

Recent Updates in Transfusion Transmitted Parasitic Diseases

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Abstract

A number of parasitic diseases have been reported to be transmitted by blood transfusion, including malaria, leishmaniasis, Chagas' disease, babesiosis, toxoplasmosis and filariasis. Majority of blood banks do not screen donor blood samples for these potentially pathogenic parasites, this poses great risk to the recipients of blood, especially immunocompromised patients and those who need regular, frequent and multiple transfusions. Transfusion-transmitted parasitic infections depend on several factors; asymptomatic parasitemia individual qualifies as a blood donor, the ability of the parasite to survive on stored donated blood, and the infected blood is transfused in a sufficient dose to a susceptible patient.

Keywords: Babesiosis; Chagas; Disease; Filariasis; Leishmaniasis; Malaria; Toxoplasmosis; Transfusion

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Transfusion-Transmitted Malaria (TTM)

Malaria is a mosquito-borne infectious disease caused by intraerythrocytic protozoa of the genus *Plasmodium*. In humans, malaria is caused by *Plasmodium falciparum* (*P. falciparum*), *P. malariae*, *P. vivax*, *P. ovale* and *P. knowlesi* [1]. Malaria infection develops via two phases: one involves the liver (exoerythrocytic), and the other involves the red blood cells

(erythrocytic). TTM differs from natural infection in the form that exoerythrocytic phase does not occur, the incubation period is shorter (2–4 days as the inoculum contains the erythrocytic forms of the parasite), relapses do not occur, and radical cure is possible [2]. TTM is a greater threat because a bite from an infected mosquito may cause malaria by introducing as few as 15 parasites. While, a single parasite identified on microscopic evaluation of a thick blood film (4 μ L) is equivalent to ~10,000 parasites in a 450-mL unit of blood [3]. Malaria parasites can survive for at least 3 weeks in refrigerated blood and even in frozen blood. Although cell-free blood components (plasma, plasma components, or derivatives devoid of intact red cells) are believed not to transmit malaria, some cases have been reported after transfusion of cryoprecipitated antihemophilic factor [4]. Moreover, transfusion of plasma and platelets may contain the exo-erythrocytic forms of malaria parasites [5].

The risk of acquiring transfusion malaria is very low (1 case per 4 million) in non-endemic countries (where the infection is imported from outside either travelers to, or immigrants from, highly endemic regions) while, it is much higher (>50 cases per million donor units) in the endemic countries. The first case of TTM reported in 1911, since then, an increasing number of cases has been reported worldwide [6-15]. The recipient develops the classic symptoms of malaria and severe malaria is usually caused by *P. falciparum* infection, particularly in the non-immune recipients, and typically arises 6–14 days after infection leading to coma and death if untreated [16].

In endemic regions, the prolonged contact of individuals to malaria parasites has been reported to decrease host symptoms

and parasite densities below the detection threshold of currently available assays; these individuals are infected asymptomatic carriers with a protective immune status who are generally the source of TTM. The transmission has been documented after the last exposure as long as 44 years for *P. malariae*, five years for *P. vivax* and eight years for *P. falciparum* [12]. Malaria antibodies were detected among blood donors by several investigators in different countries. Owusu-Ofori et al. [3] identified 17 relevant studies from the period 1980–2009 and found that the prevalence of malaria among 33,029 blood donors was 10.2% (range, 0.7% in Kenya to 55.0% in Nigeria). The high variation in prevalence rates could be the result of the combination of different and independent factors influencing the dynamics of malaria transmission, seasonal variations with higher rates observed during rainy season, the criteria for blood donor selection and the blood donor screening methods [17].

