Emergent Arboviruses and Renal Transplantation: A Global Challenge

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In recent years, Zika, Chikungunya, Dengue, West Nile Fever, and Yellow Fever epidemics have generated some concerns. Besides difficulties related to vector control, there are challenges related to behavior of pathologies not yet fully understood. The transplanted population requires additional care due to immunosuppressive drugs. Furthermore, the potential risk of transmission during donation is another source of uncertainty and generates debate among nephrologists in transplant centers. Do the clinical outcomes and prognoses of these infections tend to be more aggressive in this population? Is there a risk of viral transmission via kidney donation? In this review article, we address these issues and discuss the relationship between arbovirus and renal transplantation.

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Arboviruses comprise a group of viruses disseminated by arthropods, generally hematophagous insects and ticks. Arboviruses are endemic to all continents, except Antarctica (Figure 1). They cause several diseases, some of which are emerging and spread primarily by mosquitoes. The virus is transmitted to the mosquito during the bite, lodging in its salivary glands, and is transmitted in subsequent bites.

Current importance of arboviruses stems from the increase in global incidence of cases, especially in tropical countries. Increasing urbanization and destruction of natural habitats promoted the approximation of large population groups to vectors and their intermediate hosts.

There are approximately 500 species of mosquitoes, of which approximately 150 can cause disease in humans.² Three are arbovirus families: Reoviridae, Togaviridae, Bunyaviridae, Rhabdoviridae, and Flaviviridae.¹ The latter is responsible for yellow fever, dengue, Zika, and West Nile fever. Chikungunya virus belongs to the Togaviridae family.³,4

Arboviruses often present with similar symptoms, which may occasionally confuse the diagnosis. In such cases, a complementary laboratory serological or molecular evaluation may be necessary. The diseases produce a variety of clinical manifestations, such as hemorrhagic syndrome, neurological symptoms, arthralgia, arthritis, and mild febrile syndrome.²,³

The global spread of arboviruses is a concern because more than 30% of the world population lives in areas of risk.³,⁶,⁷ In addition to barriers to effective vector control, dealing with clinical entities that are not yet fully understood is an additional challenge. The transplanted population requires additional consideration due to immunosuppression. Moreover, potential risk of transmission during donation is another source of uncertainty and generates debate in transplantation centers.

Dengue

Dengue is probably the most studied arbovirus. It is endemic in more than 100 countries. Incidence of the classic form of the disease is estimated at 100 million cases annually.⁸

Currently, America, Southeast Asia, and Western Pacific regions are the most seriously affected by the disease.⁷ In the Americas, 581,207 cases were registered in 2017; approximately 218,337 of those cases occurred in Brazil.⁹ Public health concerns include difficulty of vector control, aggravated by the tropical climate, increasing numbers of humans infected, and potential lethality.

Dengue is caused by a flavivirus that is transmitted primarily by the Aedes albopictus and Aedes aegypti mosquitoes.¹⁰ Rarer alternative forms of transmission were also described, including percutaneous,
nosocomial, and vertical pathways. Infections transmitted by blood transfusion and organ transplantation also have been reported. In naturally acquired dengue, duration of viremia varies from 2 to 12 days, lasting 5 to 6 days in most patients. This phase of viremia may precede onset of classic clinical symptoms. Thus, blood derivatives collected during this period can transmit the pathogen to susceptible receptors. Conversely, for each case of classic dengue, it is estimated that there are at least 3 asymptomatic patients. The association of the long duration of viremia and the high percentage of asymptomatic viral carriers confers a potential risk of transmission in organ and tissue transplantation. Therefore, there are several reports of asymptomatic blood donors with viremia during periods of outbreak.

Although blood transfusion is a known transmission route for dengue virus infection, it does not pose a risk for the safety of blood transfusions. In renal transplantation, despite documented cases of transmission through donation, screening donors for dengue virus is controversial.

Active screening for dengue virus infection during evaluation of potential donors may be unnecessary. Although previous reports suggest a theoretical risk of transmission, estimated risk can be considered low, and cost-effectiveness of serological and laboratorial screening in donors is not justified.

In contrast to high rates of viremia in donors, incidence of posttransplant dengue infection does not appear to be elevated, even in times of outbreak. There are several possible explanations for this. In endemic regions, many individuals probably have already acquired antibodies with protective IgG. Prevalence of positive serology in the population exceeds 90% in some cities. Another reason could be the pathogenicity of the virus, which appears to be lower through blood transmission in organ and tissue transplantation than via direct inoculation by the mosquito of the genus Aedes. This may occur due to strong inflammatory response triggered by vector’s saliva.

