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Viral Febrile Illnesses and Emerging Pathogens

Timothy P. Endy

KEY FEATURES

- The majority of emerging diseases are caused by viruses, with many that are transmitted by insect vectors or are zoonotic.
- RNA viruses in particular have high mutation rates and can evolve rapidly in new and changing environments. This, in combination with societal factors, climate change, and rapid travel, has increased the number of epidemics from emerging pathogens in the last several decades.
- Understanding the travel history, incubation time of potential viruses, and the clinical presentation by illness day is essential in making the right diagnosis and identifying the infecting virus.

INTRODUCTION

Emerging diseases and/or pathogens is a term used frequently when describing new or spreading infections in the human population. It is a term used to describe the emergence of previously unrecognized pathogens that produce human disease or recognized pathogens expanding in different ways through the population. Emerging diseases have historically been responsible for civilization-altering events. Bubonic plague during the 14th century was responsible for the death of 60% of the European population. The Spanish flu pandemic in 1918 resulted in the death of 50 to 100 million worldwide; the rinderpest epidemic in livestock in Eastern Africa during the 19th century resulted in the starvation of 75% of the Massai population; and potato blight produced the Irish potato famine, reducing the Irish population by 25%. Our generation has had dramatic experiences in the last decade with emerging or reemerging pathogens that rapidly spread and result in death or illness in large segments of the population, to include many of the pathogens mentioned in this section and outlined in this book, such as Ebola and Zika viruses. For the clinician, the challenge is to distinguish a viral febrile illness caused by an endemic pathogen from one that is “emerging” and has the potential for human-to-human spread, requiring isolation and, if available, targeted therapy. The scenario is common: a patient presents to the emergency room, usually on a weekend, with fever and a constellation of symptoms and a recent history of travel overseas. The fear is this Ebola, Lassa fever, or another unknown contagious pathogen, and are the clinician and the staff at risk? In this section the epidemiology, clinical features, and evaluation of the patient with a potential viral febrile illness from an emerging pathogen are discussed.

EPIDEMIOLOGY

We are humbled by a 2011 editorial entitled “Microbiology by Numbers,” which estimates that “if all the $1 \times 10^{31}$ viruses on earth were laid end to end, they would stretch for 100 million light years!” Additionally in this editorial, it is estimated that there are approximately 1,400 species of human pathogens which includes viruses, bacteria, fungi, and parasites and represents 1% of the total number of microbial species on the earth. Approximately 50% of the human pathogens have an origin in the animal species. The potential of the remaining 99% of microbial species to adapt and transform into potential human pathogens is daunting and emphasizes the challenges we face in recognizing and predicting the next epidemic. Table 36.1 lists the reported outbreaks by year as reported by the World Health Organization. Conclusions that we can draw from this table are that the majority of the reported outbreaks of diseases in the world are caused by viruses, the majority of these viruses are RNA viruses, most have an animal reservoir in their life cycle, and the majority of outbreaks affect developing countries and potential “hot spots” for emerging pathogens. Jones et al. analyzed 335 emerging infectious disease events between 1940 and 2004. Emerging disease events were found to have risen significantly over time, with the peak number of events occurring in the 1980s corresponding to the HIV pandemic. Emerging disease events were predominantly zoonotic (60.3%), originated from wildlife.
(71.8%), and are increasing over time. Factors that determine the emergence of these viruses include (1) high mutation rate and adaptation of the RNA viruses; (2) human intimacy (cross-species transmission) and movement of animal species due to land development and migration from political conflicts; (3) increase in urbanization; (4) climate change with increase and spread of potential insect vectors and changes in migratory patterns of birds; and (5) societal mobility through air travel.

**CLINICAL FEATURES**

Emerging viral pathogens can, in general, present in one of the following clinical categories: (1) generalized febrile illness producing a “viral syndrome,” (2) fever with meningitis/encephalitis, (3) fever with joint pain, (4) hemorrhagic fever, and (5) birth defects.

Due to human host and viral diversity, many viruses can produce illness across the spectrum of these clinical categories. For example, dengue virus as a first infection can result in sub-clinical infection or a febrile illness that results in a self-limited fever, myalgia, bone pain, and transient laboratory abnormalities. On second infection, dengue virus in a minority of patients can produce a severe hemorrhagic disease. Chikungunya and Ross River viruses can produce a generalized febrile illness but also severe joint pains that can persist for months. Japanese encephalitis, West Nile, and the equine encephalitis viruses are classic viruses that produce a meningo-encephalitis in 1% of the persons infected. Yellow fever and the filoviruses (Ebola and Marburg) are examples of severe hemorrhagic fever viruses. The recent Zika virus outbreak and birth defects associated with infection in pregnant women have broadened our clinical categories to include those that produce birth defects. All viruses produce a constellation of signs and symptoms early in infection that are clinically the same. After infection, an incubation period of normally between 1 and 14 days can occur, with some exceptions. For example, Ebola has been reported to occur 21 days after exposure. The first onset of symptoms heralds the host immune response with fever followed by generalized symptoms of headache, muscle aches, joint pains, nausea, vomiting, and diarrhea. Early laboratory abnormalities that would indicate a viral infection include leukopenia, anemia, and thrombocytopenia. Electrolyte and renal function abnormalities can be common if the patient is volume depleted. As the disease progresses, clinical manifestations will become more specific for the clinical syndrome and provide clues on the potential virus, such as the onset of headache, neck stiffness, and altered sensorium in the case of encephalitis; severe joint pains; or bleeding internally or externally with blood loss or hemoconcentration, with plasma leakage with the hemorrhagic fevers. Specific manifestations such as diuresis, volume loss, and renal dysfunction can be an indicator for viruses that produce hemorrhagic fever with renal syndrome such as the Hantaviruses or Lassa fever. Rash is common to all the viral illnesses and in general indicates a shift in the host immune response from a cell-mediated to a humoral immune response with a rise in antibodies. It is important for the clinician to understand that viremia occurs several days before the onset of clinical illness and through the duration of early clinical symptoms. Pathogens that are spread by insect vectors, the respiratory route, blood-borne contact, or sexually can occur before the onset of clinical symptoms, and thus infect others who come in contact by that route. Contact tracing from the index patient should include the days of viremia before the onset of symptoms.

**PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS**

Understanding the incubation time of viral pathogens is the first important step in evaluating the febrile patient. A travel history in an area of an outbreak or potential hot spot for an emerging disease should be within the incubation period of these pathogens (1–21 days). For example, a febrile patient in your clinic or emergency room who had traveled overseas 3 months before fever would be unlikely to have a viral infection, and potential other etiologies such as non-falciparum malaria or a parasitic infection should be considered. An extensive travel history and exposures while traveling will help to determine the risk for the patient to acquire a local infection. An important question often not asked is “who else is sick in your travel party, and have you been in contact with anyone acutely ill?” This can often be an important clue on the risk of acquiring an infection. If the patient is within the incubation period and at risk for a viral illness, determining the clinical illness day is important when obtaining the history. Our studies in hospitalized patients with dengue infection, for example, illustrate the importance for the clinician to approach the viral febrile illness and differential of potential viruses by determining the patient’s clinical illness day and their clinical manifestations. Fig. 36.1 demonstrates an idealized patient with a viral febrile illness. In this example, after an incubation period of 3 days, the first day of viremia occurs. Viremia will continue, with the onset of fever heralding the first day of clinical illness. In general, the first 3 to 5 days of clinical illness of most viral infections will be a generalized febrile illness with no clinical signs or symptoms that will distinguish the illness to a specific viral pathogen, denoted here as a “viral syndrome.” Headache, myalgia, nausea, diarrhea, and respiratory symptoms will be common during the viral syndrome stage. Influenza, dengue, chikungunya, Ebola, or Lassa fever will all be indistinguishable from each other in the early clinical illness. By day 5 of the clinical illness day, day 9 post-infection, the manifestations will become more specific and hemorrhagic manifestations and coagulopathy will occur, along with plasma leakage and encephalitis. As the host response increases with antibody levels rising and cytokines peaking, the manifestations of a specific viral illness will become apparent as cellular damage occurs.

The diagnosis and diagnostic methods used to identify the viral pathogens are also dependent on the clinical illness day. Fig. 36.1 demonstrates the time-dependent diagnostic test that can be performed during the clinical course of the patient. In this example, viremia will start before fever and last until 6 days of clinical illness and before the onset of viral-specific IgM and IgG antibodies. During viremia, diagnostic tests should be focused on detecting the virus, whether by viral isolation, molecular techniques, or antigen detection. Viremia starts to resolve with the onset of the host response and corresponding rise in viral-specific IgM and IgG. Antibodies will continue to rise during the convalescent period, and IgG will last several years or more. Once antibodies start to rise, the diagnostics are focused on their detection, with a variety of methods that can be used, including enzyme-linked immunoassays, hemagglutination inhibition, plaque reduction neutralization, and rapid tests.

**TREATMENT AND CONTROL**

Treatment and control are virus specific, emphasizing the need for early recognition and ordering the appropriate diagnostics. Many of the viruses that are responsible for febrile illnesses and are considered emerging or emerged have no available treatment or vaccine. Reading through the specific viruses and chapters in this book will give the reader valuable information on potential treatments. For vector-borne or zoonotic viruses, control will be specific and include both aerial and larvicidal spraying for mosquito-borne viruses, personal protection practices for both mosquitoes and ticks, and animal control for zoonotic-borne viruses. Contact practices and/or isolation may be appropriate for viruses that can be transmitted human to human, such as the respiratory viruses, Crimean-Congo hemorrhagic fever, and the filoviruses Marburg and Ebola.
36.1 Dengue and Dengue Hemorrhagic Fever

Daniel H. Libraty

**KEY FEATURES**

- Dengue is the most common and significant arboviral disease throughout the world. It is caused by infection with any one of the four dengue virus serotypes (DENVs 1–4).
- The clinical manifestations of a DENV infection can range from an inapparent or mild febrile illness, to the more symptomatic and well-described dengue fever (DF), to the most severe, and sometimes fatal, form of illness, dengue hemorrhagic fever (DHF) (severe dengue).
- The distinguishing characteristic of DHF/severe dengue is a vascular leakage syndrome that develops around the time of defervescence. The relative risk for developing DHF/severe dengue is increased with sequential heterologous DENV infections.
- Patients with dengue, or suspected dengue, who manifest pre-defined “warning signs” require close monitoring and supportive care during the critical phase of illness.
- The case-fatality rate for severe dengue is <1% with early recognition and appropriate supportive care and management.

