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SKIN AND SOFT TISSUE INFECTIONS IN RETURNING TRAVELERS FROM THE TROPICS (C FRANCO-PAREDES, SECTION EDITOR)

Arbovirus Rash in the Febrile Returning Traveler as a Diagnostic Clue

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Abstract

Purpose of Review This review aims to describe briefly the general information of arboviruses dengue, Zika, and chikungunya infections and emphasize the clinical manifestations of each, to help identify and make a quick diagnosis of each.

Recent Findings The most relevant advances in the study of these arboviruses' infections have been in the epidemiological distribution, mainly due to international travel, migration, and climate change; in the clinical manifestations of these diseases, the development of clinical decision-making software, which can help improve the management and outcomes of these patients; and in the prevention of this disease.

Summary Although arboviruses infections constitute a clinical challenge for the attending physician in the scope of a febrile returning traveler, a thorough clinical history and exam can help to aid diagnostic reasoning. The characteristics of the rash are a very helpful clue in the evaluation of these patients. Currently, there are clinical decision aid tools that help to get the diagnosis more quickly.

Keywords Arboviruses · Dengue · Zika · Chikungunya · Epidemiology · Travel-related

Introduction

Arboviruses (arthropod-borne viruses) are an amazingly diverse group of viruses that survive in nature by transmission from infected to susceptible hosts by certain types of arthropods (i.e., mosquitoes, ticks, sand-flies, or biting midges) [1]. Although they are mostly zoonoses, primarily, infections of vertebrates other than humans occasionally spill over into human populations following transmission by an infected insect vector resulting in infection. The mechanism of transmission for the majority of viruses in this group, in their urban and zoonotic cycles, follows the ingestion of an infected blood meal from an infected host. Viruses then multiply within the tissues of the vector (i.e., arthropods). This period is often referred as the extrinsic incubation period, and lastly, they are passed on to humans, usually incidentally, or other vertebrates through insect biting [2]. Notable exceptions of this occasional spill to humans from enzootic cycles are the dengue viruses (DENV) for which humans are the primary vertebrate hosts [3]. Dengue, Zika (ZIKV), and chikungunya (CHIKV) are currently co-circulating in the Americas [4] and probably on tropical areas of Asia and Africa, where these viruses were first identified. Although most of the infections caused by arboviruses are asymptomatic, the small percentage of those who present symptoms are at elevated risk for severe complications during or after the course of the disease, namely dengue vascular permeability syndrome (DVPS) [5], Zika associated Guillain-Barré Syndrome (GBS) [6] and microcephaly [7], or post-Chikungunya arthralgias, which are very debilitating and usually long lasting [8].

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Dengue

Dengue infections are emerging as the most abundant vector-borne viral illness in the world [9] and are the most important arboviral disease in terms of geographical distribution, morbidity, and mortality. Dengue infections are caused by four antigenically distinct viruses (DENV1, DENV2, DENV3, DENV4) of the genus *Flavivirus* in the family *Flaviviridae.*

They are single-stranded enveloped RNA viruses 30 nm in diameter [10].

Epidemiology

Dengue virus is endemic throughout the tropical and subtropical zones between 30° N and 40° S, where environmental conditions are optimal for the DENV vector, the *Aedes* mosquitoes [11], and transmission within this area occurs throughout the year [10]. Latest estimates suggest that around 100 million symptomatic dengue infections occur annually [12]. According to the WHO/PAHO Epidemiological Update on Dengue on the Americas of Nov. 11, 2019, a total of 2,773,635 cases of dengue and 1206 deaths have been recorded throughout epidemiological weeks 1 and 42. Although it must be remembered that most of the dengue infections are asymptomatic or mildly symptomatic, probable underreport bias may be present. The most affected regions of the world are comprised by Southeast Asia, Latin America, The Caribbean, and Africa [10]. Probably the global burden of dengue follows the wide distribution that *Aedes* mosquitoes have, which probably began with the slave trade of the fifteenth through the nineteenth centuries. Following the passage of time, the *Aedes aegypti* mosquito has become widely distributed across tropical and subtropical areas [11]. This is likely a consequence of the innovation of travel by airplane, which has aided the DENV to get established as endemic in these areas. Transmission of dengue virus occurs mostly via the bite of an infected *Aedes aegypti*, an anthropophilic daytime mosquito [13].