Because dengue is an immune-mediated disease, it is possible that there are differences in clinical expression in immunocompromised patients. A definitive consensus on this issue is not easily reached. Although some reports highlight a relatively benign course of the disease in transplant patients, not unlike the healthy population, other reports present a more severe clinical scenario. There are no reports of graft rejection among dengue-infected cases.

The clinical course of dengue in secondary infections is also a concern. The main theory to justify the increased frequency of severe forms of dengue in secondary infections is the phenomenon of increased antibody-dependent enhancement. It is postulated that neutralizing antibodies from a previous dengue virus infection would be able to bind to the serotype of the secondary infection, but with low neutralization capacity. Intact viral particles would be phagocytosed via interaction of these antibodies with receptors for the IgG Fc fragment, expressed in monocytes and macrophages, where they would multiply and trigger a

Figure 1. World map representing continents affected by arboviruses. Arboviruses are endemic to all continents, except for Antarctica. This figure highlights in red the regions most affected by arboviruses.
massive release of mediators, with effects on hemostasis and vascular permeability.\textsuperscript{37}

In a 2007 retrospective analysis of 27 patients who received a renal transplant, clinical manifestations and outcomes were similar to those of the general population. All patients had fever, followed by muscle pain (90\%), malaise (75\%), and headache (68\%). One case of dengue hemorrhagic fever and 1 death were reported. Mean serum creatinine, which was 1.4 mg/dl before dengue, rose to 1.9 mg/dl during the episode but returned to baseline recovery values. Dengue virus infection was not related to long-term damage in renal graft function.\textsuperscript{38} In 2015, another series of 10 cases reported dengue hemorrhagic fever in 4 patients. Three of these patients required dialysis and only 1 of them recovered graft function. The other patient had "discrete" and nondetailed increases in serum creatinine. There were no deaths reported in this series.\textsuperscript{39}

A systematic review in 2017 identified 168 cases. When compared with the healthy population, a lower frequency of classic dengue symptoms was observed in transplanted patients. The mean increase in baseline creatinine was 67.0% and 6.5% of patients lost the graft. The authors also reported a higher mortality rate (8.9\% vs. 0.06\%) in transplanted patients, likely due to the increased incidence (16\%) of dengue hemorrhagic fever or dengue shock syndrome. It is important to emphasize a potential selection bias in this study; because mild cases are commonly not detected and treated as nonspecific viruses, there is a trend to select the more severe cases.\textsuperscript{40}

Conflicting studies have linked immunosuppressive drugs to clinical outcomes in this population. Higher doses of corticosteroids (>7.5 mg/d orally) were associated with a more severe disease in cases of primary infection.\textsuperscript{29} Patients on cyclosporine regimen had less severe disease.\textsuperscript{29} Tacrolimus was associated with increased risk of bleeding complications and increased lethality. However, a subsequent systematic review did not confirm these findings.\textsuperscript{40}

Therefore, because the intensity of immunosuppression does not determine the outcome of most patients, and because there is no specific therapy for dengue infection in transplant recipients, early diagnosis and supportive treatment are currently available tools for better clinical management.\textsuperscript{36,41}

Yellow Fever

Yellow fever (YF) is an infection with variable clinical spectrum and a high lethality. Approximately 200,000 cases of YF occur annually, 90\% of them in Africa. A dramatic resurgence has occurred since the 1980s in both sub-Saharan Africa and South America.\textsuperscript{42} There are 2 forms: the wild and urban YF. The latter was eradiated from the Americas some years ago. The wild form is transmitted by mosquitoes of the genera Sabethes and Haemagogus and it is a zoonosis that primarily affects monkeys. Humans may accidentally become infected by living in rural areas at risk.\textsuperscript{32–44}

There have been no reports of YF transmission by organs or blood. This is probably due to the small number of cases, mostly confined to rural areas, and the presence of a large vaccinated population.\textsuperscript{25}

The presentation of YF ranges from subclinical infection to systemic disease, including fever, jaundice, hemorrhage, and renal damage. The variety of clinical symptoms may be due to the different virus strains and immunological factors of the host. Viremia peaks 2 to 3 days after infection and patients who present with evolution to death usually have a longer duration of viremia.\textsuperscript{42}

