of people living with HIV/AIDS was 36.7 million. Men who engage in dangerous sexual behavior, the use of intravenous drugs, risky blood transfusions, or blood products are additional risk factors linked to an increased chance of contracting HIV [10].

HTLV-1 is present in the blood of 15 million persons globally who are chronically infected. HTLV-1 is spread sexually, perinatally (by breastmilk), and parenterally (via blood transfusions, injectable drug users, and transplants) [11].

The African continent has undergone a long-term drop in the prevalence of *Plasmodium falciparum* malaria from 40% (1900–1929) to 24% (2010–2015), however this trend has been interrupted by periods of quickly growing or declining transmission. According to the WHO, there were an estimated 216 million cases of malaria globally in 2016 [12].

There are several pathogenic West Nile virus isolates, but the two main West Nile virus lineages, L1 and L2, are responsible for the majority of documented outbreaks. While L2 encompasses indigenous strains from sub-Saharan Africa, Madagascar, and Eastern Europe, L1 comprises strains from North, Central, and South America, Africa, and the Middle East. Since 2010, outbreaks of West Nile neuro-invasive illness in Romania have been triggered by an isolated L2 strain discovered in Southern Russia in 2004. Wild birds and mosquitoes are the main vectors for the spread of this virus. Blood transfusions, perinatal exposure, nursing, and organ transplantation are among ways that individuals might be exposed to one another. Only one in every 150 cases of West Nile virus infection develops in serious neurologic disease, and the patient is usually old [13].

Classification of TTIs

TTIs are broadly classified depending on the evidence for transfusion transmissibility, the amount of danger (global or regional), and management. Category I infections (HIV, HBV, HCV, and *T. pallidum*) are those for which transfusion transmissibility is well known, risk is worldwide, and donor screening is nearly ubiquitous. Both categories II and III comprise infections for which transfusion transmissibility has been thoroughly demonstrated and mitigating strategies, albeit in limited regions. They differ in terms of danger extent, with Category II infections posing a worldwide risk and Category III pathogens posing a regional risk, albeit this difference is rather arbitrary. Pathogens of Category IV have been implicated, albeit infrequently, in instances of transfusion-transmitted illness. Risk is regarded as minimal regardless of frequency in the general population. Finally, Category V pathogens are those for which there is no clinical evidence of transfusion transmitted infectious illness [14].

Viruses

HIV: HIV has had a greater influence on blood transfusion safety than any other infectious pathogen. After immunological dysfunction developed in three hemophilia patients, the question of whether HIV and blood transfusions were related was initially addressed [15].

Similarly, at 14 months of age, a transfused newborn acquired opportunistic infections [16]. A retrospective examination indicated that one of the three blood donors died from AIDS-related complications, providing more proof of transfusion transmissibility. The failure to recognize transfusion as a means of transmission had disastrous repercussions, particularly for patients with hemophilia who relied on plasma-derived clotting factor concentrates for therapy [17].

Using a third-generation enzyme immunoassay, HIV-2 could be detected in 1992 [18]. A multiplex test for HIV and HCV called mini-pool-NAT was released in 1999. Transfusion-transmitted HIV remains uncommon in HICs even four decades after its discovery. For instance, based on a modeled incidence rather than an actual incidence, the predicted risk in the US is less than 1 in 2 million [19]. Unfortunately, this is not the case in low- and middle-income countries (LMICs), where transfusion-transmitted HIV continues to pose a serious public health threat due to the high background HIV incidence and inadequate blood donor screening and selection practices [5].

HBV: Hepatitis B virus (HBV) is a DNA virus that belongs to the *Hepadnaviridae* family that is spread by parenteral, sexual, and perinatal routes. Most infections in the US which its prevalence is 5.6% and other low-prevalence nations are horizontal, spreading from one adult to another; in nations with a high prevalence of HBV, infections can be both horizontal and vertical (i.e. perinatal). The disease's incidence has dropped due to widespread vaccination of newborns and high-risk adults (from 260,000 new infections per year in the United States to 60,000 per year). Additionally, children delivered to infected moms or for post-exposure prophylaxis can get hepatitis B immune globulin. TT-HBV can cause an acute infection that is followed by viral eradication and immunity, or it can cause a chronic infection that is accompanied by persistent viral replication. Chronic infection can either resolve with the development of immunity or reactivate, resulting in more acute illness [20].

