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Chapter 48

Other Viral, Bacterial, Parasitic and Prion-Based Infectious Complications

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INTRODUCTION

During the last decade of the 20th century, diagnostic advancements dramatically reduced the transmission of human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) by transfusion. However, simultaneously, the emergence of additional pathogens as potential blood contaminants gained attention. Some of these agents represented newly discovered entities (e.g., severe acute respiratory syndrome [SARS-CoA]). Others were known sources of transfusion complications that expanded into the United States (e.g., Chagas disease). Additionally, some agents demonstrated species jumping from animal hosts to humans (e.g., variant Creutzfeldt-Jakob disease [VCJD], Asian influenza, and West Nile virus). Increasing globalization through commerce, travel, and social interaction requires that many infectious agents, once thought exotic or of remote significance, must be considered as potential blood-component contaminants.[1,2] Alternatively, new information may reduce some concerns. For example, porcine endogenous retrovirus (PERV), previously linked to humans undergoing xenotransplantation, currently appears less threatening.[3]

This chapter addresses agents endemic to the United States and those emerging in other parts of the world that have been transmitted or are theoretically capable of transmission by transfusion, and approaches to reduce the associated risks.

BABESIA

Babesiosis, a zoonosis caused by the rodent-borne piroplasm protozoan, *Babesia microti*, is transmitted by *Ixodes scapularis*, the deer or black-legged tick. *I. scapularis* also transmits the agents of Lyme disease and human granulocyte ehrlichiosis (discussed later).[4–10]

The white-footed mouse (*Peromyscus leucopus*) is the natural reservoir for *B. microti*; once infected, a mouse remains parasitemic indefinitely. *I. scapularis* transmits the piroplasm most frequently during the nymphal stage when the tick is 1.5 mm long. Tick bites, at this stage, often go unnoticed despite the 48- to 72-hour feeding time during which infection occurs.[11] *B. microti* is the agent most frequently associated with clinical illness; MO1-type, WA1-type, and CA1-type also cause clinical disease.[12,13] Endemic areas include coastal and island areas of New England and New York as well as parts of California, Washington, Missouri, Wisconsin, and Minnesota.[6,7,9,12,13] Ticks coinfected with *B. microti* and *Borrelia burgdorferi* (the agent of Lyme disease) transmit *B. microti* less frequently than *B. burgdorferi* because the tick is a less competent host for *B. microti*. The intraerythrocytic localization of *B. microti*, however, favors transfusion transmission of this agent over that of *B. burgdorferi*.[6]

In humans, circulating *B. microti* DNA persists, on average, for 82 days in asymptomatic patients and in those not given specific treatment. Co-infection with Lyme disease does not alter the duration of parasitemia. Parasites circulate for only 16 days in persons who are treated with clindamycin and quinine; alternative antibiotic regimens include atovaquone and azithromycin.[13] Silent *Babesia* infections occur commonly. Some infected individuals develop a chronic carrier state lasing months to years. In others, recrudescence occurs spontaneously or after splenectomy or immunosuppression.[11,14] The parasite retains infectivity in red blood cell (RBC) components at refrigerated or frozen temperatures and in the residual RBCs contained in platelet concentrates stored at room temperature.[5,8]

To date, more than 50 post-transfusion cases involving *B. microti* and other *Babesia* species have been reported.[5,6,9,12,15] Several reports involve donors who transmitted infections through multiple donations given up to 6 months apart.[11,16] The overall risk of acquiring transfusion-associated babesiosis is low, but varies regionally. In Connecticut, 1.9% of seronegative donors became seropositive on a subsequent donation. In another study, 0.9% of donors in endemic and nonendemic areas of Connecticut had confirmatory indirect immunofluorescence assay (IFA)-positive test results for *Babesia* infection; the prevalence rates peaked in July when 1.2% of donors were seropositive.[15] This represents a relatively high potential threat in an endemic area because 8 of 51 recipients became seropositive after receiving blood from IFA-positive blood donors.[17]

Asplenia, older age, immunodeficiency, organ transplantation, and liver disease increase the risk of severe *Babesia* illness. In acute symptomatic cases, fatigue, malaise, weakness, and fever occur in more than 90% of the patients. Shaking chills, diaphoresis, nausea, anorexia, headaches, and myalgia occur frequently. Heart murmurs, hepatomegaly, and splenomegaly are found in 10% to 20% of patients; jaundice occurs less frequently. Renal failure, disseminated intravascular coagulation, and adult respiratory distress syndrome have been reported.[13] The average hemoglobin concentration was 11.3 g/dL in a review of hospitalized patients with community-acquired babesiosis.[4]

Examination of blood smears for intraerythrocytic ring forms and maltese cross–like tetrads (including more than two parasites per cell, contorted shapes, vacuoles, and

budding),[18] antibabesial antibody assays, and polymerase chain reaction (PCR) assays for babesial DNA provide laboratory evidence of infection.[4,14] (Fig. 48–1)

Most transfusion-associated babesia cases involve RBC transfusions, although frozen-deglycerolized RBC and platelet units have been implemented.[5,8,13] Transfusion-acquired cases have an incubation period of 2 to 6.5 weeks.[4,6,8,13,15] Blood-collection agencies ask all prospective donors whether they have ever had babesiosis. Those answering affirmatively are deferred. However, donors are not asked about a recent history of tick bites or geographic residence because of the low predictive value associated with these questions. For example, 0.4% of donors in Connecticut reporting tick bites were seropositive for babesiosis antibodies compared with 0.3% in those not reporting tick bites.[9] Serologic or PCR testing is impractical at this time. The absence of specific interventions to interdict donors capable of transmitting *Babesia* infections relegates clinical awareness and prompt antibiotic therapy as the primary modality for treating this infrequent complication of transfusion therapy.

LYME DISEASE

The *Borrelia burgdorferi* spirochete causes Lyme disease, a tick-borne zoonosis present in mice, squirrels, and other small animals. More than 20,000 human Lyme disease cases occur annually in the United States, although none has been associated with transfusion. Endemic areas include the northeastern, mid-Atlantic, and upper north-central regions of the United States.[10,19]

Ixodes scapularis, the black legged deer tick, transmits *B. burgdorferi* in the northeastern and north-central parts of the United States. *I. pacificus,* the western black-legged tick, transmits the infection along the Pacific Coast. The ticks feed predominantly in the late spring and early summer during their nymphal stage, and Lyme disease usually results from bites of infected nymphs. Deer do not become infected but rather transport and maintain the ticks.[10]

Patients with Lyme disease typically present with a characteristic erythema migrans rash accompanied by fever, malaise, headaches, myalgia, arthralgia, or Bell's palsy. The rash occurs 3 to 30 days after a tick bite. *B. burgdorferi* spirochetes disseminate from the entry site via cutaneous, lymphatic, and blood-borne routes. In one study, spirochetes were isolated from the blood of 44% of patients with symptomatic Lyme disease.[20] *B. burgdorferi* has also been isolated from erythema migrans lesions.

The diagnosis of Lyme disease is based primarily on characteristic symptoms, physical examination findings, and a history of possible tick exposure.[10,20–23] Serologic tests, including enzyme-linked immunoassays and IFA tests, become positive 4 to 6 weeks after infection. Western blot testing is used to confirm the results of reactive screening tests. Treatment with antibiotics clears the infection, but additional treatment to relieve symptoms is prescribed when arthritis persists after two antibiotic courses and for post–Lyme disease syndrome.[20–23]

Despite documentation that the spirochete survives routine RBC and frozen plasma storage, testing blood donors is not under consideration because no reports exist of transfusion-associated Lyme disease.[10] Of note, transfusion of RBCs or platelets collected during peak deer tick activity to 155 patients undergoing cardiothoracic surgery resulted in no serologic or clinical evidence of Lyme disease.[5] Individuals with a history of Lyme disease are accepted as blood donors provided they have been treated and are asymptomatic 12 months after the last dose of antibiotics.

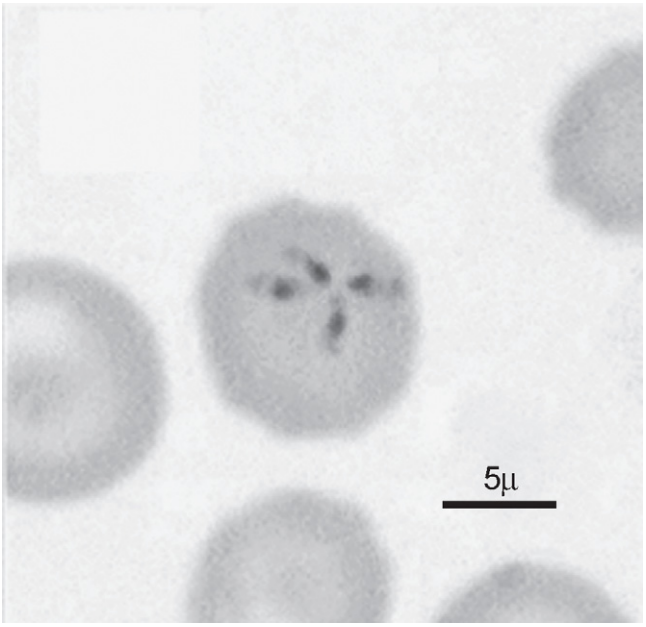

Figure 48–1 *Babesia microti* parasites infect up to 5% of red cells. Although more common in infections with *B. gibsoni* (WA-1) than *B. microti,* tetrad or Maltese cross structures are pathognomonic for *Babesia* infections. They result from budding with four nucleated intraerythrocytic merozoites remaining attached to each other after division. (From Pantanowitz L, Monahan-Earley R, Dvorak A, et al. Morphologic hallmarks of *Babesia*. Transfusion 2002;42:1389.)