In immunocompetent patients, YF vaccine is effective and relatively safe. The risk of side effects increases with age. Severe adverse reactions, such as Guillain-Barré syndrome and encephalitis, are rare and affect 1 individual every 125,000 vaccinations. Although rarer, acute viscerotropic disease has clinical manifestation similar to YF itself and can be fatal. In the most recent estimate, incidence of this reaction was 0.3 per 100,000 doses.\textsuperscript{45}

Vaccination against YF in transplanted patients is contraindicated\textsuperscript{46,47} because it is an attenuated live virus vaccine.\textsuperscript{47} Although there were no reports of YF in transplant patients, due to the increasing reports of the vaccine in this population, some questions were raised regarding the prohibition of vaccination in this group.\textsuperscript{48}

Transplanted patients are occasionally vaccinated inadvertently. A questionnaire-based study aimed to investigate side effects of vaccination in this population. Nineteen cases of YF vaccination were identified in transplant patients, 14 of whom were renal transplant recipients. Only one patient had a mild reaction at the puncture site. No serious adverse events were reported. Despite promising results, some considerations should be made. Its retrospective nature and small sample size are limitations of the study.\textsuperscript{48}

There is evidence that corroborates these observations and suggests that the YF vaccine in immunocompromised patients is relatively safe. No severe adverse events were reported in patients with rheumatologic disease,\textsuperscript{49,50} bone marrow transplant recipients,\textsuperscript{51,52} and patients with HIV.\textsuperscript{53–57}

In areas of high incidence, the risk-benefit ratio may weigh in favor of vaccination.\textsuperscript{44} Because vaccination is not innocuous, vaccination should be applied only to people who are at real risk or meet the migration requirements. In clearly at-risk individuals, especially
the elderly, the potential effects should be carefully weighed. 

Although there are persistent YF antibodies in suitable medium- and long-term titers in previously vaccinated transplant recipients, experts recommend that seroprotection of these patients be verified in cases of travel plans to places of risk. 

Candidates for transplantation preferably should be vaccinated at least 1 month before transplantation.

Additional studies are needed to attest the safety of YF vaccine in transplant patients. Conversely, it is also necessary to emphasize the lack of data indicating the opposite and, thus, sustain the contraindication.

In situations of major epidemics, benefits of YF vaccination are likely to outweigh the harm, even in transplant patients. Therefore, it is possible to consider YF vaccine in transplant patients as a relative contraindication. Despite current guideline recommendations, it could be considered in particular cases.

**West Nile Fever**

Despite absence or low prevalence in some countries, West Nile Fever (WNF) is the main arboviruses in other countries, such as the United States. In addition to the high incidence in this country, it is an important cause of morbidity, representing a high economic and social impact. In 2013, it was the main neuroinvasive arbovirus, responsible for 1267 events in the United States alone.

WNF is a zoonosis that primarily infects mosquitoes and birds. Horses and humans are accidental hosts. Infection in humans has an average incubation period of 3 to 5 days but may range from 2 to 14 days and is usually subclinical. Some comorbidities, such as diabetes mellitus and old age, increase the risk of a more severe clinical manifestation, presenting with muscle weakness and encephalitis. Only 20% of immunocompetent patients infected with WNF virus present clinical signs and symptoms. Of these, an even smaller portion develops severe neurological complications of the disease: encephalitis and meningitis. The usual presentation is a febrile syndrome, lymphadenopathy, ocular pain, and headache.

Long incubation and high percentage of asymptomatic cases increase the risk of transmission by transfusion or transplantation during an epidemic. In the 1990s epidemic in New York, it was statistically estimated that the maximum and average transfusion risk would be 2.7 and 1.8 per 10,000 transfusions, respectively.

The first reported transmission of WNF virus occurred in 2002. Four patients who received organs from the same donor developed fever and altered mental status between 7 and 14 days after transplantation and were diagnosed with WNF. Three patients developed encephalitis. One recipient had brief illness and 2 patients suffered long illness but survived, and 1 kidney recipient died. The donor had received blood products from 63 different donors and one of them had positive viremia.