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INTRODUCTION

Dengue is the most prevalent and widespread human arboviral disease in the 21st century. It is caused by infection with any one of four dengue viruses (DENVs 1–4), single-stranded RNA viruses that belong to the genus Flavivirus, family Flaviviridae. The DENVs are transmitted to humans through the bite of infected urban and peri-urban mosquitoes (female *Aedes* [Stegomyia] *aegypti* and *Aedes* [Stegomyia] *albopictus*). Outbreaks of dengue-like illnesses were recognized and recorded in the 17th and 18th centuries, and perhaps even earlier. There has been a dramatic increase in the incidence and global spread of dengue over the past 50 years.

EPIDEMIOLOGY

The areas at risk for dengue essentially correspond to the global distribution of *A. aegypti* mosquitoes (Fig. 36.1.1). In the Asian tropics, all four DENV serotypes co-circulate, creating a large region of hyper-endemicity. Dengue outbreaks occur with predictable seasonality and periodicity. The majority of dengue cases are seen during the rainy season in a given year. Through a complex interplay of population immunity, vector biology, and environmental conditions, a shift in the dominant circulating DENV serotype typically occurs every 4 to 6 years. The shift in the dominant circulating DENV serotype often leads to waves of large-scale epidemic dengue activity. Historically, the Americas were characterized by isolated and interspersed dengue outbreaks of a single infecting serotype. Over the past several decades, Asian genotype DENV strains have spread throughout the Americas accompanied by increased co-circulation of multiple DENV serotypes. As such, the dengue disease and transmission patterns in the Americas are shifting toward the Asian hyper-endemic patterns. The global burden of symptomatic dengue is on the order of 100 million cases/year.

NATURAL HISTORY, PATHOGENESIS, AND PATHOLOGY

The human dengue cycle is maintained by DENV transmission back and forth between mosquito vectors and viremic individuals. After the bite of a DENV-infected mosquito, there is local viral replication in Langerhans cells and cutaneous dendritic cells and spread to regional lymph nodes. Thereafter, the virus rapidly disseminates, leading to viremia. The likely DENV factories are tissue macrophages, dendritic cells, and adipocytes. The incubation period between a mosquito bite and symptom onset is 3 to 10 days. Viremia generally lasts for 4 to 5 days, and the disappearance of viremia correlates with fever resolution. The distinguishing characteristic of DHF/DSS is a transient and rapid increase in vascular permeability. The plasma leakage syndrome is often characterized by hemoconcentration and transudate accumulation across serosal surfaces (i.e., pleural effusions and ascites). In its extreme form (DSS), hypovolemic shock ensues. The plasma leakage syndrome of DHF/DSS develops rapidly at the time of defervescence and clearance of viremia, and is transient (hours to days). Primary infection with a DENV serotype produces long-term protective immunity against re-infection with the homologous serotype (homotypic immunity), but only short-term protective immunity against heterologous serotypes (heterotypic immunity). The relative risk of developing DHF/DSS (severe dengue) is increased 15- to 100-fold with sequential heterologous DENV infections (secondary DENV infection) compared with primary DENV infections. Most individuals with secondary DENV infections do not develop severe dengue. Primary DENV infections in infants <12 months old also appear more likely to lead to DHF/DSS (severe dengue) than primary DENV infections in children or adults.
Numerous risk factors have been identified for the development of severe dengue. They can be divided into three general steps, and multiple risk factor combinations can take place to produce the three steps. The first step includes factors that can increase the dengue viral load. These include antibody-dependent enhancement of viral infection, impairment of CD8+ T-cell and natural killer cell anti-viral immune responses, adiposity, virus genetics/serotype differences, and host genetics. The second step includes factors that can promote anti-DENV pro-inflammatory immune responses. These include cross-reactive anti-DENV T-cell responses, anti-DENV IgG/DENV immune complexes, adiposity, and host genetics. The final step includes factors that tip the balance in favor of permeability-inducing conditions in the serosal cavities. Several pro-inflammatory cytokines/mediators can promote endothelial paracellular permeability, and virus-induced type I interferon signaling can augment the endothelial barrier function. Each of the three steps described here is necessary, but not sufficient by itself, to produce severe dengue.

**CLINICAL FEATURES**

The most likely outcome of a primary or secondary DENV infection is either asymptomatic infection or a mild undifferentiated febrile illness. The mild febrile illness is often characterized by non-specific constitutional symptoms. This is particularly true in children, whereas DENV infections may be more likely to present as classic DF in adults.

Classic DF begins with the abrupt onset of fever, retro-orbital headache, backache, and severe myalgias (“breakbone fever”). The febrile illness typically lasts for 5 to 7 days and can be accompanied by anorexia, nausea/vomiting, and prolonged asthenia. There is accompanying leukopenia, thrombocytopenia, and often mild hepatic transaminase elevation. Petechiae may develop spontaneously but, most commonly, can be elicited in a positive tourniquet test. Clinically significant bleeding is much less common, but can occasionally be severe or life threatening. Toward the end of the febrile period, the classic rash of dengue may appear (Herman’s rash). It is a confluent, erythematous, macular rash over the extremities with scattered, well-circumscribed areas of sparing. The appearance of this rash is pathognomonic for a DENV infection.

DHF/DSs is the dengue clinical syndrome whose distinguishing feature is abrupt plasma leakage from the intravascular to the extravascular space. The World Health Organization (WHO) case definition for DF/DSS incorporates three additional clinical criteria beyond DF and has established a grading scale of I to IV for DHF severity (Table 36.1.1). Despite the moniker “hemorrhagic fever,” most often the hemorrhagic manifestations may only be a positive tourniquet test or spontaneous skin or mucosal petechiae. Severe coagulopathy is nearly always seen in the context of profound shock and multi-organ failure. Recent WHO guidelines have moved away from the DHF case definition and, instead, proposed a new case definition termed severe dengue (see Table 36.1.1). Whether defined as DHF/DSS or severe dengue, the majority of serious morbidity and mortality caused by DENV infections is due to a vascular leakage syndrome with hypotension and shock. Clinically significant hemorrhage can sometimes occur in the absence of vascular leakage, particularly in adults. Other uncommon complications of DENV infections include hepatic necrosis, encephalopathy/encephalitis, and chorioretinitis. Unlike Zika virus infections, DENV infection during pregnancy has not been associated with congenital malformations.

**TABLE 36.1.1 Case Definitions for Dengue Hemorrhagic Fever/Dengue Shock Syndrome, Severe Dengue, and the Warning Signs for Severe Dengue**

| Case Definition for Dengue Hemorrhagic Fever (DFH) and DHF Severity Classification | Case Definition for Severe Dengue | Warning Signs for Severe Dengue |
|---|---|---|
| Signs/symptoms of dengue fever and: 1. thrombocytopenia (platelet count <100,000/mm³), and 2. evidence of plasma leakage (hematocrit rise ≥20% from baseline, pleural effusion, or ascites), and 3. hemorrhagic manifestation | Probable or laboratory-confirmed dengue and: 1. severe plasma leakage (shock or fluid accumulation with respiratory distress), or 2. severe hemorrhage (as evaluated by clinician), or 3. severe organ impairment: • liver: AST or ALT ≥1000 U/mL • central nervous system: impaired consciousness • heart and other organs | Abdominal pain or tenderness Persistent vomiting Clinical fluid accumulation Mucosal bleed Lethargy, restlessness Liver enlargement >2 cm Increase in hematocrit concurrent with rapid decrease in platelet count |
| DFH grade I = criteria 1 + 2 + positive tourniquet test | DFH grade II = criteria 1 + 2 + spontaneous bleeding | |
| DFH grade III = DFH grade I/II criteria + circulatory failure (hypotension, weak pulse) | DFH grade IV = DFH grade I/II criteria + profound shock | |

ALT, Alanine aminotransferase; AST, aspartate transaminase.

**PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS**

Dengue should be considered in all individuals in endemic regions, particularly children, who present with an abrupt-onset febrile illness of <10 to 14 days’ duration during the DENV transmission season. The initial clinical findings in DENV infections are fairly non-specific and can be difficult to distinguish from other common febrile illnesses in the tropics. The differential diagnosis for dengue-like illnesses includes typhoid fever, leptospirosis, rickettsial infections, or malaria. In the appropriate clinical setting, measles, influenza, chikungunya, or Zika virus infections are also possibilities.

Early in the febrile course, the suspicion for a DENV infection can be heightened by the presence of leukopenia, thrombocytopenia, mild aspartate aminotransferase elevation, and a positive tourniquet test or spontaneous petechiae. The positive predictive value for combinations of these early clinical findings has generally been good when dengue is highly prevalent (i.e., during the rainy season).

The critical phase of any DENV infection is the 24 to 48 hours surrounding defervescence—generally around days 5 to 7 of the febrile illness in a secondary DENV infection. This is the time period when plasma leakage will take place in patients developing DHF/DSS. A challenge in patients with dengue, or suspected dengue, is to identify those at risk for severe disease before the critical phase is reached. A group of warning signs and symptoms have been identified in DENV-infected patients that often presage the deterioration to DHF/DSS (severe dengue) (see Table 36.1.1). These patients require close monitoring and supportive care during the critical phase of illness.

Laboratory diagnosis remains the most reliable way to identify a DENV infection. Reverse transcriptase polymerase chain reaction (RT-PCR) can detect viral RNA in the blood for up to 5 to 7 days after the onset of fever in primary infections and 3 to 4 days in secondary infections. However, DENV RT-PCR is not routinely available in most clinical settings. Viremia can also be detected by antigen-detection assays that measure circulating levels of a DENV non-structural protein, NS1. The timeline for detectable circulating soluble NS1 lags viral RNA RT-PCR detection by 1...
to 2 days. The most widely used serologic assay for dengue is IgM/IgG enzyme-linked immunosorbent assay (ELISA). A single positive dengue IgM or high-titer IgG can only provide a presumptive diagnosis of dengue. Definitive serologic diagnosis requires paired acute and convalescent sera. Anti-DENV IgM antibody levels do not generally become positive until the fifth or sixth day of illness and can be affected by other flavivirus infections (e.g., Japanese encephalitis virus, Zika virus). Therefore the diagnostic sensitivity and specificity of anti-DENV IgM ELISA assays often depend on the timing of the blood sample, co-circulating flaviviruses in the region, and the manufacturer.