TRANSFUSION TRANSMISSION OF OTHER TICK-BORNE PATHOGENS

The rickettsial agents human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE) are intracellular organisms that survive in stored blood and cause mild to severe illnesses.[10] *Ehrlichia chaffeensis* causes HME and is transmitted to humans through the bite of the Lone Star tick (*Amblyomma americanum*) previously infected by contact with deer or possibly dogs.[9,10] Most of the reported cases have occurred in the south-central and southeastern United States.

Anaplasma phagocytophila causes HGE and is related closely to species infecting horses (*Ehrlichia equi)* or ruminants (*Ehrlichia phagocytophila*). This illness occurs predominantly in the northeastern, upper midwestern, and northwestern areas of the United States and is transmitted to humans by *I. scapularis* or *I. pacificus* ticks.[5,9,24–26] Fifty percent of ticks examined in one study in Connecticut were infected with the HGE agent, but none was infected with *E. chaffeensis.*[27]

Patients with HME and HGE present similarly, with fever, headache, myalgia, thrombocytopenia, leukopenia, and elevated liver enzyme concentrations. A rash occurs in one third of patients with HME but in fewer patients with HGE. Membrane-bound intracytoplasmic ehrlichia aggregates, or morulae, are present in monocytes. Complications include respiratory distress, renal failure, neurologic disorders, and disseminated intravascular coagulation. Septicemia, vasculitis,

and thrombotic thrombocytopenic purpura should be considered in the differential diagnosis.[5,10,24,25] Doxycycline is the treatment of choice.

Because ehrlichia are present in blood, transfusion transmission must be considered. One case of transfusion-associated HGE occurred 9 days after an RBC transfusion donated by an asymptomatic donor who had been exposed to extensive deer ticks 2 months previously. The infected RBCs were stored for 30 days before transfusion.[28] An in vitro study suggested that leukocyte reduction may not be completely effective at preventing *E. chaffeensis* transmission because some pathogens are found in the cell free plasma fraction.[29]

An extensive epidemiologic study in Arkansas involving military trainee blood donors who had been exposed to tick bites and unknowingly infected with the agents of ehrlichiosis and Rocky Mountain spotted fever (RMSF) found no clinical illness among the recipients of RBCs and platelets donated by these soldiers. However, possible seroconversion to RMSF occurred in one of the recipients.[30]

A single case report has been published of clinical illness associated with transfusion-transmitted RMSF infection. The donor developed symptoms of RMSF 3 days after donation and died 6 days later. The recipient, who developed fever and headache 6 days after receiving the implicated *Rickettsia rickettsii*–infected transfusion, was notified about the donor's illness and was treated effectively.[10]

Other tick-borne agents implicated in transfusion-associated cases include Colorado tick fever virus and tick-borne encephalitis virus.[10] Although the risk of transfusion transmission of these agents is low, clinical suspicion is important as a mechanism for determining infection by these organisms.

MALARIA

Etiology, Life Cycle, Diagnosis

Malaria is a protozoan disease caused by four species of the genus *Plasmodium: P. falciparum, P. vivax, P. ovale,* and *P. malariae* (Table 48–1). These protozoa are transmitted to humans by the bite of an infected female mosquito of the genus *Anopheles.* Infection of the human host, absent treatment, results in a chronic intraerythrocytic infection that can be transmitted by blood transfusion.

The two-host life cycle of the malaria parasite is diagrammed in Figure 48–2.

Although the signs and symptoms of malaria are variable, most patients are febrile, and many also manifest headache, chills, sweating, nausea, vomiting, diarrhea, back pain, myalgia, and cough. A diagnosis of malaria should be considered for any patient with these symptoms who has a history of travel to a malaria-endemic area or recent blood transfusion. Given the periodic reports of local mosquito-borne transmission, malaria should also be considered in the differential diagnosis of patients who have fever of unknown origin regardless of their travel history.

Malaria is diagnosed microscopically by finding intraerythrocytic parasites on Giemsa-stained peripheral blood smears. Properly prepared thick and thin smears must be examined by trained laboratory personnel to make an accurate laboratory diagnosis. Patients with negative smears suspected of having malaria should have additional smears examined daily for 3 days. PCR can be a useful adjunct in cases in which serial testing of smears yields negative results.

Epidemiology

Malaria is a huge global public health problem with an estimated annual incidence of 300 to 500 million cases and 3 million deaths per year.[31] Malaria-endemic areas include parts of Africa, Asia, Central America, Hispaniola, North America, Oceania, and South America.

During the early part of the 20th century, specifically 1914, an estimated 600,000 cases of malaria occurred in the continental United States, but since the 1940s, improved socioeconomic conditions, water management, vector control, and case management have prevented endemic malaria transmission.[32] Ongoing malaria surveillance in the United States by the Centers for Disease Control and Prevention (CDC) continues to identify cases in immigrants and in residents and travelers to areas of the world where malaria transmission still occurs. Additionally, each year, a few cases are reported that might represent local mosquito-borne transmission.[33] For example, seven cases of locally acquired, mosquito-transmitted *P. vivax* malaria were reported in Palm Beach County, Florida. Multilocus genotyping of the ribosomal RNA of the isolates from the seven patients revealed that they were infected by the same strain.[34] Congenital infections and transfusion-acquired infections round out the sources of malaria cases diagnosed each year in the United States.

Of 1337 cases of malaria in the United States with onset of symptoms in 2002, one was due to transmission of *P. malariae* by blood transfusion.[35] Of 1278 cases reported in 2003, one was due to transmission of *P. falciparum* after a blood transfusion.[36] The overwhelming majority of reported cases in both years were imported (i.e., acquired outside the United States).

Data from 1979 through 1986 showed that cases were more frequently identified in foreign civilians than in U.S. civilians.

Table 48–1 **Transfusion-transmitted Malaria in the United States 1963–2004***

	Plasmodium falciparum	*Plasmodium vivax*	*Plasmodium ovale*	*Plasmodium malariae*
Transfusion-associated cases, 1963–2004 (% of total)	34 (36%)	25 (27%)	5 (5%)	26 (28%)
Average incubation period (days)	17 (range, 8–36)	20 (range, 11–42)	24 (range, 18–30)	51 (range, 8–90)
Relapse	No (manifests clinically within 1 yr)	Yes (usually within 3 yr)	Yes (usually within 3 yr)	Yes (prolonged)

*Three cases were due to mixed infections. The etiologies of two cases were unknown.

