

Transfusion–Transmitted Parasites

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ABBREVIATIONS: CDC = Centers for Disease Control; ELISA = enzyme linked immunosorbent assay; HGE = human granulocytic ehrlichiosis; HME = human monocytic ehrlichiosis; HRP-2 = histidine-rich protein 2; IFA = indirect fluorescent antibody; PCR = polymerase chain reaction; pLDH = lactate dehydrogenase; RBC = red blood cells.

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The incidence of transfusion-transmitted parasitic infections is even lower when compared to that of bacterial and viral contamination; but nonetheless, these organisms may pose a significant risk of illness, especially in immunocompromised recipients. Unlike bacterial contamination, which can occur at multiple points during the collection and transfusion process, transfusion-transmitted parasitic diseases originate from the donor. The most common parasitic organisms implicated in transfusion-transmitted infections are: *Plasmodium* sp., the causative agent of malaria; *Trypanosoma cruzi*, the agent responsible for Chagas' disease; and *Babesia microti*, the etiologic agent of babesiosis. These organisms are gain-

ing prominence due to global travel and increased exposure to habitats where insect vectors reside. Population migration from endemic countries to the U.S. also contributes to the recent increases in parasite transmission.¹ In this article we will discuss the organisms and their prevalence as well as detection methods as they relate to transfusion transmission.

Despite the fact that organisms such as *Ehrlichia* are bacteria, they will be discussed in this section because they are obligate intracellular organisms that can be transmitted via cells present in a transfusion. They are not normal flora or environmental contaminants – they are primarily insect-transmitted, as are the parasites discussed. These organisms, which have the potential to be transfusion-transmitted, but have limited evidence documenting transmission via blood components, merit discussion.

MALARIA

Transmission of malaria via blood transfusion is relatively uncommon in the U.S. Over the past 30 years the incidence has decreased and is now estimated at less than one case/million units.^{2,3} In most cases, the implicated donor had visited an endemic area or had emigrated from such an area. There were 1,402 cases of malaria reported in the U.S. in 2000. Two of the cases were congenital and two were blood related.⁴

A comprehensive review of transfusion-transmitted malaria identified 93 cases that had been reported to the Centers for Disease Control (CDC) between 1963 and 1999.² Of these patients, 11% (10/93) died. Sixty-five percent of all cases came from the following areas in order of number of cases—New York City (NYC), Texas, California, New York State (excluding NYC), Pennsylvania, and Florida. During this period, the total number of cases caused by each species was: *P. vivax* – 25, *P. malaria* – 25, *P. ovale* – 5, and *P. falciparum* – 33, with the remainder either reported as a mixed infection or as *Plasmodium* sp.² Table 1 gives the distribution of cases by decade. The percentage of cases due to *P. falciparum* increased from 47% during 1963–69 to 71% in the period 1990–99. This is probably attributable to increased immigration from areas such as sub-Saharan Africa where *P. falciparum* is the primary species and where drug resistant strains have developed. Most cases were associated with trans-

fusion of erythrocytes, but approximately 6% were linked to platelet transfusion.² This is most likely due to the presence of residual red blood cells (RBC) in the platelet concentrates.

At the present time, there are no approved methods to screen blood donors for malaria in either the U.S. or Canada. Medical and travel history elicited through the questions asked of the donor prior to donation is the only way to determine if the donor poses a risk of transmitting malaria (Table 2). The questions asked however, have not proven to be totally effective in preventing transmission. In one study it was determined that 62% of the accepted donors who were implicated in transfusion-transmitted malaria should have been excluded based on the donor guidelines in place during the time periods studied.² In the remainder of the cases, however, the donor had returned from travel to endemic areas or had been in the U.S. longer than the minimum deferral period.