**TREATMENT**

No specific anti-viral therapies are available for dengue. The vast majority of uncomplicated dengue can be managed on an outpatient basis with rest, oral rehydration solution, and analgesia/antipyretics. The use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, as they can exacerbate platelet dysfunction and mucosal bleeding. Patients and the parents of affected children should be notified of the warning signs and symptoms that should prompt an immediate return to medical attention.

In-hospital management should be arranged for patients with the pre-defined warning signs, early evidence of plasma leakage (including narrow pulse pressure), bleeding or severe hematologic abnormalities, co-morbid conditions, or those with unreliable access to outpatient follow-up care. For hospitalized patients without frank hypotension or shock, the key aspect of supportive therapy is judicious intravascular volume replacement as the critical phase is entered. This is accomplished by the careful administration of intravenous isotonic crystalloid solutions (e.g., 0.9% saline, Ringer's lactate, Hartmann's solution) with frequent re-assessment of intravascular volume status and urine output. The overly aggressive use of intravenous fluids or the failure to adequately monitor therapy can lead to serious complications of fluid overload during the critical phase of illness. Treatment guidelines are shown in Fig. 36.1.2.

Prophylactic platelet transfusions have not proven to be useful in dengue and should be avoided. Platelet transfusions can be considered in patients with thrombocytopenia and clinically significant hemorrhage. Intramuscular injections, multiple large-bore intravenous lines, and diagnostic or prophylactic placement of nasogastric tubes should be avoided, except as needed in the most severe cases. If possible, complicated or unusual severe dengue cases should be transferred to experienced referral centers in the

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**Compensated shock (systolic pressure maintained but has signs of reduced perfusion)**

Fluid resuscitation with isotonic crystalloid

5–10 mL/kg/h over 1 hour

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**Check HCT**

If HCT increases, consider bolus fluid administration or increase fluid administration; if HCT decreases, consider transfusion with fresh whole transfusion.

Stop at 48 hours.

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**Fig. 36.1.2** Treatment guidelines for dengue and dengue hemorrhagic fever.
area. The case-fatality rate for severe dengue is <1% with early recognition and appropriate supportive care and management.

**PREVENTION**

Dengue prevention can be approached by strategies to minimize human–vector contact and control mosquito–vector populations. Functioning screens and insecticide-treated bed nets for daytime sleeping (e.g., in infants) can reduce mosquito–vector contact indoors. Personal measures that afford some protection against the daytime biting habits of female *A. aegypti* include wearing clothing that minimizes skin exposure and appropriate use of repellants on exposed skin or clothing. Effective repellants should contain N,N-diethyl-3-methylbenzamide (DEET), 3-(N-acetyl-N-butyl)-aminopropionic acid ethyl ester (IR3535), or 1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester...

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**Fig. 36.1.2, cont’d.** Treatment guidelines for dengue and dengue hemorrhagic fever.
DENV transmission in many endemic regions. opens up the possibility of severely halting, or even eradicating, virus vaccine, and a plasmid DNA vaccine. The combination of recombinant envelope protein vaccine, an adjuvanted inactivated phase III clinical trials. Other dengue vaccine products that are another tetravalent live-attenuated dengue vaccine (attenuated the subsequent disease severity with a natural DENV infection. to truly dengue-naïve individuals, it appears to be able to enhance licensed in several countries. However, if this vaccine is administered to truly dengue-naïve individuals, it appears to be able to enhance the subsequent disease severity with a natural DENV infection. Another tetravalent live-attenuated dengue vaccine (attenuated by a deletion in the DENV2 3' untranslated region [UTR]) is in phase III clinical trials. Other dengue vaccine products that are in pre-clinical or early clinical phases include an adjuvanted recombinant envelope protein vaccine, an adjuvanted inactivated virus vaccine, and a plasmid DNA vaccine. The combination of effective dengue vaccination with vector-control strategies will open up the possibility of severely halting, or even eradicating, DENV transmission in many endemic regions.

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36.2 Chikungunya Fever
Ann M. Powers

KEY FEATURES
• Chikungunya fever is a significant arboviral disease with nearly global distribution. Infection is characterized by the abrupt onset of high fever with severe arthralgia and rash.
• The disease is nearly always self-limiting and rarely fatal but may result in long-term arthralgia affecting quality of life.
• There is no specific treatment, and supportive care consists of treatment for the fever and pain. No vaccine yet exists, but both vaccines and therapeutic options are under development.
• The virus is transmitted in urban settings by infected Aedes aegypti and A. albopictus mosquitoes. Endemic maintenance of the virus is by forest-dwelling Aedes species mosquitoes.

INTRODUCTION
Chikungunya (CHIK) fever is an arboviral disease that is characterized by the rapid onset of high fever, rash, and severe joint pain (Fig. 36.2.1). Its name is derived from the Makonde word meaning “that which bends up” in reference to the stooped posture that develops as a result of the arthritic symptoms of the disease. The disease is nearly always self-limiting.1 The causative agent, chikungunya virus (CHIKV), is a single-stranded, positive-sense RNA virus belonging to the family Togaviridae, genus Alphavirus. Molecular characterization has demonstrated three distinct genotypes (West African, Central/East African, and Asian) that historically were geographically limited to Africa and Asia.2 Recent spread has made the pathogen a nearly global concern (Fig. 36.2.2). A zoonotic cycle is known to exist in Africa involving a range of vertebrate hosts, including non-human primates, and forest-dwelling Aedes (Stegomyia) mosquitoes. The virus is transmitted to humans primarily by Aedes aegypti and A. albopictus mosquitoes.
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EPIDEMIOLOGY

The first recorded epidemic occurred in Tanzania in 1952–1953. In Asia, CHIKV was first detected in Bangkok, Thailand, in 1958. In India, well-documented outbreaks occurred in 1963 and 1964 in Calcutta and southern India, respectively. Thereafter, a small outbreak of CHIK was reported from the Sholapur district, Maharashtra, in 1973. Cases of CHIK continued to be reported in Africa and Southeast Asia, although no additional major outbreaks were reported for nearly three decades. The virus emerged in East Africa (Kenya) and the islands of the Indian Ocean, including Comoros, La Réunion, Mayotte, Mauritius, and Seychelles, beginning in 2004. CHIKV then re-emerged in India in December 2005. The 2005–2006 outbreak in India involved approximately 1.35 million suspected cases in 12 states. The attack rate reached up to 45% due to the lack of herd immunity, a large susceptible population, and the ability of certain strains containing an alanine to valine mutation in the E1 gene to more efficiently infect the secondary vector, A. albopictus.

Imported cases of CHIKV infection were reported from Europe and North and South America in returning travelers from areas with high incidence rates. In 2013 the virus emerged in the Caribbean island of St. Martin and quickly spread throughout the Caribbean and Latin America. In the first year alone in the Americas, an estimated >1 million cases occurred in over 40 countries (Fig. 36.2.3). Although massive outbreaks have subsided, the virus continues to circulate on a nearly global scale.

PATHOGENESIS

After the bite of an infected mosquito, the virus replicates in fibroblasts and epithelial cells leading to a viremia that can reach up to 8 log_{10}/mL. The skin, joints, and muscles are the primary affected organs, whereas the nervous system, heart, and liver are less frequently involved. Macrophage appear to be susceptible to infection during the viremic phase. Mouse models have shown that type 1 interferon response appears to be associated with control of infection.

CLINICAL FEATURES

CHIK is an acute infection of abrupt onset, heralded by high fever and severe arthralgia, followed by other constitutional symptoms and rash (typically maculopapular) lasting for a period of 1 to 7 days. The incubation period is usually 3 to 7 days, with a range of 2 to 12 days. Fever rises abruptly, often reaching 39°C to 40°C. This acute phase lasts a few days to 2 weeks. In some cases, the temperature may remit for 1 to 2 days after a gap of 4 to 10 days, resulting in a “saddle back” fever curve that is characteristic of arthropod-borne virus infections.

The arthralgias are polyarticular, symmetric, and predominantly affect the small joints of the hands, wrists, ankles, and feet (see Fig. 36.2.1) with lesser involvement of larger joints. During the acute phase, joint pain can be incapacitating. Patients with milder articular manifestations are usually symptom free within a few
weeks, but more severe cases require months or years to resolve entirely. One study indicated that one third of patients had chronic joint symptoms that persisted for at least 9 months. Cutaneous manifestations are typical with many patients. This is usually a maculopapular rash, but bullous lesions can occur in infants. The trunk and limbs are most commonly involved, but the face, palms, and soles may also show lesions. During the acute phase, some patients will have headache, but it is not usually severe, and retro-orbital pain, commonly found in dengue infections, rarely occurs. Conjunctival redness is present in some cases. Pregnant women can pass the virus to their infant, most commonly during the intrapartum phase. The Reunion South Hospital Group observed 84 pregnant women who had laboratory-confirmed CHIK infection. In 88% of these women (all involving infections relatively distant from delivery), the newborns appeared asymptomatic. Conversely, 10 newborns developed disease soon after birth (4 with meningoencephalitis and 3 with intravascular coagulation) and required intensive care support. Severe cases of CHIK, including neurologic complications, myocarditis, or nephritis, can occur, most commonly in the elderly, newborns, and immunocompromised individuals. CHIK outbreaks typically result in several hundred or thousands of cases, but deaths are rarely encountered.

DIAGNOSIS

Symptoms of CHIKV infection can be clinically indistinguishable from dengue fever. Other causes in the differential diagnosis of CHIK include malaria, O’nyong nyong, Sindbis, Ross River, West Nile, and Zika virus infections. The clinical laboratory findings in CHIK are not remarkable. A few patients may present with leukopenia with relative lymphocytosis; however, most patients will have normal blood counts. The platelet count may be moderately depressed. The erythrocyte sedimentation rate and C-reactive protein levels are typically elevated in acute cases. A definitive diagnosis can only be made by laboratory testing, but CHIK should be suspected when epidemic disease occurs with the characteristic triad of fever, rash, and arthralgia.

Virus-specific IgM antibodies typically can be detected by 5 to 7 days of illness using enzyme-linked immunosorbent assay (ELISA). Because viremia is so high and persists for several days post-illness onset, blood samples for virus isolation and reverse transcriptase polymerase chain reaction (RT-PCR) should be collected within the first 5 days of illness when viremia is detectable. Frequently, diagnosis can be definitively confirmed by virus isolation or molecular techniques such as RT-PCR, for which a wide range of tests now exist.

