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WHAT'S NEW IN INTENSIVE CARE

Key points on Zika infection for the intensivist

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Introduction

Zika virus (ZIKV) infection or Zika is a new emerging arboviral disease in rapid geographic expansion, related to congenital malformations and neurological complications in adults. ZIKV was first isolated in 1947 in the blood of a sentinel rhesus monkey in the Zika Forest (Uganda) [1] and later from human samples in Nigeria in 1956. Until recently human infections were reported sporadically, with no major outbreaks. In 2007, the first major outbreak outside of its traditional endemic areas took place on the island of Yap (Micronesia) [2]. Subsequently, an outbreak in French Polynesia was recorded in 2013 with more than 30,000 cases [3]. Autochthonous transmission of ZIKV has been reported in South America since April 2015 [4]. Until March 2016, active transmission of ZIKV was observed in more than 40 countries and territories worldwide.

ZIKV is a member of the flavivirus family, which also includes yellow fever, dengue, Japanese encephalitis, and West Nile virus. The genome is an approx. 10.6-kilobase-long, positive RNA strand that encodes a polyprotein with three structural proteins (capsid, premembrane/membrane, and envelope) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Phylogenetic analyses of ZIKV sequences revealed the existence of two main virus genotypes (African and Asian). The present outbreak is related to the circulation of the Asian genotype [5]. The virus transmission is associated with the bite of an infected *Aedes* species mosquito (*A. aegypti*, *A. albopictus*, and others). The incubation time is not yet clearly defined, but is probably around 3–14 days. Interpersonal transmission, in particular sexual transmission, has been demonstrated [6].

Clinical characteristics

The disease course is usually mild and its symptoms consist of pruritic rash (typically maculopapular), mild fever, conjunctivitis, headaches, arthralgia, myalgia, and asthenia. Zika infection may be indistinguishable from dengue, chikungunya, or other viral infections with fever and/or rash. Asymptomatic infections seem common and it is estimated that only one in four infected people develops symptoms. In a recent series of 58 non-pregnant adult patients PCR-positive for ZIKV from Rio de Janeiro, Brazil [7], exanthema was the most common clinical presentation (98.2 %), arthralgia was observed in 61 %, and conjunctivitis in 38.6 % of the cases. Fever was present in only 60 % of cases, with median low-grade temperature of 38 °C.

Association of ZIKV with microcephaly

The initial observation of clusters of microcephaly cases simultaneously to the ZIKV outbreak in the northwest of Brazil warned of the possibility of association between ZIKV and congenital malformations [8]. These observations were critical to World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC) at the beginning of February 2016 [9]. Robust evidence of this association has emerged, e.g., the isolation of the virus from fetal brain tissue [10] or the presence of the virus in amniotic fluid [11]. In a recent publication in *The New England Journal of Medicine* [12], from a cohort of pregnant woman PCR-positive for ZIKV, the authors identified 29 % with abnormalities on fetal ultrasonography, including intrauterine growth restriction, CNS alterations, and fetal death.

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Guillain–Barré syndrome (GBS) and other neurological complications

Apart from the microcephaly cases, neurological complications have been reported as the most severe complications of the ZIKV infection. An increased incidence of GBS was noticed in countries experiencing recent outbreaks of Zika, such as French Polynesia, Brazil, Colombia, among others. In a case–control study recently published in *The Lancet* [13], the authors demonstrated a strong association between Zika and GBS. In this series of 42 GBS patients diagnosed during the outbreak in French Polynesia, the large majority of patients had positive IgM or IgG antibodies (98 %), as well as neutralizing antibodies against Zika (100 %), compared to only 56 % in the control group (patients admitted to hospital with other syndromes). Additionally, symptomatic Zika was reported by 88 % of the GBS patients preceding the neurological symptoms. No other associated risk factor was observed.

The clinical picture of the cases included a rapid progression of disease (1–15 days, with an average of 6 days from the beginning of symptoms to the nadir) and more frequently an electrophysiological pattern of acute motor axonal neuropathy (AMAN). The outcome was generally favorable, with only 38 % of patients admitted to the ICU, 22 % with progression to respiratory support, and no deaths. All patients were treated with immunoglobulin [13].

The GBS incidence in French Polynesia during the Zika outbreak was estimated to be 24/100,000 people infected, compared with 1–4/100,000 person-years globally. In the recent outbreaks in Polynesia and Brazil other neurological complications including encephalitis, myelitis, and optical neuritis have been observed [14].

Differential diagnosis

The differential diagnosis for ZIKV infection is extensive and can include other arboviruses (dengue, chikungunya, Mayaro, West Nile fever, etc.), as well as infections by group A streptococcus, rubella, measles, among others. The main clinical features contrasting Zika with dengue and chikungunya are presented in Table 1.

In its most severe form, dengue progresses with hypotension or shock associated with increased vascular permeability and thrombocytopenia. Hemorrhagic events can be observed but are in general related to late evolution and poor prognosis. These manifestations have not yet been described to be associated with ZIKV infection.

Neurological complications have been related to CHIKV including GBS, encephalitis, and neuritis and it is a relevant differential diagnostic for Zika, especially by the co-circulation of these two viruses in several countries. Previous neurological disease, immune suppression, and extreme of age have been associated with more severe forms of arbovirus infection.

Table 1 Clinical differential diagnostic among Zika and other arbovirus

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	–	–
Arthralgia	++	+	+++
Adenomegaly	++	–	–
Myalgia	+	+++	+
Headache	+	+++	++
Petechiae or hemorrhage	–	++	–

Diagnostic confirmation

Case definitions and laboratory diagnostics for ZIKV are rapidly evolving, and clinical diagnosis is therefore important. A conclusive diagnosis is often difficult with current diagnostic tools, and most often the diagnosis is presumptive in many countries. The main strategy for diagnostic confirmation of Zika infection is based on virus detection from clinical specimens (blood, urine, cerebrospinal fluid, tissues, amniotic fluid, saliva, or semen) using molecular techniques such as real-time RT-PCR. Though diagnosis by RT-PCR from blood provides a definitive result, it is only valid for up to about 7 days after the illness onset, since viremia is usually low and of short duration. ZIKV RNA has been detected at higher titers and for longer periods (up to 20 days) in urine and this may represent a good option for diagnosis [15]. Reports of the virus presence in semen for more than 60 days reinforce the relevance of the sexual transmission. After 5 days from the beginning of symptoms, serological detection of IgM antibodies can often be detected. Cross-reactivity of ZIKV antibodies with other flaviviruses (including dengue) has complicated the development and interpretation of serological tests, especially in a previously exposed dengue population. Confirmation of Zika infection in neurological cases may be difficult because usually these complications occur when viral RNA is no longer present in the blood.

General aspects in the intensive care setting

Although the need for hospitalization and the evolution of severe diseases are relatively rare in ZIKV infection, the rapid geographic expansion with large outbreaks with thousands of cases turned ZIKV into a global concern. Additionally, the simultaneous expansion of other arboviruses like dengue and CHIKV forces the intensivist

community to be on alert for complications of common arboviruses. At the moment no specific therapy is available for these arbovirus. The clinical management includes general measurements and treatment of complications. No specific biosafety measures are necessary.

Conclusions and perspectives

The rapid spread of ZIKV and the identification of severe complications associated with this infection have generated a rapid response from the scientific international community and the public health authorities. However, several critical questions still need to be answered, including the main aspects of the natural history of disease, frequency of major complications and their risk factors, as well as the best strategies for diagnosis and management.

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