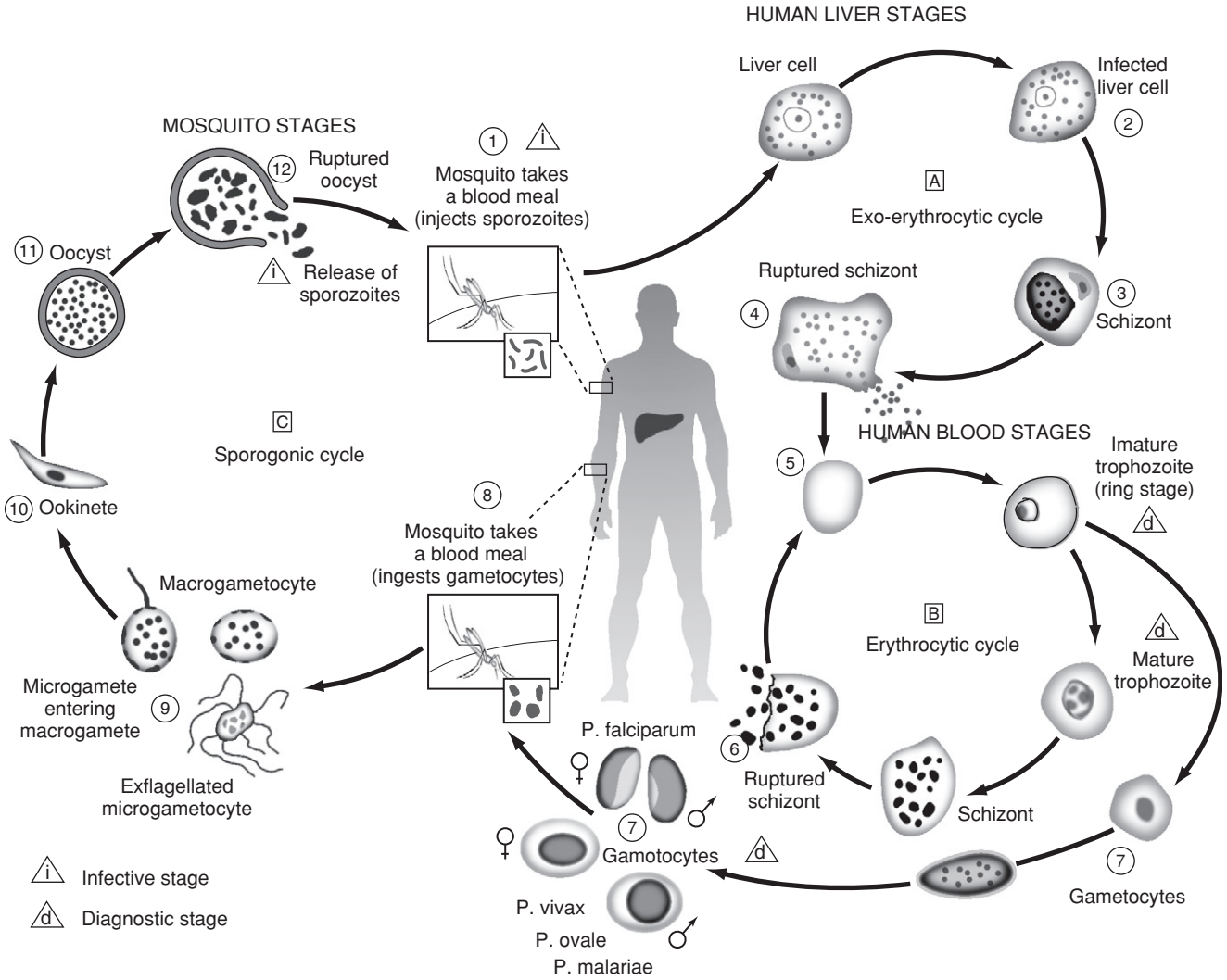

Figure 48–2 The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host. Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites. (Of note, in *Plasmodium vivax* and *P. ovale,* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). Merozoites infect red blood cells. The ring-stage trophozoites mature into schizonts, which rupture, releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). Blood-stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal. The parasites' multiplication in the mosquito is known as the sporogonic cycle. While in the mosquito's stomach, the microgametes penetrate the macrogametes, generating zygotes. The zygotes in turn become motile and elongated (ookinetes) and invade the midgut wall of the mosquito where they develop into oocysts. The oocysts grow, rupture, and release sporozoites, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle. (Figure and legend are taken from the Centers for Disease Control and Prevention [CDC] website http://www.cdc.gov/malaria/biology/life_cycle.htm.)

However, since 1997, the situation has reversed. Cases in United States civilians are now reported at 2.5 to 3 times the number in foreign civilians, most likely due to increased travel by U.S. civilians to endemic areas and decreased immigration since 2001.[36] From 75% to 90% of the cases among U.S. civilian travelers occurs in persons who failed to take prophylactic drugs, had not taken CDC-recommended drugs, or were noncompliant with a recommended drug.

Mosquitoes of the genus *Anopheles*, with few exceptions, feed between dusk and dawn. The exceptions are daytime feedings in densely shaded woodlands or dark interiors of houses or shelters. Therefore, travelers who visit malarial areas during bright daylight hours are at little or no risk for acquiring malaria if they return to a nonmalarial area before dusk.

Transmission by Transfusion and Risk Reduction

Transfusion-transmitted malaria occurs at an estimated rate of 0.25 cases per 1 million blood units collected.[37] Because of this low incidence and the lack of a laboratory test approved by the U.S. Food and Drug Administration (FDA), prevention of transfusion-transmitted malaria continues to depend solely on the donor-deferral guidelines established by the FDA and most recently updated in 1994.[38] Currently, prospective donors who are residents of countries where malaria is not endemic but who have traveled to a malaria-endemic area are temporarily deferred until 1 year after their departure from the endemic area if they have remained free of symptoms suggestive of malaria. Immigrants, refugees, citizens, and residents of malaria-endemic areas are deferred for 3 years after

their departure from the endemic area if they have remained free of symptoms suggestive of malaria. Prospective donors who were diagnosed and treated for malaria are deferred for 3 years after becoming asymptomatic.

Between 1996 and 1998, three cases of post-transfusion malaria due to *P. falciparum,* two of which were fatal,[39] were diagnosed in the United States, prompting a review by the CDC of all cases of transfusion-transmitted malaria reported between 1963 and 1999[40] (see Table 48-1, which has been updated to include reported cases in 2002 and 2003[35,36]). In total, 95 cases (2.5 per year) were reported through 2003. Thirty-four (36%) cases were caused by *P. falciparum*, 25 (27%) by *P. vivax*, 26 (28%) by *P. malariae*, 5 (5%) by *P. ovale*, 3 (3%) by mixed species, and 2 (2%) by an undetermined species. *P. falciparum* cases increased in frequency over the period 1990 to 2003, accounting for 11 (73%) of 15 cases during that interval, compared with 15 (24%) of 62 cases reported between 1970 and 1989. Of 10 (11%) fatal cases overall, 6 were associated with *P. falciparum*, 2 with *P. vivax*, and 2 with *P. malariae*.

The incubation period in these cases ranged from 8 to 90 days, with *P. falciparum* having the shortest time (mean, 17 days; range, 8 to 36 days) and *P. malariae* having the longest (mean, 51 days; range, 8 to 90 days). The period between onset of symptoms and the time of diagnosis ranged from 1 to 180 days, with a median of 10 days. Ninety-four percent of the cases were associated with transfusion of whole blood or RBCs; 6% were platelet-associated.

Implicated donors were defined as having met one or more of the following criteria (1) a blood smear that demonstrated malaria parasites, (2) a positive result on malaria serology, and (3) being the only donor. Ninety-three donors were implicated in the 95 cases. The median number of donors per case was seven (range, 1 to 192). Donors were overwhelmingly male (90%) and ranged in age from 19 to 59 years (median, 27 years). Foreign-born donors accounted for 60% (64% of those from Africa); 40% were born in the United States.

Of 60 donors implicated in the cases for which epidemiologic follow-up was complete, serology was the most effective tool for identifying transmitting donors (73%); only 10% were identified by a positive blood smear. Serology and blood smear were both positive in 15%, and 3% were implicated as the only donor to a case.

Analysis of all cases using current donor deferral guidelines revealed that 23 (24%) cases occurred despite proper application of the guidelines. When reviewed against the guidelines in place at the time they occurred, 3 cases could not be evaluated because their dates of onset were before 1970 when guidelines were vague; 18 of the remaining 20 cases would still have occurred, but 2 would have been prevented if then-current guidelines had been applied properly. Not surprisingly, most (65%) of the cases that occurred despite following guidelines were caused by *P. malariae*.

The continued occurrence of cases in the face of current history questions highlights the reality that malaria risk from transfusion, although low, cannot be fully prevented by questioning of donors. Although the deferral guidelines currently in place are based on the biology of the four species of *Plasmodia* that cause malaria, they represent a balance struck between maximizing safety and minimizing donor loss. *P. vivax* and *P. ovale*, species that give rise to relapsing infections, rarely persist longer than 3 years.[42] However, some infections do persist, and individuals with these prolonged infections will transmit malaria if their blood is transfused. Likewise, disease caused by *P. falciparum*, a nonrelapsing species, manifests within 1 year after departure from a malarious area 99% of the time, but a report of falciparum malaria occurring 13 years after departure from a malarious area has been published.[41] The well-known ability of *P. malariae* to persist asymptomatically for decades in some individuals further highlights the difficulty of eradicating the risk of post-transfusion malaria through questioning of donors.[42]

The AABB has advocated the use of uniform donor screening questions to elicit malaria risk from prospective donors, including questions that inquire about a history of malaria and about the prospective donor's travel history within the past 3 years. A "yes" answer to travel outside the United States and Canada triggers further inquiry to pinpoint travel destinations in malarious areas.

The FDA is in the process of revising its guidelines for deferral of blood donors because of risk of malaria. However, it is unclear when the agency will issue the new guidelines. The proposed guidelines were discussed at the FDA's Blood Products Advisory Committee meeting in June 1999.[46] In addition to retaining the provisions for donor deferral outlined in the FDA memo of July 26, 1994,[38] the revised guidelines recommend adding the following question sequence to the donor history form: (1) "Were you born in the United States?" If yes, ask: (2) "In the past 3 years, have you been outside the United States or Canada?" If the answer to (1) is no, ask: (3) "When did you arrive in the United States, and, since your arrival, have you traveled outside the United States or Canada?" If the answer to question (2) or the second question in (3) is yes, follow-up questions will be asked of the donor to determine when and which country or countries were visited. The impetus for revision of the guidelines includes the increased number of imported malaria cases in the United States, the large number of postdonation events related to malaria reported to the FDA, and the recognition that eliciting an accurate donor history is the only currently available defense against transfusion-transmitted malaria.

From time to time, proposals to test donors for evidence of malaria have been advanced, but no FDA-approved tests or policies for screening donors are currently in place. Selective screening of high-risk donors has been suggested as an alternative to universal screening.[43] Blood-smear diagnosis is both impractical and insensitive as a donor-screening technique. The IFA test is useful diagnostically but is unsuitable for large-scale donor screening, although it could be used to test high-risk donors and to determine their suitability.[43] Although antibody assays detect most individuals with parasitemia, they also are positive in treated persons who are no longer parasitemic.[44] Hence, noninfectious donors would also be deferred if selective antibody screening were implemented. PCR is a promising approach that may have the required sensitivity and specificity, but it is currently not standardized and not available outside research laboratories.[45]

CHAGAS DISEASE

Life Cycle

American trypanosomiasis, or Chagas disease, is a zoonosis caused by the hemoflagellate protozoan parasite *Trypanosoma cruzi*. The life cycle of *T. cruzi* involves transmission from

insect vectors to mammalian hosts including humans. *T. cruzi* infects humans when triatomid (reduviid) or kissing bugs ingest a blood meal from the host and deposit infected feces into the wound or when contaminated feces contact the mucosal surface of the eye or mouth. Hematogenous spread occurs subsequently. In addition, *T. cruzi* crosses the placenta and can cause congenital disease[47–51] (Fig. 48–3).