All three cases of transfusion-transmitted malaria in Canada during 1994–99 were due to *P. falciparum*.⁵ Two of the cases were due to contaminated RBC and one due to contaminated platelets. The infections were detected in recipients by a positive blood smear. All implicated donors had met screening guidelines for donation, yet two of

the three donors had a positive smear.⁵ As a result of these cases, Canadian guidelines were changed in 1995 to permanently defer a person who has a past history of diagnosis of and/or treatment for malaria. Conversely, a review of three U.S. cases of transfusion-transmitted malaria during 1996–1998 showed that donors had been accepted for donation based on their responses to questions, but in actuality they did not meet guidelines in place at the time of donation.⁶

The problem of individuals who meet donor guidelines for travel, yet become implicated in transfusion transmitted malaria may be due to low levels of ongoing parasitemia. Persons in highly malarious areas may have persistent asymptomatic parasitemia due to an acquired immunity or inadequate treatment. In most instances, parasitemia due to *P. falciparum* is eliminated in two years, while *P. vivax* and *P. ovale* parasitemia may persist three to five years. *P. malariae* has recurred after 40 years.⁷ In one report there was a 15-year gap between exposure to malaria and a blood donation that transmitted *P. falciparum*.²

Aside from donor screening, other options to identify infected donors include use of tests primarily designed to detect parasites in symptomatic individuals or antibody screening tests. Tests for detection of parasites include:

thick/thin blood smears, fluorescent staining techniques, tests for circulating malarial antigen, or polymerase chain reaction (PCR) for detecting malarial DNA.^{8,9,10}

Examination of thick blood smears is not cost effective for screening large numbers of donors, nor is it sensitive enough (limit of detection is approximately ten organisms/μL) to detect low levels of parasitemia that might exist in donors. Less than 50% of implicated donors in studies had positive smears, which is probably related to low levels of circulating parasites.^{2,6} Fluorescent stains such as acridine orange that stain nucleic acids can also be used for examination of a thick film for parasites or in systems that employ capillary tubes filled with blood (QBC™). Commercial systems, however require expensive equipment and do not allow for retention of the specimen.⁸ With these systems, the species identification must be done using a thin blood smear.

In recent years, there has been increased use of dipstick tests for rapid screening/diagnosis of acute malaria in rural endemic areas. These tests which use monoclonal antibody fixed to nitrocellulose strips detect circulating *P. falciparum* histidine-rich protein 2 (HRP-2) antigen or *Plasmodium* lactate dehydrogenase (pLDH).^{9,10} The level of detection required in acute cases is approximately 500 parasites / μL, which may be greater than the level of circulating parasites in an asymptomatic blood donor.⁹

On the other hand, serologic tests identify antibody positive individuals, but do not indicate parasitemia because antibody levels can remain elevated up to ten years after infection. In general, when used in a donor population with a low prevalence of malaria, antibody

Table 1. Number of cases of transfusion transmitted malaria 1963-1999

Years	<i>P. vivax</i>	<i>P. ovale</i>	<i>P. malariae</i>	<i>P. falciparum</i>	Other*
1963-69	2	1	5	8	1
1970-79	14	1	8	10	1
1980-89	8	2	10	5	3
1990-99	1	1	2	10	—

*Mixed infections or *Plasmodium* sp.

tests have poor positive predictive value. Laboratories in France, however, use an indirect fluorescent antibody (IFA) method to detect antibodies to *Plasmodium* sp. in at-risk donors. There has not been a reported case of transfusion-transmitted malaria since the test was instituted in 1994.⁷ One study evaluating an enzyme linked immunosorbent assay (ELISA) test that used *P. falciparum* antigen indicated that the test may be sensitive and specific enough to screen for antibodies in at-risk donors whose medical history indicated they might have been exposed to malaria.¹¹

Silvie used a combination of a *P. falciparum* HRP-2 antigen test and an enzyme immunoassay (EIA) antibody test to test plasma specimens from patients with confirmed *P. falciparum* infection.⁷ Results in patients with confirmed malarial infection indicated that the combination of tests detected more positives than either test alone. Again, there is concern whether even this combination can detect the very low levels of parasitemia often seen in donors; especially since small amounts of blood are used.⁷

PCR methods to detect plasmodium DNA or RNA may be the most sensitive (one parasite/50 µL) and specific but are technically demanding and the most expensive. One study, however, has indicated even this method may not be able to detect organisms below the level of 10 parasites/10µL blood.¹¹