The clinical presentation of WNF in transplant patients seems to be different and more severe than in the general population. In 2014, another case series of 4 infected recipients from an asymptomatic donor were described. A literature review identified 23 exposed recipients. Of these, 3 remained asymptomatic and 20 developed disease. The mean time to symptoms was 13 days and the most common presentation was fever not responsive to antibiotics, followed by rapid onset of neurological symptoms (dysarthria, flaccid paralysis, seizures, and coma). There was a high incidence of neuroinvasive manifestations (70%) and death or permanent coma (30%).

There is no specific antiviral treatment for WNF. Usual treatment consists of reduction of immunosuppression, associated with polyclonal or specific IgG and interferon.

As there are few cases and some patients recover without any intervention, it is not possible to address therapeutic recommendations.

In countries where it is not endemic, WNF is considered an arbovirus with real and imminent risk of emergence. In the absence of effective therapies, the current treatment is prevention, which includes barriers that increase the safety of blood and organ donation and nonacceptance of donors from areas of WNF with fever and rapid onset neurological symptoms.

**Zika**

This arbovirus remained unnoticed for a long time, despite its isolation in a sample from a monkey on Zike Island, Uganda, in 1947. Zika attracted greater attention only after epidemics in Micronesia, Gabon, and French Polynesia in 2007, 2010, and 2013, respectively. In the West, infection with Zika virus (ZV) occurred initially in 2014. In 2015, it was detected in Brazil.

Both ZV and chikungunya virus (CHIKV) infection have become a concern in recent years. Because they are new, the implications are not yet fully known, especially regarding clinical evolution in transplant population and the risk of transmission through organ donation.

ZV transmission forms include the natural route through the mosquito bite, vertical transmission, breastfeeding, and sexual contact. Current data showed transmission by blood products and by transplants.

Typical presentation of ZV is a fever with arthralgia, headache, myalgia, and exudative conjunctivitis. A maculopapular erythematous rash is also
characteristic. The infection is related to neurological complications such as Guillain-Barré syndrome, meningoencephalitis, and microcephaly and other cerebral abnormalities in neonates.

Little is known about the natural history of ZV infection in organ recipients or immunodeficient individuals. One report describes 4 solid organ recipients, 2 of kidney and 2 of liver, which were studied after febrile illness. No patient had cutaneous manifestations, conjunctivitis, or neurological involvement. In 2 of these patients, the febrile syndrome was associated with adynamia and myalgia. All patients had thrombocytopenia, and 3 had anemia. There was an acute worsening of renal or hepatic function in all patients. Although clinical evolution was more severe than usual in immunocompetent patients, there were no deaths or long-term clinical sequelae.

Another case report is about a heart recipient, who developed fever, adynamia, headache, and seizures, without cutaneous lesions, 8 months after transplantation. The patient presented a severe evolution, with acute neurological deterioration, hemodynamic instability, and coma, followed by death. The autopsy showed a pseudo tumoral form of meningoencephalitis from ZV.

Reports of ZV transmission through blood transfusion and transplanted organs are rare. Severe clinical presentation in this population is a concern. Subclinical infections and oligosymptomatic cases that do not require specialized medical attention increase the risk of transmission. Potential risk was confirmed by the report that approximately 3% of blood donors who were asymptomatic tested positive for ZV in routine screening of blood donors during outbreak.

A retrospective study conducted in the United States showed that 2 kidney recipients from an IgG-positive donor for ZV had no signs of rejection 6 months after transplantation.

Some guidelines are still based on fragile evidence of small case series and reports. It is currently recommended to contraindicate transplantation with a deceased donor in at-risk areas if symptoms suggestive of donor infection have occurred in the past 6 months, as well as postponing donation for at least 4 to 6 months after the onset of symptoms in living donors with prior history of infection.

Unfortunately, a laboratory test for routine screening is not currently available in many countries. Prevention of infection induced by blood or organs depends on clinical screening to identify signs and symptoms suggestive of previous infection by ZV. As infection is endemic to countries, a contraindication policy would not be beneficial because it would greatly reduce the availability of donors. Thus, active surveillance systems, with access to retrospective diagnosis in donors and transplant recipients where the disease is highly prevalent, should be established.

Another prominent point is viral persistence in organs in absence of viremia. It is unclear whether the presence of viral RNA in organs represents active infection, intact virus, or residual viral RNA after elimination of the infection. Therefore, it is still uncertain whether positive blood tests for ZV may represent real risk in organ donation.