TREATMENT

There is no specific treatment for CHIK. The illness is usually self-limiting and resolves with time. Supportive care with rest is
indicated during the acute joint symptoms. Movement and mild exercise may decrease stiffness and arthralgia, but heavy exercise may exacerbate rheumatic symptoms. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for chronic pain. A number of therapeutic options are in development, as are several vaccine candidates.

Because no vaccine or specific medication is yet available against CHIKV infection, vector control is very important in controlling or preventing transmission. Elimination of breeding sites or source reduction is an important control approach. *A. aegypti* is typically a container-habitat species (Fig. 36.2.4) and breeds primarily in artificial containers and receptacles. Therefore all water tanks, cisterns, barrels, trash containers, etc., need to be covered tightly with a lid. Old tires, tin cans, buckets, drums, bottles, etc., should be removed, as mosquitoes may breed in these containers if they accumulate water. In ornamental garden water tanks, larvivorous fish (e.g., gambusia, guppy) can be introduced. In case water containers cannot be emptied on a daily or weekly basis, larvicidal treatments can be applied.

Both primary vectors, *A. aegypti* and *A. albopictus*, are principally daytime biters. Insect repellent containing N,N-diethyl-m-toluamide (DEET) or another registered active ingredient should be applied on exposed skin (Table 36.2.1). People should be advised to wear long sleeves and pants and have secure screens on windows and doors to keep mosquitoes out. Insecticide-treated bed net use during daytime resting can help prevent mosquito bites. Infected persons should be protected from further mosquito exposure (staying indoors and/or under a mosquito net during the first few days of illness) so that they cannot contribute to the transmission cycle.

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**TABLE 36.2.1** Environmental Protection Agency–Registered Insect Repellents

| Active Ingredient | Other Names |
|-------------------|-------------|
| DEET              | N,N-diethyl-m-toluamide |
| Picaridin         | Known as KBR 3023 and icaridin outside the US |
| IR3535            | 3-[(N-butyl-N-acetyl)-aminopropionic acid |
| Oil of lemon eucalyptus (OLE) | Para-menthane-diol (PMD), p-menthane-3,8-diol |
| 2-undecanone      | Methyl nonyl ketone |

Higher percentages of active ingredient provide longer protection. The EPA’s search tool is available at www.epa.gov/insect-repellents/find-insect-repellent-right-you.
36.3  Zika

Lin H. Chen, Mary E. Wilson

KEY FEATURES

- Zika virus, a flavivirus, has re-emerged with intense outbreaks in the Americas since 2013.
- It is transmitted by *Aedes* mosquitoes, primarily the species *Aedes aegypti*, but sexual transmission and transfusion-related transmission have also occurred.
- It is often a mild or asymptomatic illness, but infections can manifest with rash, fever, conjunctivitis, and myalgias; severe manifestations have occurred and include Guillain–Barré syndrome (GBS). In utero transmission has led to microcephaly and other severe birth defects.
- There is no anti-viral agent to treat Zika virus infection; supportive care is indicated.
- There is no effective vaccine yet; prevention relies on avoidance of vector mosquitoes and sexual contact with infected persons, which are particularly important for pregnant women and persons who are planning conception.

INTRODUCTION

Zika virus, a single-stranded RNA virus of the Flaviviridae family, genus *Flavivirus*, originally isolated in Africa, gained worldwide attention in 2015 and 2016 when massive outbreaks in Brazil were followed by a marked increase in infants born with severe microcephaly and congenital abnormalities. The virus subsequently spread throughout the Americas. Intense research activities have answered key questions about Zika virus, its spread, and control, but gaps in knowledge remain.

EPIDEMIOLOGY

Zika virus, first isolated from a sentinel rhesus monkey in the Zika forest in Uganda in 1947, was found in the same area in 1948 in *Aedes* mosquitoes. The first human infection was identified in the 1950s. In subsequent decades it was identified sporadically in animals and in mild human infections in Africa and Asia. In 2007 Zika virus caused a large outbreak on Yap Island (western Pacific), initially thought to be caused by dengue virus; the virus was estimated to infect 70% of the population. It subsequently caused a major outbreak in French Polynesia in 2013 to 2014. Zika virus was first associated with recognized outbreaks in Brazil in 2015, but recent analyses using sequencing, molecular mapping, and modeling suggest Zika reached the Americas as early as 2013, with cryptic transmission before the disease was detected. From northeast Brazil the virus spread to the Caribbean, Central America, and throughout South America (except Chile and Uruguay where local vector transmission has not been documented); many countries in Asia and Africa have also documented transmission (Fig. 36.3.1). Local vector transmission in the continental United States has occurred in Florida and Texas (226 cases as of December 2017; https://www.cdc.gov/zika). A 2016 outbreak in Singapore (455 cases confirmed) shows the potential for outbreaks in many tropical and sub-tropical regions where competent mosquito vectors are present and ecoclimatic conditions are favorable.

PATHOGENESIS AND PATHOLOGY

Perinatal transmission of Zika virus was reported to occur in the French Polynesia outbreak in 2013 to 2014, but the association between Zika virus and microcephaly was not recognized until the observations had been made in Brazil and a retrospective study was done in 2016 based on serologic and surveillance data. Zika virus can infect the placenta, reach the developing fetus, and can target neural precursors. Maternal infection disrupts fetal central nervous system development and causes intrauterine growth retardation and fetal loss. Infection is associated with cortical malformations and intra-cranial calcifications. The congenital malformations include ventriculomegaly, dystrophic calcifications, severe cortical neuronal depletion, decreased brain weight, congenital contractures, marked early hypertonia with symptoms of extrapyramidal involvement, and ocular and hearing problems.

TRANSMISSION

Infection is spread primarily via infected female mosquitoes, with *A. aegypti* being the primary vector in the Americas. *A. albopictus*, which can survive in more temperate areas, can also transmit Zika virus. These mosquito vectors infest most sub-tropical and tropical regions globally, including urban areas (areas with a total population of about 3.6 billion people). Seasonality of transmission is linked to local temperature and rainfall patterns. The same mosquitoes can also transmit dengue and chikungunya (and co-transmission can occur). In the past 10 years, Zika transmission has been reported from at least 84 countries. Zika virus can be transmitted vertically in *A. aegypti* mosquitoes. The transmission cycle in the Americas has been person–mosquito–person. It is not known whether the virus will become established in an animal reservoir host in the Americas, as occurs in Africa, where the virus infected animal hosts and occasionally spilled over into the human population—at least in the past. The growth of urban areas infected with *A. aegypti* provides a suitable environment for transmission.

Of the 5413 Zika virus disease cases (excluding congenital cases) reported in the United States for January 2015 to December 6, 2017, 95% were travel related and 99% were vector borne. Of the 51 cases that were not vector borne, 94% were attributed to sexual transmission, 1 due to laboratory transmission, and 1 unknown route (https://www.cdc.gov/zika).

Virus can be found in blood, urine, saliva, semen, and vaginal or cervical secretions. Sexual transmission can occur during or after symptomatic or asymptomatic infection from male to female, male to male, and female to male (possibly via oral sex). Virus is found in vaginal secretions, and viral RNA has been documented in semen up to 188 days after infection and infectious virus up to 69 days. In a longitudinal assessment of Zika virus RNA in body fluids, 95% of men had cleared the virus from semen after about 3 months. In areas infested with competent vectors, it is difficult to assess what percentage is vector borne and how much infection is sexually transmitted. Zika virus particles and RNA have been found in breast milk, but transmission via breastfeeding has not been documented to date. Virus persists longer in whole blood than in plasma, which may be relevant for diagnosis and in testing blood or tissue donations for transfusion/transplantation. Transmission via platelet transfusion was reported from Brazil, and RNA Zika–positive asymptomatic donors were identified in Florida and Texas in the United States. Screening of blood donors in Puerto Rico during an outbreak on the island found 1.1% viremic.
Pathologists also identified pulmonary hypoplasia and pathologic changes consistent with viral infection of multiple organs, including liver and kidneys. Ongoing follow-up will reveal the extent of other developmental problems.

Based on data from the U.S. territories (2464 live-born infants from completed pregnancies with laboratory evidence of possible Zika virus infection), about 5% had Zika-associated birth defects. The likelihood varied by trimester and was highest during the first trimester (8%, 5%, and 4%, respectively, for first, second, and third trimesters).  

**TABLE 36.3.1** Comparison of Proportions of Symptoms in Samples of Zika-Infected Persons

|                     | Yap1 | French Polynesia2 | Brazil20 | Puerto Rico21 | U.S. Travelers22 | GeoSentinel Travelers23 | Singapore7 | U.S. Pediatric Travelers24 |
|---------------------|------|-------------------|----------|---------------|------------------|-------------------------|------------|---------------------------|
| Sample size, N      | 31   | 297               | 119      | 683           | 115              | 91                      | 149 adults | 14 children               | 158         |
| Rash                | 90   | 93                | 97       | 74            | 98               | 88                      | 93         | 100                       | 82          |
| Fever/sweats        | 65   | 72                | 36       | 63            | 82               | 76                      | 79         | 93                        | 55          |
| Arthralgia          | 65   | 65                | 63       | 63            | 66               | 72                      | 23         | 14                        | 28          |
| Headache            | 45   | 46                | 66       | 63            | 57               | 61                      | 23         | 21                        | +           |
| Myalgia             | 48   | 65                | 61       | 68            | 55               | 60                      | 42         | 29                        | +           |
| Fatigue             | –    | 78                | 73       | –             | –                | 47                      | –          | –                         | –           |
| Conjunctivitis      | 55   | 64                | 56       | 20            | 37               | 40                      | 23         | 29                        | 29          |
| Pruritus            | –    | –                 | 79       | –             | –                | 23                      | –          | –                         | –           |
| Retro-orbital pain  | 39   | 16                | 45       | 51            | –                | 1                       | –          | –                         | –           |
| Edema/swelling      | 19   | 47                | 29       | –             | –                | 8                       | –          | –                         | –           |
| Gastrointestinal    | +    | +                 | +        | +             | +                | +                       | –          | –                         | +           |
| (nausea, vomiting,  |      |                   |          |               |                  |                          |            |                           |             |
| diarrhea, or        |      |                   |          |               |                  |                          |            |                           |             |
| abdominal pain)     |      |                   |          |               |                  |                          |            |                           |             |

– = Not reported specifically; + = reported.