Acute infection has an incubation period of 60-150 days. The majority of infected people are asymptomatic, but 30–50% of infected children under the age of five may exhibit jaundice, fever, appetite loss, nausea, vomiting, and stomach discomfort, and 0.5–1% of infected people, mostly those under the age of 60, will have a fulminant acute infection that will result in death. Serologic findings in acutely infected people show HBs-Ag positivity, anti-HBc positivity, IgM anti-HBc positivity, and anti-HBs negativity. The emergence of anti-HBs and the removal of HBs-Ag suggest the development of immunity in the absence of additional clinical illness. The chance of chronic infection is connected to the patient's age at the time of infection, with 90% of those infected in infancy developing chronic illness, while only 6% of those infected after age 5 get chronic disease [20].

Chronic infection can be asymptomatic, but in certain cases, cirrhosis and hepatocellular carcinoma can lead to severe and deadly illness. Rashes, arthritis, vasculitis, and glomerulonephritis are the most common extra-hepatic symptoms of cryoglobulinemia. Serologic findings in individuals with chronic active hepatitis show HBsAg positivity, anti-HBc positivity, IgM anti-HBc negativity, and anti-HBs negativity. Interferon, lamivudine, adefovir, and other antiviral drugs are used to treat chronic infection [20].

HCV: Hepatitis C virus (HCV) is an RNA virus of the *Flaviviridae* family that is transmitted parenterally, most notably via blood transfusions (prior to testing) and intravenous drug use. Using current NAT testing, the risk is predicted to be 1:1.4 million goods or less [20].

Hepatitis C virus (HCV) infection is asymptomatic in 80% of individuals. After a 7-8 week incubation period, around 20% may have acute infection symptoms (fever, jaundice, lack of appetite, exhaustion, and nausea). Chronic infection affects 75-85% of infected people, with cirrhosis affecting 20-30% (after an average of 20 years) and hepatocellular cancer affecting 30% (after an average of 30 years) [20].

The probability of transfusion transmission is currently less than 1:1.4 million donors when using the latest enzyme immunoassay assays and NAT. According to the FDA, when a donor tests positive for HCV antibodies, a "look-back" is required to find, notify, test, and, if necessary, treat recipients of products donated in the past by the same donor, at a time when those recipients did not test positive for HCV, either because they had not yet contracted the infection or because their markers of infection were below the test's detection threshold [20].

Hepatitis G: Hepatitis G is widespread in the general population; 3-15% of healthy people have antibodies to the virus, and viral RNA is found in 1-3%. The virus is spread by transfusion, as evidenced by a high incidence of infection in several transfused people. There is currently no sickness linked with this virus, hence no testing is necessary [20].

HEV: HEV is a single-stranded, positive-sense, non-enveloped RNA virus. There are four Genotypes (G1-4), each with its own major method of dissemination and epidemiology. G1 and G2 specifically transmit by the fecal-oral pathway, which explains outbreaks in low-income countries (LICs) due to water-borne dissemination. G3 and G4 are zoonoses (porcine viruses) that are transferred to humans by eating contaminated meat. Globally, HEV is a significant cause of acute hepatitis [21]. It has received attention while being mostly ignored (in comparison to HBV and HCV) because of the steady rise of HEV in several regions of Western Europe. While it produces a moderate self-limiting illness in immune-competent people, it can cause severe or even deadly disease (acute fulminant hepatitis) in pregnant women and the immune-compromised. The fast development of cirrhosis is widely reported together with persistent infection and chronic hepatitis.

Observed sero-prevalence values in Nepal (47%), Bangladesh (50%), France (53%) and the Netherlands (27%) represent significant rates of background exposure in several regions of the world, according to surveillance studies [22]. Transfusion-transmitted HEV poses a risk to RBCs, platelets, granulocytes, and plasma. The chance of infection for recipients is between 40 and 50 percent when the lowest infectious viral dosage (2 104 IU) and 55% of components are used to transmit the virus [23]. Molecular monitoring in the donor community reveals varying frequencies of G3 viremia, such as 1 in 762 in the Netherlands, 1 in 9,500 in the United States, 0 in 13,993 in Canada, 1 in 4,997 in Ireland, and 1 in 3,830 in England [24]. Surveillance has most certainly influenced donor screening policy: HEV NAT is now regularly conducted on donors in Japan, the Netherlands, France, Germany, the United Kingdom, and Ireland [25].

CMV: Cytomegalovirus (CMV) is spread by transfusion, HPC, and solid-organ transplantation. CMV transmission in the community is often through intimate contact with a CMV carrier. The sero-conversion rate in blood donors is about 1% each year. The prevalence ranges from 40 to 90%; it rises with age and is higher in lower socioeconomic categories, cities, and developing nations. Immuno-competent people get a moderate self-limiting illness course that includes fever, malaise, hepatosplenomegaly, and rash. The immune response does not eradicate the virus, but it does cause the virus to become dormant in peripheral blood leukocytes [20].

