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Transplant-Associated and Blood Transfusion-Associated Tropical and Parasitic Infections

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KEYWORDS

• Transplantation • Blood transfusion • Tropical diseases • Parasites • Transmission • Donors

KEY POINTS

- Laboratorial and epidemiological screening is fundamental in assuring safe blood and organs for transfusion and transplantation.
- Due to the intense movement of people, animals and vegetables, tropical diseases are no longer restricted to the tropics.
- Knowledge of the life cycle of infectious agents and vectors are instrumental in promoting surveillance.
- Advanced molecular biology methods and fast communication are human weapons to prevent and fight emerging and re-emerging diseases that may threaten the blood and organ supply.

Most of the developing countries are located in tropical or subtropical regions, which have epidemiologic characteristics different from those of developed countries with temperate climates. These countries are characterized by the occurrence of endemic infections and diseases that are absent or rare in developed countries and may not be prepared to diagnose or manage them. Tourism, international commerce, and immigration are important factors for the emergence and reemergence of specific infectious diseases. Migrant populations may naturally become part of blood bank donor, transplant donor, or transplant recipient populations in destination countries and may represent an unintentional threat to blood or transplant recipients.[1] In this increasingly globalized world, the transmission of infectious diseases has no boundaries. Consequently, the interest in blood- and donor-derived disease transmission is growing globally.

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Blood transfusion is an efficient mechanism to spread infectious agents in naive populations; thus several measures are taken worldwide to ensure the safety of the blood supply. However, physicians are constantly surprised by cases of transfusional transmission (TT) of new and reemergent agents. Recent waves of immigration from the South to the North took several asymptomatic carriers of tropical agents, potentially blood donors, to countries where tropical diseases are recognized exclusively in returning travelers. Cases of TT parasites, such as *Trypanosoma cruzi* (Chagas disease) and *Plasmodium* sp (malaria), in Europe and North America provoked changes in the policies for blood donor screening in these countries (discussed later). In parallel, technologies that may inactivate pathogens (pathogen reduction technologies [PRT]) by targeting nucleic acids in a nonspecific mode are in a late stage of development and in regular use for plasma and platelet units in some countries.

There are several differences among countries on the agents that require mandatory testing and the allowed assays. In limited-resource regions, testing by thick smear or antigenic rapid test is restricted to antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and malaria parasitemia. This portfolio is adopted in many African countries. Syphilis and hepatitis C virus (HCV) come next in the order of importance. Enzyme immunoassays (EIAs) for anti–*Treponema pallidum* antibodies are mostly used, and, possibly, the discard rate for reactive donations may be high. No case of TT syphilis has been reported in the last 15 years, even when less sensitive assays were routinely used. Donors are also screened for antibodies to human T-lymphotropic virus 1/2 (HTLV-1/2) in many countries, mainly countries in which the prevalence is significant, such as the United States, Brazil, and Japan. HCV should get the same status as HIV because it has a high prevalence among donors, and it may be an extremely harmful infection. However, anti-HCV screening is not universally performed so far. Other agents of restricted geographic occurrence are screened only locally, such as the West Nile virus (WNV) in the United States and Canada and the Q-fever agent in the Netherlands. Cytomegalovirus (CMV) antibody–negative blood is given to newborns and immunocompromised patients. Bacterial contamination is controlled in some countries, differing on the principle mentioned earlier, because testing is performed in blood products after processing, as most contamination is environmental and occurs during processing and storage. Platelets present the highest concern because they are stored at room temperature and under shaking, conditions that may foster growth of many bacterial species. Laboratory methods include automated hemoculture and other disposable rapid tests that are to be performed just before platelet release.

In the beginning of this millennium, automated nucleic acid testing (NAT) became available, and it was possible to be incorporated into the blood screening scheme. The aim of NAT introduction was to reduce the so-called window period that precedes the development of detectable antibodies in the recently infected host. HCV NAT and HIV NAT became mandatory in most developed countries, but hepatitis B virus (HBV) NAT was introduced later, and, up to 2011, this NAT was not as widespread as the NATs for HCV and HIV.

An international network for biovigilance of organ recipients would be desirable in the transplantation setting. Although national systems are already available in some countries, in many others the systems are still under development. The higher rate of incident infection transmitted by organ donors compared with that transmitted by blood donors emphasizes the need for such networks.[2] At present, the following screening tests are generally required for organ, tissue, and hematopoietic stem cell donors: anti–HIV-1/2, HIV NAT, syphilis (by either a treponemal or nontreponemal test), anti–HTLV-1/2, anti-CMV, anti–Epstein-Barr virus, anti–hepatitis B core (anti-HBc), HBsAg, anti-HCV, and HCV NAT.[3]

This article describes the epidemiologic characteristics of tropical and parasitic diseases that can be transmitted by blood and/or transplantation. **Table 1** shows the tropical and parasitic diseases with widespread transmission, epidemic activity, or high risk for infection according to the region. The diseases associated with blood and/or transplant transmission are highlighted in bold.