Prevention of TTM is based on travel-based risk assessment and includes donor deferral for 4–12 months for visitors from low-endemic areas to high-endemic countries, and 3–5 years or permanently for donors with a history of residency in an endemic area. However, this deferral policy leads to an extensive loss of blood donations; for this reason screening tests have been introduced in a number of countries [12]. Screening of blood donors is routinely made by the microscopic examination of blood using thick/thin blood films, but its sensitivity decreases in parallel with low parasite densities found in the blood of infected asymptomatic carriers. In most situations it is not sufficiently sensitive for blood bank screening. Therefore, several methods can be used alternatively including serological immunoassays [18, 19], antigen-based rapid diagnostic tests and molecular amplification methods [20, 21]. Also, administration of antimalarials to all transfusion recipients may help to prevent transmission [3].

Transfusion-Transmitted Babesiosis (TTB)

Babesiosis is a zoonotic disease caused by protozoa of the genus *Babesia*, which parasitize erythrocytes of both domestic animals and human. Most human infections have been acquired in temperate regions of the United States and Europe. In

Europe, *Babesia divergens* and *Babesia bovis* are cattle strains that cause a severe and often fatal disease, particularly in people who have undergone splenectomy, whereas *Babesia microti* (*B. microti*) in North America, infects patients with intact spleens and produces a milder and often asymptomatic disease [22]. *Babesia duncani*, formerly termed WA-1 that affects immune competent patients is described in Washington State and California and it was reported to be associated with TTB [23, 24]. *Babesia* parasites are transmitted by the bite of Ixodid ticks that inject sporozoites into the bloodstream of their hosts. The sporozoites enter the host erythrocytes; undergo asexual budding into 4 merozoites, followed by perforation of the Red Blood Cell (RBC) membrane, leading to hemolysis. The merozoites then infect other RBCs; the parasites become trophozoites and can divide by binary fission, creating the ring forms and tetrads seen in erythrocytes in stained blood smears [22].

Another mode of transmission to humans is via blood transfusion; following the transfusion of infected packed red cells [25], glycerol cryopreserved red cell units [26] and platelet concentrates that contain residual erythrocytes (up to 0.5 ml) routinely found in platelet bags or extracellular parasites [27]. The parasites can remain viable under blood bank conditions, at 4°C for up to 35 days [28]. TTB has a longer incubation period (6-9 weeks) compared with 1-4 weeks in naturally acquired illness, depending on the recipient's immune status, the parasite species and/or strain implicated in transmission, and infectious dose [25].

Clinical features of TTB cases range from asymptomatic infection to fulminate disease. These may be malaise, myalgia, nausea, night sweats, chills, fever, weight loss, jaundice, hematuria, mild hepatosplenomegaly, normochromic normocytic anemia, thrombocytopenia, and occasionally leukopenia. In advanced age, HIV, asplenia and immunocompromised patients, the disease fulminates causing severe hemolytic anemia, disseminated intravascular coagulation, acute renal failure, and acute respiratory distress syndrome [29].

The first case of TTB reported in 1980 from Boston, and involved the transmission of *B. microti* to a 70-year-old patient after the transfusion of 20 platelet units [30]. Since that initial report, numerous cases of TTB have been reported with an increasing in number, particularly in the United States [25, 31-33]. Also, Senanayake et al. [34] reported the first human case of babesiosis in Australia after the multiple blood products that the patient received during his admission. Furthermore, there have been two cases of babesiosis in recipients of solid-organ transplants (renal and cardiac) that were not directly attributable to the transplanted organ, but, blood transfusions at the time of transplantation or shortly thereafter were implicated as the source of the *Babesia* infection [35, 36]. The incidence of reported TTB has been estimated at about 1.1 cases per million RBC units distributed for transfusion [25]. However, the actual incidence is expected to be higher because of under-detection and under-reporting of transfusion-associated cases. Several factors likely contribute to the apparent increase in TTB case frequency. Firstly, recipients of blood transfusions increasingly represent in an aged and immunocompromised population, since increasing marrow and solid-organ transplants are performed each year. Secondly, education efforts and published case reports have raised the awareness of TTB, leading to an increased recognition of cases by physicians and hospital transfusion services. Lastly, the geographic range of the parasite is expanding, beyond its historical foci in endemic areas [26].