**Chikungunya**

Chikungunya fever, like Zika, is a recent disease. CHIKV has been identified in more than 60 countries in Asia, Africa, Europe, and the Americas. CHIKV is believed to have originated in Tanzania in the 1950s. The first large outbreak in the Americas occurred in 2013 in the Caribbean islands. In 2016, there were approximately 350,000 suspected and 146,914 confirmed cases in the Americas. Brazil was the country with the highest number of suspected cases, approximately 265,000.

There are 4 distinct CHIKV genotypes currently in circulation. Incubation period varies from 2 to 4 days and viremia lasts, on average, from 5 to 7 days and can reach up to 3 weeks. Infection can be transmitted through the mosquito bite by vertical, intrapartum, and blood transmission. Most cases of CHIKV infection are asymptomatic or self-limiting, although polyarthritis and arthritis are usual presentations.

Increased risk of disease has been described in patients with underlying medical conditions, including immunosuppressed individuals. It is difficult to assess the actual prevalence of the disease in this population because many oligosymptomatic cases were probably treated without serological confirmation.

In the few available reports in renal transplant patients, CHIKV infection has been reported to be a mild disease, with no apparent damage to the graft. The largest study of CHIKV infection in transplant recipients was performed in an endemic area, with 13 cases (9 kidney and 4 liver recipients). All patients had arthralgia and 84.6% had fever. There were no deaths or complications, and all individuals fully recovered.

Although these reports suggest a benign course of the disease in transplant recipients, CHIKV infection may lead to complications with high mortality rates. Serious or atypical cases have been reported, including neurological and cardiovascular disorders and renal and ocular diseases.

A characteristic of CHIKV is tissue persistence after the acute viremic phase of infection. An experimental model in monkeys observed persistence of viable CHIKV in joints, muscles, lymphoid organs, and...
liver, and identified macrophages as the main cellular reservoir. \(^\text{104}\) Recently, mice have been shown to maintain viral RNA in joint tissues for at least 16 weeks. In humans, during a 2005 to 2006 epidemic, CHIKV was isolated in corneas from deceased donors. \(^\text{105}\) Possibility of recipient infection was suggested even with negative viremia in the donor. Although kidneys were apparently spared from harboring the virus, \(^\text{104}\) persistence of active virions in tissue "sanctuaries" is a concern for transplants with solid organs. These concerns led to the recommendation to screen potential donors who died in or on returning from areas of endemic CHIKV infection. \(^\text{100,106}\)

Despite global spread of this arboviruses and presence of CHIKV in up to 2% of blood donors during epidemics, \(^\text{107}\) there are no documented cases of virus transmission via transfusion or organ transplantation. \(^\text{25,108}\) Clinical screening, the relatively short viremic phase, as well as occasional bans on potential donors from at-risk areas may have contributed to this favorable outcome.

Living and deceased donors from nonendemic areas can be assessed for risk of exposure through screening for recent trips. It is suggested that the donation be postponed for at least 30 days if the donor lives or has traveled to endemic areas and has symptoms or laboratory confirmation of CHIKV. Living donor candidates should be advised to avoid travel to endemic areas. \(^\text{25,26}\)

In live kidney donation, transplantation could theoretically be postponed until development of protective immunity. However, due to the phenomenon of tissue persistence, it is unknown what the safe window of time would be to allow transplantation without exposure of the recipient to the risk of a disease transmitted by the graft.

Recently, this dilemma was evidenced during the evaluation of a living kidney donor. On the day of hospitalization, the donor had fever, generalized malaise, and joint pain, resulting in surgery cancellation. In laboratory investigation, CHIKV was diagnosed. The donor candidate has progressed satisfactorily with complete resolution of symptoms and, after 6 weeks, serological conversion was observed. Four months later, the transplantation was performed with good late evolution. \(^\text{109}\)

Conclusions

Despite increasing spread of arboviruses worldwide, the level of evidence for decision-making involving various aspects of transplantation is still incipient. Most recommendations from medical societies, committees, or groups of experts are based on only case reports or small series.

There are still uncertainties related to arboviruses. For greater safety in a still very unknown scenario, health care practitioners should consider the epidemiological data of the region of residence or travel of patients, heightened clinical surveillance, careful investigation of cases of undiagnosed fevers, especially when there is rapid and unfavorable evolution, and laboratory follow-up of suspected cases.

DISCLOSURE

All the authors declared no competing interests.

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