BACTERIAL INFECTIONS

Tuberculosis

Epidemiology

Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. According to the World Health Organization, in 2009, there were an estimated 9.4 million incident cases (range, 8.9 million–9.9 million) of TB globally, equivalent to 137 cases per 100,000 population. Most of the estimated number of cases occurred in Asia (55%) and Africa (30%), with smaller proportions of cases occurring in the Eastern Mediterranean region (7%), the European region (4%), and the region of the Americas (3%). India alone accounts for 21% of all TB cases worldwide, and China and India together account for 35%.[4]

The HIV pandemic has contributed to these numbers because 1.0 to 1.2 million (11%–13%) cases of TB were reported in HIV-positive people. Because the rate of cure in new cases of smear-positive TB is lower among HIV-positive patients (<40%) than among HIV-negative patients (>60%), transmission is facilitated in places where HIV infection

Table 1
Distribution of tropical and parasitic diseases according to the region

Region	Viruses	Bacteria	Parasites
Mexico, Central America	**Dengue**, hepatitis A	Leptospirosis, typhoid, and paratyphoid fever	**Leishmaniasis**
Latin America	**Dengue, yellow fever, rabies,** hepatitis A, **hepatitis B**, measles, hantavirus, other viral hemorrhagic fevers	**Tuberculosis**, leprosy, leptospirosis, plague	**Leishmaniasis, malaria, schistosomiasis, trypanosomiasis**
North Africa	Hepatitis A, **rabies**	Plague, **tuberculosis**, typhoid, and paratyphoid fever	**Leishmaniasis**
Sub-Saharan Africa	**Dengue, rabies**, hepatitis A, **hepatitis B,** yellow fever, poliomyelitis, other viral hemorrhagic fevers	Diphtheria, plague, **tuberculosis**, leprosy	**Leishmaniasis, schistosomiasis, malaria, trypanosomiasis**
Southeast Asia	**Dengue,** hepatitis A, **hepatitis B**	Leptospirosis, plague, **tuberculosis**	**Filariasis, malaria, schistosomiasis**
South Asia	**Filariasis,** hepatitis A, **rabies, hepatitis B**	Leptospirosis, plague, **tuberculosis**	**Filariasis, leishmaniasis, malaria**
East Asia	Hantavirus, hepatitis A, **hepatitis B**	Leptospirosis, plague, **tuberculosis**	—
Northern Asia	Hantavirus, hepatitis A, **hepatitis B, rabies**	Diphtheria, **tuberculosis**	—
Middle East	Hepatitis A, **hepatitis B**	**Tuberculosis**	**Leishmaniasis**

Blood- and/or transplant-transmitted infections are in bold.

is highly prevalent.[1,4] Of these HIV-positive TB cases, approximately 80% were in the African region.[4] Other immunocompromised hosts, including solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients, are also more prone to reactivation of latent *Mycobacterium tuberculosis* infection (LTBI).[5]

Transmission in transplant recipients

TB among transplant recipients may arise from reactivation of the quiescent foci of *M tuberculosis*, transmission by the graft, or contamination by actively infected persons. The risk of TB in transplant recipients is estimated to be 20 to 50 times higher than in the general population, even in developed countries,[6,7] and mortality rates vary from 20% to 40%.[8] Most reports of TB are in SOT recipients, especially after renal transplantation. The prevalence of LTBI among renal transplant recipients in North America is 0.5% to 1%, in Northern Europe is 1% to 4%, and in India and Pakistan can reach 15%.[9] In Brazil, TB is number one among the neglected tropical diseases after transplantation, with an incidence of around 1% in HSCT recipients and 2% in SOT recipients.[10,11]

Reactivation of LTBI accounts for most TB cases reported in transplant recipients and largely reflects the local incidence.[1] Graft transmission has been documented in renal, lung, and hepatic transplantation but accounts for less than 5% of all TB cases in transplant recipients. In one international study, 4% of TB infections in recipients were considered donor derived.[8] Recently, a case of donor-derived TB that resulted in the infection of 2 of the 3 transplant recipients (with 1 death) has raised the discussion regarding the need for donor TB screening with new blood tests (interferon gamma release assays [IGRAs]) to diagnose LTBI.[12]

Screening and prevention

Pretransplant evaluation of the epidemiologic risk of TB should be made for donors and recipients in countries where TB is highly prevalent. However, in the evaluation of donor eligibility, no standard assessment is conducted to determine if the potential donor is at risk of having previously undiagnosed TB or LTBI. In addition to selected laboratory testing (mentioned at the beginning of the article), the donor's medical record is reviewed for specific conditions (including known active TB), a social history is obtained with a close relative (or another person familiar with the donor), and chest radiography is performed. Although the screening process might reveal symptoms or risk factors for TB or LTBI, no further investigation or diagnostic testing is required.