As with bacterial contamination, the best approach may be to find agents that will inactivate the parasite in donor blood. A report describing a recent pathogen inactivation system for bacteria (INTERCEPT™) that uses a psoralen-type compound and ultraviolet light showed that *P. falciparum* is susceptible to inactivation with this system.¹²

CHAGAS' DISEASE (AMERICAN TRYPANOSOMIASIS)

Chagas' disease, caused by the hemoflagellate, *Trypanosoma cruzi* is endemic in Central and South America and parts of Mexico. It is transmitted by an insect vector commonly called the 'kissing bug' (a member of the *Reduviidae* family). In order to understand why there is potential risk of transfusion transmission, the life cycle of the organism needs to be reviewed. The disease is initially acquired when the infective trypomastigote stage is deposited on human skin in the insect's feces after it takes a blood meal. The organism enters the human circulation through a break in the skin. The acute stage of the illness is short-lived and characterized by fever, anorexia, hepatosplenomegaly, and circulation of the trypomastigote form in blood. About 10% to 30% of those infected will develop chronic trypanosomiasis with intracellular invasion by the organism.¹³ This intracellular amastigote stage is responsible for the chronic form of the disease which is characterized by neurological disorders, progressive damage to heart muscle – resulting in cardiomyopathy, or damage to the digestive system – resulting in megacolon or megaeosophagus. During the chronic stage infective trypomastigotes circulate in low numbers in the individual's blood and make the blood potentially capable of transmitting the disease by transfusion.

In endemic areas the seroprevalence of the disease varies from less than 1% to 62% (depending on the country) with estimates of 16 to 18 million persons infected overall.¹⁴⁻¹⁷ Blood donors in endemic areas are commonly tested for antibodies before donation and the risk of acquiring transfusion-transmitted Chagas' disease from seropositive donors in endemic area ranges from 12% to 48%.^{13,15,18}

Table 2. Sample donor questions related to risk of parasitic infection

Question	Action
Have you ever had: malaria? Chagas' disease? babesiosis?	Follow up questions to determine how long ago and treatment. Indefinite deferral Indefinite deferral
In the past three years have you: traveled outside the U.S.? resided in another country?	Follow up questions to assess risk of exposure to malaria or Chagas': country(ies) visited, length of time, rural or urban area return date to U.S.
Have you ever had chest pain, heart disease or lung disease?	May be indicative of symptoms of chronic Chagas' disease

Transfusion transmission is the second most common method of acquiring the disease, followed by transplant-transmitted and finally transplacental (congenital). There have been four reported cases of transfusion-transmitted Chagas' disease in the U.S. and two in Canada, with the majority due to *T. cruzi* contaminated platelets.¹⁹ The recipients were all immunocompromised and all but one of the donors was from a country endemic for *T. cruzi*.^{19,20} In one case the donor, who had emigrated to the U.S. 33 years ago, demonstrated circulating trypomastigotes.¹⁹

Transmission by solid organ transplantation (especially renal transplant) is also common in Latin American countries and has now been documented in the U.S.²¹⁻²³ Three individuals, all of whom had received organs from same donor, developed Chagas' disease including the presence of circulating trypomastigotes.²³

Despite the few documented cases of transfusion-transmitted *T. cruzi* infection, there is concern about the safety of the U.S. blood supply because of increased immigration from endemic areas. It is estimated that 25,000 to 100,000 Latin American immigrants in the U.S. may be infected with *T. cruzi*.²⁴ In addition, trypomastigotes have been shown to remain viable in stored whole blood for seven days, in platelets for four days, and in RBCs for two days with PCR testing for *T. cruzi* DNA remaining positive throughout the storage of the units.²⁵

Several studies involving blood donors or recipients of blood donations have been carried out to determine risk status and/or seroprevalence in the U.S.^{17,26-29} In one study, donors in the American Red Cross Southwest region were tested for antibody to *T. cruzi* using a screening test and repeatedly reactive results were confirmed using recombinant immunoprecipitation assays. There was a confirmed positive rate of 1 in 33,000 (0.003%).¹⁷