**CLINICAL FEATURES**

Zika virus seroprevalence studies in Yap and French Polynesia estimated that asymptomatic infections ranged from 29% to 80%. Clinical syndromes among residents from outbreak areas such as Yap, French Polynesia, Brazil, and Puerto Rico and returned infected travelers appeared to be alike ([Table 36.3.1](#table3631)). The most frequently reported symptoms were rash (74%–100%), fever, arthritis and/or arthralgia, myalgia, conjunctivitis, and fatigue. The most common finding, rash, was usually described as
Maculopapular. Pruritus was reported from Rio de Janeiro, Brazil, and travelers evaluated in the GeoSentinel Surveillance Network, but not from other series. Fatigue was frequently reported from French Polynesia and Brazil (78% and 73%, respectively) but possibly not solicited or recorded in some other series. Proportions with retro-orbital pain or edema/swelling were variable. Presenting symptoms among children infected postnatally resembled those in adults, mainly with rash, fever, conjunctivitis, and arthralgia.

Rarely, some severe complications in adults have been attributed to Zika virus infection, particularly neurologic disorders (GBS, myelitis, demyelinating polyneuropathy, meningoencephalitis, autoimmune disorder, and immune-mediated thrombocytopenia). GBS occurred in about 1/4000 Zika infections in studies from French Polynesia and Brazil, at least six times that of the global baseline incidence; males had higher risk. Patients with Zika-associated GBS or encephalitis have died (6%), and 51% have chronic pain. As described earlier, congenital Zika syndrome resulting from infection during pregnancy is associated with devastating abnormalities in the newborn and has the most significant impact.

**PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS**

During acute infection with Zika virus, laboratory findings may reveal leukopenia, lymphopenia, thrombocytopenia, and less frequently, leukocytosis. C-reactive protein may be mildly elevated, as well as transaminases.

Recommendations for confirmatory Zika virus testing vary among countries and have evolved over the course of its rapid spread in the Americas. In the United States testing has been constrained by availability of diagnostic tests and laboratory capability. The guidelines consider the pregnancy status of the patient or partner, exposure history, and symptoms, with strongest focus on pregnant women.

Definitive Zika diagnosis can be made by detection of viral RNA during acute infection by reverse transcription polymerase chain reaction (RT-PCR) or by detection of Zika virus antibodies such as IgM, IgG, or neutralizing antibodies.

**Fig. 36.3.2** Testing recommendations and interpretation of results for symptomatic persons with possible Zika virus exposure. (A) Pregnant women. (From Oduyebo T, Polen KD, Walke HT, et al. Update: interim guidance for health care providers caring for pregnant women with possible Zika virus exposure – United States (including U.S. territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017;66(29):781–93.)
RNA appears to be detectable longer in whole blood and urine samples compared with serum samples. These molecular tests can be performed on serum, whole blood, or urine up to 2 weeks after symptom onset; in pregnant women, NATs may be performed up to 12 weeks after symptom onset or exposure. 

Detection of Zika IgM by IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) followed by confirmation with plaque reduction neutralization test (PRNT) can also establish the diagnosis. Zika IgM may be reactive when performed 2 to 12 weeks after exposure, but can persist longer. Unfortunately, Zika serology cross-reacts with other flaviviruses, and PRNT, which is needed to differentiate among the flaviviruses, is labor intensive, time consuming, and challenging to interpret. Unlike dengue and chikungunya, where IgG is available to assess past infection and immunity, Zika IgG is not available in the United States.

There are no Food and Drug Administration (FDA)-licensed diagnostic tests for the diagnosis of Zika virus infection, but several diagnostic tests are available under Emergency Use Authorization. The Centers for Disease Control and Prevention (CDC) and state laboratories perform testing with PCR or IgM, and the CDC performs PRNT. In October 2017, the FDA approved the first Zika test for screening blood donations.

The main differential diagnoses for Zika virus infection are other viruses transmitted by <i>Aedes</i> mosquitoes, especially dengue (also a flavivirus) and chikungunya (an alphavirus). Because Zika, dengue, and chikungunya cause similar symptoms and each may have important consequences, distinguishing among the flaviviruses by molecular test or serology followed by PRNT is desirable. Other diagnoses that may resemble Zika virus infections include rubella, rubella, parvovirus, West Nile virus, and many other viruses, as well as leptospirosis, rickettsiosis, and malaria.

**TREATMENT AND PREVENTION**

Treatment for the typical uncomplicated Zika virus infection aims to provide symptomatic relief. There is no known specific medication targeting Zika virus. However, research is underway to assess the effect of some existing drugs on Zika virus. Preliminary investigations have identified some candidate drugs: emricasan, niclosamide, sofosbuvir, chloroquine, azithromycin, and bovine

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**Fig. 36.3.2, cont’d. Testing recommendations and interpretation of results for symptomatic persons with possible Zika virus exposure. (B) Non-pregnant women. (From CDC. Guidance for US laboratories testing for Zika virus infection, July 24, 2017. Available at [https://www.cdc.gov/zika/laboratories/lab-guidance.html](https://www.cdc.gov/zika/laboratories/lab-guidance.html).**

| Specimen collected <14 days post-symptom onset | Specimen collected ≥14 days post-symptom onset |
|------------------------------------------------|------------------------------------------------|
| Positive Zika virus NAT | Negative Zika virus NAT |
| Zika virus IgM serology | Non-negative Zika virus IgM |
| Plaque reduction neutralization test (PRNT) | Negative Zika virus IgM |
| Zika virus PRNT ≥10 AND dengue virus PRNT <10 | Zika virus PRNT ≥10 AND dengue virus PRNT ≥10 |
| Zika virus PRNT <10 | Zika virus PRNT <10 |

1NAT testing is not recommended for specimens obtained ≥14 days post-symptom onset.

2Acceptable specimens for NAT testing include serum, or patient-matched serum and urine. Repeat NAT testing of a positive result is not indicated. Dengue and chikungunya virus NAT testing should be performed for patients at risk of exposure, and with clinically compatible illness.

3Dengue IgM serology should also be performed for patients at risk of exposure, and with clinically compatible illness.
lactoferrin. Further evaluation is needed regarding their potential activity against Zika virus.

Currently there is no vaccine to prevent Zika virus infection but multiple candidate vaccines are under development and testing. Therefore avoidance of mosquito bites and sexual transmission is fundamental in prevention. The impact of Zika virus infection is most consequential during pregnancy; thus preventing infection in pregnant women is crucial. The key messages for pregnant women, their partners, and persons planning conception include:

- Taking measures to avoid mosquito bites, and practice safe sex to reduce risk from sexual transmission. In areas with active Zika virus transmission, vector control measures are essential. Updated epidemiology and testing recommendations on the CDC website (www.cdc.gov/zika) are valuable in guiding clinical practice.

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## 36.4 O’nyong Nyong Fever

**Gregory Deye, Michael Koren**

### KEY FEATURES

- Alphavirus transmitted by anopheline mosquitoes in sub-Saharan Africa.
- Typically reported in large epidemics with high attack rates.
- Fever and severe symmetric arthralgias are nearly universal. Pruritic maculopapular rash is common.
- Lymphadenitis (especially posterior cervical) is common but not universal.
- Diagnosis is by polymerase chain reaction (PCR) in the first 3 days or by serology.
- Treatment is supportive, with acute symptoms resolving in 5 to 7 days.

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**PART 2**  
**Viral Diseases**  
**340**
INTRODUCTION

O’nyong nyong fever (ONN) is an arboviral disease caused by an alphavirus of the Semliki Forest complex and closely related to chikungunya virus (CHIKV) (Fig. 36.4.1). Like other members of this complex, O’nyong nyong virus (ONNV) causes a febrile arthralgic illness. It is unique among alphaviruses in its adaptation to Anopheles mosquito vectors, which are primarily responsible for its transmission.

The disease was first recognized in 1959 when an epidemic began in northwestern Uganda. By the end of the epidemic in 1962, it had involved 2 million people in a bandlike distribution across Uganda, Kenya, and Tanzania. Investigation of this epidemic led to the discovery of the novel virus, which was named after an Acholi term meaning “the joint breaker.”

EPIDEMIOLOGY

ONN has largely been described as occurring in epidemics in sub-Saharan Africa. After the end of the initial epidemic in 1962, no clinical cases were recognized until a subsequent epidemic occurred in Uganda in 1996 to 1997 resulting in several hundred cases. However, sporadic cases have been reported from several regions in sub-Saharan Africa outside of recognized epidemics. Furthermore, a recent serosurvey from coastal Kenya demonstrated 13% prevalence of ONNV antibody presence despite no reported recent outbreaks in the region. An illness with clinical features very similar to ONN has been described in Nigeria with the causative agent originally named Igbo Ora virus. Subsequent studies have shown that Igbo Ora is actually a strain of ONNV. The genetic similarities of Igbo Ora and the 1996 to 1997 ONNV to the 1959 ONNV, together with serosurveys from Kenya, Cameroon, and West Africa, suggest at least some level of unrecognized endemic transmission occurs during interepidemic periods.

During recognized epidemics, rates of infection have been very high in some areas; up to 68% in some affected villages. The virus is principally transmitted by Anopheles funestus and A. gambiae, both of which also serve as important vectors of malaria. No vertebrate reservoir has been identified. Risk factors for infection are likely to be related to risk of mosquito exposure and are likely to be similar to risk factors associated with malaria.

CLINICAL FEATURES

The ratio of symptomatic to inapparent infections is roughly 2 : 1. The incubation period is estimated to be 8 days. Clinical symptoms typically begin with sudden onset of fever and joint pains. Joint involvement is generally symmetric, involving knees (90%), ankles (83%), elbows (75%), wrists (75%), or fingers (63%). Joint pain lasts for an average of 6 days, although durations as long as 90 days have been reported. Arthralgia was sufficiently severe to lead to immobilization in 78% of cases for an average of 4 days. Headache and rash are also very commonly reported in clinical cases. The rash is described as maculopapular and descending in progression from head to trunk to extremities. It typically lasts for 4 to 7 days.

Lymphadenopathy has also been commonly described and occurs most often in the cervical region but also in inguinal and axillary areas in some cases. This has been suggested as a distinguishing factor in ONN, but it notably only appears to occur in 40% to 50% of cases. Conjunctival suffusions have also been reported in approximately half of cases.

A mild neutropenia has been reported during the acute phase of the illness. In both the 1959 to 1962 epidemic and the 1996 to 1997 epidemic, there were no reported fatalities, despite a total of more than 2 million cases.