LTBI can also be evaluated through the tuberculin skin test (TST), a delayed-type hypersensitivity reaction to an intracutaneous injection of antigens isolated from culture filtrate by protein precipitation. For living donors, the TST result should be interpreted as positive or negative according to the Centers for Disease Control and Prevention (CDC) guidelines for the general population.[13] However, the specificity of the TST is impaired in donors from developing countries because the delayed-type hypersensitivity reaction may indicate infection with nontuberculous mycobacteria or previous vaccination with the BCG vaccine, a live attenuated mycobacterial strain derived from *Mycobacterium bovis*. IGRAs are more specific alternatives and should be interpreted according to manufacturer instructions. If LTBI is confirmed, then active TB should be ruled out. Treatment of LTBI should be considered before organ donation, especially for recent seroconverters. Organs from potential donors, whether living or deceased, with active TB disease should not be used.[14]

Brucellosis

Epidemiology

Brucellosis is a common zoonotic disease caused by *Brucella* spp, which mainly infect cattle, swine, goats, sheep, and dogs. It can be transmitted to people via direct

contact with livestock or through drinking unpasteurized milk from an infected animal. In humans, *Brucella* causes a wide range of clinical manifestations involving various body systems. The main symptom is recurrent bouts of high temperature. Therefore, it is frequently misdiagnosed as drug-resistant malaria in tropical countries.

Transmission in transplant recipients

Few cases of brucellosis have been reported after renal transplantation and as a donor-derived infection during HSCT, in endemic regions.[15] Fever, anemia, and pancytopenia are often observed and may mimic several other diseases in the immunocompromised patient. In general, the diagnosis is made by the detection of *Brucella* species in blood cultures, after extensive investigation of other causes. Consequently, complications may develop in case of delay in the diagnosis or administration of appropriate antimicrobial treatment. Fluoroquinolones, doxycycline, and streptomycin are successful therapeutic options. More recently, tigecycline was demonstrated to be safe and effective in the control of brucellosis after liver transplantation.[16]

PROTOZOAN INFECTIONS

Malaria

Epidemiology

Malaria is an acute systemic illness caused by infection with *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, or *Plasmodium ovale.* About 3.3 billion people, half of the world's population, are at risk of malaria. In 2010, there were an estimated 216 million episodes of malaria and nearly 655,000 deaths due to malaria, mostly among children living in Africa. People living in the poorest countries are the most vulnerable. In Africa, every 45 seconds a child dies of malaria; the disease accounts for 20% of all childhood deaths.[17]

Endemic malaria cases have been reported in Central and South America, sub-Saharan Africa, India, Southeast Asia, and part of Oceania. Awareness of *Plasmodium* species endemicity is important for early introduction of appropriate treatment. *P falciparum* is found in sub-Saharan Africa, Southeast Asia, and the Indian subcontinent as well as in South America, Haiti, the Dominican Republic, Jamaica, and areas of Oceania. *P malariae* and *P ovale* are present in sub-Saharan Africa. *P vivax* is prevalent in areas of Southeast Asia, the Indian subcontinent, and Central and South America.[18]

Malaria may be transmitted through infected blood products, by natural exposure to *Plasmodium*-infected mosquitoes in endemic regions, or via an infected organ or tissue.

Transmission through blood products

In contrast to the large number of cases of malaria transmitted through *Plasmodium*-infected mosquitoes worldwide, transmission by blood transfusion has scarcely been reported, and the majority comes from nonendemic countries. A recently published international forum report informs that only 5 TT cases were reported in the last 10 years: 2 in Italy, 2 in Brazil, and 1 in the United States.[19] This may be partially explained by the difficulty in distinguishing transmission by transfusion from vector-borne cases in endemic countries.[20] Another aspect is that malaria may be more harmful for naive patients than exposed semi-immune patients who are recipients of blood and organs in nonendemic and endemic regions, respectively.