Clinical Manifestations

Dengue has a wide spectrum of clinical manifestations, ranging from asymptomatic to severe disease, varying according to infecting virus (DENV1, DENV2, DENV3, DENV4), epidemiology, immune status, genetic makeup [5], and previous infections status by DENV or other flaviviruses (i.e., ZIKV), and in those who are symptomatic, the infection can be further divided in febrile, critical, and recovery phase. The frequency of symptomatic dengue fever is about <10% according to a Colombian prospective longitudinal study conducted in 2010 [14], but underreporting bias should be addressed because much of dengue symptomatic infections are mild and perceived by the patients as a common viral illness not necessary for physician consult.

Incubation period of DENV ranges from 5 to 8 days following a mosquito bite with high viral load [10]. Following the incubation period, symptomatic patients enter the febrile phase, which usually lasts 4–7 days [9], is usually self-limited, and consists of the following symptoms: sudden onset of high fevers (up to 40 °C), headache, retro-orbital pain, nausea/vomiting, myalgia, arthralgia [9], and rash. Face, neck, or trunk flushing is the first dermatologic manifestation occurring in the first 24–48 h following symptom onset. Subsequently, a faint morbilliform rash, which may be mildly pruritic, occurs in 50% of the cases [13]. Also, minor hemorrhagic manifestations such as petechiae and ecchymoses may be present on the skin [15]. Following the febrile phase, the course of the disease may be uncomplicated, in which case it will be followed by a defervescence phase, in which the patient successfully recovers, or may be complicated by a critical phase, which usually begins around day 5 of defervescence and is characterized by an increase of capillary permeability, massive plasma leakage, and intravascular volume depletion that can lead to severe complications such as shock and end organ damage, possibly resulting in death [10]. There is no way to tell which patient is going to develop the critical phase, so continuous monitoring of these patients is required. What is known about the pathogenesis of this critical phase is that it is the result of an immunological process called antibody-dependent enhancement (ADE) and NS1 toxicosis; both converge in the development of DVPS, and patients that are most likely to develop this critical phase are those who have a history of a previous DENV infection. The critical phase usually lasts for 24–48 h, after which time the plasma leakage begins to reabsorb and the initiation of the recovery phase begins. The recovery phase usually last 48–72 h, which is clinically characterized by returning appetite, hemodynamic stability, and increasing diuresis.

Diagnosis

Diagnosis is based on clinical suspicion and can be confirmed by serological testing and virus detection by molecular techniques. A detailed travel history is vital, focusing on timing and duration of stay in endemic areas, dengue seasonality, and epidemic activity of countries visited [16]. The choice of confirmatory diagnostic method is based on the time between patient arrival and symptom onset. During the first 7 days of symptoms onset, identification of viral RNA using reverse transcription polymerase chain reaction (RT-PCR) and detection of dengue non-structural protein 1 (NS1) using enzyme linked immunosorbent assay (ELISA) [17] are useful techniques. Rapid tests, often combining NS1 detection with an antibody test, are also available and have a reasonably good window of detection.

Treatment

No specific antiviral treatment is actually available or approved. Appropriate management relies primarily on the classification of these patients according to the degree of severity of the disease, as stated in the WHO/PAHO guidelines for dengue in the Americas [18]. The mainstay of treatment is supportive, with basis on the severity of the disease.

Adequate fluid resuscitation has been demonstrated to result in better outcomes in severe dengue, but this should be carefully monitored throughout administration, because of the risk of complication developing as a result of fluid overload, mostly in the recovery phase. NSAIDS or steroids are not recommended in the management of the disease [19]. Most individuals with dengue infections develop thrombocytopenia, which can result in severe bleeding. It may be appropriate to administer platelet transfusions as a prophylactic measure to prevent bleedings. However, there is no evidence that this practice improves outcomes but offer a very definite risk for both acute and long-term complications [20].