Trans placental infection causes intrauterine growth retardation, deafness, mental impairment, blindness, and thrombocytopenic hemorrhage in 5-15% of affected newborns. Pneumonitis, hepatitis, retinitis, and multisystem organ failure are all possible outcomes of infection in immune-compromised individuals, including preterm newborns, those who have had solid organ or HPC transplants, and people with AIDS. Antivirals including ganciclovir, cidofovir, and foscarnet are used to treat CMV infection [20].

Anti-CMV antibodies, the CMV antigenemia test, and the CMV PCR are all methods for identifying CMV infection. CMV antigenemia assays have mainly been supplanted by PCR, allowing for early identification of CMV [20].

WNV: The WNV flavivirus is a member of the *JE antigenic Complex*, which is spread via mosquitoes. The vast majority of infections (80%) remain asymptomatic; nevertheless, 1% will develop neuro-invasive illness, including meningo-encephalitis [14].

WNV NAT was quickly designed and deployed in 2003. When a positive donor is found in a certain area code, a system was developed that uses mini-pool NAT year-round with a reflex to ID-NAT. ID-NAT is maintained for a certain amount of time in the geographic location where the infected donor

originated. This method is used to increase the likelihood of finding donors with low levels of viremia who might otherwise go undetected using MP-NAT. MP-NAT is then restarted if no new positive donors are found. Based on area monitoring and seasonal activity, the ID-NAT term may be extended. WNV positive donors are postponed for 120 days following donation. The present testing technique has been lauded as one of the triumphs of contemporary blood banking, having successfully intercepted hundreds of potentially infected blood products [14].

Bacteria

Transfusion-transmitted bacterial infection (TTBI) was determined to be 24.7 per million platelet concentrates (PCs) and 0.39 per million red cells transfusion. The fatal TTBI rate in PCs transfusion is 5.14 per million. Bacterial contamination is more likely in PCs since they are maintained at 20-24°C, a temperature that promotes bacterial development. 0.02-1.2% of PCs and 0.1-0.2% of packed red blood cells (PRBCs) are contaminated. Bacteria can be found in donors, the surroundings of a blood bank or hospital, infected bags and tubing, and the donor's or recipient's skin. Although both streptococcus and coagulase-negative staphylococcus are spread by frozen platelets, the bacteria are mostly skin contaminants like these types of bacteria [26].

Red cells are more prone to be infected than platelets. The longer red cells are retained, the greater the risk of infection. Gram-negative bacteria such as *Yersinia*, *Serratia*, *Escherichia*, *Pseudomonas*, *Proteus*, *Klebsiella*, and *Acinetobacter* are the most common species found in Bacthem studies. These bacteria can thrive at temperatures ranging from 1-6°C, which is the range at which red blood cells are kept. *Staphylococcus aureus*, *Klebsiella*, *Propionibacterium*, and *Pseudomonas* have all been discovered. The likely source is water baths used to defrost plasma [26].

Transfusion-transmitted bacterial infection can cause high fever, chills, rigour, tachycardia, hypotension, nausea, vomiting, dyspnea, backache, and abdominal discomfort, which might be mistaken for a febrile non-haemolytic transfusion response.

Gram-negative endotoxaemia can produce severe symptoms, including a fever of 109°F, and can develop to fulminant sepsis, shock, disseminated intravascular coagulation, and even death. Transfusion should be halted promptly if TTBI is suspected, followed by the delivery of broad-spectrum antibiotics and symptomatic care of the patient. It is necessary to notify the blood bank. Gram staining and bacterial culture of both the donor and the recipient should be performed. A Coombs test of the recipient's blood is required to rule out a hemolytic transfusion response. Syphilis transmission has become extremely infrequent with the advent of a serological test for antibodies to *Treponema pallidum* [26].

Parasites

Plasmodium spp. malaria, *T. cruzi* sickness, and babesiosis are three parasite illnesses that put the blood supply at risk. Reports of other parasitic illnesses (such toxoplasmosis and leishmaniasis) being transmitted through transfusions are extremely uncommon and sometimes have unclear causality [27].