Transmission in transplant recipients

Although not an opportunistic disease, malaria is relevant in the transplant setting because more patients either with a history of malaria or residing in an endemic malaria region are undergoing transplantation, more residents from endemic regions are being

considered as donors, and more recipients are being exposed to malaria after transplant. The washing of organ blood during the transplantation procedure may not be enough to eliminate possibly parasitized red cells within the organ, and transmission may occur. In transfusion-associated malaria, symptoms generally develop earlier (1–3 days) than if the infection is transmitted through infected cells within the organ (>1 week).[18] *Plasmodium* species are capable of surviving for more than 24 hours in blood at 4°C. Therefore, the cold preservation time is generally not enough to prevent transmission, especially in heart and liver transplantations, which require shorter cold preservation time (3–4 hours for heart, <12 hours for liver) than kidney transplantation (24–48 hours). The reports of malaria cases after multiorgan donation have supported the hypothesis of the graft as a source of *Plasmodium* in transplant recipients.[21–23]

Screening and prevention

Investigation of the epidemiologic risk for malaria is mandatory for blood and transplant donors and recipients in endemic regions. If possible, routine serologic and blood smear tests should be considered for all individuals with exposure risk. In developing countries, a past history of malaria is not a contraindication for organ or stem cell donation.

Clinicians must be aware that malaria does not always follow the typical paroxysmal or cyclic pattern in transplant recipients, and a high index of suspicion should be maintained when caring for patients with identifiable risk factors. If donors or recipients have a history of mosquito exposure in regions of *P vivax* or *P ovale* infection, clinicians should bear in mind that the parasites' exoerythrocytic schizogony in the liver makes eradication more difficult. These dormant hypnozoite forms can cause relapse up to 12 months later.

Guidelines from developed countries recommend that donors from nonendemic areas who have traveled to an area where malaria transmission occurs should be deferred from donating for 12 months after their return. Similarly, persons who have lived or are living in malaria areas should be deferred for 3 years. If these deferral times are not possible to maintain, the donor should receive empirical treatment of malaria before donation. Blood smear and immunochromatogenic tests and polymerase chain reactions (PCRs) are all inappropriate tests for evaluating asymptomatic potential donors.[24]

Chagas Disease (American Trypanosomiasis)

Epidemiology

Chagas disease is caused by *T cruzi*, a protozoan parasite first described by Carlos Chagas in 1909. Chagas disease is endemic in the Americas, from the south of the United States to the south of Latin America. As a consequence of the initiatives of the South and Central American countries since 1991 in the control of Chagas transmission, the disease prevalence has been reduced from the 1990 estimates of 16 to 18 million people infected to 9 to 12 million people in 2004.[25] The parasite is generally transmitted through the feces of infected triatomine insects by penetration of the parasite into the bite wound, conjunctiva, or other mucous membranes.[26] Transmission can also occur by organ transplantation, blood transfusion, from mother to child during pregnancy, and laboratory incident. More recently, some outbreaks due to the ingestion of contaminated food or drink have been reported.[27–29]

Transmission through blood products

Blood transmission is considered as the second most important method of acquiring Chagas disease. With the exception of blood derivatives, all blood components are infective. Transmission by blood transfusion was first suggested by Mazza in

Argentina in 1936, and the first cases of transfusion-associated Chagas disease were published in 1952.[30] The true number of reported cases is also underestimated because no more than 350 cases have been published.[31] In nonendemic countries, cases of transfusion-associated transmission can go undetected because acute infections are often asymptomatic and the level of awareness of Chagas disease among clinicians is low.[28] In endemic countries where mandatory screening tests have been implemented since 1991, the residual risk of infection is calculated to be around 1:200,000 units.[32]

Transmission in transplant recipients

Transplant recipients from nonendemic countries are more likely to acquire *T cruzi* infection through blood transfusion or by an infected graft, whereas infected recipients from endemic regions are at risk for reactivation of latent infection during immunosuppression. More than 7.5 million individuals are infected by *T cruzi* in endemic countries.[33]

The first strong evidence of transmission via graft was reported in Brazil in 1983. Four renal transplant recipients developed Chagas disease; all 4 had received graft from infected donors in the chronic phase of *T cruzi* infection.[34] Other series have been published, mostly from Argentina and Brazil.[35,36] In the United States, 3 cases of *T cruzi* transmission via graft were reported to the CDC in 2001. Three SOT recipients, 1 liver and 2 kidney, who received organs from the same donor developed Chagas disease.[26] In 2006, two other cases were reported in heart transplant recipients. In both cases, investigation of the source of infection showed that the blood donors tested seronegative for *T cruzi*, whereas the organ donors tested seropositive.[37]

Screening and prevention

Serologic screening of donors is routine in highly prevalent countries, and 2 positive results in different serologic tests are necessary to consider a patient infected. Hemagglutination assays, which were used as the screening method in the past, are being replaced by EIAs, which are now the standard for donor screening.