Prevention

For the prevention of these vector-borne diseases, two approaches have been utilized: (a) vector control and (b) vaccine development. Vector control programs have been the mainstay in efforts to control different vector-borne diseases such as dengue, Zika, chikungunya, yellow fever, just to name a few, since they all share common vectors (i.e., arthropods). These interventions mainly refer to vector eradication strategies by means of widespread uses of insecticides, elimination of artificial water bodies, and novel genetically modified *Aedes* mosquitoes infected by the Wolbachia bacteria. Although these strategies are categorized as effective, they are not sustainable because of high degree of effort needed to implement all of these strategies in the tropical and subtropical areas [21]. Therefore, a massive effort is under way to develop a vaccine, aiming for an integrative way to address the vector population, as well as the rate of infections occurring by arboviruses. Currently, there is only one dengue vaccine approved by the FDA for prevention of dengue disease caused by DENV serotypes 1–4, Dengvaxia. Its use is approved for use in individuals 9 through 16 years of age with laboratory confirmed previous dengue infection and living in endemic areas [22]. The Takeda, TAK-003 vaccine, is undergoing phase 3 randomized clinical trial (RCT). Recent analysis on the first part of this RCT found an overall vaccine efficacy of approximately 80% against symptomatic and virological confirmed dengue cases [23•]. Final results of this study are expected in December 2021 [24]. A third vaccine, being developed at the National Institute of Allergy and Infectious Diseases in Bethesda and the Johns Hopkins Bloomberg School of Public Health, consists of a live-attenuated tetravalent dengue vaccine. This vaccine is currently undergoing a phase 3 RCT in Brazil [25]. The outlook for live-attenuated tetravalent dengue vaccine, based on phase 2 clinical trials in humans, is that a single dose of this vaccine will raise a durable, solid, protective immunity in both seronegative and seropositive patients [26].

Zika

After an exponential increase of cases in 2015 in Brazil, Zika is considered of international concern because of its relationship with possible fatal complications such as GBS and microcephaly, when the infection is contracted by pregnant women. ZIKV is a positive sense RNA flavivirus of the genus *Flavivirus* in the family *Flaviviridae* [27].

Epidemiology

Historically, ZIKV spread eastward from equatorial Africa and Asia to the Pacific Islands during the late first decade of the twenty-first century and then invaded the Caribbean and most of Latin America in 2015 and reached North America in 2016 [28, 29]. ZIKV is transmitted to humans primarily by the bite an infected *Aedes* mosquito. Other documented modes of transmission include sexual, intrauterine, perinatal, laboratory exposure, and probably via blood transfusions. [29]. From January 2015 to March 2017, a total of 754,460 suspected and laboratory-confirmed autochthonous cases of ZIKV diseases had been reported to the Pan American Health Organization from countries and territories all around the Americas. During this period of time, 20 deaths among ZIKV infected patients (excluding those patients with GBS or congenital ZIKV infection) occurred, accounting for a case fatality rate of < 0.003% [30].

Although the fatality rate is not as high for ZIKV infections as for other arbovirus infections, the complications associated with this infection (i.e., GBS and microcephaly) require active surveillance in order to reduce the global burden of ZIKV infections.

Clinical Manifestations

Up to 80% of ZIKV virus infections are asymptomatic. In symptomatic patients, the incubation period is about 3–14 days. The infection is typically a mild illness, with a duration of up to 1 week, manifesting as low-grade fever, arthralgia, myalgias, and non-purulent conjunctivitis [13, 28, 31]. Approximately 90% of symptomatic ZIKV infections will develop a rash [32]. Based on the most recent data of the epidemic in the Americas, the Pan American Health Organization defined a suspected-case for ZIKV infection as a patient with a rash (usually pruritic and maculopapular) with two or more of the following signs or symptoms: elevated body temperature (~38.5 °C), arthralgia/myalgia, non-purulent conjunctivitis or conjunctival hyperemia, headache/malaise, and periarticular edema. A confirmed case is a case with clinical suspicion and a positive laboratory confirmation of ZIKV [33]. Skin manifestations appear within 24–48 h of symptom onset and are usually characterized by a pruritic maculo-papular rash predominantly localized to the trunk, extremities, face, palms, and soles [13, 34]. The rash is the most

common dermatologic feature of ZIKV infection [35], and conjunctivitis is generally considered one of the most common ZIKV infection signs. (A key feature of ZIKV infected patients is that they appear to be in good clinical status as compared with patients infected from other arboviruses.) [36]. Probably, the most important features of the ZIKV disease are the associated complications. The incidence of ZIKV-associated GBS is estimated to be 2–3 cases per 10,000 ZIKV infections, which is similar to the risk associated with *Campylobacter* infection [37]. The pathogenic mechanism for this GBS remains unclear, but it is hypothesized to result from the production of neutralizing antibodies against ZIKV target peripheral nerve glycolipids, thereby inducing injuries to myelin sheets or axonal membranes, further leading to demyelinating polyneuropathy [38]. Vertical transmission during pregnancy of ZIKV can lead to teratogenic effects on the fetus CNS [7]. The clinical phenotype of congenital ZIKV infection includes cerebral calcifications, microcephaly, intrauterine growth restriction, and fetal demise [38].

