

NHS BLOOD AND TRANSPLANT
ORGAN DONATION AND TRANSPLANTATION

ZIKA VIRUS AND TRANSPLANTATION OF SOLID ORGANS FROM DECEASED DONORS

KEY POINTS

- Zika virus is endemic in parts of Africa and Asia and is currently causing an epidemic in most parts of South and Central America. It is a Flavivirus of the same family as Dengue, Yellow Fever and West Nile virus and is spread to humans mainly through a bite from an infected mosquito.
- Viral infection is usually asymptomatic or associated with very mild symptoms but there is now scientific consensus that Zika virus is a cause of microcephaly and other neurological disorders.
- Evidence suggests preferential viral tropism for neural progenitor cells but pathogenesis is being elucidated.
- Infected people are usually viraemic only for a short period (5-7 days) after onset of symptoms, but the virus may be found in other sites after the virus goes undetectable in blood. Virus RNA has been detected in saliva, urine and sperm. Less is known about the virus dynamic in asymptomatic cases.
- There are reports of possible transmission by blood transfusion. Transmission through solid organ allografts has not been reported, but current evidence indicates that this is possible.
- The impact of immunosuppression on the natural history of Zika virus infection is unknown.
- To date, there has been one report of an asymptomatic infection in a liver recipient following a possible transfusion-transmitted infection¹. A small case series described 4 SOT recipients with symptomatic Zika infection, who all recovered.² Another report described an asymptomatic course of a possible transfusion acquired infection in a stem cell transplant recipient³
- Donor characterisation includes a full recent travel history; when the potential donor has been to affected areas, the SNOD will enquire about dates and places, compatible illness in the donor or immediate contacts, as per routine patient assessment practice.
- Exposure to other geographically – restricted infections will also be assessed in context, as required.
- Routine screening of deceased organ donors with positive travel history is not currently a SaBTO recommendation.
- Each case should be assessed individually and specialist advice should be sought at the earliest possible opportunity to allow time for discussion and planning.
- Antibody tests for Zika virus are available for diagnostic use but serology is complex. They do not have a role in organ donor screening.
- In the UK, diagnostic testing for Zika RNA in suspected clinical cases is only carried out in one reference laboratory, on a daily basis, and during normal working hours.
- Recipient clinicians should balance the risk and possible consequences of a donor-transmitted infection and the risks of harm by declining the organ.

Note: The knowledge base of Zika virus continues to change and users should interpret these notes accordingly. They are for information and do not constitute a substitute for balanced clinical judgement.

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ZIKA VIRUS AND SOLID ORGAN TRANSPLANTATION

The Zika virus epidemic continues in the Americas and Caribbean. The risk of local vector-borne transmission in Europe is also being monitored and remains low.

This is an emerging situation that has evolved relatively rapidly. Diagnostic tools are not widely available yet and the complexity of host immune response to Flaviviruses makes interpretation of results difficult. Currently, there is no role for serological tests in the screening of asymptomatic deceased organ donors.

There is now strong evidence of an association between Zika virus infection and congenital CNS malformations⁴, as well as Guillain–Barré syndrome⁵. The exact extent of the problem and pathogenic mechanisms remain to be elucidated.

To date, no cases of transmission through transplantation of cells, tissues or organs have been reported. Transfusion-associated and sexual transmission have been described.

In the UK, cases will be seen amongst travellers returning from affected areas as the vector is not present here. As of 1st September 2016, 113 cases have been confirmed in UK travellers since 2015. Every year, approximately 1.4 million UK travellers go to areas where Zika transmission is currently ongoing. An additional 1.6 million travel to Florida alone, an area in the USA where autochthonous cases are occurring.

Understanding of ZIKV pathogenesis and associated clinical presentation and complications is evolving rapidly. Viraemia is believed to be short lived and only 1 in 5 infected people develop symptoms. Excluding foetal and neonatal cases, deaths are exceedingly rare.

Currently in the UK, there is no recommendation for routine NAT screening for any Flavivirus in asymptomatic deceased donors who have been to an area where there is ongoing transmission. However, this is a new and rapidly evolving situation where there are significant gaps in knowledge and growing understanding about the neurotropic nature of Zika virus. The following precautionary measures may be considered, subject to revision, as more information becomes available:

Potential donor scenario	Points to consider	Comment
Asymptomatic traveller returning from affected area	<p>The travel history should include: area visited with dates, diurnal mosquito bites, symptoms and contact with anybody who had compatible symptoms before or after the given contact. *(see foot note below)</p> <p>Take sample (blood in EDTA) from the donor if <28 days from date of return or exposure.</p> <p>Discussions will inform the possibility of <i>post hoc</i> molecular testing, which can be facilitated by the ODT microbiologist.</p> <p>Case by case assessment is required and consideration of risk-benefit needs to be made independent of any specific testing.</p> <p>Discuss all cases as other geographically restricted pathogens may also need to be considered.</p>	<p>No evidence currently available; seek specialist advice and assess individual cases in context.</p> <p>Urgent testing is not possible for various reasons but early identification of cases may enable timely testing, if appropriate.</p> <p>A negative NAT in plasma may inform assessment but does not exclude recent infection.</p>

Potential donor scenario	Points to consider	Comment
Recent, proven or highly likely Zika infection: i)Laboratory confirmed ZIKV infection OR ii)Compatible symptoms whilst in affected area or within 28 days from return or exposure to proven case	Prolonged viraemia beyond 15 days from onset of symptoms is not thought to occur but ZIKV dynamics not fully clarified. Distribution of virus within body compartments is not known. Virus shedding in urine, sperm and saliva is well documented. A cautious approach should be used for donation within the first 6 months from disease resolution. Discuss.	No evidence currently available; seek specialist advice and assess individual cases in context. A negative NAT in plasma may inform assessment but does not exclude recent infection
Current symptomatic illness high likely or confirmed to be caused by ZIKV	Decline for deceased donor organ transplantation except in exceptional circumstances.	