Donor/recipient pretransplant investigation of the epidemiologic risk for Chagas disease is mandatory. Risk factors for *T cruzi* infection are being part of the native population from endemic areas (continental countries of Latin America), having received blood transfusion in endemic countries, being born to mothers who are natives of endemic areas with unknown serology for Chagas disease, or having lived in an endemic area for more than a month.[33] EIAs for *T cruzi* are recommended in the case of a positive test result.[38] Donors who died of acute Chagas disease should be excluded. In the case of cardiac transplantation, the heart from a patient with chronic Chagas disease is contraindicated because of the risk of chagasic myocarditis. Similarly, the use of intestines from a donor with Chagas disease is contraindicated.[33]

In Latin America, donors chronically infected by *T cruzi* are not excluded from donation of other organs, except the heart and intestines. However, a close follow-up with serologic and parasitologic methods is strongly recommended, and immediate treatment with benznidazole for 30 to 60 days or nifurtimox for 90 to 120 days should be started if parasitemia is detected. Pretransplant treatment of infected living donors with benznidazole may be considered.[33] Based on the experience in South America, the Chagas in Transplant Working Group from the United States considered that kidneys and livers from *T cruzi*–infected donors can be transplanted with informed consent from recipients and followed up by close monitoring.[38] Surveillance includes pretransplant parasitologic studies (quantitative PCR, Strout method, direct parasitologic tests) weekly up to day 60, bimonthly between days 60 and 180, and annually thereafter.[33]

The recommendation for prophylaxis is controversial both in cardiac and other transplant recipients.[33,39] Prophylactic treatment to prevent disease reactivation should be considered in patients with chagasic cardiomyopathy who undergo cardiac transplantation from a healthy donor. In other transplant recipients, early treatment should be started if monitoring shows evidence of reactivation.

Leishmaniasis

Epidemiology

Leishmaniasis is primarily a zoonotic infection, which includes animal reservoir hosts in the transmission cycle. Anthroponotic forms of leishmaniasis have been increasingly observed as humans enter the transmission cycle of the parasite and get infected. In anthroponotic forms, man is the sole source of infection for the vector.[11] The protozoan is transmitted to humans through the bite of an infected female mosquito from the genus *Phlebotomus* (in the Old World) or *Lutzomyia* (in the New World). However, incidental transmission through blood transfusions or needle sharing among intravenous drug addicts has also been described.[40]

Leishmaniasis is prevalent in 4 continents and considered endemic in 88 countries, of which 72 are developing countries: 90% of all visceral leishmaniasis (VL) cases occur in Bangladesh, Brazil, India, Nepal, and Sudan; 90% of mucocutaneous leishmaniasis cases occur in Bolivia, Brazil, and Peru; and 90% of cutaneous leishmaniasis cases occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria.[41] An estimated 12 million people worldwide are presently infected, with 1 to 2 million estimated new cases occurring every year.

Transmission through blood products

TT of VL with clinical features and outcomes similar to those of the natural infection has been described in endemic and nonendemic areas.[42] In a recent study, *Leishmania* DNA was found in up to 36% of asymptomatic blood donors who tested positive for anti-*Leishmania* antibodies, and, therefore, a theoretical risk of TT VL is present.[43]

Transmission in transplant recipients

More than 100 cases of leishmaniasis have been described in transplant recipients. VL is the most frequently observed clinical presentation. Most cases occurred in SOT recipients, mainly kidney and liver, with few cases reported in HSCT recipients.[11] The geographic distribution of leishmaniasis cases among transplant recipients reflects the endemic areas of human leishmaniasis disease and the number of transplantations performed. More than two-thirds of the reported cases are from Spain, Italy, and France.[44]

In transplant recipients, leishmaniasis may occur due to reactivation of latent infection in a previously infected recipient or due to de novo infection in transplant recipients living in or traveling to areas of endemicity, by blood transfusion, or via an infected graft.[45] This route of transmission is rare and more likely to occur in organs that form part of the reticuloendothelial system, such as the liver.

Screening and prevention

At present, routine serologic screening of organ donors from endemic countries is not recommended. If a donor is known to be positive for leishmaniasis, monitoring of the recipient in the posttransplant period is advised. In suspected cases, serologic tests and direct detection of *Leishmania* amastigotes in bone marrow biopsy samples should be performed. Fluorescent antibody technique or enzyme-linked immunosorbent assay should be used, with Western blot confirmation.[45]

VIRAL INFECTIONS

HIV Infection

Epidemiology

HIV is a zoonosis that originated from simian viruses and transmitted to man probably in the beginning of the twentieth century in Africa. Urbanization favored the adaptation of these viruses to the human host, with sexual transmission being the main route of spread. From Africa, HIV reached several countries, including the United States where the first AIDS case was described in the 1980s. It has been estimated that there are approximately 33 million persons infected worldwide, the majority in Africa. HIV-1 is responsible for more than 95% of the cases and is present in all countries.

Transmission through blood products

Transmission through blood transfusion became evident by the large number of infected individuals among persons exposed to blood products. In the United States, the risk decreased from 1:100 units before any test was available to 1:1,500,000 units after NAT was introduced.[46] Thousands of TT cases occurred worldwide, with incidence and AIDS-related mortality dramatically affecting patients demanding multiple transfusions or constant use of plasma products, such as those with hemophilia. Fear of TT HIV infection and the enormous impact on the society were the driving forces that led to the current level of safety, achieved by many technological developments and massive investments in the blood industry.