Clinical Course

Acute Chagas disease is associated with fever, facial edema, generalized lymphadenopathy, and hepatosplenomegaly. Symptomatic myocarditis and meningioencephalitis can occur, and fulminant illness can develop in immunologically immature children or immunocompromised adults. However, in more than 95% of patients, the illness is mild and symptoms resolve in 4 to 6 weeks. If untreated, hosts then enter an indeterminate phase. Ten percent to 30% of patients progress from the indeterminate asymptomatic phase to a chronic symptomatic phase associated with cardiac enlargement, apical aneurysms, mural thrombi, megaesophagus, or megacolon, appearing years to decades after infection.[48–51]

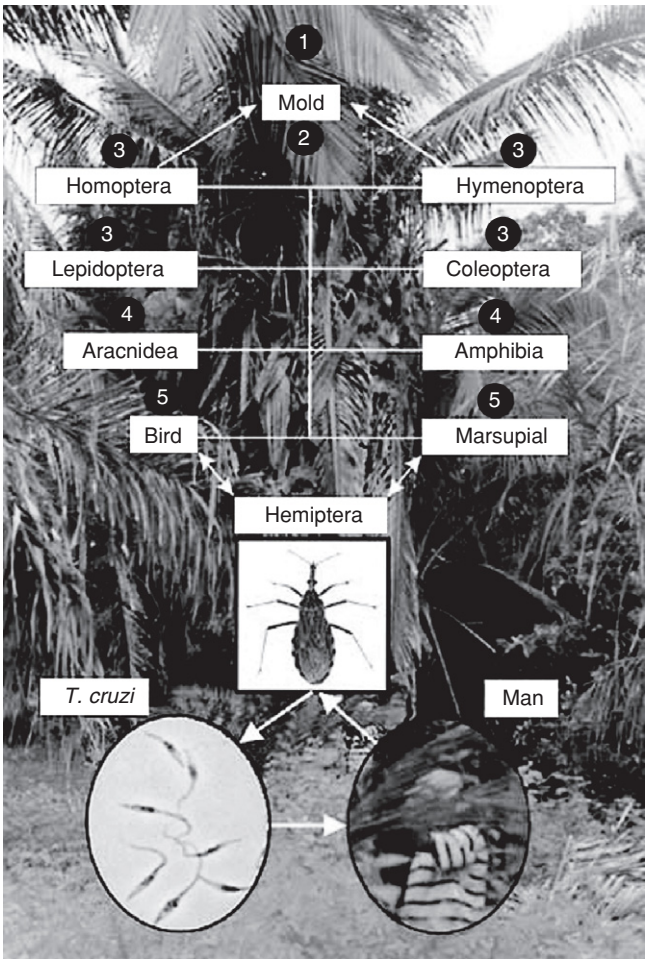

Figure 48–3 Triatomia bugs (Reduvidae), infected with *Trypanosoma cruzi*, reside in palm-tree frond clefts. Whereas birds are refractory to *T. cruzi* infections, marsupials and other residents of palm trees serve as reservoirs of infection. During the wet season when birds and mammals are scarce, triatomine bugs seek humans as a source of feeding, thereby spreading infection. (From Teixera ARL, Monteiro PS, Rebelo JM, et al. Emerging Chagas disease: Trophic network and cycle of transmission of *Trypanosoma cruzi* from palm trees in the Amazon. Emerg Infect Dis 2002;7:100–112).

Epidemiology

An estimated 16 to 18 million people are infected in South America, Central America, and Mexico, where Chagas disease is endemic and, historically, triatomid insects reside in cracks of rural and suburban houses with adobe walls. In the United States, an estimated 25,000 to 100,000 persons and 1 in 25,000 blood donors may be infected with *T. cruzi*.[48] Almost all are immigrants from Central and South America. Chagas disease is responsible for 50,000 deaths worldwide annually.[53]

Lifelong low-grade parasitemia persists in approximately 50% of those infected, and up to 63% of seropositive blood donors have parasitemia.[52] This presents a risk of transfusion transmission and of vertical transmission to infants. Between 12% and 48% of recipients of parasitemic blood become infected.

Transmission by Transfusion

Estimates of risk for transfusion-associated Chagas disease are related to immigration patterns from endemic regions. During the mid-1980s, 4.9% of 205 Nicaraguan and Salvadorian immigrants living in Washington, D.C., had serologic evidence of *T. cruzi* infection. Parasites were isolated from half.[54] In the early 1990s, 0.11% of a selected blood-donor population in California and the U.S. southwest was seropositive for *T. cruzi* antibodies. At least 50% of these donors were of Hispanic origin.[55] During the mid-1990s, 39.5% of donors at a hospital in Los Angeles responded affirmatively to questions inquiring about birth in Chagas disease–endemic areas or residing in dwellings constructed of palm leaf–thatched roofs or walls made of mud,[56] and 0.5% tested positive for *T. cruzi* antibodies. In a study conducted in the mid-to-late 1990s involving more than 1.1 million blood donors, 1 in 7500 in Los Angeles and 1 in 9000 in Miami were *T. cruzi* seropositive.[52]

Although a correlation exists between the percentage of immigrants from endemic areas and the percentage of blood donors with serologic evidence of *T. cruzi* infection, investigators have also identified seropositive blood donors who were born in the United States.[57] Congenital transmission may explain infection in these individuals. In addition, autochthonous transmission has been reported in the United States,[58] and an infestation of triatomines has been reported in Texas.[59]

Since 1989, seven cases of transfusion-associated Chagas disease have occurred in the United States and Canada.[61–65] Symptoms developed approximately 2 to 3 months after transfusion. In at least six of the cases, platelets were the implicated blood component; however, in the seventh case, the implicated unit was not identified.[63] Centrifugation may sediment *T. cruzi* into the platelet layer during component preparation, accounting for the association with platelet transfusions. Whereas room-temperature storage of platelets may favor parasite survival, *T. cruzi* has been shown to survive in refrigerated RBCs and whole blood for at least 18 to 21 days.[51] In six of the North American transfusion-associated cases, a donor emigrating from a *T. cruzi*–endemic region (Bolivia, Mexico, Paraguay, Chile) was identified. Four of the donors emigrated between 16 and 33 years before the implicated donation. Given this small number of cases, transfusion transmission of Chagas disease may be inefficient. In a study of 18 patients receiving blood from blood donors

subsequently found to be *T. cruzi* seropositive, none of the recipients became seropositive after transfusion. However, only two received platelet transfusions.[52] A report of Chagas disease also has been reported after transplantation involving an organ donor who emigrated from Central America appeared in 2002.[60] The recipient of a kidney and pancreas died of acute Chagas myocarditis 5 months after transplant. The recipients of the other kidney and the liver were both also infected with *T. cruzi*.

Transfusion Risk Reduction

Interventions to reduce the risk of transfusion-transmitted Chagas disease include questioning donors about geographic location of birth, extended stay or transfusion in areas endemic for Chagas disease, and serologic testing.[51,66,67] Donor history questions may be only 75% effective.[51] At least one candidate serologic screening assay has undergone clinical trials in the United States and is currently under review at the FDA. The U.S. FDA has indicated that it will require testing for Chagas disease if an appropriate screening assay achieves licensure. This decision reflects the reported transfusion- and organ transplant–associated cases and the concern that up to 600 transmissions may occur annually in the United States.[52] Leukocyte reduction by filtration is modestly effective, reducing *T. cruzii* transmission by 50% to 70% in a mouse transfusion model.[68]

SYPHILIS

Serologic testing of blood donations for syphilis was instituted in 1938 and required by regulation in 1958. No cases of transfusion-associated syphilis have occurred in the United States since 1966.[69] Multiple factors—improved donor selection, uniform serologic testing, lack of spirochete viability in blood stored at refrigerated temperatures, and widespread antibiotic use—apparently contribute to the current absence of transfusion-transmitted syphilis cases.[69-71] In 1978, the AABB Standards Committee deleted the requirement for syphilis testing, and an FDA advisory panel proposed eliminating the requirement for serologic syphilis testing in 1985. However, these changes were not made because of the belief that such testing might identify those at risk of transmitting the HIV. Subsequently, observational data did not support this assumption. Nonetheless, a National Institutes of Health Consensus Statement, issued in January 1995, recommended continuation of syphilis testing because its role in preventing transfusion-transmitted syphilis was not "understood."[70] A lack of complete laboratory data also supports test retention. Although spirochetes survive 96 to 120 hours at refrigerated temperatures,[72,73] viability at room temperature (e.g., in platelet concentrates) has not been studied. Furthermore, loss of viability during storage is an incomplete protection mechanism.

No single optimal laboratory test exists for syphilis. The infectious agent, *Treponema pallidum*, is an anaerobic organism that cannot be cultured in vitro.[73] During treponema infection, nontreponemal and treponemal antibodies are produced. The nontreponemal antibodies (reagin antibodies) react against phospholipid isolated from beef heart or cardiolipin. These antibodies are detected by the Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR), and other tests in response to the interaction of infected host tissue with *T. pallidum*. They parallel the pathologic course but have no relation to immunity. Treponema-specific antibodies have a higher serologic sensitivity in the early stages of syphilis but are less effective indicators of disease activity. During the first 3 weeks after primary infection, the VDRL is positive in 30% of cases, and the fluorescent treponemal antibody-absorption (FTA-ABS) test is positive in 50%. Other treponemal antibody tests, often used to confirm nontreponemal tests, include *T. pallidum* particle aggregation (TP-PA) and recombinant antigen tests. An automated test for treponemal antibodies, PK (TM) treponema pallidum (PK-TP), performed on the Olympus PK 7200, is widely used.[74–76] Reaction patterns characterized by positive RPR or PK-TP tests and negative FTA-ABS reactions (so-called false-positive reactions) may be caused by hepatitis, mononucleosis, viral pneumonia, chickenpox, measles, immunizations, pregnancy, or laboratory error. Persistent false-positive reactions have been reported in patients with rheumatoid arthritis, cirrhosis, ulcerative colitis, vasculitis, and older age.[74–76] Among PK-TP– and FTA-ABS–positive blood donors, approximately half give a prior history of a treated syphilis infection.[75] A history of lupus, rheumatoid arthritis, and diabetes did not provide an explanation for nonconfirmed PK-TP results.