Leiby and colleagues tested donors in Los Angeles and Miami from 1994-98.^{20,29} To establish risk status, donors were first asked a question about residence in, or travel to, a country where Chagas' disease is endemic. Testing of plasma samples from those who responded 'yes' gave an overall confirmed seroprevalence of 0.14%. The seroprevalence of Miami donors stayed relatively constant - 0.09% - during the study period. In contrast, seroprevalence of Los Angeles donors increased from 0.15% to 0.19% during the last two years. This approximates to 1 in 7500 donors who were seropositive in Los Angeles, and 1 in 9000 donors in Miami.²⁰

Look back studies of donors who tested positive showed that no recipient of blood products from these donors became seropositive for antibodies to *T. cruzi*.²⁰ Another large look back study involving more than 11,000 cardiac surgery patients who received blood showed that only six recipients had antibody to *T. cruzi* present and all had acquired the infection prior to transfusion.³⁰ Despite these figures, the frequency of transfusion-transmitted *T. cruzi* is most likely underestimated due to the mild acute symptoms, long interval until chronic symptoms develop, and lack of testing.²⁰

Acute infection is usually diagnosed by observation of the trypomastigotes on a Wright-stained blood smear. However, in the chronic stage the circulating level of trypomastigotes is too low to be detected and therefore seropositivity is used as evidence of infection. Serologic tests using ELISA methodology are sensitive and specific in detecting parasitemia when seroprevalence of the organism is relatively high but they cannot readily distinguish between acute and chronic infection.¹⁷ In non-endemic areas such as the U.S., the positive predictive value of the test is poor.

Another problem with current serologic tests is that the antigens used are derived from whole organisms and some antigens may be shared with other parasites such as *Leishmania* sp. This yields cross-reactions and false positive results, which may be of more concern in areas such as South and Central America where leishmaniasis is also endemic. A serologic test using four recombinant *T. cruzi* antigens was evaluated and showed greater than 99% sensitivity, greater than 98% specificity and that it could be used in blood donor screening.³¹

In endemic countries gentian violet (crystal violet) is used to inactivate the organisms.³² Gentian violet with or without ascorbic acid is added to the blood unit. The reaction of the compound when exposed to light produces a superoxide ion, which further releases products that will kill the protozoan.¹⁴ Use of this product does not appear to affect metabolism or preservation of red cells.

Currently in the U.S., aside from donor questions that may defer at-risk donors, there is no way to identify at-risk donors or prevent transmission. There is no policy requiring serologic testing of donors for antibodies to *T. cruzi*. Although there are two EIA kits available in the U.S., neither is licensed for screening blood donors. PCR, which is not available for general testing, may someday be used to detect circulating antigens in at-risk donors.

BABESIOSIS

Babesiosis, an arthropod transmitted disease, is endemic in the Northeast (New York, Connecticut, Massachusetts) and parts of the upper Midwest including Minnesota and Wisconsin. After malaria, it is the most common transfusion-transmitted parasitic disease.^{33,34} It is an intraerythrocytic parasite that like malaria, can be transmitted not only by RBC transfusion but also by the few RBC present in a unit of platelets.³³ The organisms usually associated with human infection, *Babesia microti* and *B. divergens*, are transmitted by the bite of a tick (*Ixodes* sp.). In the last five years, WA1-type and MO1-type *Babesia* sp. were also identified as etiologic agents of babesiosis and the WA1-type has been linked to transfusion-transmitted babesiosis.³⁵⁻³⁷ Although over 30 cases of transfusion-transmitted babesiosis have been reported in the U.S. since 1979, the overall incidence is less than one per one million units of blood.³⁸ However in endemic areas the risk is higher—up to six cases/million units.³⁹ Reports of seroprevalence from areas such as New York and Connecticut vary widely from 0.6% to greater than 6.9% of donors positive for antibodies in endemic areas to less than 2% positive in non-endemic areas.^{33,39-41}