Transmission in transplant recipients

The first report of HIV infection transmitted by organ transplantation was in 1989.[47] Other cases were extensively documented, forcing donor testing to be mandatory in most countries.[3] Since laboratory screening for HIV infection became available in 1985, only 1 case of HIV transmission through organ transplantation was documented in the United States, emphasizing the success of the initiative.

Screening and prevention

The fourth-generation antibody tests, which are able to detect both anti-HIV antibodies and the presence of the p24 capsid antigen in a conjugated format, provide a high degree of safety to organs available for transplantation. However, they require obtaining plasma or serum from donors, which may not be possible from cadaveric donors. Because a single organ donor may infect several recipients, all guidelines strongly recommend using organs exclusively from negative donors. NAT also contributes to reducing the window period and increasing protection for the transplant recipient. After the introduction of NAT, the risk of TT of HBV, HCV, and HIV in the United States was 1:600, 1:1149, and 1:1467, respectively.[48] Nevertheless, the additional yield obtained by NAT over a fourth EIA is minimal and becomes significant only in regions where HIV prevalence and incidence are high, such as in South Africa.[49]

However, the risk of transmission through organ transplantation must be balanced against the risk of recipients dying while waiting for an organ. Due to organ shortage and because organ transplantation is often lifesaving, organs from donors with elevated risk of HIV infection may be accepted (with informed consent from the recipient) whenever the benefit of transplantation is considered to outweigh the risk of potential disease transmission.[50] Recipients of organs from increased-risk donors are recommended to undergo testing 1, 3, and 12 months after transplantation.[51]

Hepatitis B

Epidemiology

HBV is a small DNA virus, with efficient transmission by blood and sexual contact. It is prevalent globally, with an estimated 370 million carriers. Infection in adults is relatively harmless, in that 95% of the exposed population clear it without any symptoms. When it becomes chronic, infection may lead to liver inflammation, cirrhosis, and hepatocellular carcinoma. A vaccine that was developed and introduced in the 1990s led to a reduction in the prevalence of infection among vaccinees, which is observed nowadays as these vacinees are becoming young adults and being sexually exposed. However, liver failure caused by HBV is still an important indication for transplantation.

Transmission through blood products

Before the introduction of HBsAg testing for blood donors, TT HBV was observed in approximately 6% of patients with multiple transfusions. Improvement of this test and further introduction of the anti-HBc test significantly decreased this rate. However, HBV is still the most frequently transmitted viral infection, and several cases of transmission continue to be reported in countries of low and high endemicity,[52] and it may have an aggressive course in immunocompromised hosts.[53]

Transmission in transplant recipients

HBV transmission was reported from the transplantation of not only organs such as the kidney and liver but also the cornea and bone marrow. Because the presence of HBV is an important indication for liver transplants, in certain circumstances it is difficult to distinguish a new infection on the liver graft from a reactivation of the recipient's previous infection. Without any prophylaxis, in almost all cases, HBV-infected recipients present recurrence after transplantation. The availability of high-titer anti–hepatitis B surface immunoglobulins and oral antiviral drugs, such as lamivudine, greatly reduced the incidence of HBV-related posttransplantation morbidities.

Screening and prevention

Anti-HBc is a marker of exposure, whereas HBsAg is a marker of virus replication, precluding donation of blood and organs by donors reactive for the latter. Due to organ scarcity, it is acceptable to transplant organs when both the donor and the recipient are reactive for anti-HBc, and, in some centers, HbsAg-positive organs are transplanted into recipients with anti-HBsAg titers that are considered to be protective, that is, more than 100 IU/L. However, this situation is associated with a worse prognosis and frequent reactivation of HBV, leading to graft loss. In endemic countries, such as Italy, Greece, China, and Taiwan, blood donors are screened by the HBsAg test because the prevalence of a high anti-HBc titer would considerably affect the pool of available donors. Other countries such as the United States, Germany, and Brazil use both HBV markers for screening. More recently, NAT was extended to HBV-DNA and incorporated in a multiplex format to HCV and HIV NAT platforms. NAT not only identifies donors on the HBV window period but also interdicts donations regarded as having occult B infection (OBI), thus deeming individuals negative for HBsAg but harboring HBV-DNA as potentially infectious. OBI is common in areas where HBV is endemic and is responsible for the few transfusional cases verified before the introduction of NAT. The current risk of TT HBV in the United States, where 3 parallel tests are performed (NAT, anti-HBc, and HBsAg), is estimated as greater than 1:500,000. Whenever possible, NAT of organ donors should be accomplished because this group usually presents a higher risk for infectious markers.[54]