In the United States, the most serious threat is *Babesia*, a vicious intra-erythrocytic parasite. In immune-competent hosts, naturally acquired infection by tick bite is often moderate or even subclinical, but it can lead to an asymptomatic carrier status that can last for years. In contrast, other *Babesia* species, such as *Babesia duncani* 64, are found in various regions of the United States but seldom cause TTB. *B. microti*, the main cause of human babesiosis, is extensively endemic, notably in the northeast and upper mid-west. A high mortality rate (>20%) in TTB may be explained by an overrepresentation of high-risk clinical subgroups among transfusion patients, such as those who are extremely old, asplenic, and/or immune-compromised. Clinical investigations have shown decreased TTB in endemic locations, and molecular donor screening techniques (DNA or RNA NAT) have been established. Despite FDA approval of a combined antibody/PCR-based method in 2018, these tests are not commercially accessible [27].

Donor screening is currently being conducted selectively by experimental NAT in various US endemic locales. These NAT techniques amplify highly repetitive *babesia* RNA sequences in donor whole blood that has been lysed, achieving detection of 2 to 3 parasites per milli-litre of blood, matching the infectious dose via blood transfusion, 69 and possibly eliminating the requirement for concurrent serological screening. *T. cruzi*, which causes Chagas disease and is spread by Triatomine vectors, is largely prevalent in Latin America, where donor screening with several serological tests was effectively adopted decades ago [27].

Emerging infections

Dengue fever, SARS, influenza, and LCMV are only a few of the many potentially new illnesses that need for ongoing monitoring of the blood supply and assessments of therapies [20].

Prevention of transfusion transmitted infections

The goal of a restrictive BT approach should be to transfuse blood components based on individual needs rather than transfusing based on transfusion trigger. To limit blood loss, autologous blood donation, recombinant human erythropoietin, and appropriate surgical and anesthetic techniques should be used. TTD can be largely avoided by taking safety precautions like postponing donors who have recently had dental work done, minor surgery, or a fever at presentation, carrying out proper skin disinfection on donor arms, and making sure the first 30–40 ml of whole blood from the collection bag is diverted. Bacterial testing methods should be used on preserved blood closer to the time of transfusion. Before transfusion, preserved blood should be Gram-staining, screened for contamination indicators, and cultured. Before blood is released for transfusion, it should have a negative culture for at least 24 hours [28]. Pathogen reduction techniques, such as the usage of synthetic psoralen, riboflavin, pre-storage leukocyte reduction, and apheresis generated platelet, should be used to reduce transmissible infections. Efforts should be made to enhance patient blood management modalities and multicomponent apheresis, a patient-centered paradigm in transfusion medicine that aims to keep transfusion risk as low as reasonably practicable. Vaccinating the entire population will provide protection against some TTDs. 'Look Back' projects might be implemented in poor nations. Artificial oxygen carriers and recombinant clotting factors should be developed [29].

Blood safety

The majority of low- to middle-income countries (LMICs) do not have the same high degree of transfusion safety as HICs. LMICs have challenges across the blood safety chain, from donor screening to post-transfusion monitoring [30]. LMICs are frequently located in locations where TTIs are prevalent. Notable instances are HIV and malaria in Sub-Saharan Africa, HBV in Asia, HCV in North and West Africa, and HTLV in the Caribbean. Given the unpredictable donor pool, high complexity, and high expense of recruiting voluntary donors, donor selection, the first line of defense against TTIs, frequently falls short of expectations, necessitating the use of whole blood transfusions, family replacement donors, or paid donors. Replacement donors who are sought out in times of need, such as after blood loss resulting from accidents or childbirth, are generally thought to be at a higher risk for TTIs than voluntary non-remunerated blood donors [31]. According to research conducted in Africa, where rates of contamination as high as 17.5% have been documented, collecting in hot, humid circumstances increases the likelihood of bacterial contamination [32].

TTI testing is also inadequate. Rapid diagnostic tests (RDTs) are frequently used, especially in remote areas, but their use is hampered by systemic issues like a lack of national regulatory oversight, a lack of proficiency testing, poor supply chains, expensive reagents, unstable cold-chain management, unstable electricity, and a shortage of skilled personnel [33]. RDTs, on the other hand, have not been validated for the blood donor population and have frequently exhibited limited sensitivity and specificity in detecting the main TTIs. Since serological tests are frequently used exclusively, WP infections in the nations with the greatest TTI prevalence are often ignored. Last but not least, because there is a lack of post-transfusion surveillance, patients who contract TTIs are highly unlikely to be identified as such; instead, these infections will be ascribed to acquisition through other modalities [34].

4. Conclusion

Transfused patients are at significant risk of morbidity and death from bacterial, viral, and parasitic infections. The epidemiology of transfusion transmissible illnesses in the general population will help determine population prevalence. There is a danger of disease transmission and immunosuppression following blood transfusion. It may be feasible to limit the occurrence of TTI by implementing tight donor selection criteria, using sensitive screening tests, and following safety strict blood transfusion standards.

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