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

Clinical features such as lymphadenopathy, fever, and arthralgia are important characteristic features but are not sufficiently specific to exclude other similar arbovirus infections such as chikungunya. Careful history and physical examination should be directed at excluding other illnesses, as well as finding supportive features such as rash. Virus can be detected in whole blood by molecular amplification (polymerase chain reaction [PCR]), with greatest sensitivity during the first 3 days after the onset of illness. Serology can help to establish the diagnosis, which can be made by the detection of specific IgM or by paired acute and convalescent sera showing development of specific IgG. IgM typically appears during the second week of illness and persists for about 2 months, but can be as long as 6 months in some cases. IgG titers begin to rise by day 21 and are long-lasting.

Care must be taken in the interpretation of serologic results because of a well-known, one-way cross-reactivity with CHIKV (i.e., patients previously infected with chikungunya will develop cross-reactive antibodies against ONNV, but antibodies generated by ONNV infection will not reliably cross-react with chikungunya virus).

Fig. 36.4.1 Alphavirus phylogenetic tree. (From Bessaud M, Peyrefitte CN, Pastorino BA, et al. O’nyong-nyong virus. Chad. Emerg Infect Dis 2006;12:1248.)
TREATMENT AND CONTROL

The illness is self-limited, but therapy with non-steroidal anti-inflammatory drugs (NSAIDs) may benefit joint symptoms. Preventive measures against exposure to malaria vectors—for example, insecticide-treated bed nets and indoor residual insecticides—should also be effective in controlling epidemic ONN. Additionally, vaccine efforts aimed at prevention of chikungunya may provide protection against ONNV infection due to production of cross-reactive antibodies.10

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36.5 Ross River Virus Disease

David Harley, Andreas Suhrbier

KEY FEATURES

• Synonyms include epidemic polyarthritis and Ross River fever.
• Endemic and epidemic transmission in Australia and Papua New Guinea, with a mean of 4600 cases per annum in Australia (2000–2015).
• Notable clinical features include peripheral symmetric polyarthralgia or polyarthritis, predominantly involving joints of the appendicular skeleton. The disease usually progressively resolves within 3 to 6 months.
• Diagnosis is usually made by pathology services using commercially available IgM/IgG enzyme-linked immunosorbent assay (ELISA).

INTRODUCTION

Ross River virus (RRV) is a mosquito-borne virus that causes several thousand human cases per year in Australia, with polyarthralgia or polyarthritis being the predominant clinical feature. This single-stranded, positive-sense RNA virus (11.8 kb genome) belongs to the genus Alphavirus and the family Togaviridae. The virus was first isolated from *Aedes vigilax* mosquitoes trapped beside the Ross River in Queensland (Fig. 36.5.1) in 1959.1 After a series of outbreaks, the disease was originally called epidemic polyarthritis.2

EPIEMIOLOGY

RRV disease is notifiable to public health authorities in Australia and is the most common arboviral disease in Australia. There has been a mean of 4600 (range 1451–9554) reported cases per year (2000–2015), equating to a mean national incidence of 21.3 (range 7.4–40.2) per 100,000 per annum in the same period (data available via http://www9.health.gov.au/cda/source/rpt_4.cfm). Disease typically occurs in adults between 25 and 39 years old, with no clear predominance in males or females. Symptomatic infections are rare in children.3

RRV is endemic in Australia and Papua New Guinea. Most cases occur in northern Australia during the wet season (usually December–February) when mosquito numbers are high. In 1979–1980, RRV caused a large epidemic in the South Pacific (see Fig. 36.5.1) where the virus may still be circulating.

NATURAL HISTORY, PATHOGENESIS, AND PATHOLOGY

RRV is transmitted in enzootic cycles with macropods (kangaroos and wallabies) as the natural vertebrate hosts. The virus is transmitted to humans from other vertebrates (and humans during epidemics) by mosquitoes, principally *A. vigilax*, *A. camptorhynchus*, and *Culex annulirostris*.1 Enzootic transmission, complex ecology involving multiple hosts and vectors, and different modes of transmission in different biogeographic areas make the disease difficult to model and predict and hence hinder disease control.3

Rheumatic disease is believed to arise from adaptive and innate immune responses directed at RRV antigens and RNA persisting in affected tissues. These responses produce arthritogenic pro-inflammatory mediators.5,6 Joint effusions predominantly contain mononuclear cells, and RRV RNA has been detected in synovial fluids by polymerase chain reaction (PCR). However, joint aspirations and PCR have limited value for diagnosis.7 RRV infections can be sub-clinical, with the asymptomatic-to-symptomatic ratio between 1.2:1 and 3.0:1.7

Virus-specific antibodies, probably neutralizing antibodies, are believed to be the principal protective adaptive immune response to RRV. Naturally acquired immunity appears to be lifelong, with no reports of re-infection.
CLINICAL FEATURES

The incubation period for RRV is usually 7 to 9 days, with a range of 3 to 21 days. Acute disease typically involves polyarthritis or polyarthralgia (80%–100% of patients), fever (20%–60%), rash (40%–60%, usually maculopapular), and/or myalgia (40%–80%). The joints most commonly affected are multiple peripheral small joints and the knees, usually with a symmetric pattern (Table 36.5.1). Effusions are often present but are usually small. Other symptoms include fatigue (>50%), headache, photophobia, and lymphadenopathy. RRV encephalitis cases have been reported; however, causal links to the virus are unsupported.

A popular misconception is that RRV disease symptoms persist for years. However, prospective studies using validated questionnaires illustrated that in patients with RRV disease (and no other diagnoses), symptoms usually progressively resolve over 3 to 6 months with no long-term sequelae.

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

A detailed history is helpful, especially with regard to residence, domestic and international travel, and season. Rapid onset of arthritic symptoms is usual, with pain on movement, tenderness, and slight swelling (which can be hard to detect) the most common signs. Tenderness, swelling, heat, redness, and intolerance to movement or pressure can be extreme. The rash is usually maculopapular, occurs within a few days after the onset of symptoms, and resolves within 5 to 10 days. Rash distribution varies considerably, with the trunk and limbs most affected. The face is less affected and, rarely, the rash may be confined to palms, soles, and/or digital webs. Lymphadenopathy is frequently present, if sought. Aside from fatigue, constitutional symptoms usually resolve within a week.

Diagnosis is usually made by a primary-care physician aided by a commercial serodiagnostic enzyme-linked immunosorbent assay (ELISA)-based test (widely available in Australia). Two serologic tests at least 10 to 14 days apart are recommended. Peripheral blood counts are usually normal except for a possible slight neutrophilia. An elevated erythrocyte sedimentation rate can occur, but decreases within a few weeks. Serum C-reactive protein levels are rarely elevated. If erosive changes are seen in x-rays, alternative diagnoses should be sought.

The differential diagnoses at initial disease presentation include related Old World alphaviruses (e.g., chikungunya, Barmah Forest, or Sindbis virus), dengue, and Epstein–Barr virus. Other viral arthritides may also be considered, for example, rubella or parvovirus B19. Drug reactions, autoimmune arthritides (e.g., rheumatoid arthritis), and other infectious arthritides may also be among the differential diagnoses. Persistent distinct monoarticular arthritis is inconsistent with RRV disease.

## TABLE 36.5.1 Joint Involvement in Ross River Virus Disease.

| Joint                        | Percentage With Involvement |
|------------------------------|----------------------------|
| Wrist                        | 36–100                     |
| Knee                         | 39–100                     |
| Ankle                        | 50–97                      |
| Interphalangeal (fingers)    | 50–81                      |
| Elbow                        | 17–71                      |
| Cervical spine               | 12–70                      |
| Shoulder                     | 38–62                      |
| Interphalangeal (thumb)      | 53–58                      |
| Thoracolumbar spine          | 36–56                      |
| Tarsus                       | 36–49                      |
| Interphalangeal (toes)       | 47                         |
| “Hand,” including metacarpophalangeal joints | 45 |
| Hip                          | 4–27                       |
| Temporomandibular joint      | 10–15                      |

The percentage of patients who have arthritis/arthralgia in the indicated joint(s) is shown, with the range reflecting the data obtained from several studies. Data from Harley D, Sleigh A, Ritchie S. Ross River virus transmission, infection, and disease: a cross-disciplinary review. Clin Microbiol Rev 2001;14:909–32; and papers cited therein.
In patients diagnosed with RRV disease but in whom symptoms last longer than 3 to 6 months, other differential diagnoses should be actively sought. In a survey of RRV disease patients, about half the patients reported disease lasting longer than 6 months. However, in nearly all these patients, other rheumatic conditions (primarily autoimmune) or depression were subsequently diagnosed. There is no evidence that RRV disease predisposes to other rheumatic diseases, but it may contribute to post-infective depression or fatigue.

PREVENTION AND TREATMENT

Preventing mosquito bites prevents RRV infection. Insect repellents containing DEET are recommended (except for infants <2 months). Insect screens; bed nets; and long-sleeved, loose-fitting, light-colored clothes are also protective.

RRV disease is generally treated with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), with many patients being satisfied with this treatment. Anecdotal evidence suggests different NSAIDs may need to be tried. Standard risks and contraindications for NSAID use in patients with conditions including asthma, peptic ulcer, cardiovascular and renal disease should be considered. Aspirin is used by some patients (but is not recommended for chikungunya). Steroids are not generally recommended. Although a vaccine has been tested in phase III human trials, this is not commercially available.

36.6 Oropouche Virus

Marcio R. T. Nunes, Pedro F. C. Vasconcelos

KEY FEATURES

- The most prevalent arboviral disease in South America, after dengue and chikungunya fever viruses.
- More than 30 epidemics reported in the last three decades in the Brazilian Amazon region, Peru, Panama, and Trinidad and Tobago, with an estimated occurrence of over 500,000 infections.
- Clinical picture caused by Oropouche fever virus is an acute febrile disease with headache, chills, myalgia, nausea/vomiting, retro-ocular pain, and dizziness.
- Some patients develop aseptic meningitis, and virus can be recovered from blood but also from cerebrospinal fluid.
- Four genotypes of Oropouche fever virus (I, II, III, and IV) are recognized.
- Urban cycle is responsible for outbreaks and transmission, and is transmitted by the midge Culicoides paraensis.
- Diagnosing of Oropouche fever virus is by IgM enzyme-linked immunosorbent assay (ELISA) virus isolation and molecular biology techniques, mainly reverse transcription polymerase chain reaction (RT-PCR) and real-time PCR, and nucleotide sequencing.
- There is no vaccine available to prevent Oropouche fever virus, and personal protection is recommended during epidemics.