The typical first sign of syphilis, a chancre, appears 3 to 90 days (average, 21 days) after exposure. The exact timing of spirochetemia and *T. pallidum* dissemination from the chancre and of seroconversion is not known. Secondary syphilis, characterized by a disseminated rash and spirochetemia, occurs 6 to 8 weeks after infection. Serologic tests are almost universally positive. If patients remain untreated, recurrent fulminant secondary syphilis recurs within 2 years in approximately 20%. Subsequently, patients become immune to reinfection and become noninfectious. VDRL titers decrease over time. Unless patients are treated in the primary stage, treponemal antibodies persist in both treated and untreated patients. Tertiary syphilis develops after a variable length of time. Reactivation is clinically and serologically noticeable via anticardiolipin and treponemal antibody detection.[72,74,76]

Currently, donations with reactive syphilis screening tests are unsuitable unless nonreactive in a confirmatory test. If the confirmatory test is positive, donors are deferred for 1 year; they are then allowed to donate again, provided that they have undergone adequate treatment for syphilis, and a nontreponemal assay is negative.[76]

HUMAN PARVOVIRUS

Clinical Findings and Epidemiology

Human parvovirus B19 was discovered serendipitously in human plasma during blood-donor screening for hepatitis B surface antigen in 1975. Initially, parvovirus was linked causally with transient aplastic crises in patients with sickle cell anemia and subsequently in patients with other inherited hemolytic diseases, as a result of severe reticulocytopenia and anemia. B19 was later found to be the etiologic agent of fifth disease or erythema infectiosum, a common childhood illness that manifests as an erythematous rash.[77,78] The rash occurs less often in infected adults than children. Fever and nonspecific symptoms precede the rash and arthralgia, both

of which probably result from immune complex deposition in the skin and other organs. Hepatitis, myocarditis, vasculitis, and the gloves-and-socks syndrome have also been linked to B19 infection (Fig. 48–4).

B19 infects only humans, and transmission occurs most commonly via the respiratory route. In addition, transplacental transmission of parvovirus B19 occurs in 30% of women infected during pregnancy. In women infected during weeks 9 to 20 of pregnancy, hydrops fetalis and fetal death occur in approximately 11%.[79] The virus is highly tropic for erythroid progenitor cells, gaining access to cells through the blood group P antigen, or globoside, which has been identified as the virus receptor.[77,78,80] The viral genome consists of single-stranded DNA that codes for three proteins. The nonstructural protein, NS1, is cytopathic to host cells. Viral protein 1 and viral protein 2 code for α-helical loops that appear on the capsid surface. Neutralizing antibodies recognize VP1. The nonenveloped virus consists of symmetric particles 25 mm in diameter.

B19 infection is ubiquitous in human populations and is already prevalent in pediatric age groups. Seroprevalence studies show antibody frequencies of 50% in high school–age children and up to 90% in older adults.[77,78] Epidemics and sporadic infections may occur at any time of year, with major outbreaks of erythema infectiosum occurring every 3 to 6 years. Persistent parvovirus infection, including pure RBC aplasia, occurs in those not developing neutralizing antibodies to VP1. The virus circulates at high titer, greater than 10^{12} genome copies per milliliter.[77,78] Patients receiving cytotoxic chemotherapy, immunosuppressive drugs, organ transplant recipients, and patients with immunodeficiency and the acquired immunodeficiency syndrome (AIDS) are at higher risk of developing chronic infections. The therapeutic approach for persistent parvovirus infection involves discontinuing immunosuppressive therapy, administering intravenous immunoglobulin (IVIG) preparations, instituting antiviral therapy for AIDS patients, and giving repeated courses of IVIG as needed.[77,78]

Transmission by Transfusion

The transient 1- to 2-week, high-titer viremia accompanying acute asymptomatic B19 infection allows virus transmission by blood, blood derivatives, and organ transplantation.[77,78,81] The infrequent recognition of transfusion-associated cases reflects the short viremic phase and the high frequency of immunity among transfusion recipients.

In contrast to recipients of blood transfusions, almost all recipients of plasma-derived factor VIII and IX concentrate are at risk for B19. Parvovirus circulates in the blood of approximately 1 in 800 plasma donors.[90] Fourteen percent had titers between 10^4 and 10^7 genome equivalents per milliliter, and 1 in 13,000 had greater than 10^7 genome equivalent per milliliter. Not surprisingly, in plasma derivatives

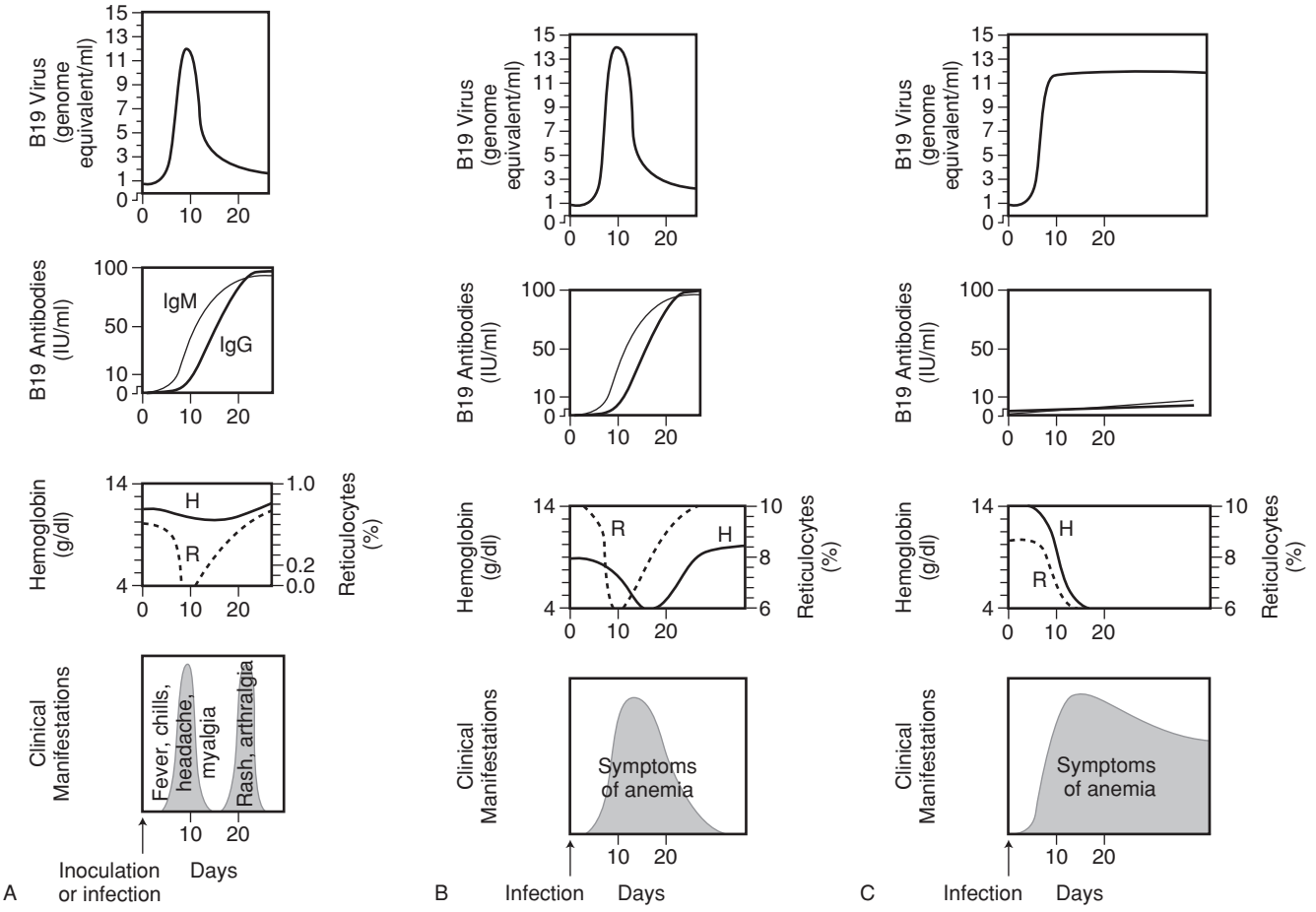

Figure 48–4 Parvovirus B19 infection: The viral titer progression, antibody response, hemoglobin and reticulocyte levels, and symptom complex vary among those with transient infections (**A**), patients with transient aplastic crisis (**B**), and patients developing red cell aplasia (persistent infection) (**C**). (From Young NS, Brown KE. Mechanisms of disease: Parvovirus B19. N Engl J Med 2004;350:586–597.)

prepared from large-scale plasma pools, PCR testing detects parvovirus B19 in most lots. In observational studies, recipients of solvent/detergent–treated plasma seroconverted after infusion of products with high-titer parvovirus DNA, $10^{7.5}$ to $10^{8.5}$ genome copies per milliliter, suggesting that the presence of anti-B19 antibodies was not protective against large viral loads. Seroconversion did not occur among recipients of lots with viral titers between $10^{0.5}$ and $10^{3.5}$ genome copies per milliliter.[78] The virus is resistant to viral-inactivation steps such as solvent/detergent treatment and heat after lyophilization or in the vapor stage. Heat may reduce infectivity if applied in the liquid state. Children receiving plasma-derived factor VIII concentrates were at least 1.9- to 7.6-fold more likely to be B19 seropositive than were those receiving no product or recombinant-derived anti-hemophilic factor.[87] Parvovirus seemingly becomes concentrated in the plasma fraction used in factor VIII preparations. Despite the high frequency of parvovirus exposure, long-term sequelae appear subtle.[82,87] For example, parvovirus B19–seropositive hemophilic children had an 8-degree loss in joint range of motion, a 0.48% difference, compared with seronegative children. Unlike factors VIII and IX, albumin has not transmitted parvovirus B19.[82–88] One report implicated parvovirus transmission by IVIG based on detection of viral DNA by PCR.[89] However, no documentation showed the same viral genotype in the recipient and the immunoglobulin preparation.

