Objectives

- Describe the mechanisms of chikungunya virus transmission in humans.
- Outline the risk factors associated with the transmission of the chikungunya virus.
- Recognize the key clinical signs and symptoms of chikungunya virus infection.
- Understand the use of specific diagnostic tests for chikungunya virus infection.
- Describe the available treatments and forms of prevention for chikungunya virus infection.

Case Study

A 42-year-old woman reentered the United States via Miami 2 days ago, returning from a vacation trip to the Caribbean islands. She had noted malaise, fever, and severe joint pain for the past 3 days. Once she reached home, she went to an urgent care clinic. Her vital signs there were: blood pressure 110/60 mm Hg, heart rate 100 beats/min, temperature 39.5°C (103.1°F), and respiratory rate 20 breaths/min. Physical examination revealed a diffuse maculopapular rash on the trunk and extremities, conjunctival suffusion, cervical shotty lymphadenopathy bilaterally, and swollen tender joints at her hands, wrists, and ankles.
I. INTRODUCTION

World globalization and the ease of international travel have made it possible for diseases of the past to reemerge, thus impacting their geographical distribution and increasing their morbidity and mortality rates. This is the case for chikungunya virus (CHIKV) infection, a disease restricted to Africa and Asia until 2004, when an outbreak that started in Kenya spread to the islands of the Indian Ocean (Comoros, Mauritius, Madagascar, and Réunion). The virus affected thousands of people, and even reached a small community in Italy via mosquitoes that were breeding in old tires coming from these islands.

In December 2013, the first local transmission of CHIKV in the Western Hemisphere was reported, beginning with autochthonous cases on St. Martin Island in the Caribbean Sea. The rapid spread of the virus was probably due to a lack of population immunity and the broad distribution of the disease vectors.

CHIKV infection shares some of its clinical signs and symptoms with other vector-borne diseases, such as dengue and malaria, making it difficult to establish a clinical diagnosis in areas where these diseases are endemic. Chikungunya does not have high mortality, but it has high morbidity because of its long-term debilitating effect on the joints.

The word *chikungunya* is derived from the Kimakonde language root verb *kungunyala*, which means “to become contorted.” This described the severe joint pain and the posture of patients who acquired the disease. The first CHIKV outbreak was recorded in 1779 and was limited to the Asian and African continents; infection had a low prevalence and was possibly mistaken for dengue or malaria. In 1955, Robinson and Lumsden described an outbreak of chikungunya
in the Makonde Plateau, an area in southeast Tanzania. It was there that Lumsden wrote, “People habitually store water in their houses which in consequence are infested with *Aedes aegypti* and *Culex fatigans*.” This description helped to establish the causative vector for the disease.

CHIKV is a single-stranded RNA virus, a spherical, enveloped virion with a diameter of 60 to 70 nm. The virus is classified as an arbovirus, a group of viruses that are transmitted by arthropod vectors.

CHIKV belongs to the Togaviridae family and Alphavirus genus. It can be subclassified as either an arthritic or encephalitic virus. CHIKV is sensitive to temperatures above 58°C (136.4°F) and to desiccation. Six viruses are classified under the arthritic group: Semliki Forest virus, Ross River virus, Sindbis virus, Mayaro virus, o’nyong-nyong virus, and CHIKV. Phylogenetic analysis has revealed three distinct groups based on partial sequences of *NS4* and *E1* genes: West African, East Central South African, and Asian.

CHIKV originated in Central East Africa, where it is maintained in nature by the sylvatic cycle involving wild primates and forest mosquitoes (*Aedes furcifer*, *Aedes luteocephalus*, and *Aedes taylori*). Subsequently, CHIKV was introduced in Asia, transmitted from human to human by *Aedes aegypti* and, to a lesser extent, by *Aedes albopictus* (the Asian tiger mosquito). Both species are aggressive daytime biters and are widely distributed throughout the tropics. *A albopictus* is also present at more temperate latitudes. Once the mosquito acquires the virus, and after an extrinsic incubation period of 10 days, the mosquito is able to transmit the virus to a naive host.

II. CLINICAL PRESENTATION

After being bitten by an infected mosquito, between 72% and 97% of patients become symptomatic. The disease can have an acute and a chronic phase. The acute phase begins with an incubation period that can last from 3 to 7 or even 12 days. Patients usually develop the abrupt onset of fever (>39°C [102.2°F]), which can be associated with chills and rigors. Fevers can be continuous or intermittent, last
for several days to 1 week, and may be associated with bradycardia. The presence of fever coincides with viremia in CHIKV infection, and asthenia is an important symptom.