Diagnosis

The definitive diagnosis relies on nucleic acid or serologic testing since the clinical presentation of ZIKV infection is similar to other arboviruses (e.g., dengue, chikungunya). Nucleic acid testing should be performed on whole blood or serum samples obtained during the first days of illness [31•]. Zika virus nucleic acid amplification test (NAAT) can be used on serum, plasma, whole blood, cerebrospinal fluid, urine, or amniotic fluid. Serologic diagnosis is complicated by false positive results owing to cross-reactivity in persons who have been exposed to other flaviviruses. Zika IgM levels generally become positive within the first week of exposure and may remain positive for up to 12 weeks after infection. Plaque reduction neutralization tests (PRNT) are quantitative assays that measure the virus specific neutralizing antibody titers. The CDC states that if Zika virus IgM antibody is positive and definitive diagnosis is needed, confirmatory PRNT should be done against Zika and other flaviviruses [39].

Treatment

There are no specific antiviral treatments or vaccines approved to cure ZIKV infection, and patients' care is mainly focused on treating symptoms [13, 38]. Treatment of ZIKV-associated GBS is the same as the usual management which consists of immunotherapy [40]. Regarding infants with congenital ZIKV infection, their management requires a multidisciplinary team throughout their lifespan to monitor for the early recognition of complications as well as to provide early interventions [41].

Prevention

Preventive measures for the ZIKV infection are the same as with other members of the arbovirus groups. They consist of personal protective measures aimed at preventing the *Aedes* mosquitoes bite, such as using mosquito repellent, wearing long sleeve shirts, and long trousers, using mosquito nets while sleeping in high endemic areas, and using condom while staying at a Zika endemic area with known active transmission [42]. Sexually transmitted ZIKV preventative measures include abstinence after suspected infection for 2 months, if the partner with the suspected infection is female, and for 3 months if male [31•] since ZIKV RNA has been demonstrated to persist in semen for up to 4 months [43]. Since the major ZIKV epidemic in Brazil in 2015, the international health care system has called for the development of candidate vaccines against the virus. Several candidates are being tested, including ZIKV-purified inactivated virus vaccine [44], adenovirus-based vaccines, and nucleic acid vaccines [38].

Chikungunya

Chikungunya infection is caused by chikungunya virus (CHIKV), an arbovirus of the genus alphavirus of the *Togaviridae* family. CHIKV is an enveloped, positive-strand RNA virus. The virus got its name from a word in the local dialect of the Makonde area in Tanzania and is literally translated as "bent over pain" [45], which typically describes the posture acquired by those who suffer from severe joint pain and arthralgias, which are hallmarks of the disease [8].

Epidemiology

Over 70 CHIKV epidemics have occurred in several countries across many continents between 1959 and 2016 [8]. Prior to 2013, CHIKV cases and outbreaks had been identified in countries in Africa, Asia, Europe, and the Indian and Pacific oceans; however, in late 2013, the first local transmission of CHIKV was identified in the Americas [46]. As of September 2015, 1.7 million cases and 240 deaths were reported from 45 of the 53 countries or territories reporting to the Pan American Health Organization [47]. Transmission of the CHIKV mainly occurs through the bite of an infected *Aedes* mosquitoes (i.e., *Aedes albopictus* and *Aedes aegypti)* [48].

Clinical Manifestations

The incubation period for CHIKV can vary from 1 to 12 days, and a high level of viremia usually lasts for 4–6 days after the onset and correlates with the severity of the clinical presentation. Unlike DENV and ZIKV infections, less than 15% of patients develop an asymptomatic seroconversion; this is because of the high replication rate of the CHIKV within the body and consequent strong immune response [48, 49]. The

acute phase of the illness usually lasts for 1 week following the onset of symptoms and is characterized by high fever, intense myalgia and arthralgia, nausea, fatigue, and rash (in 50% of the cases) [48]. The most common dermatologic manifestation is a maculopapular rash involving the trunks and limbs that appear 2 to 5 days after the fever starts, and it can be slightly pruritic and affect the palms and soles [13, 48]. The presence of rash is variable and ranges from 30 to 75% of cases. Another common dermatologic manifestation is hyperpigmentation of the skin, which affects 16–42% of the patients [50]. This hyperpigmentation is usually centrofacial and when it comprises the "Chik sign" when it predominantly involves the nose [51]. Atypical manifestations can be seen more frequently in vulnerable groups such as neonates and older adults and those with comorbidities. Some of these are bullous dermatosis, xerosis, stomatitis, meningoencephalitis, encephalitis, seizures, hemorrhages, myocarditis, fulminant hepatitis, and ocular disease [46]. Severe CHIKV infection has been associated with nasal skin necrosis and multiple organ dysfunction syndrome [52•]. Special mention has to be made of arthralgias, which are a hallmark of the disease and have a positive predictive value greater than 80% [49]. The joint pain is usually symmetric in both arms and legs and affects mostly the large joints [47, 48]. The post-acute phase usually develops from the fourth week to the end of the fourth month and is characterized by persistence of the initially inflamed areas (i.e., synovitis, tenosynovitis, bursitis) which slowly regress, and it is often associated with decompensation of pre-existing arthropathy. The chronic stage is defined by the absence of return to pre-existing condition more than 3 months after the onset of the disease [49, 53].