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INTRODUCTION

Oropouche virus (OROV), a member of the Orthobunyaviridae genus, is the causative agent of Oropouche fever. The first case of Oropouche fever was described in 1955, when the virus was isolated from the blood sample of a febrile patient in the West Indies and from a pool of Coquillettidia venezuelensis mosquitoes. A large epidemic was recorded in the 1960s in Belém, Brazil, involving an estimated 11,000 people. Over the past five decades, it is estimated that more than half a million people have been infected by the virus in the tropical areas of South and Central America, mainly in the Amazon region of Brazil and Peru.

EPIDEMIOLOGY

OROV has been found in Brazil, Panama, Peru, and Trinidad and Tobago, and is basically maintained by two different life cycles. One occurs in urban areas of tropical cities in the Amazon basin and involves humans as the vertebrate hosts, with Culicoides paraensis midges as the major arthropod vector. Transmission in general occurs outdoor in the daytime, especially during sunrise and sunset. The other described life cycle is sylvatic and not well understood and is based on serologic prevalence involving wild mammals (especially sloths and monkeys) and birds as the potential vertebrate hosts. The arthropod vector in the sylvatic life cycle is unknown, but may include C. paraensis.

Many outbreaks of Oropouche fever have been characterized by epidemics spreading in numerous villages within one geographic area and over a short period; these episodes essentially occur in new colonized areas and in the suburbs of large Amazonian urban
centers. The spread of the virus is probably a consequence of the circulation of viremic people in localities where the transmitting vector can be found and where there is a large concentration of susceptible individuals.

NATURAL HISTORY, PATHOGENESIS, AND PATHOLOGY

Oropouche fever is a self-limiting, febrile illness with no fatalities recorded. Using molecular typing methods, four different OROV genotypes have been described in the Americas. Little is known about the pathogenesis of the Oropouche fever in humans—most of the information on pathogenesis has been obtained in experimental studies on golden hamsters. As in humans, the viremic period in these animals is brief and reaches titers high enough to easily infect C. paraensis midges. In lethal infections in hamsters, intense encephalitis is observed with a prominent hepatitis, the probable mechanism of animal deaths.

CLINICAL FEATURES

Clinically, Oropouche fever is characterized by the sudden onset of high fever, headache, myalgia, arthralgia, anorexia, dizziness, chills, and photophobia. Some patients present with a morbilliform exanthem that resembles rubella or dengue. Nausea, vomiting, diarrhea, conjunctiva congestion, epigastric and retro-ocular pain, and other constitutional symptoms are also common. Some patients may display a picture of aseptic meningitis, and others temporary encephalitis. A recrudescence of mild symptoms several days after waning of the initial febrile episode is commonly seen (biphasic illness). Recovery is complete in all individuals without apparent sequelae, even in the most severe cases. There are no reports of proven lethality caused by Oropouche fever.

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other causes of febrile illness, particularly dengue fever, chikungunya fever, and malaria. Blood samples collected during the acute phase of illness (up to 5 days after the onset of the symptoms) can be used for virus detection methods. The most commonly applied molecular method is reverse transcription polymerase chain reaction (RT-PCR), and recently a real-time PCR showed excellent results. Virus isolation can be attempted in newborn mice or hamsters (1–3 days), or in Vero or C6/36 cell cultures. For virid identification, suspensions prepared from brains of mice or supernatants of infected Vero or C6/36 cells are used as antigens in complement fixation or immunofluorescence assays with OROV hyper-immune serum. More recently the molecular approaches have been used for genotyping and identification of isolates. For specific identification of OROV, neutralization and hemagglutination inhibition tests can be also performed.

TREATMENT AND PREVENTION

Treatment is supportive, common analgesics should be used to relieve the headache and muscle and joint pains, in particular to treat retrobulbar pain that in general is severe. No vaccine is available to prevent Oropouche fever; only personal control measures are recommended, including use of repellents.

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36.7 Mayaro Virus

Pedro F. C. Vasconcelos, Marcio R. T. Nunes

KEY FEATURES

- Mayaro fever virus is an alphavirus responsible for sporadic cases and several outbreaks of illness with fever, arthralgia, and rash in northern South America.
- Some infected patients develop severe arthralgia during the defervescence period that can last up to a year.
- Three Mayaro fever virus genotypes are recognized.
- Mayaro fever virus is transmitted by Haemagogus mosquitoes, particularly H. jantinomys.
- The main vertebrate hosts are non-human primates.
- In the Brazilian Amazon, the specific antibody rate ranges from 5% to 60%; it is higher among closed communities (South American Indians) in the forests.
natural hosts. 7 The virus has been isolated several times from Haemagogus spp. mosquitoes, mainly from H. janthinomys species, which is considered the primary vector potential. There are three distinct genotypes of the virus. In addition, a unique strain of Mayaro virus has been recovered from Coquillettidia venezuelensis in Trinidad, two others from Sabethes spp., and one from Culex spp., which can represent spillover from the virus from the hosts.

EPIDEMIOLOGY

Mayaro virus has been isolated from patient residents in tropical areas of Central and South America, mainly in Brazil, Trinidad and Tobago, Bolivia, Surinam, and Haiti. The virus has also been isolated in French Guiana, Colombia, Panama, and Peru. Detection of antibodies to the virus has been also demonstrated in certain populations of these countries, as well as in Guyana, Colombia, and Peru. 7 Most cases occur in forest workers, who are typically adult males. In the Brazilian Amazon, the specific antibody rate ranges from 5% to 60%; it is higher among closed communities (South American Indians).

Only a few major Mayaro fever epidemics have been reported in the Americas: two in Brazil, one in Bolivia, and one in Peru. 2,6 Between 1955 and 1991, epidemics of Mayaro fever were restricted to Brazil, beginning in the municipality of Guamá, Pará state (1955), and spreading toward other localities in the São Miguel do Pará state, such as Belterra (1978), Conceição do Araguaia (1981), Itaruma in Goias state, the central region of Brazil (1981), Benevides, Pará state (1991), and Peixe, Tocantins state (1991). In the following years, the agent reached other Peruvian Amazon counties (Tumbeu, Acayacu, and Huanuco in 1995). 6 In 2008 the virus re-emerged in Pará state causing an outbreak in the municipality of Santa Bárbara, Pará state, 50 km from Belem in northern Brazil, 4 and in 2014 to 2016 small outbreaks were also reported in central Brazil in the states of Mato Grosso and Goiás, where this agent is considered an emerging virus.

NATURAL HISTORY, PATHOGENESIS, AND PATHOLOGY

Little is known about the pathogenesis of Mayaro fever in humans, as the virus has not been associated with deaths. Thus no material is available for histopathologic examination. 7 The data regarding its pathogenesis are a result of experimental in vitro studies using Vero cell cultures. These have indicated intense cytopathic effects and cell death, with casein kinase 2 (CK2) having an important role during the Mayaro virus infection cycle. 7

CLINICAL FEATURES

Mayaro fever is clinically characterized as an acute febrile illness, generally accompanied by headache, myalgia, rash, chills, and photophobia. Dizziness, eye pain, nausea, and vomiting are less frequently reported. Arthralgia, predominantly affecting the wrists, fingers, ankles, and toes, as well as a cutaneous rash, are also commonly observed on the trunk and extremities. 2,3 Occasionally, there may also be painful joint swelling that can persist. In some patients, arthralgia lasts up to a year. An aspect to consider is the possibility of co-circulation of MAYV and chikungunya virus (CHIKV) in the same area, because both viruses are members of the Semiliki Forest group in the Alphavirus genus, and a high cross-reactivity is present in serologic tests even on IgM-ELISA (enzyme-linked immunosorbent assay). Thus the molecular biology approaches are more indicated to confirm MAYV and/or CHIKV infection; indeed, the real-time polymerase chain reaction (PCR) is the gold standard diagnostic test to make a confirmation of infection by both viruses.

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

Leukopenia is a common finding in unspecified laboratory tests within the first week of illness, and a white cell count of about 2500/mm³ is commonly observed; platelet counts and liver function tests are usually normal. 1 The differential diagnosis includes other causes of fever, arthralgia, and rash, particularly dengue, Oropouche, chikungunya, and Zika fever viruses. The laboratory diagnosis of Mayaro fever either depends on virus isolation attempts or serologic diagnostic and molecular methods for genome detection. For virus isolation, biologic samples (serum or blood) obtained from viremic patients (up to 5 days after the onset of the symptoms) are used for inoculation in newborn mice or in Vero cells. Suspensions prepared from brains of mice or supernatants of infected cells are used as antigens in either complement fixation tests or an immunofluorescence assay against hyperimmune sera of different arboviruses circulating in the region. Specific identification of Mayaro virus is carried out using neutralization and hemagglutination inhibition tests 1 and by reverse transcription (RT)–PCR, 2,3 as well as by real-time PCR, that has showed excellent results. 2

TREATMENT AND PREVENTION

Treatment is supportive. Some patients require hospitalization, but no deaths have been reported. In theory, personal protection against mosquito bites (insect repellent and long sleeves and trousers) should be protective, but this is not practical for most forest workers. Bed nets and window screens are of little benefit because Haemagogus mosquitoes are day biters. In addition, no vaccine is available to prevent Mayaro fever.

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36.8 Pathogenic Phleboviruses: Severe Fever With Thrombocytopenia Syndrome, Heartland Virus Disease, and Sandfly Fever

Keun Hwa Lee, Sung-Han Kim, In-Kyu Yoon

KEY FEATURES

- Phleboviruses belong to a genus of arboviruses that can cause human diseases, including Rift Valley fever, sandfly fever, and the more recently emerged severe fever with thrombocytopenia syndrome (SFTS) and Heartland virus disease.
- SFTS virus (SFTSV) is transmitted by the *Haemaphysalis longicornis* tick, and is endemic in central and eastern China, Japan, and South Korea, with hundreds of cases occurring annually.
- SFTS presents as a non-specific febrile illness that can progress to multi-organ failure with up to 12% to 30% mortality.
- Heartland virus disease has occurred in a small number of older men in the Midwestern United States with a history of tick exposure.
- Heartland virus is thought to be transmitted by the Lone Star tick, and fatal infections have occurred with multi-organ dissemination.
- Sandfly fever viruses are transmitted by *Phlebotomus* sandflies, endemic to the Mediterranean region, Middle East, and South Asia.
- Sandfly fever viruses usually cause self-limited febrile illness; however, Toscana virus is unique by primarily causing central nervous system disease.