Most tick-caused infections are asymptomatic or exhibit non-specific symptoms such as fever, fatigue, chills, and anorexia. In elderly, asplenic, or immunocompromised patients a severe malaria-like illness with hemoglobinuria, hemolytic anemia, and renal failure can occur. Asymptomatic parasitemia in untreated patients persists for at least a year.⁴² *B. microti* organisms can survive at 4 °C and at 25 °C. One study demonstrated that organisms in blood stored at 4 °C were viable at day 17; those in blood held at 25 °C were viable for three days.⁴³ Results from a study that monitored *Babesia*-infected subjects every three months for up to 27 months demonstrated organisms in the circulation (blood smear) for approximately a week but PCR assays for circulating babesial DNA were positive for 82 days.⁴²

In a cluster of incidents in New York, five of eight patients who received infected blood became infected.^{39,44} Two recipients, each a chronically transfused patient, were infected by single donor and developed smear positive evidence of infection. The third case in the cluster involved a single donor who infected six patients from the same unit, four of the infected were neonates who received aliquots of blood from the unit. A blood smear from the unit demonstrated a single infected cell.⁴⁴ Transfusion-transmitted cases have also been reported in transplant patients who receive large quantities of blood products.^{45,46} Just recently, a case of transfusion-transmitted babesiosis was identified in Canada.⁴⁷ The im-

plicated donor had a positive blood smear and a 1:1024 antibody titer. A case from the upper Midwest involved a donor who infected multiple individuals over a six-month period through blood donations. Four of seven individuals who received components from this donor became infected. A review of donor's medical history showed that he had most likely been parasitemic for at least ten months.⁴⁸

As with malaria and Chagas' disease, there are no approved serological tests for donor screening and donor questions may not always elicit correct history since the infection is often asymptomatic.^{40,42,48} Current diagnostic tests for babesiosis are not suited to large-scale donor screening. Examination of peripheral blood smears, indirect fluorescent antibody tests, PCR for detection of *B. microti* specific targets, or inoculation of animals are slow, costly, and/or labor-intensive methods. Efforts are underway to develop EIA tests for detection of babesial antibodies that might be suitable for donor screening.⁴⁹ Methods for pathogen inactivation to prevent transmission of babesiosis have been reported.⁵⁰ At the present time, however, any donor with a history of babesiosis is indefinitely deferred because of the possibility of persistent parasitemia.

EHRlichiosis

There are two human ehrlichioses – human monocytic ehrlichiosis (HME) caused by *Ehrlichia chaffeensis* and human granulocytic ehrlichiosis (HGE) caused by organisms that resemble *E. equi* and *Anaplasma phagocytophila* (formerly *E. phagocytophila*). The human ehrlichioses are characterized by clinical symptoms that are similar to Lyme disease and Rocky Mountain spotted fever. One distinguishing factor, however, is the presence of intracytoplasmic inclusions in white blood cells. These morulae, as they are called, are actually intracellular bacterial microcolonies that can be seen on a Wright's stained blood smear.

Although there are several cases of HGE and HME linked to transplant transmission, only one case of HGE has been linked to transfusion transmission.⁵¹⁻⁵⁵ However, *E. chaffeensis* can remain viable in blood for up to 11 days and *A. phagocytophila* for up to 18 days.^{56,57} A seroprevalence study of antibodies using an IFA technique to detect antibodies to *A. phagocytophila* in random blood donors was conducted in Wisconsin and Connecticut. Seropositivity ranged from 0.5% in Wisconsin donors to 3.5% in Connecticut donors.⁴¹ At this time there are no screening questions asked of the blood donor to determine at-risk status for ehrlichiosis.

OTHER POTENTIAL TRANSFUSION-TRANSMITTED DISEASES

Ticks are effective vectors of disease and are responsible for transmission of a number of viral, spirochetal, and rickettsial agents that cause serious diseases.^{33,34} In addition to *B. microti*, and the etiologic agents of ehrlichiosis, ticks can transmit the causative agents of Lyme disease and the spotted fever group, all of which have the potential to be transfusion-transmitted.