Diagnosis

Chikungunya virus infection should be considered in patients with acute onset of fever and polyarthralgia, especially in those patients who have a history of recent travel to areas of known virus transmission. Laboratory diagnosis is generally done by testing of serum or plasma to detect viral nucleic acid, viral specific IgM antibodies, and neutralizing antibodies. During the first 8 days of the illness, CHIKV RNA can often be identified in serum. IgM antibodies normally develop toward the end of the first week of illness, and to definitely rule out the diagnosis, convalescent-phase samples should be obtained from patients whose acute phase samples were negative [54]. IgM antibodies may persist up to 1 year but generally persist for 3 to 4 months [49].

Treatment

There is no effective antiviral treatment; therefore, the mainstay of treatment is focused on reliefs of symptoms. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) remains a key disease management approach. The therapeutic strategy to manage these patients is aimed at reducing inflammation and preventing long-term complications such as stiffness, loss of muscular tone and function, and loss of physical fitness [53].

Prevention

The most effective way to prevent CHIKV infection is to prevent mosquito bites. *Aedes* mosquitoes are known to be anthropophilic and daytime mosquitoes. The CDC recommends personal protective measures such as the use of insect repellent containing proven active ingredients (i.e., DEET, picaridin, IR3535, PMD), wearing long sleeve shirts and long trousers, eliminating artificial water bodies, and using mosquito nets while traveling to an endemic area if sleeping outdoors or in a room that does not have screens or windows [55]. The attempt to develop a vaccine started in the 1960s not long after the virus was first isolated; however, there is no CHIKV vaccine licensed for use [56].

Approach to febrile returning traveler with suspected arbovirus infection

A returning traveler with fever constitutes one of the most complicated clinical challenges any physician can face. Initial approach should include an extensive clinical history that should be aimed to inquire for travel destination; length of stay in visited country; purpose of travel; any kind of possible exposure to

Table 1 Clinical manifestations of dengue, Zika, and chikungunya

	Dengue	Zika	Chikungunya
Incubation period	5–8 days	3–14 days	1–12 days
Frequency of symptoms	~10% of infected patients.	~20% of infected patients.	~85% of infected patients.
Skin manifestations	- Facial, neck, and trunk flushing. - Morbilliform rash. - *Hemorrhagic manifestations*: petechiae and ecchymoses.	- Maculopapular rash involving, trunk, face, palms and soles. - *Highly pruritic*.	- Maculopapular rash involving trunk and limbs. - May be pruritic. - *Centro facial hyperpigmentation of the skin (Chik sign)*
Other important manifestations of disease	- High fevers (up to 40 °C). - Retro-orbital pain. - Nausea and vomiting.	- Non-purulent conjunctivitis. - Guillain-Barré Syndrome. - Microcephaly in neonates.	- High fevers (39–40 °C). - Severe polyarthralgia.

febrile causing pathogens; mosquito bites; thick bites; the patient's immune status; if pregnant, in case of women in gestational age; and current immunization status. Subsequently, a complete physical examination should be done searching for the fever focus, and in the special case of an arboviral infection, the presence of a rash with the associated findings depicted above. This information should be combined with up to date epidemiological information on outbreaks and transmission status, and incubation period of the possible pathogens, which help to narrow the differential diagnosis of a febrile returning traveler. Epidemiological information is freely available on the internet in the Center for Disease Control and Prevention (CDC) website. There are also clinical decisions aid tools developed to help clinicians on the challenge that a febrile returner traveler represents. Some of these are the Swiss guidelines for primary care physicians on the management of febrile illness in travelers (available at http://www.fevertravel.ch), and KABISA, developed by the Institute of Tropical Medicine of Antwerp, Belgium. Recently, a diagnostic algorithm was published in the New England Journal of Medicine for the evaluation of the febrile returning traveler based on the clinical history, Quick Sepsis Related Organ Failure Assessment (qSOFA) score (severity of the disease), and possibility of a highly transmissible pathogen [57•]. The presence of a rash is indicative for requiring investigations for arboviruses. Initial investigations for a returning febrile traveler with a rash should include general blood tests, such as complete blood count, liver and renal function tests, blood cultures, malaria and dengue rapid tests, RT-PCR for arboviruses, and human immunodeficiency virus tests. A rapid diagnosis of an arboviral infection can be the line that separates life and death, in the picture of severe dengue, or can be the clinical cue to be aware of possible complications such a GBS and chikungunya arthritis.