INTRODUCTION

The genus Phlebovirus, within the family Phenuiviridae (formerly Bunyaviridae) of the order Bunyavirales, contains viruses that cause human diseases, including Rift Valley fever, sandfly fever, and the more recently emerged severe fever with thrombocytopenia syndrome (SFTS) and Heartland virus (HRTV) disease. Phleboviruses are enveloped, negative-sense, single-stranded RNA viruses with a tri-segment genome (large [L], medium [M], and small [S]), containing over 70 viruses grouped into 10 species. This chapter will briefly summarize SFTS virus (SFTSV), HRTV, and the sandfly fever viruses.

SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME

**Epidemiology:** SFTSV was first isolated from a patient in central China in 2009 and reported in 2011. Since then, hundreds of SFTS cases have been reported in central and eastern China where the disease is endemic. SFTS was first reported in Japan and South Korea in 2013. Retrospective studies have subsequently documented SFTS cases in Japan in 2005, rural areas of central China in spring 2006, and South Korea in 2010. Transmission occurs through tick vectors, mainly *Haemaphysalis longicornis*, with animals such as goats, cattle, sheep, yak, donkeys, pigs, cats, deer, rats, mice, hedgehogs, weasels, brushtail possums, chickens, and some birds thought to serve as animal reservoirs. Migratory birds can act as carriers for *H. longicornis*-borne SFTSV and may be important in long-distance dissemination. SFTS occurs mainly during the spring and summer months when tick density is highest in endemic areas and human contact with infected ticks is most likely. High-risk groups include farmers, ranchers, forest workers, and others who live in rural, hilly, wooded areas. Person-to-person transmission through direct contact with blood or bloody secretions has been reported. SFTSV is phylogenetically separated into two clades, Chinese and Japanese, with viruses usually (though not always) consistent with their geographic origin. Korean strains fall within the Japanese clade.

**Pathogenesis:** SFTSV infection generally has four overlapping stages: incubation, febrile illness, multi-organ involvement, and convalescence (all four stages may not occur in milder infections). The incubation period is generally 5 to 14 days, and can be affected by viral dose and route of infection. Viremia peaks during the febrile illness stage at about 7 to 10 days after fever onset, and high viremia may be associated with poor outcomes. Very high viremia can occur, accompanied by uncontrolled systemic inflammatory response. During the multi-organ involvement stage, viremia gradually falls in survivors, but remains high in fatal cases. Viral components have been detected in the liver, spleen, lymph nodes, and bone marrow. The marked thrombocytopenia typical of SFTS has been proposed to be due to splenic macrophage clearance of circulating virus-bound platelets.

**Clinical features:** SFTS presents as a non-specific febrile illness with sudden onset of fever lasting for 5 to 11 days, headache, fatigue, malaise, muscle and joint pain, nausea/vomiting, and diarrhea, accompanied by thrombocytopenia and leukopenia, which occur in almost all patients, and abnormal liver function tests. Multi-organ involvement can occur about 5 days after illness onset, lasting for 7 to 14 days, with progressive failure in fatal cases or a self-limited course in survivors. Progressive organ failure can be rapid, first in the liver and heart, then the lungs and kidneys. About one fifth of patients can have central nervous system (CNS) manifestations, including apathy, seizures, muscle tremors, and/or coma. Death can occur in 12% to 30% of cases, with the average time between illness onset and death being 9 days.

Poor outcomes are more likely in patients with advanced age, decreased consciousness, underlying disease, bleeding tendencies, elevated lactate dehydrogenase (LDH) and creatinine kinase, prolonged activated partial prothrombin times, and elevated C-reactive protein during the disease course. The convalescence period in survivors begins about 11 to 19 days after illness onset.

**Diagnosis:** SFTS should be considered in patients presenting with fever, thrombocytopenia, and leukopenia between spring and fall, with a history of exposure to ticks or relevant animals in endemic areas of China, Japan, and South Korea. Laboratory diagnosis consists of reverse transcriptase polymerase chain reaction (RT-PCR) (if available) during the first week of illness, or virus-specific IgM/IgG enzyme-linked immunosorbent assay (ELISA) after the first week. Because the clinical presentation is non-specific, the differential diagnosis is broad and may include scrub typhus, rickettsial infections, anaplasmosis, leptospirosis, Q fever, dengue fever (where endemic), and other etiologies.

**Treatment and prevention:** No specific therapy has been proven to improve outcomes in SFTS. Treatment is supportive, consisting of early diagnosis and management of complications such as bacterial and fungal infections. Ribavirin has been shown to have in vitro antiviral activity against SFTSV. However, clinical benefit...
has not been demonstrated by ribavirin alone, perhaps due to sub-optimal doses and/or late timing of intervention. Plasma exchange has been proposed to have some benefit when administered early. Ribavirin and plasma exchange in combination has been used in some SFTS patients who have recovered. Plasma exchange followed by convalescent serum therapy has been used to successfully treat a case of SFTS encephalopathy. All of these therapies need to be confirmed with further studies. No vaccine is available for SFTS, and prevention consists of avoidance of tick bites. Health care providers should adhere to strict contact and droplet precautions due to the risk of environmental contamination and person-to-person transmission, especially when treating critically ill patients.

HEARTLAND VIRUS DISEASE

Epidemiology: HRTV was first isolated from two patients from Missouri in 2009. A handful of cases have been documented since then, mainly in older men from the Midwestern United States with a history of tick bite exposure during the summer months. Transmission is thought to occur through the Lone Star tick (Amblyomma americanum). No animal reservoir has yet been confirmed, although neutralizing antibodies have been detected in a variety of animals, including horses, deer, raccoons, and coyotes.

Pathogenesis: The pathogenesis of HRTV is not well understood, given the low number of cases. HRTV has been detected in the brain (thalamus), liver, gallbladder, pancreas, heart, lung, large and small bowel, kidney, and testes, in addition to bone marrow, lymph node, and splenic tissue.

Clinical features: HRTV disease presents with fever, fatigue, headache, cough, joint and muscle pain, nausea, and diarrhea, with leukopenia and thrombocytopenia. Patients can have confusion with short-term memory loss lasting up to several months. Death has occurred in at least two confirmed cases with wide dissemination of virus and multi-organ failure.

Diagnosis: HRTV disease should be considered in older men from the Midwestern United States with non-specific febrile illness and a history of tick bite exposure. Laboratory diagnosis can be performed at specialized laboratories using RT-PCR, IgM/IgG ELISA, and neutralization assays. Differential diagnosis may include ehrlichiosis, anaplasmosis, West Nile virus infection, rickettsial infection, leptospirosis, and other etiologies.

Treatment and prevention: No specific therapy is available, and clinical management is supportive. Prevention consists of sandfly control measures and avoidance of sandfly bites.

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36.9 Sindbis Fever
Gregory Deye, Michael Koren

**KEY FEATURES**

- Self-limited febrile illness with rash and polyarthropathy.
- Arthritis may persist for longer than 12 months.
- Broad geographic range.

**INTRODUCTION**

Sindbis virus (SINV) is an alphavirus within the Western equine encephalitis virus complex. Like other alphaviruses, it has a single-stranded, positive-sense genome contained within a small, enveloped virion. The virus was first isolated in 1952 from *Culex univittatus* mosquitoes trapped in the Sindbis district of Egypt. It was first isolated from human whole blood from a febrile patient in Uganda in 1961. The first major recognized outbreak occurred in South Africa in 1974 causing hundreds of cases. During the 1980s a disease characterized by rash and arthritis was described in Sweden, Russia, and Finland and named *Okelbo disease*, *Karelian fever*, and *Pogosta disease*, respectively. Subsequent analysis has shown all of these clinical syndromes to be caused by SINV. Six genotypes have been described spread across four continents.

**EPIDEMIOLOGY**

The virus is transmitted primarily from *Culex* species of mosquitoes to multiple avian species, which serve as amplifying hosts and perpetuate the cycle of transmission. However, *Aedes cinctus* and *A. communis* are capable carriers and may function as bridging vectors from infected birds to humans.

Outbreaks of clinical cases due to SINV infection have primarily been reported from South Africa and Scandinavia. However, reports of seropositive individuals have been described from several countries in South and Southeast Asia, the Middle East, Central Europe, and several other countries across multiple geographic regions of Africa.

In South Africa and Finland, disease incidence tends to be clustered in discrete outbreaks occurring on a background of sporadic endemic cases. The seasonality of cases mirrors changes in local *Culex* mosquito populations. Overall incidence has been noted to be steadily rising in Finland from 0.4 cases per 100,000 in 1982 to 2.0 cases per 100,000 in 2010 to 2012.
Seroprevalence rates vary significantly between various endemic regions, with some of the highest rates reported in areas of Finland (17%) and South Africa (18%).

Sindbis fever outbreaks have notably been reported in conjunction with outbreaks of West Nile virus infection as they share the same Culex mosquito vectors.

**CLINICAL FEATURES**

The majority of infections result in asymptomatic or sub-clinical infection, with only approximately 6% of cases manifesting clinical symptoms.

The incubation period is estimated to be 8 to 9 days. The most common symptoms reported by patients are rash and arthralgia, both of which occur in more than 90% of cases. The rash typically appears on the trunk and limbs first, as macules and progressing to papules, with all lesions usually in the same stage of development. Distribution may include all four extremities, including palms and soles; the face is usually spared. The rash may persist for more than 5 days.

Arthropyathy is often symmetric and may occur with or without effusion. The joints most commonly involved include ankles, knees, fingers, and wrists, with less frequent involvement of hips, shoulders, neck, and back.

Other symptoms often reported include fever, fatigue, myalgias, and headache, which are reported in approximately half of symptomatic cases.

Joint symptoms can persist 3 years or longer, and may cause a significant degree of disability. The presence of the HLADRB1*01 allele has been significantly associated with the manifestation of clinical disease and with a higher rate of chronic joint pain.

**PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS**

Differential diagnosis should include consideration of chikungunya or Ross River virus infection based on geographic location. Other important considerations include parvovirus B19, varicella, or measles, along with non-infecious rheumatic conditions.

Reverse transcriptase polymerase chain reaction (RT-PCR) usually is ineffective for diagnosis because viremia is low level and transient. Diagnosis is typically based on serologic confirmation.

Elevation of specific IgM is typically detectable within 1 week of symptom onset and persists for up to 6 months. IgG is generally elevated 8 to 9 days after symptom onset and is persistent.

**TREATMENT**

There are no specific therapies. Symptomatic therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and rest may provide some relief, although effectiveness may vary in individuals. Preventive measures include avoidance of the bites of Culex mosquitoes.

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