Several surveys have investigated the presence of *Babesia* antibodies in asymptomatic blood donors. Among donors from highly endemic areas of the northeastern United States, the overall seropositivity for *B. microti* antibodies of approximately 1.1% - 1.4% was reported [37]. Some studies have reported rates as high as 4.3% in Shelter Island, New York [38], 8% in German blood donors [39] and 20.8% in a northern California community [24]. As observed above, the seroprevalence estimates were markedly influenced by geographic variations.

Detection of *Babesia* parasites in donating blood is dependent upon direct identification of intraerythrocytic ring forms or the pathognomonic “Maltese cross” finding of *Babesia* organisms in Wright-or Giemsa-stained blood smears [34]. Due

to morphological similarities with *Plasmodium* species, it is critical to distinguish these two parasitic infections. Thus, serological demonstration of antibodies using IFAT [40] or the detection of *B. microti* antigen by Enzyme-Linked Immuno Sorbent Assay (ELISA) [41] may help to determine the risk of TTB. Alternatively, PCR is considered more sensitive for detecting the presence of circulating parasites and should be used if the clinical suspicion of TTB is high [42, 43]. Donors with a history of babesiosis or laboratory evidence of *Babesia* infection are deferred indefinitely from the blood donation [43].

Transfusion -Transmitted Leishmaniasis (TTL)

Leishmaniasis, a vector-borne parasitic disease, is caused by obligate intracellular protozoa of the genus *Leishmania*. *Leishmania* infection is naturally transmitted by the bite of phlebotomine sandflies, also the parasite can be transmitted through the placenta from mother to fetus, sexual intercourse, blood transfusion and laboratory acquired infections. The infection presents with a wide range of clinical forms. Visceral Leishmaniasis (VL), also known as kala-azar, is the most severe form of the disease, that caused by the *Leishmania donovani* complex, which includes three species: *Leishmania donovani* (*L. donovani*), *L. infantum* and *L. chagasi*. It is characterized by prolonged fever, anemia, weight loss and hepatosplenomegaly that caused by the multiplication of the parasite in the reticulo-endothelial system and if untreated, has a mortality rate of almost 100% [44]. Cutaneous leishmaniasis is caused by *L. tropica* and *L. braziliensis*, it produces skin ulcers on the exposed parts of the body, such as the face, arms and legs, causing serious disability and leaving the patient permanently scarred. The third form is mucocutaneous leishmaniasis or espundia. It can lead to extensive and disfiguring destruction of mucous membranes of the nose, mouth and throat cavities and can involve the cartilages [45].

The development of disease starts with an asymptomatic subclinical period in which parasites may already be circulating in the peripheral blood within large mononuclear cells and polymorphonuclear leukocytes for an undefined period between the bite of sandfly and their final localization to the target

organs. Different reports documented parasitemia in asymptomatic *L. donovani* and *L. tropica* infections [46], in cured *L. braziliensis* infection [47] and in asymptomatic *L. infantum* infection among blood donors from an area of southern France [48]. The duration of asymptomatic parasitemia varies with the infecting species, for *L. donovani* this period varies from 1-14 months [46]. For other species this period varies from 2-8 weeks, although some cases have been reported following a one-year incubation period [47]. The parasitemic individuals usually have a very low parasite density and may serve as a source of TTL. In-vitro studies have clearly shown that viscerotropic *L. tropica* survived as intracellular forms in monocytes for 30 days in unprocessed whole blood kept at 4°C, for five days in the platelet fraction kept at 24°C and for 35 days in the red blood cell fraction frozen with glycerol. Identical experiments with *L. donovani* resulted in comparable survival data [46].