Conclusion

Although all 3 of these arboviruses' infections are clinically very similar, they each exhibit unique characteristics, which are grouped in Table 1. This article summarizes some of the key clinical features that can help to raise clinical suspicion of these infections and give a brief description of the newly developed clinical decision aid tools that have been recently developed for diagnosis these diseases which, as noted above, can result in deleterious outcomes including impairment on quality of life and even death.

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Both Laura Naranjo and Maria Castrejòn-Alba declare that this work is not linked to their current jobs at GSK company.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Arthropod-borne and rodent-borne viral diseases. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1985;719:1–116.
2. Young PR, Ng LF, Hall RA, Smith DW, Johansen CA. Manson's tropical diseases. In: Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White NJ, editors. Arbovirus infection. Amsterdam: Elsevier: SAUNDERS; 2014. p. 129–61.
3. Young PR. Arboviruses: a family on the move. In: Hilgenfeld R, Vasudevan SG, editors. Dengue and Zika: control and antiviral treatment strategies. Singapore: Springer Singapore; 2018. p. 1–10.
4. Jones R, Kulkarni MA, Davidson TMV, Talbot B. Arbovirus vectors of epidemiological concern in the Americas: a scoping review of entomological studies on Zika, dengue and chikungunya virus vectors. PLoS One. 2020;15(2):e0220753. https://doi.org/10.1371/journal.pone.0220753.
5. Halstead S. Recent advances in understanding dengue. F1000Res. 2019;8:1. https://doi.org/10.12688/f1000research.19197.1.
6. Katz I, Gilburd B, Shovman O. Zika autoimmunity and Guillain-Barré syndrome. Curr Opin Rheumatol. 2019;31(5):484–7. https://doi.org/10.1097/bor.0000000000000629.
7. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med. 2016;374(10):951–8. https://doi.org/10.1056/NEJMoa1600651.
8. Mascarenhas M, Garasia S, Berthiaume P, Corrin T, Greig J, Ng V, et al. A scoping review of published literature on chikungunya virus. PLoS One. 2018;13(11):e0207554. https://doi.org/10.1371/journal.pone.0207554.
9. Yacoub S, Wills B. Dengue: an update for clinicians working in non-endemic areas. Clin Med (Lond). 2015;15(1):82–5. https://doi.org/10.7861/clinmedicine.15-1-82.
10. Yacoub S, Farrar J. Dengue. In: Manson's tropical infectious diseases. Philadelphia: WB Saunders; 2014. p. 162–70.
11. Simmons CP, Farrar JJ. Nguyen v V, Wills B. Dengue. N Engl J Med. 2012;366(15):1423–32. https://doi.org/10.1056/NEJMra1110265.
12. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7. https://doi.org/10.1038/nature12060.
13. Martinez JD, Garza JAC, Cuellar-Barboza A. Going viral 2019: Zika, chikungunya, and dengue. Dermatol Clin. 2019;37(1):95–105. https://doi.org/10.1016/j.det.2018.07.008.