Measures to Reduce Transfusion Transmission

In light of these data, in 1999, regulatory agencies and manufacturers of plasma derivatives sought to reduce B19 DNA levels below 10^4 genome copies per milliliter in plasma pools containing 1000 to 3300 plasma donations. However, subsequent reports showed that parvovirus transmission occurred in a recipient of solvent/detergent–treated antihemophilic factor containing 1.3×10^3 genome equivalents per milliliter[83] and a recipient of a dry-heat–treated factor VIII product containing 4×10^3 genome equivalents per milliliter.[85] In these cases, smaller plasma batches with high viral loads were combined to form larger pools used in manufacturing the antihemophilic factor concentrates.

Currently, manufacturers conduct "in-process" testing to eliminate plasma donors with high-titer B19 levels. For example, "recovered plasma" (plasma obtained from whole-blood donations) that is intended for fractionation into plasma derivatives undergoes B19 DNA testing via nucleic acid amplification testing (NAT) assays on aliquots from pooled samples. Subpool analyses are performed to determine which of the samples contained the high-titer donor. These high-titer units, approximately 1 per 10,000 donations, are withheld from product manufacture. Because the infection is transient and a carrier states does not exist, the infected donor is not identified specifically or permanently deferred. Because whole-blood donations rarely transmit parvovirus infections, testing of single unit RBCs, platelets, or plasma for parvovirus B19 is not under consideration in the United States.

CREUTZFELDT-JAKOB DISEASE

Transmissible spongiform encephalopathies (TSEs) occurring in humans include kuru, CJD, Gerstmann-Sträussler-Scheinker disease (a phenotypic variant of CJD), fatal familial insomnia, and variant CJD (vCJD). TSEs occurring in animals include scrapie (sheep and goats), wasting disease of deer and elk, transmissible mink encephalopathy, and bovine spongiform encephalopathy.[91–93]

The TSE infectious agents are classified as prions, or proteinaceous infectious particles that lack nucleic acid. TSEs resist inactivating agents such as alcohol, formalin, ionizing and ultraviolet irradiation, proteases, and nucleases but are disrupted by autoclaving, phenols, detergents, and extremes in pH that affect proteins. The normal host membrane prion protein PrP (designated PrP^c), whose function is unknown, is protease sensitive, soluble, and has a high α-helix content. All prion diseases appear to involve conformational modification of PrP^c to a protease-resistant altered isoform that forms amyloid fibrils (designated PrP^{sc}). The conversion of PrP^c to PrP^{sc} results in refolding of a portion of the α-helical and coil structure of PrP^c into β-sheets. Neuronal loss and vacuolization leads to a spongioform appearance in the brain cortex and deep nuclei.

CJD occurs at an incidence of 0.5 to 1.5 cases per 1 million population worldwide. This rate has increased slightly over the past decade presumably on the basis of improved diagnostic accuracy and greater numbers of older individuals.[92,94] Fewer than 300 cases per year are reported in the United States. Sporadic CJD, causing approximately 85% of CJD cases, occurs in persons 40 to 80 years of age (average age at onset is 60 years) and is manifested by disordered sleep and decreased appetite, behavioral or cognitive changes or focal signs such as visual loss, cerebellar ataxia, asplasia, and motor deficits.[91] The mean survival time is 5 months. The mode of infection for sporadic CJD is uncertain. Approximately 10% to 15% of CJD cases occur in patients with a family history of CJD, suggesting an autosomal dominant inheritance pattern and mutations in the *PRMP* gene that codes for the prion protein. More than 50 mutations in this gene, located on the short arm of chromosome 20, have been identified, but 4 point mutations at codons 102, 178, 200, and 210 occur in 95% of familial cases.[91] Approximately 1% of CJD cases involve iatrogenic transmission. For example, CJD was transmitted by a corneal transplant from a patient with undiagnosed CJD, whereas stereotactic electroencephalographic silver electrodes previously implanted in a patient with CJD subsequently resulted in two iatrogenic CJD cases.[91,92] More than 130 young adults have died 5 to 30 years after receiving intramuscular human growth hormone injections prepared from cadaveric pituitary glands from donors with unsuspected CJD.[91,95] Cadaveric dura mater grafting with a commercial product prepared by batch processing resulted in at least 100 CJD cases worldwide, some occurring 18 years after graft placement.[91,96] In sporadic and iatrogenic cases of CJD, a polymorphism involving codon 129 in the PrP gene appears to affect susceptibility. Normally 37% of the population are methionine/methionine homozygous, and 11% are valine/valine homozygous at codon 129. The remaining 52% are heterozygous. Homozygous individuals represent almost 90% of sporadic and iatrogenic CJD cases.[96,100] Those homozygous for methionine are at risk for fatal familial insomnia, whereas those homozygous for valine are at risk of clinical CJD.[91]

In experiments involving mice infected with a strain of Gerstmann-Sträussler-Scheinker disease, blood-component infection was demonstrated.[97] In contrast, no evidence of transfusion-associated CJD was documented in case-control

studies involving more than 600 patients with CJD or in recipients of blood from persons who subsequently developed CJD.[98–100] Examination of brain tissue from deceased hemophilia patients showed no evidence of CJD.[91,101,102] No transfusion-associated CJD cases have been reported to date. Nonetheless, the occurrence of iatrogenic cases and the theoretical risk of CJD transmission by blood led the FDA to issue a recommendation to defer donors if they have one or more blood relatives with CJD or if they have received human pituitary–derived growth hormone injections or a dura mater transplant. All in-date products from donors with these risk factors must be quarantined and destroyed, and the previous recipients of blood from implicated donors, with the exception of those who have only one family member with CJD, must be notified.[92]

VARIANT CREUTZFELDT-JAKOB DISEASE

In the spring of 1985, several dairy cows in the United Kingdom displayed aggressive behavior, ataxia, and falling. These "mad cows" were found to have spongiform lesions in brain tissue resembling scrapie that was subsequently termed *bovine spongiform encephalopathy* (BSE). More than 180,000 cattle succumbed to BSE, but almost 1 million may have been infected. Because the mean incubation period for BSE is 5 years and most cows were slaughtered between 2 and 3 years of age, most cattle did not manifest disease.[91–93] Approximately 50,000 BSE-infected cattle entered the food chain before the first BSE case was recognized in 1986. Subsequently, the onset of the BSE epidemic was traced to a meat-and-bone cattle feed made from sheep, cattle, and pig offal. The rendering process presumably resulted in the feeding of scrapie-infected material to cows. Use of sheep offal or other tissues from ruminant animals as feed for other ruminant animals was banned in 1989. The annual incidence of clinical cases in cattle peaked in 1992. After March 1996, only animals younger than 30 months were eligible for food preparation.[93]

Surveillance for human CJD cases heightened in the United Kingdom after recognition of the BSE epidemic. Ten of 207 CJD patients in 1994 and 1995 had unusual neuropathologic changes.[103,104] They had predominantly psychiatric and sensory symptoms, ataxia, dementia, and myoclonus. All were younger than 45 years, a distinctly unusual characteristic for CJD. Electroencephalographic features were not typical of CJD, and florid PrP plaques were seen on neuropathologic examination. Median survival time was 14 months, in contrast to 4 months for CJD. These cases were considered a new variant of CJD (vCJD). The median incubation period for food-borne vCJD is 13 years.[105] Extensive investigations using animal models provided evidence that the same prion strain causes BSE and vCJD.[106] Ingestion of British beef, therefore, was identified as a risk factor for BSE.[107]

As of June 2006, 159 cases of vCJD have been reported in the United Kingdom, 17 in France, 4 in Ireland, 1 each in Portugal, Spain, Italy, the Netherlands, Saudi Arabia, Japan, and Canada, and 2 in the United States. The latter three plus one Irish patient were thought to result from exposure in the United Kingdom. The Japanese patient spent only 24 days in the United Kingdom. All patients tested were homozygous for methionine at PrP codon 129. By 2000, the incidence of human vCJD cases peaked, suggesting that clinical manifestations among methionine/methionine homozygotes may be less than anticipated after extensive exposure to cattle with subclinical disease.[105,108,109]

Concern about transfusion transmission of vCJD increased because PrP^{sc} is found consistently in the lymphoreticular system of vCJD patients, the possibility that circulating prions transfer the infection from the gut to the brain, and eventually because of animal studies.[105,108,109] In animal model experiments, sheep were fed aliquots of brain obtained from BSE-infected cattle. Subsequently, the sheep underwent phlebotomy at periodic intervals. Among 24 sheep receiving blood from iatrogenically infected donor sheep, 2 given blood from donors in the preclinical BSE phase developed BSE, and 2 receiving blood from clinically affected sheep showed clinical signs of BSE. Among 21 sheep transfused with blood from natural scrapie-infected animals, 4 demonstrated clinical signs of scrapie.[110,111]