A few cases of transfusion-associated VL with clinical features and outcome similar to those of the natural infection have been reported in endemic and non-endemic areas. The first report of TTL came from China in 1948. The blood was donated from asymptomatic infected mother to two daughters (4 and 6 years old) as a prophylaxis for measles prevention. Both the daughters were developed kala-azar 9 and 10 months after receiving the transfusion, respectively [49]. Some reports of TTL have been detected from France, Sweden, Belgium, United Kingdom and India [50-55]. The time between the transfusions of the *Leishmania* infected blood and first clinical manifestation was variable in these reports; and the mean incubation period was 7.4 months. In all patients, fever was the absolute symptom, present in all patients following hepatosplenomegaly (82%), isolated splenomegaly and severe anemia (9% each). In addition, *Leishmania* transmission by blood has been demonstrated experimentally from infected patients to experimental animal [56]. In a veterinary report, three cases of *L. donovani* transmission to anemic dogs through blood transfusion were reported [57].

Donors should be questioned regarding recent cases of VL in the household; in cases where this had occurred, they could

be temporarily deferred. Regular screening could be proposed in areas where VL is more prevalent, discarding seropositive donors. Usually, screening of donated blood is performed through immunological methods or PCR as microscopic examination is not a sensitive tool due to the low level of parasitemia in immunocompetent individuals with VL. *Leishmania* infection was detected in blood donors from a Spanish endemic area using various methods; 2.4% were positive by ELISA, 7.6% by western blot, 22.1% by amplification of *L. infantum* DNA used nested-PCR, 22.3% by delayed-type hypersensitivity test and 4.5% by cultures [58]. Moreover, the prevalence rate of *L. chagasi* infection in a cross-sectional study sets up in Sabará country, southeastern Brazil was 10.7%, by using IFAT and strip test [59]. Another strategy to protect recipients against TTL comprises blood treatment with psoralens or riboflavins [60]. Because white blood cells are the parasite target, the preparation blood products using leukoreduction by filtration minimizes the potential risk of *Leishmania* transmission [48]. The use of such blood protection procedures should be considered mandatory in the case of immune suppressed recipients.

Transfusion -Transmitted Chagas' Disease (TT-CD)

Chagas' disease is a parasitic infectious disease caused by the flagellate protozoan, *Trypanosoma cruzi* (*T. cruzi*). The disease is widespread in Latin America. The natural infection is transmitted by the contact of broken human skin with metacyclic trypomastigotes present in contaminated feces of blood-sucking triatomine insect (reduviid bug). *T. cruzi* may also be transmitted by transfusion of infected blood, via the placenta or by breastfeeding for newborn infants, organ transplantation, laboratory accidents or ingestion of contaminated food [61]. The parasite has been shown to remain viable at 4°C in store whole blood for 7 days, in platelets for 4 days, and in frozen plasma components for 24 hours or less. Although frozen strains are viable in cryopreserved vials, there are no clear evidences of transmission through frozen-thawed blood components. The probability of transmission of the parasite per contaminated donation may be increased by

separation of the blood into components [62]. The incubation period of acute Chagas' disease following an infected blood unit varies from 20 to 40 days and approximately 20% of infected recipients are completely asymptomatic, raising no suspicion of the diagnosis [63].

Chagas' disease has an acute stage, typically asymptomatic or with mild symptoms (fever, malaise, lymphadenopathy or hepato- and splenomegaly) during the first 6-8 weeks after infection. If not treated, infection is lifelong with low-level, intermittent parasitemia. The majority of infected persons remain asymptomatic in the chronic indeterminate phase with intracellular invasion by the organism. These individuals are potentially at risk of transmitting the parasite via transfusion [64].

Transmission of *T. cruzi* by blood transfusion was first suggested by Mazza in Argentina in 1936, but the first two cases of TT-CD were reported in 1952 in Sao Paulo, Brazil. Further cases have been described in all Latin American countries in the following years; it was estimated that about 10,000 new cases of *T. cruzi* infection occurred per year in Brazil through transfusional transmission [65]. A few cases of infection mediated by transfusion have been documented in the United States and Canada during the past years; all occurred in immunocompromised recipients and involved *T. cruzi* infected donors from *T. cruzi*-endemic areas [66-68]. It was believed that a substantially larger number of such cases have occurred because of the large number of immigrants from endemic areas of Latin America, but the actual number of cases has not been recognized because the newly infected recipients were immunocompetent and presented with relatively few signs and symptoms.