14. Restrepo BN, Piedrahita LD, Agudelo IY, Parra-Henao G, Osorio JE. Frequency and clinical features of dengue infection in a schoolchildren cohort from medellin, Colombia. J Trop Med. 2012;2012:120496–9. https://doi.org/10.1155/2012/120496.
15. Arenas Guzmán R. Dengue. In: Arenas Guzmán R. Dermatología-Atlas Diagnóstico y Tratamiento. New York: McGraw-Hill; 2019. p. 620–7.
16. Wilder-Smith A, Schwartz E. Dengue in travelers. N Engl J Med. 2005;353(9):924–32. https://doi.org/10.1056/NEJMra041927.
17. Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti-Infect Ther. 2012;10(8):895–907. https://doi.org/10.1586/eri.12.76.
18. Pan American Health Organization. Dengue: guidelines for patient care in the region of the Americas, 2016. https://iris.paho.org/handle/10665.2/31207. .
19. Patterson J, Sammon M, Garg M. Dengue, Zika and chikungunya: emerging arboviruses in the New World. West J Emerg Med. 2016;17(6):671–9. https://doi.org/10.5811/westjem.2016.9.30904.
20. Lye DC, Archuleta S, Syed-Omar SF, Low JG, Oh HM, Wei Y, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. Lancet. 2017;389(10079):1611–8. https://doi.org/10.1016/s0140-6736(17)30269-6.
21. Pang T, Mak TK, Gubler DJ. Prevention and control of dengue-the light at the end of the tunnel. Lancet Infect Dis. 2017;17(3):e79–87. https://doi.org/10.1016/s1473-3099(16)30471-6.
22. FDA: Dengvaxia https://www.fda.gov/vaccines-blood-biologics/dengvaxia (2020)
23.• Biswal S, Reynales H, Saez-Llorens X, Lopez P, Borja-Tabora C, Kosalaraksa P, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. N Engl J Med. 2019;381(21):2009–19. https://doi.org/10.1056/NEJMoa1903869 **Important because it gives preliminary data on the research of the Takeda vaccine, which found an overall vaccine efficacy of approximately 80% against symptomatic and virological confirmed dengue cases**.
24. ClinicalTrials.gov, U.S. National Library of Medicine. 2019 https://clinicaltrials.gov/ct2/show/NCT02747927?term=den-301&rank=1
25. ClinicalTrials.gov, U.S. National Library of Medicine. 2020. https://clinicaltrials.gov/ct2/show/NCT02406729
26. Halstead SB, Dans LF. Dengue infection and advances in dengue vaccines for children. Lancet Child Adolesc Health. 2019;3(10):734–41. https://doi.org/10.1016/s2352-4642(19)30205-6.
27. Kostyuchenko VA, Lim EX, Zhang S, Fibriansah G, Ng TS, Ooi JS, et al. Structure of the thermally stable Zika virus. Nature. 2016;533(7603):425–8. https://doi.org/10.1038/nature17994.
28. Song BH, Yun SI, Woolley M, Lee YM. Zika virus: history, epidemiology, transmission, and clinical presentation. J Neuroimmunol. 2017;308:50–64. https://doi.org/10.1016/j.jneuroim.2017.03.001.
29. Pan American Health Organization: timeline of the emergence of Zika virus in the Americas. https://www.paho.org/hq/index.php?option=com_content&view=article&id=11959:timeline-of-emergence-of-zika-virus-in-the-americas&Itemid=41711&lang=en (2016)
30. Pan American Health Organization: Zika cumulative cases. https://www.paho.org/hq/dmdocuments/2017/2017-dec-21-phe-ZIKV-cases.pdf
31.• Musso D, Ko AI, Baud D. Zika virus infection - after the pandemic. N Engl J Med. 2019;381(15):1444–57. https://doi.org/10.1056/NEJMra1808246 **Important review of the data published for the Zika epidemic in the Americas, especially Brazil on 2015**.
32. Derrington SM, Cellura AP, McDermott LE, Gubitosi T, Sonstegard AM, Chen S, et al. Mucocutaneous findings and course in an adult with Zika virus infection. JAMA Dermatol. 2016;152(6):691–3. https://doi.org/10.1001/jamadermatol.2016.1433.
33. Pan American Health Organization. Zika case definitions. http://www.paho.org/hq/index.php?option=com_content&view=article&id=11117%3A2015-zika-case-definitions-&catid=8424%3Acontents&itemid=41532&lang=en (2016)
34. Paniz-Mondolfi AE, Blohm GM, Hernandez-Perez M, Larrazabal A, Moya D, Marquez M, et al. Cutaneous features of Zika virus infection: a clinicopathological overview. Clin Exp Dermatol. 2019;44(1):13–9. https://doi.org/10.1111/ced.13793.
35. Watts Santos A, Ocampo Candiani J. Manifestaciones dermatológicas en dengue, zika y chikungunya. *Dermatología Cosmética, Médica y Quirúrgica*. 2019;*17*(1):52–9.
36. Burillo-Martínez S, Fernández-Ruiz M, Pérez-Rivilla A, Zarco-Olivo C. Zika virus infection: an emerging disease the dermatologist must know about. Actas Dermosifiliogr. 2016;107(8):687–9. https://doi.org/10.1016/j.ad.2016.04.012.
37. Mier YT-RL, Delorey MJ, Sejvar JJ, Johansson MA. Guillain-Barré syndrome risk among individuals infected with Zika virus: a multi-country assessment. BMC Med. 2018;16(1):67. https://doi.org/10.1186/s12916-018-1052-4.
38. Ferraris P, Yssel H, Missé D. Zika virus infection: an update. Microbes Infect. 2019;21(8-9):353–60. https://doi.org/10.1016/j.micinf.2019.04.005.
39. Center for Disease Control and Prevention: testing for Zika virus infection https://www.cdc.gov/zika/laboratories/types-of-tests.html (2019)
40. Assessment and management of Guillain-Barré syndrome in the context of Zika virus infection: interim guidance update 18 August 2016.
41. Adebanjo T, Godfred-Cato S, Viens L, Fischer M, Staples JE, Kuhnert-Tallman W, et al. Update: interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection - United States, October 2017. MMWR Morb Mortal Wkly Rep. 2017;66(41):1089–99. https://doi.org/10.15585/mmwr.mm6641a1.
42. Center for Disease Control and Prevention: Zika virus prevention and transmission https://www.cdc.gov/zika/prevention/index.html (2019)
43. Paz-Bailey G, Rosenberg ES, Doyle K, Munoz-Jordan J, Santiago GA, Klein L, et al. Persistence of Zika virus in body fluids - final report. N Engl J Med. 2018;379(13):1234–43. https://doi.org/10.1056/NEJMoa1613108.
44. ClinicalTrials.gov, U.S. National Library of Medicine. 2018. https://clinicaltrials.gov/ct2/show/NCT02952833
45. Halstead SB. Reappearance of chikungunya, formerly called dengue, in the Americas. Emerg Infect Dis. 2015;21(4):557–61. https://doi.org/10.3201/eid2104.141723.
46. Center For Disease Control and Prevention chikungunya geographic distribution https://www.cdc.gov/chikungunya/geo/index.html (2019)
47. Petersen L, Powers A. Chikungunya: epidemiology [version 1; peer review: 2 approved]. F1000Research. 2016;5(82):1. https://doi.org/10.12688/f1000research.7171.1.
48. Silva LA, Dermody TS. Chikungunya virus: epidemiology, replication, disease mechanisms, and prospective intervention strategies.