Hepatitis C

Epidemiology

HCV is an RNA virus belonging to the Flaviviridae family. It is transmitted by contact with blood, and, in contrast to other members of the Flaviviridae family, HCV transmission to humans by arthropod vectors was never reported. HCV was first cloned from the plasma of individuals experiencing posttransfusion hepatitis not associated with hepatits A viruses (HAVs) or HBVs. After HCV was cloned and characterized in 1989, a laboratorial tool for identification of infected patients was rapidly developed and used in epidemiologic studies and for screening blood and organ donors.[55]

It is estimated that approximately 2% of the world population are carriers of HCV.[56] A population-based survey has shown that the true prevalence is 1.42% in the United States. Egypt has the highest prevalence (15%–20%), and this has been attributed to massive spread of this virus during campaigns for the treatment of schistosomiasis along the Nile River from 1961 to 1986.[57]

Transmission through blood products

HCV was identified in the search for a cause of hepatitis that is frequently observed in transfusion recipients in whom HBV and HAV infections were ruled out by laboratory tests. Before anti-HCV tests were made available in 1990, the so-called non-A non-B hepatitis had an incidence greater than 10% in patients with multiple transfusions. Nowadays, the risk is about 1 in 1,000,000 transfused units when NAT and antibody testing are performed.[58]

Transmission in transplant recipients

To date, HCV is the main cause for the failure of kidney transplantation, and the use of organs from HCV-positive donors is acceptable and common, mainly for kidney recipients whose anti-HCV test result is also positive. However, HCV and HIV cotransmissions have also been observed in HCV-negative recipients, presumably by a donor in the window period.[50] Although the use of NAT could have prevented such cases, its use is not recommended because it may cause delay in transplantation and increase organ shortage, which strongly contrasts the policies on blood transfusion.

Screening and prevention

Detection of antibodies to several HCV antigens in the EIA format is the test of choice for screening blood and organ donors. At present, these EIAs are in their fourth generation, which, similar to the anti-HIV assay, allows the simultaneous detection of both antibodies and HCV core antigen. A difficulty associated with excluding donors at risk for HCV infection by predonation interviewing is that up to 50% of the infected donors do not report any obvious source of transmission (eg, use of intravenous drug, previous transfusion, needle sharing), and hence prevention of TT HCV infection largely relies on laboratory testing. Because of the longer time to seroconversion, approximately 90 days, HCV was the first agent to be targeted by NAT. The yield of NAT-only donors worldwide is about 1:250,000 donations, with important regional variations.[59]

Arbovirus

Epidemiology

Arboviruses are a heterogeneous group of agents transmitted to humans by arthropods, most significantly mosquitoes and ticks. By feeding on human blood, several species of female mosquitoes transmit the pathogens present in their digestive system to the individual from whom blood is sucked. *Aedes aegypti* and *Aedes albopictus* have adapted to living close to humans by reproducing in water accumulated

near human habitats. Being spread worldwide, dengue is the most important human-arthropod–borne viral disease. Autochthonous cases have been described from the United States (Florida) to Argentina, and there is no vaccine available. At present, the incidence has been estimated at more than 50 million cases globally and is rising every year, mainly in the Americas.

There are 4 dengue serotypes. Infection by one serotype provides lifelong immunity against that serotype but only partial and transient protection against subsequent infection by the other 3 serotypes. There is compelling evidence that secondary and tertiary dengue infections tend to be more severe than primary dengue infection. After being bitten by an infected mosquito, symptoms develop in approximately 7 to 10 days, lasting for a maximum of 15 days.

Transmission through blood products

The contrast between the huge number of cases of dengue fever in endemic countries and the rare reports of transfusion-transmitted dengue is astonishing. Only 3 well-documented episodes of dengue virus transmission by blood transfusion, and only 1 of them resulting in clinically evident disease (dengue hemorrhagic fever) in the recipient, have been reported so far,[60] much less than what would be expected from the prevalence projected from blood donors, although transient asymptomatic dengue viremia is a potential risk to the blood supply. In a recent publication, dengue viremia was detected in 0.04% and 0.30% of asymptomatic blood donors from Brazil and Honduras, respectively.[61] Because recipients are not systematically investigated, the detection of transfusion/organ transmission occurs only when they present with overt symptoms. Further studies are needed to establish the rates of TT by viremic donations and the clinical consequences in recipients.

Transmission in transplant recipients

The transmission of dengue in transplant recipients living or traveling to endemic areas is, by far, via a mosquito bite. In most of the published cases, dengue was acquired by vector transmission.[11] Dengue transmission via graft has also been reported in HSCT and renal transplant recipients.[62–64] The disease has certainly been underdiagnosed in transplant populations from endemic areas because most of the cases are mild and present as a flulike syndrome. Consequently, the actual incidence, morbidity, and mortality associated with dengue and its complications are difficult to estimate.