The risk of acquiring TT-CD from seropositive donors ranges from 12% to 48% in endemic areas and 13–23% in nonendemic areas depending on several factors; immune status of the recipient, the concentration of parasites in the donor's blood, the blood component transfused, amount of transfused blood and the parasite strain [69]. It has been estimated that the seropositivity of infected donors was much lower in the USA (0.01%) than in certain Bolivian cities (60%) [70,71]. Along the

same lines, Assal and Corbi [72] screened blood donors in the 17 French blood centers by two different ELISA techniques and found that the estimated prevalence of anti-*T. cruzi* antibodies was one in 32,800 donations (0.85%).

To alleviate the risk TT-CD, all blood donors should be screened for *T. cruzi* infection. Acute *T. cruzi* infection is usually diagnosed by observation of the trypomastigotes on a Wright / or Giemsa stained blood smear. However, in the chronic stage the circulating level of trypomastigotes is too low to be detected; therefore serological screening tests have become an alternative to detect specific antibodies to *T. cruzi* antigens in silent, chronic carriers of *T. cruzi*-infection [73-75]. Moreover, PCR techniques may be useful for the screening of blood donors as it able to detect one parasite in 20 ml of blood [76].

TT-CD can be prevented by donor education and identification of putatively infectious blood donors by risk history. Pathogen inactivation methods such as chemical treatment of whole blood with crystal violet, platelet inactivation by amotosalen and ultraviolet light (INTERCEPT) or riboflavin and ultraviolet light, and for plasma either INTERCEPT or methylene blue have been proved to be effective [77-79]; all of them acting by irreversible linking to nucleic acids under light action, promoting DNA transcription impairment. As *T. cruzi* is an intracytoplasmatic pathogen then the removal of white blood cells by leukoreduction will indirectly remove this agent. However, leukocyte filters could not promote full protection in animal models and should not be considered as a main prevention strategy [63].

Transfusion-Transmitted Toxoplasmosis (TTT)

Toxoplasmosis is an opportunistic infection caused by the obligate intracellular protozoan; *Toxoplasma gondii* (*T. gondii*). This organism is worldwide in distribution and infects up to one third of humanity [80]. It is found in 2 forms, the actively proliferating tachyzoites are usually seen in the early, more acute phases of the infection and the slowly dividing bradyzoites which form long lived cysts in skeletal muscle and

the central nervous system, probably as a result of the host immune response [81].

T.gondii is found in the blood during the phase of parasitemia early in the acute phase of infection and also in reactivating disseminated cases. If *T. gondii* present in blood at the time of donation, it could survive in citrated whole blood for up to 50 days at 4°C, thus refrigeration of blood units during storage cannot prevent transmission [82]. Experimentally, blood from humans collected into heparin or citrate was inoculated with *Toxoplasma* organisms. After storage at 4 °C up to 28 days, samples were injected into the ear veins of rabbits. The test rabbits developed toxoplasmosis. Similar results were obtained by transfusing rabbits with blood obtained from rabbits subcutaneously injected with *Toxoplasma* organisms [83].

With the availability of advanced medical facilities for bone marrow, renal and hepatic transplantation, cardiac surgery, children with thalassemia, sickle cell anemia and aplastic anemia, and the high prevalence of the HIV positive immunocompromised population, the need for *Toxoplasma* seronegative blood is crucial for reducing the impact of this infection [84]. Many epidemiological studies screened the blood donors for toxoplasmosis. The prevalence of asymptomatic human infection as reflected by seropositivity for IgG/ or IgM anti- *T. gondii* antibodies varies widely among different regions of the globe from a low of 4.1% in Thailand [85] to 75% in Brazil [86]. These variations in *T. gondii* positivity might be attributed to the differences in the characteristics of the blood donors, differences in virulence of strains of *T. gondii* prevalent in different areas of the world, host immune function, sociocultural habits, geographic and environmental factors, the state of hygiene in the society and routes of transmission in the population studied [87].