An active investigation to determine whether transfusion associated-vCJD transmission occurs in humans began in the United Kingdom in 1997 by identifying vCJD patients who donated blood before illness. Eventually, 48 recipients of blood from 15 donors with vCJD were identified. Three of the 48 recipients, to date, have evidence of vCJD. One, at age 62 years, received non–leukocyte-reduced RBCs from a 24-year-old donor who developed vCJD 3.5 years after the blood donation. The transfusion recipient developed vCJD 6.5 years after transfusion.[112] The second patient received a transfusion of non–leukocyte-reduced RBCs in 1999.[113] The donor developed vCJD 18 months later. The asymptomatic recipient died of a ruptured abdominal aortic aneurysm 5 years after transfusion. At autopsy, protease-resistant prions were present in the spleen and cervical lymph nodes. Prions were not detected in the brain. The recipient, found to be heterozygous (methionine/valine at codon 129), did not have clinical vCJD, raising concern that the incubation period may be longer in codon 129 heterozygotes. In animal studies, a primary challenge with vCJD prions resulted in a significantly reduced transmission rate in mice with valine at codon 129 compared with that in animals homozygous for methionine.[114] Additional data are needed to confirm whether the incubation period varies among methionine homozygous and heterozygous individuals. The third case developed vCJD approximately 8 years after receiving non-leukocyte-reduced red cells from a person who developed vCJD 20 months postdonation.[114a]

The U.K. National Blood Service also determined that approximately 100 people donated blood to four patients who subsequently showed clinical signs of vCJD. These donors were notified that they may be at higher risk of developing vCJD despite the uncertainty of whether the patients contracted vCJD through food or blood transfusion. In addition, UK authorities notified recipients of factor XI concentrates that donors of these components developed vCJD after donation on the ethical tenet of transparency. The United Kingdom currently imports plasma from the United States for patients younger than 16 years and uses apheresis-derived platelets in these patients to reduce donor exposures.[94,116]

The identification of presumed transfusion-associated vCJD cases appears to validate the steps taken in response to the precautionary principle to decrease the risk of transmitting vCJD by transfusion.[92] Donors who visited or resided in the United Kingdom for a cumulative period of 3 months or longer between 1980 and 1996 are deferred indefinitely. Donors who spent 5 years or more in Europe before 1980 and the present are also deferred. In addition, donors are indefinitely deferred if they injected bovine insulin after 1980, received transfusions in the United Kingdom and France

between 1980 and the present, or served in the military on bases in Europe for 6 months or more between 1980 and 1996. This geography-based donor-deferral protocol evolved in various phases beginning in 1999. Approximately 3.5% of potential donors in the United States have been deferred as a result of this policy.[117] The impact was higher in Canada.[118] In-date blood components and plasma intended for derivative production from these donors must be recalled, quarantined, and destroyed. Ongoing surveillance of vCJD cases, which increased after identification of a Texas cow with BSE, is currently being conducted, including a recommendation to notify the CDC about all patients younger than 55 years who are diagnosed with CJD.[115]

In addition to geographic exclusion policies, other strategies for preventing vCJD transmission include removal of the infectious agent and testing. In the United Kingdom, all blood components undergo leukocyte reduction by filtration, based on observations that prions associate with leukocytes. Leukocyte reduction, however, is only partially effective, removing only 42% of total prion infectivity.[120] Filters that specifically remove prions and laboratory tests that detect infectious prions are currently being developed and evaluated. The latter, if implemented, will be accompanied by significant ethical concerns.[119]

LEISHMANIASIS

Visceral forms of leishmaniasis result from infection with *Leishmania donovani* or *Leishmania infantum*. Cutaneous lesions occur in persons infected with *Leishmania braziliensis* or *Leishmania tropica*, the cause of Old World cutaneous leishmaniasis. However, at least eight soldiers returning from eastern Saudi Arabia after Operation Desert Storm developed visceral leishmaniasis that was attributed to *L. tropica*.[121,122]

The leishmania organisms, transmitted primarily by bites from infected sand flies, are endemic in the tropical and subtropical regions of the Sudan, Eastern India, Bangladesh, Nepal, Brazil, and the Mediterranean.[123]

After transmission by sand fly bite, parasites reside intracellularly in monocytes, which circulate before taking up residence in internal organs. In the most severe manifestation of visceral leishmaniasis, kala-azar, patients have marked hepatosplenomegaly, pancytopenia, hypergammaglobulinemia, and cachexia. The incubation period is approximately 6 months.[123] Anti–*L. donovani* antibodies form shortly after infection. In studies conducted in Brazil, 21 seropositive asymptomatic blood donors were found to have positive PCR results for *L. donovani*, demonstrating the ongoing potential of transfusion transmission in endemic areas.[124]

At least 10 transfusion-associated cases of leishmaniasis attributed to *L. donovani* have been reported in endemic regions. Most of those infected were young children or neonates. A probable case of platelet transfusion–transmitted *Leishmania* was reported recently.[125] Transfusion-transmission also appears to occur in dogs receiving transfusions of RBCs from seropositive dog-blood donors.[126]

Veterans of Operation Desert Storm who served in the Persian Gulf region between August 1990 and December 1992 were deferred from blood donation for 1 year, after the report of *L. tropica*–related viscerotropic leishmaniasis. The patients had nonspecific clinical manifestations, including prolonged fever, malaise, abdominal pain, and intermittent diarrhea, which occurred up to 7 months after they returned to the United States.[121] *L. tropica* was found in the bone marrow of seven patients and in a lymph node in one patient. Intracellular amastigotes were seen in the peripheral blood of the one patient in whom this was studied.[127] After reports of hundreds of cases of cutaneous leishmaniasis and two cases of visceral leishmaniasis in troops involved in the Iraq war, a similar 1-year deferral after departure from Iraq was instituted in October 2003.[127] *L. tropica* within human monocytes survives in blood stored at 1° C to 6° C, in frozen RBCs, and in platelet concentrates stored at room temperature. However, *L. tropica* has not been detected in relatively cell-free fresh frozen plasma. Animal studies demonstrate transmission by contaminated blood.[126]

No cases of transfusion-transmitted leishmaniasis have been reported in the United States to date. For this reason, surveillance and targeted donor deferral appear to be appropriate. Use of leukocyte filters to reduce *Leishmania* transmission is under investigation.[128]

TOXOPLASMOSIS

Toxoplasma gondii is a ubiquitous parasite whose usual host is the domestic cat. Infection sometimes results in lymphadenopathy, malaise, fever, headache, sore throat, splenomegaly, hepatomegaly, and rash. Retinopathy and lethal infections occur in immunocompromised hosts.

Transfusion transmission was reported in 1971. However, the cases occurred among leukemia patients given granulocyte transfusions obtained from other leukemic patients. Another case report suggested that a patient undergoing chemotherapy for a leukemic relapse 3 years after receiving an allogeneic marrow transplant developed toxoplasma pneumonitis. A person with serologic evidence of recent toxoplasma infection donated one of the units of blood transfused to the patient.[130] In addition, a 52-year-old woman with drug-induced thrombocytopenia developed toxoplasma retinochoroiditis, presumably related to a platelet transfusion.[130] A case further emphasizing the importance of nontraditional routes of infection in immunocompromised patients involved a renal transplant recipient who developed toxoplasmosis.[131] The infection was presumably transmitted by a kidney obtained from a seropositive organ donor.

DENGUE

Dengue, transmitted by *Aedes* mosquitoes, has infected at least 77 U.S. travelers to Caribbean islands (including Puerto Rico and the U.S. Virgin Islands), Pacific islands, Asia, Central America, Africa, and Hawaii between 2001 and 2004.[132,133] The incubation period is 3 to 14 days. Infections cause either no symptoms, mild illness, or severe disease including hemorrhagic manifestations and shock.[134] Transmission by bone marrow transplantation and several reports of transmission after needle-stick injuries involving symptomatic patients raise the possibility of transfusion transmission by asymptomatic travelers returning from endemic areas.[135–137]

SIMIAN FOAMY VIRUS

More than 70% of nonhuman primates in zoos or in animal research facilities are infected with simian foamy virus (SFV),

an endogenous, cell-associated retrovirus found in New and Old World primates.[138] Surveillance studies indicate that approximately 5% of zoo and biomedical research personnel working with chimpanzees and baboons are infected with SFV. Evaluation of archival samples documented infection for 8 to 26 years (median, 22 years). All subjects remained healthy, and each of three spouses undergoing testing for SFV were nonreactive. In addition, 1% of bush hunters in central Africa and 1% of those exposed to free-ranging nonhuman primates in Asia tested positive for SFV.[139,140] Presumably, those infected were inoculated through exposure to saliva from bites or close contact through exposure to body fluids.

Only limited information is available about transfusion transmission. One occupationally exposed SFV-infected individual donated blood 6 times during an interval when SFV test results, conducted retrospectively, were positive. None of the tested recipients of RBCs, leukocyte-reduced RBCs, or platelets was SFV positive. Three of these blood components were stored for less than 8 days.[141]

LYMPHOCYTIC CHORIOMENINGITIS VIRUS

Infections with lymphocytic choriomenigitis virus (LCMV), a rodent-borne arenavirus, usually cause mild, self-limited illness or aseptic meningitis in nonimmunosuppressed patients. Human infections typically follow exposures to body fluids or infected animal excretions. Vertical transmission occurs, but LCMV is not considered to be communicable from person to person. LCMV has been transmitted to four organ transplant recipients via an asymptomatic organ donor who had a cerebrovascular accident and subsequent brain death.[142] The donor apparently became infected by exposure to a pet hamster. Within 3 weeks of transplantation, the recipients of the liver, lungs, and two kidneys developed fever, rash, or diarrhea; three of the four recipients died. A previous case also involving four transplant recipients was unrecognized until this case was reported. Transfusion transmission has not been reported but is a possibility, given transmission by solid-organ transplantation.