Lyme disease, caused by spirochete *Borrelia burgdorferi*, can be transmitted concurrently with *B. microti* or ehrlichiosis by the same insect vector.^{33,34,58} Individuals who show symptoms of one disease often have positive antibody titers to both organisms. Despite the numerous cases of transfusion-transmitted babesiosis, however, there have been no reported cases of transfusion-transmitted Lyme disease. Although *B. burgdorferi* can survive in red cells stored at 4 °C up to a month and in platelets stored at room temperature, it appears to circulate in the blood for a relatively short time.⁵⁹

Rocky Mountain Spotted Fever is caused by the obligate intracellular bacillus *Rickettsia rickettsii*. Despite potential for transfusion transmission, it is not common. There is only a single case of documented transfusion transmission in the late 1970s.⁶⁰ A report concerning 377 donors from a National Guard unit who were exposed to ticks and who developed symptoms of tick-borne illness (Rocky Mountain spotted fever or ehrlichiosis) demonstrated that none of the recipients of components from the 12 confirmed cases developed serologic evidence of exposure.⁶¹

Leishmania donovani, the etiologic agent of visceral leishmaniasis is transmitted by the bite of a sandfly. The organism is an intracellular parasite that is present primarily in cells of the reticuloendothelial tissue and cells of the mononuclear phagocytic system. In endemic areas such as Africa, Asia, and South America there is a relatively high seroprevalence (24% to 43%) of antibodies to the organism. After the 1980s Gulf War, returning military personnel were deferred from donating blood due to fears of possible transfusion-transmission of the organism, as well as from a viscerotropic *L. tropica*.⁶²⁻⁶⁴ Studies in animals have shown that it can be transfusion-transmitted, but documented cases are rare.^{62,65-67} Because the organism is present in circulating phagocytic cells, one study compared the presence of parasite DNA in blood pre- and post-leukodepletion. Results demonstrated that after leukodepletion, there was no parasite DNA present in the blood.⁶⁸

In summary, the transmission of parasitic organisms through transfusion is relatively rare. Of the three major transfusion-transmitted diseases, babesiosis and Chagas' disease pose the greatest threat to donors in the U.S. In both cases, this is due to the increased number of potentially infective donors. There are no serologic tests available to screen donors for any of these organisms and the focus for prevention remains on adherence to donor screening guidelines that address travel history and previous infection with the etiologic agent. One goal is the development of tests that are able to screen for and identify donors potentially infectious for *T. cruzi* or *B. microti*, without causing the deferral of a large number of noninfectious donors or significantly increasing costs. Ideally, methods to inactivate the infectious organism will provide an element of added safety to the blood supply.

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\$6.2 billion immunodiagnostics market. The immunodiagnostics division makes tests that can detect thyroid problems, infertility, tumor markers, infectious disease, and cardiac markers. In an interview with Dow Jones, Prondzynski noted that the deal allows Igen to go forward as its own company with applications such as food testing and defense contracts which held no interest to Roche, while Roche gets full access to Igen's Origen technology, for which it had to pay royalties in the past.

Dade Behring, the largest company in the world solely devoted to clinical diagnostics, today released the findings of a benchmark survey on the diagnostic industry's reputation among U.S. consumers, healthcare professionals, and others. The intent of the summer 2003 survey was to develop further under-

standing of the expectations of consumers and healthcare and industry professionals, so that the industry could address their needs. Among findings, the survey indicated that half of the consumers interviewed (51 percent) consider that the diagnostics industry has a strong impact on the quality of their health care, and more than half (56%) consider that laboratory testing professionals have a "strong impact" on the quality of health care they receive. More than four out of five (84%) say that early-stage testing to assess one's risk of developing a disease is important.

Correlogic Systems, Inc., developer of promising new cancer detection tests that use just a single drop of blood from a patient, has entered into an agreement with Advion BioSciences, a leading provider of mass spectrometry services and

products, to explore the use of Advion's NanoMate™ System as a component of Correlogic's upcoming ovarian cancer clinical trials. Correlogic's test, called Proteome Pattern Blood TestSM, scans a drop of blood for protein patterns generated by a mass spectrometer. In February 2002, Correlogic Systems earned international recognition when its joint research with the National Cancer Institute (NCI) and the U.S. Food and Drug Administration revealed that the Correlogic test successfully detected all of the ovarian cancer patients in a study of 216 women, including cancers that were still in Stage 1. The goal of the Correlogic-Advion research is to determine whether results similar to those published in February 2002 can be replicated on the NanoMate system and employed in the NCI-sponsored clinical trials.

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