Screening and prevention

Patients who had dengue are eligible for blood and organ donation after recovery, when development of IgM and IgG indicates virus clearance. The risk of transmission by blood and organ donation stems from asymptomatic hosts and the short incubation period preceding viremia/fever. It has been observed that for each case of dengue fever, there are 2 other asymptomatic infected cases. Not unexpectedly, dengue RNA has been detected among blood donors in endemic areas.[64] So far there are no screening tests validated for blood and organ donation. Testing strategies, in analogy to the WNV, belonging to the Flaviviridae family, include NATs or antigenic assays with high sensitivity.

Rabies

Epidemiology

Rabies is a zoonotic viral disease, which infects domestic and wild animals. It is distributed worldwide, but few countries are free of rabies: Japan, New Zealand, Sweden, Norway, Greece, Portugal, Barbados, Fiji, Seychelles, Maldives, Uruguay, and Chile. Rabies is most prevalent in developing countries and is certainly underreported.

Several countries that are considered endemic for canine rabies (among them India and Pakistan) do not include rabies among notifiable diseases, and hence the actual incidence is unknown.

Dog bites are the most frequent mode of transmission in most countries in Africa, Asia, Latin America, and the Middle East. In contrast, in North America, most documented human rabies deaths occurred as a result of infection from the bat rabies virus.[65] The contact of infected saliva with scratches, licks on broken skin, and mucous membranes may also cause rabies.[66] Human-to-human transmission occurs almost exclusively as a result of organ or tissue transplantation.

The rabies virus causes acute viral encephalomyelitis, which is virtually 100% fatal. The virus may remain latent near the inoculation site, then replicate in muscle or dermal cells (in the case of some bat variants).[67] Around 55,000 rabies deaths occur annually and are generally associated with dog bites. Bat rabies variants may cause clinical manifestations different from what is seen in humans infected with canine rabies.

Rabies in transplant recipients

Human-to-human transmission of rabies has occurred in 16 organ and tissue transplant recipients (8 corneas, 7 solid organs, 1 vascular tissue). The 16 cases occurred in 6 countries: 5 in the United States, 4 in Germany, 2 in Thailand, 2 in India, 2 in Iran, and 1 in France.[67,68] In all cases, the donors died of an illness compatible with rabies, even though the diagnosis was only suspected when the recipients died of rabies.[68] These cases illustrate how easily the diagnosis of rabies may be missed if a clear investigation of rabies exposure is not done. In the SOT cases, the donors had a recent history of bat and dog bites, which were not elicited or considered important. Because bat teeth are very fine, bat bites and bat-inflicted scratch marks may be undetectable and the epidemiologic risk underestimated. In the United States and Canada, the incidence of bat-variant rabies cases increased from 2.2 cases per billion person-years from 1950 to 1989 to 6.7 cases per billion person-years from 1990 to 2007.[65]

Screening and prevention

A detailed history of contact with bats should be obtained from the organ donors' relatives and friends. In the absence of a clear history, physical signs, and reliably performed rabies diagnostic tests, the safest strategy is to exclude any donor with neurologic signs and symptoms of unknown cause. In the case of exposure (suspected history or rabies diagnosed postmortem in the donor), postexposure prophylaxis with human rabies immunoglobulin should be immediately started (20 IU/kg), as well as the first dose of rabies vaccine. Additional doses should then be administered on days 3, 7, 14, and 28 after the first dose. The vaccination should always be administered intramuscularly in the deltoid area (adults) or in the anterolateral aspect of the thigh (children).[68]

SUMMARY

In the previous century, the discovery and successful introduction of penicillin and further development of antibiotic therapy led the medical community to predict that infectious diseases would decline as a leading cause of death worldwide, giving place to cancer and circulatory illnesses. Surprisingly, in 2012, infectious diseases, mainly malaria, continue to kill thousands and affect millions around the world. Chaotic urbanization, waste accumulation, global warming, tourism, and human migrations have all contributed to the dissemination of infectious agents and associated vectors. Autochthonous dengue cases in the United States and France and the chikungunya

outbreak in Italy illustrate this new scenario of the diseases that were previously named tropical.

As long as reliance on humans as donors of blood and tissues for transplantation continues, issues with transmissible agents and the fact that several agents are no more restricted to the tropics have to be dealt with. Technological advances in molecular diagnostics and vaccine production provide tools for active surveillance and quick response, as seen recently for severe acute respiratory syndrome and influenza H1N1 threats when appropriate measures avoided potential pandemics of these lethal agents. Permanent research and active communication is the effective answer, and the authors hope to give a small contribution with this article.

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