H5N1 AVIAN INFLUENZA VIRUS

The avian influenza A/H5N1 virus has spread epidemically among birds and poultry since emerging in Hong Kong in 1997.[143] Since that time, more than 100 million birds and poultry have died or been culled to prevent epidemic progression via bird migration in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, Vietnam, Malaysia, Turkey, Romania, and Russia. Transmission to humans via contact with infected poultry or contaminated surfaces has resulted in more than 60 deaths.

To date, human-to-human transmission has occurred infrequently.[144] However, concern exists that mutations, reassortments, or recombinant rearrangements of the virus with pathogenic human influenza viruses could produce a virus capable of jumping the species barrier and causing a worldwide pandemic. Influenza viremia is infrequent, although highly pathogenic avian influenza can be transmitted via blood.[145] Although transfusion transmission is a theoretical risk, a more likely impact would be large-scale donor illness and blood shortages.

SEVERE ACUTE RESPIRATORY SYNDROME

SARS, caused by a novel enveloped RNA coronavirus, infected more than 1800 patients in 17 countries in February and March 2003.[146] This highly contagious illness dominated worldwide public health attention, resulting in rapid identification, travel advisories, patient quarantine, and eventual eradication of the epidemic.[147] The 2-week asymptomatic incubation period fostered spread of the virus through close person-to-person contact and raised the possibility of blood-borne infection. For this reason, the U.S. FDA issued a guidance document in April 2003 requiring blood-collection agencies to defer anyone from donating blood for at least 14 days after possible exposure to SARS.[148] Those with a suspected SARS illness were deferred for at least 28 days after recovery. Notices were posted in blood centers apprising donors about SARS-affected areas, and donors were asked about recent travel history. Those traveling to affected areas, including transit in an airport at these locations, were deferred from blood donation. The epidemic subsided within months. No reports of transfusion-associated SARS exist.

WEST NILE VIRUS

West Nile Virus (WNV) is a mosquito-borne, lipid-enveloped, RNA virus in the Japanese encephalitis flaviridae complex. The viral genome codes for capsid, membrane, envelope, and nonstructural proteins.[149]

The virus, transmitted from bird to bird by mosquito vectors, infects humans as incidental hosts. The virus was identified in the West Nile district of Uganda in 1937. Outbreaks occurred subsequently in the Mid-East, South Africa, and Europe. The first North American cases were recorded in New York City in 1999.[150–153] WNV infections in humans have occurred predominantly between June through October, peaking in August through late September and remitting during the winter. Starting in July 2000, WNV cases were reported in Mid-Atlantic states. In July 2001, 66 cases occurred in the eastern one third of the United States. In 2002 the epidemic spread to the Midwest and eastern Plains states; 4156 cases were reported including 2946 with meningoencephalitis. In 2003, further western spread saw the majority of cases in the Plains states of Nebraska, Colorado, North and South Dakota, and Wyoming; 9862 cases were reported, including 2775 with neuroinvasive complications. In 2004, the epidemic spread farther westward to include Arizona and southern California. WNV activity was reported in 47 states, involving 2470 reports. WNV cases in 2005 progressed farther down the West Coast; 2435 cases were reported through October 2005.[154] In addition, 372 viremic blood donors were identified.

WNV activity in birds and mosquitos occurs throughout the year, especially in warmer regions. The virus becomes detectable in blood 1 to 3 days after a mosquito bite, followed by an increase in viral loads. However, peak titers are relatively low (median of 3500 copies per milliliter) compared with HIV and HCV (10^5 to 10^7 per milliliter). RNA levels decrease markedly 7 to 10 days after infection when immunoglobulin M (IgM) antibodies, and subsequently IgG anitibodies, appear. IgM antibodies persist for more than 398 days in approximately two thirds of those infected.[155] The mean duration of viremia is 6 days. However, WNV RNA

was detected up to 104 days after infection in one blood donor.[157–162] (Fig. 48–5)

Approximately 80% of persons infected with WNV remain asymptomatic. The 20% with symptomatic infections report abdominal pain, chills, fever, generalized weakness, headache, joint pain, muscle weakness and pain, new macular rash on the trunk and extremities, new difficulty thinking, painful eyes, and swollen glands.[163] One in 150 infected persons develops meningitis, encephalitis, or asymmetric flaccid paralysis. Fatal outcomes occur in 4% to 14% of those with severe disease.

WNV transmission in four recipients of organ donations was reported in 2002.[163] The organ donor, in turn, received blood transfusions from 63 donors, one of whom subsequently was found to be WNV infected. A sample from the organ donor subsequently tested WNV RNA positive, but WNV IgM negative. Initial reports of transmission by blood transfusion in 2002 eventually resulted in confirmation of 23 cases of transfusion-associated WNV infection.[162] The interval between transfusion and symptom onset was 10 days (median interval range, 2 to 21 days). Nine of 14 implicated blood donors reported WNV-associated symptoms before donation.

After intense collaboration among U.S. public health authorities, test manufacturers, and blood-collection agencies, NAT for WNV RNA was implemented before the 2003 WNV season. As a direct result of testing, more than 1000 donors were found to be WNV RNA positive in 2003, preventing WNV transmission to approximately 1500 recipients of RBCs and components prepared from these donations.[156,157,159] During the summer months, approximately 1 per 7000 units was WNV RNA positive. In high WNV endemic areas, 1 in approximately 150 donors was WNV viremic. In 2003, six transfusion-associated WNV cases were reported.[158] All of the implicated donors had extremely low-level viremia that escaped detection by routine testing in minipools containing aliquots from 6 to 16 donations. Testing of individual samples in high-incidence areas increases test sensitivity by approximately 7% and was introduced in 2004 when incident cases exceeded preestablished thresholds (approximately 1 WNV-positive donor per 1000 donations). Only one confirmed transmission occurred in 2004. Among the 30 confirmed transfusion cases, all implicated donations were WNV IgM antibody negative.[164,165]

A second transplant-associated incident involving three of four organ recipients who developed WNV infection after transplant was reported in 2005.[166] Of note, the organ donor (infected through mosquito bites) was WNV RNA positive and IgM antibody positive. This report raises concern that organ-transplant recipients and other heavily immunosuppressed patients are at extremely high risk for severe WNV complications and that the virus remains viable in organ/tissue reservoirs despite a humoral immune response.

Overall, the rapid implementation of WNV testing within months of the initial transplant and transfusion-associated cases resulted in dramatic reduction of further transfusion-transmitted cases. Assuming that RNA-positive, IgM antibody–positive donors do not transmit WNV through blood transfusion, the residual risk of transfusion-associated WNV after implementation of NAT is approximately 1 per 350,000 donations.[164,165]

RABIES

In June 2004, the CDC confirmed the diagnosis of rabies in recipients of a liver and two kidneys from an organ donor subsequently found infected with rabies via a bat bite. The recipients developed tremors, myoclonic jerks, altered mental status, or anorexia 21 to 27 days after transplant. All died. It is unlikely that these transplant-related cases portend a risk for transfusion-transmission, in that exposure to infected neuronal tissue appears to be the vector in these cases. The rabies virus is not transmitted hematologically, and contact with blood, urine or feces is not considered an exposure risk.[167]

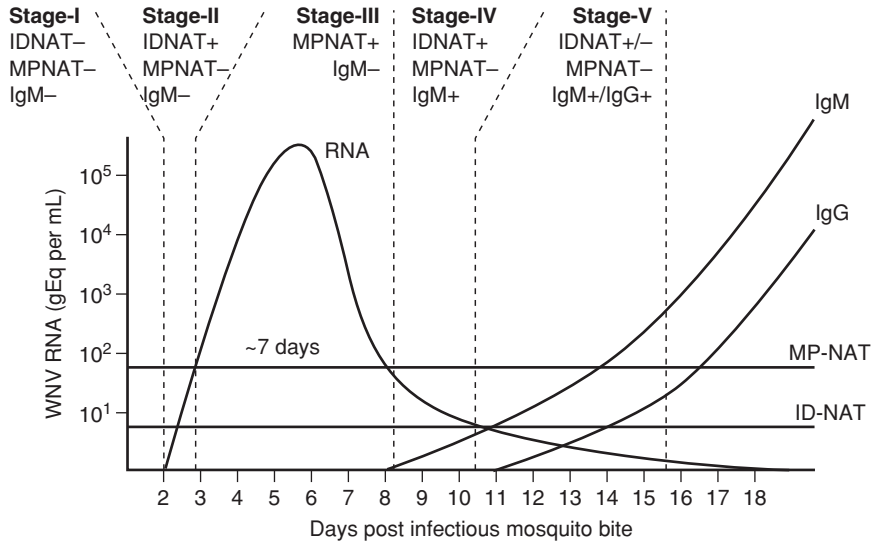

Figure 48–5 West Nile virus (WNV) RNA circulates at relatively low levels for 7 to 10 days after the bite of an infected mosquito. Minipool nucleic acid testing (MP-NAT) detects 43 to 309 viral copies per milliliter within a few days of infection. In contrast, individual donation NAT (ID-NAT) detects 3.4 to 29 copies per milliliter and reduces the window period between infection and test detection. All transfusion-associated WNV cases have occurred in the NAT-positive/IgM antibody–negative stages. (From Busch MP. West Nile virus window period. Transfusion 2005;45:cover figure.)

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