Screening of blood donors has been based mainly on serological tests including, ELISA, IFAT and IHAT [84, 88, 89] for detection of anti-*Toxoplasma* IgG and /or IgM antibodies in serum. However, these antibodies may not be produced until after several weeks of parasitemia [90]. Therefore the risk of TTT may be undetected because the donor might test negative during the active phase of *T.gondii* infection. For these reasons,

molecular screening have been used for specific detection of active *T.gondii* infection [91] in asymptomatic blood donors and should be carried out on the blood being transfused to immunocompromised patients, pregnant women and in intrauterine and neonatal transfusion. Using leucocyte-reduced blood and providing packed cell or platelet transfusions to the immunocompromised recipients may be effective to reduce the high risk of TTT [92].

Transfusion-Transmitted Microfilariasis

Filariasis is a parasitic disease that is caused by threadlike nematodes. It is transmitted from host to host by blood-feeding arthropods, including mosquitoes. The blood filarial nematodes that may be transmitted by blood transfusions are divided into three groups according to the niche within the body they occupy. Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* which occupy the lymphatic system, and in chronic cases these worms lead to the elephantiasis disease. Subcutaneous filariasis is caused by *Loa loa* (the eye worm) which occupy the subcutaneous and fat layers of the skin. Serous cavity filariasis is caused by the worms *Mansonella perstans* and *Mansonella ozzardi*, which occupy the serous cavity of the abdomen. In all species, sexually mature female worms release microfilariae, which are pre-larval stages into the bloodstream. If the blood from microfilaremic individuals is transfused, the transfused microfilariae may persist in the recipient's circulation for up to 3 years [93]. *Microfilaria* may survive in refrigerated blood units for 2-3 weeks. Transfusion-transmitted microfilaremia is self limited because transfused microfilariae do not develop into adult filarial worms. It is possible that adult worm may be present in blood collected from an asymptomatic blood donor but, the possibility of its transmission is remote because it cannot pass through routine blood transfusion. In both instances, the recipients may not suffer from clinical filariasis, but they usually develop post transfusion allergic reactions to dying microfilariae [94].

The association of post-transfusion reactions and filarial infections has been reported in sporadic cases. The first warning

of possible problematic transfusional filariasis in a nonendemic area by Weller et al. [95] who reported on tourism-acquired *Mansonella ozzardi* microfilaraemia from a blood donor. Also, Bregani et al. [94] described a case of post-transfusional *Mansonella perstans* microfilariasis in an infant from an endemic zone in south Chad. This infant with malaria-related severe anemia received blood from his parent carrying *Mansonella perstans* microfilariae. The patient's follow-up showed a progressive clearance of microfilariae from the blood without any occurrence of symptoms or eosinophilia for 4 months. A Nigeria based study evaluated blood-borne parasites in prospective blood donors; in addition to malaria, there was prevalence of 1.3% *Loa loa*, 15.6% *Mansonella perstans*, and 0.2% coinfection of both parasites [96]. According to another study, 1% in Nigerian blood donors had microfilaria parasitaemia (*Mansonella perstans*) [97]. Moreover, Choudhury et al. [98] reported that filarial antibody was detected in 55.3% of Indian blood donors, but microfilaria was detected in 8.5%.

In endemic areas, all donor blood should be screened for filarial parasites by concentration technique, filarial antigen / antibody detection (both by ELISA) and if possible the combined diethylcarbamazine plus mebendazole was recommended for treatment [98]. Blood donors with an active history of filarial infection should be deferred from donating blood.

Conclusion

Blood donation policies should incorporate screening of blood and blood products for transfusion transmitted parasitic infections, especially in immunocompromised patients, neonates and pregnant women. Moreover, molecular screening should be combined with serology for decreasing the residual risk.

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