Shortly after the onset of fever, patients develop polyarthralgia that is usually symmetric, most commonly affecting the wrists, elbows, fingers, knees, and ankles. Approximately 27% of patients present with asymmetric oligoarthralgia that mostly affects the proximal joints. Joint swelling can occur and can be associated with tenosynovitis. Patients have reported pain that is worse in the morning and sometimes relieved by mild exercise. Some studies have shown that arthralgia can be present in about 60% of patients and can last up to 36 months after the acute infection appears. Patients with long-term effects on the joints do not have positive markers for autoimmune or rheumatic disease.

Chronic arthralgia that persists months after the acute infection is believed to be associated with mechanisms involving host-derived inflammatory cytokines, or perhaps the presence of the virus in the synovial macrophages can explain a delayed inflammatory reaction. (There is evidence that infected monocytes do not have an increased expression of common adhesion molecules. Thus, mononuclear infiltration can turn some areas into sanctuaries, allowing the virus to escape the immune response.) Some studies also suggest that CHIKV infection affects cartilage and connective tissue metabolism. Radiologic images, such as radiograph or magnetic resonance imaging, from these patients can show bone erosions, joint effusions, bone marrow edema, tendinitis, synovial thickening, and tenosynovitis. Musculoskeletal disorders associated with CHIKV infection include multiple tendinitis, tenosynovitis, plantar fasciitis, tunnel syndromes, and rheumatoid arthritis.

A maculopapular rash can be present in 50% (20%-80%) of patients, usually affecting the trunk and extremities, but sometimes involving the soles, palms, and face. The rash usually starts 2 to 5 days after the onset of fever and lasts 3 to 4 days; some patients can present with a diffuse blanching erythema. In infants, vesiculobullous lesions with desquamation have been described, as well as aphthous ulcerations and subungual hemorrhages.
Other symptoms can also be present, including pharyngitis, photophobia, headache, retro-orbital pain, anorexia, nausea, vomiting, and abdominal pain. Atypical clinical presentations that have been reported include pericarditis, myelitis, uveitis, retinitis, myocarditis, nephritis, hepatitis, pancreatitis, cranial nerve palsies, meningoencephalitis, and Guillain-Barré syndrome. Elderly patients and those with comorbidities, such as diabetes, end-stage renal disease, and underlying neurologic conditions, can present with these atypical symptoms and have an increased risk of morbidity and mortality.

There is no difference in the clinical outcome of pregnant patients; however, spontaneous abortions have been reported. The highest transmission risk to the fetus seems to be during the intrapartum period, during which the rate of vertical transmission could be as high as 49%; there is no evidence of the virus in breast milk. Neonates are also at risk for severe infection associated with neurologic signs.

After 10 days, most patients improve, but some have a post-viral reactive arthritis that can cause a relapse in symptoms, especially joint pain and tenosynovitis. Some patients also may have peripheral vascular problems, such as Raynaud syndrome. The presence of all of these symptoms establishes the beginning of the chronic phase of the disease, defined as symptoms persisting for more than 3 months.

III. DIFFERENTIAL DIAGNOSIS

The presence of fever with arthralgia is a common clinical presentation in viral infections, especially arboviruses. Other diseases that share this trait are malaria, leptospirosis, rickettsia, group A streptococcus, rubella, measles, parvovirus, HIV, enterovirus, and adenovirus. In regions endemic for dengue and Zika virus infections, a patient can have similar clinical signs and symptoms and even be infected with more than one virus. In CHIKV infection, the onset of fever is more acute and the duration is shorter. Patients with dengue infection do not report arthralgia or tenosynovitis, but they can present instead with hemorrhagic manifestations and shock.
IV. LABORATORY TESTING

Early diagnosis is a result of a high index of clinical suspicion based on epidemiology (place of residence, travel history, and exposure) and the clinical presentation of the triad of high fever, rash, and rheumatologic manifestations. Thrombocytopenia, leukopenia, and elevated liver function tests have been also reported. Inflammatory markers such as sedimentation rate and C-reactive protein are elevated.

The “gold standard” test for CHIKV infection is a viral culture, but often this is not feasible due to its difficulty, lack of availability, and time needed. The culture must be performed on serum samples acquired in the acute stage (<8 days); results are available in 1 to 2 weeks. Sample processing requires a biosafety level 3 facility. A faster test is the reverse transcription-polymerase chain reaction for CHIKV, which is performed using serum obtained within the first week of infection; results can be available in 1 or 2 days.