J Clin Invest. 2017;127(3):737–49. https://doi.org/10.1172/JCI84417.

49. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: epidemiology, pathogenesis, clinical features, management, and prevention. Infect Dis Clin N Am. 2019;33(4):1003–25. https://doi.org/10.1016/j.idc.2019.08.006.
50. Handler MZ, Handler NS, Stephany MP, Handler GA, Schwartz RA. Chikungunya fever: an emerging viral infection threatening North America and Europe. Int J Dermatol. 2017;56(2):e19–25. https://doi.org/10.1111/ijd.13439.
51. Singal A. Chikungunya and skin: current perspective. Indian Dermatol Online J. 2017;8(5):307–9. https://doi.org/10.4103/idoj.IDOJ_93_17.
52.• Torres JR, Córdova LG, Saravia V, Arvelaez J, Castro JS. Nasal skin necrosis: an unexpected new finding in severe chikungunya fever. Clin Infect Dis. 2016;62(1):78–81. https://doi.org/10.1093/cid/civ718 **Important because it describes recent atypical manifestations of chikungunya fever, which can lead to poor outcomes**.
53. Zaid A, Gérardin P, Taylor A, Mostafavi H, Malvy D, Mahalingam S. Chikungunya arthritis: implications of acute and chronic inflammation mechanisms on disease management. Arthritis Rheum. 2018;70(4):484–95. https://doi.org/10.1002/art.40403.
54. Center For Disease Control and Prevention: Chikungunya Diagnostic Testing https://www.cdc.gov/chikungunya/hc/diagnostic.html (2018)
55. Center for Disease Control and Prevention: chikungunya prevention https://www.cdc.gov/chikungunya/prevention/index.html (2019)
56. Gao S, Song S, Zhang L. Recent progress in vaccine development against chikungunya virus. Front Microbiol. 2019;10:2881. https://doi.org/10.3389/fmicb.2019.02881.
57.• Thwaites GE, Day NPJ. Approach to fever in the returning traveler. N Engl J Med. 2017;376(6):548–60. https://doi.org/10.1056/NEJMra1508435 **Important publication that states clinical diagnosis algorithim for the returning febrile traveler**.