*Sexual exposure to Zika-infected partner: A specific question has not been added to the PA1 questionnaire but the existing content includes contact, including sexual, with an individual with an infectious disease or illness. Questions 22 and 32e, in particular, address these points. Any information captured through these questions or volunteered by the NoK must be noted by the SNOD and discussed.

Zika Virus – General Information

Zika virus (ZIKV) is a Flavivirus related to Yellow Fever, Dengue, West Nile, and Japanese Encephalitis viruses. In 2007 ZIKV caused an outbreak of relatively mild disease characterized by rash, arthralgia, and conjunctivitis on Yap Island in the southwestern Pacific Ocean. This was the first time that ZIKV was detected outside of Africa and Asia. This arboviral disease has emerged in tropical areas of Latin America, particularly in Brazil and Colombia, as a public health threat in 2015 and has spread into areas to which dengue virus (DENV) and chikungunya virus (CHIKV) are endemic. In 2016, it reached southern areas of the USA.

Transmission: ZIKV is transmitted primarily by *Aedes aegypti* mosquitoes. This vector also transmits dengue and chikungunya virus and is found throughout much of the Americas. Vertical transmission is known to occur but the determinants of foetal abnormalities are still being elucidated. There have been few reports of possible transfusion-associated transmission and several reports of spread of the virus through sexual contact. Of note, prolonged shedding in semen is known to occur, with virus RNA being detected up to 181 days after resolution of acute symptoms.⁶

Pathogenesis: Knowledge regarding pathogenesis of ZIKV is evolving but mosquito-borne flaviviruses are thought to replicate initially in dendritic cells near the site of inoculation then spread to lymph nodes and the bloodstream. The incubation period for Zika virus disease is a few days to a week. As with other Flaviviruses, detectable plasma viraemia is short-lived and last only a few days. To date, infectious ZIKV has been detected in human blood as early as the day of illness onset; viral nucleic acid has been detected as late as 11 days after onset. Zika virus is an intensely neurotropic virus that particularly targets neural progenitor cells but also – to a lesser extent – neuronal cells in all stages of maturity^{7,8}. It has been isolated from the brains and cerebrospinal fluid of neonates born with congenital microcephaly and identified in the placental tissue of mothers who had had clinical symptoms consistent with Zika virus infection during their pregnancies.

Clinical presentation: An estimated 80% of persons infected with Zika virus are asymptomatic. Symptomatic disease is generally mild and may include rash with or without fever and at least one of the following: arthralgia, myalgia or non-purulent conjunctivitis. Symptoms usually last from several days to 1 week. Severe disease requiring hospitalization is uncommon, and fatalities are rare. Neurological symptoms consistent

with Guillain–Barré Syndrome (GBS) are known to occur; other neurological syndromes such as acute flaccid paralysis, myelitis, meningitis and meningoencephalitis should be considered. Clinical distinction amongst cases of dengue, Chikungunya and Zika, in areas where these viruses are co-circulating, may be very difficult.

Clinical course in the immunocompromised: There have been two case reports of stem cell and liver recipients^{1,3}, possibly infected through transfusion of blood components; the liver recipient received 12 units of FFP intraoperatively, together with the implicated infectious unit and the serological profile of the other donors was not described in the report. These, together with the first case series of 4 SOT recipients in Brazil² account for the limited published data on the experience with immunocompromised patients. To date, the precise clinical course in the immunosuppressed has not been described in great detail and it is not known whether there are groups of individuals at particular risk of complications; so far, asymptomatic to symptomatic course with recovery has been documented in these very few cases.

Specific prevention and treatment: There is no specific antiviral. Vaccines are under development.

Laboratory diagnosis: Limited number of commercially available tests for Zika virus antibodies and nucleic acid are available and require detailed validation. The PHE Rare and Imported Pathogens Laboratory (RIPL) is currently the only laboratory in England that offers some arboviral testing for the diagnosis of clinically symptomatic cases; these tests have not been validated for screening of asymptomatic individuals. During the first week after onset of symptoms, Zika virus RNA may be detected in serum, saliva or urine. Cross-reaction with related flaviviruses (e.g., dengue and yellow fever viruses) is common and pose a diagnostic challenge. Immune memory response in those who have previously been exposed to dengue is quite strong, adding to the diagnostic complexity of closely-related viruses.

Up to date information: The situation is evolving rapidly and up to date information should be assessed through websites such as

http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.asp

<https://www.gov.uk/guidance/zika-virus>

<http://www.who.int/mediacentre/factsheets/zika/en>

<http://www.cdc.gov/zika/index.html>

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