SeroLogic testing, based on immunoglobulin (Ig) G and IgM, should be performed after the fourth day of the clinical onset of infection and at the convalescent phase of the disease (usually 10 to 14 days after the infection; Figure 1). IgM antibody levels are present on enzyme-linked immunosorbent assay after the fourth day, reaching the highest level 3 to 5 weeks after clinical onset and staying elevated for about 2 months. The diagnosis of chikungunya is made when there is a four-fold increase in the antibody level in the convalescent serum.
Figure 1. Algorithm for Arbovirus Detection in Suspected Cases of Chikungunya, Dengue, or Zika

Tiered algorithm for arbovirus detection for suspected cases of chikungunya, dengue, or Zika (Testing only performed if patient symptomatic and travel history indicates travel to affected area.)

Molecular testing¹
(<7 days after symptom onset)

<table>
<thead>
<tr>
<th>RT-PCR / NS1 dengue</th>
<th>(Real time) PCR- Zika virus</th>
<th>(Real time) PCR- chikungunya virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: dengue virus Confirmed</td>
<td>Negative: Zika virus Confirmed</td>
<td>Positive: chikungunya virus confirmed</td>
</tr>
<tr>
<td>Perform antibody testing ²</td>
<td>Perform antibody testing ²</td>
<td>Perform antibody testing ²</td>
</tr>
</tbody>
</table>

Antibody testing¹
(≥4 days after symptom onset)

<table>
<thead>
<tr>
<th>IgM dengue</th>
<th>IgM Zika virus</th>
<th>IgM chikungunya virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: Presumptive dengue virus³</td>
<td>Positive: Presumptive Zika virus³</td>
<td>Positive: Presumptive chikungunya virus</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>PRNT⁴</td>
<td>PRNT⁴</td>
<td>PRNT</td>
</tr>
</tbody>
</table>

¹ Due to extensive cross-reactivity in flavivirus serological assays, for samples collected ≥7 days post illness onset, molecular detection should be performed first.

² Perform if sample ≥4 days after symptom onset.

³ Extensive cross-reactivity would be expected in samples from DENV/ZIKV circulation areas. A positive IgM assay with either antigen should be confirmed by using PRNT against both ZIKV and DENV as well as any other flavivirus (e.g., SLEV, ZIKV, WNV, etc.) that might be found in that geographic area (including travel areas).

⁴ PRNT should include any flavivirus (e.g., SLEV, DENV, WNV, etc.) that might be found in that geographic area (including travel areas).

V. TREATMENT

There is no specific antiviral treatment for CHIKV. Management and therapy during the acute period should focus on providing supportive care to maintain the hemodynamic status using hydration, antipyretics, and physiotherapy. Analgesics and antipyretics such as acetaminophen can be used without problems. Nonsteroidal anti-inflammatory agents can be used once dengue has been ruled out. Based on experience with past outbreaks, corticosteroids and antiviral medications are not recommended. Ribavirin, ribavirin plus interferon, and favipiravir have not been demonstrated. For acute and chronic joint problems, several treatments have been investigated, including chloroquine and methotrexate, alone and in combination, with variable results.

VI. PREVENTION

Neither specific treatment nor vaccine is yet available for CHIKV infection. Vector control is necessary to eradicate the virus. Public awareness through community education on elimination of mosquito breeding sites and the use of insecticides play important roles in curbing infection.

Travelers to endemic or epidemic areas should avoid mosquito bites by applying repellents containing DEET to exposed skin, wearing long-sleeves and long pants, and staying in rooms with air-conditioning or with screens on windows and doors.
KEY POINTS

- Chikungunya infection is caused by an RNA arbovirus from the Togaviridae family and the Alphavirus genus.

- It is a vector-borne disease transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes.

- The acute phase of the disease is characterized by fever, polyarthralgia, arthritis, tenosynovitis, and a maculopapular rash.

- Atypical presentations can occur, especially in elderly patients and those with chronic conditions.

- Some patients will develop a chronic phase, which can present with severe and debilitating arthritis.

- The diagnosis relies on the clinical presentation, epidemiologic data (place of residence, travel history, and exposure), and molecular and serologic testing.

- Therapy during the acute stage is focused mainly on controlling symptoms using nonsteroidal anti-inflammatory agents or acetaminophen, fluids for hydration, bed rest, and monitoring the patient’s hemodynamic status.

- Several medications have been used to treat chronic joint problems, such as chloroquine and methotrexate, with variable results.


