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Selected mosquito-borne illnesses— Chikungunya



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Background

In the last several years another mosquito-borne pathogen—Chikungunya virus (CHIKV) has evolved into a significant public health threat, from a relatively unknown and geographically isolated pathogen. It is now found in Africa, Asia, Central- and South-America, with the very real potential for spread into North America.^{1–9} By December 2013 the first local transmission of Chikungunya virus was reported in the Western Hemisphere; likely first with autochthonous cases in St. Martin.^{9,10} As of 08/08/14 over 500,000 suspected/laboratory confirmed cases have been reported in the Americas. Local transmission has been reported extensively throughout the Americas, including the United States and US territories in the Caribbean. As the vector is highly adaptable to a variety of geographic regions, further spread is to be expected, especially as the CDC cautions there is a risk the virus will be imported to new areas by infected travelers.⁸

Chikungunya virus (CHIKV), the causative agent for Chikungunya fever (CHIKF) is a single-stranded RNA virus, member of the genus Alphavirus, and family Togaviridae.^{2,4,6,10,11,13} Its name is derived from the Kimakonde language and means “to become contorted”⁷ as patients often experience severe arthralgias. Other translations, from a dialect found in the Madoke language of Tanzania, means “the one bowing.”³ CHIKV was initially isolated over 60 years during an epidemic in Tanzania; interestingly the illnesses were first thought to be Dengue. That notwithstanding, the actual timeline of CHIKV may go back into the 18th century. Typically infection resulted from enzootic and local outbreaks in Africa, and Asia, but the epidemiology has changed as a result of demographic shifts, overcrowding, travel, and the ability of vectors to adapt.^{14,15} Large-scale epidemics affecting millions in Africa, Asia, Europe, and the Pacific regions have occurred, such that more than 45 countries, including ones in the Americas are at risk from CHIKF. Not surprisingly the risk of CHIKV can both influence and be influenced by tourism and travel.¹⁶

It is a mosquito-borne disease transmitted to humans by the ubiquitous *Aedes mosquitoes*, including *A aegypti* (Fig. 1) and *A albopictus*.^{1,6,9,17,18} In Africa other mosquitoes may be involved in disease transmission, such as *A. fuscifer-taylori*, and *A. luteocephalus*. Because of a mutation in an African lineage of CHIKV, it became adaptable to *A. albopictus*, increasing the spread and geographic

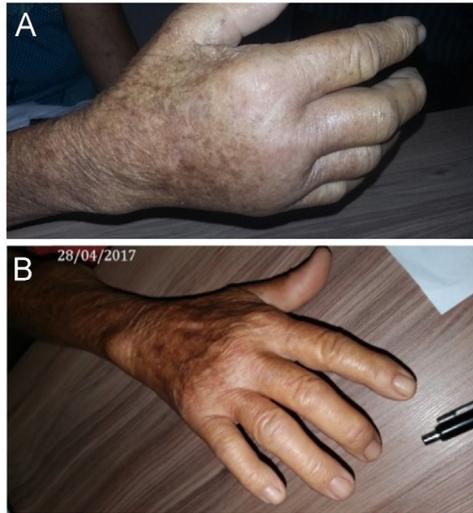


Fig. 1. (A) Hand arthritis in a 71-year-old woman, previously without joint complaints, 1 year after CHIKF. Prior to methotrexate therapy. (B) After methotrexate 7.5 mg po eq week was given for 4 weeks.³

range for infection—urban and peri-urban from the Indian Ocean islands to the continent as well as other tropical, subtropical, and temperate regions.⁶ This has led to near pandemic expansion in 2003. The autochthonous transmission has placed CHIKV in the Caribbean since 2013 and Brazil in 2014.¹⁶ The rapidity through which CHIKV spread resulted in Brazil establishing a state of public health emergency.¹ Outbreaks have occurred in North-Eastern Italy, and the United States. Co-infection with other similarly co-circulating and transmitted arboviruses, such as DENV or Zika is possible.^{1,6}

Chikungunya was first described in 1952, during an outbreak in Tanzania.^{11,12} Chikungunya disease has been diagnosed in Africa, Asia, the Indian subcontinent, as well as Europe and the Americas. In 2007 a localized outbreak was reported in north-eastern Italy—the first time in Europe. Although human infection has been historically at consistently low levels, by 1999–2000 a large outbreak occurred in Africa, and by 2005 further large outbreak occurred in islands of the Indian Ocean, resulting in cases imported to Europe.^{5,19} India experienced a large outbreaks in 2006 and 2007. Subsequently over 1.9 million cases have been reported from India, Indonesia, the Maldives, Myanmar, and Thailand.^{1,6,16} Cases have been noted in France in 2013, and Croatia. Local transmission has been reported since then in over 40 countries. More than 1,379,700 suspected cases have been recorded in the Caribbean, South America, and the United States, with nearly 200 deaths reported, that were attributed to Chikungunya. The US has recorded imported cases as well.



Fig. 2. *Aedes aegypti*.

By 2015 there were 693,489 suspected cases, reported to the Pan American Health Organization (PAHO), with 37,480 confirmed cases.²⁰

According to the CDC, in 2015 Chikungunya virus disease became a nationally notifiable illness.⁸ A total of 896 Chikungunya virus cases were reported to Arbo-NET from US States, and 237 from US territories, of these 227 were locally transmitted reported from Puerto Rico and the US Virgin Islands. One locally transmitted case was reported from Texas; other cases resulted from travelers returning from affected regions (Fig. 2).⁸

There is a risk that the virus will be imported to new areas by infected travelers.

Clinical overview

As with other arboviral infections, symptoms can range from mild to severe.^{1,2,7–11,22} Fatalities have been noted, although initially considered uncommon. The epidemic on Reunion Island underscored the risks associated with CHIKV, where encephalitis causing death or adverse long-term sequelae were reported.^{1,2} Perinatal transmission resulting in encephalitis and limitations in neuropsychomotor development in children were reported.^{1,21,23} CHIKV disease can also evolve into chronic illness, characterized by persisting polyarthralgia and joint stiffness.^{7,9,11,22} This chronic CHIKV stage has been reported to severely incapacitate patients for a duration of weeks, and in some cases even several years after the initial infection.^{1,2,7,9–12} It is often referred to as an arthritogenic alphavirus.²²

The acute phase of Chikungunya (CHIKF) often comes on abruptly, although it can also take a couple of days.^{7,8,11,22–24} CHIKV causes high fever, and severe multi-joint pain, as well as muscle pain, headache, nausea, fatigue, and a rash (Tables 1 and 2) that follows an average incubation period of 5–7 days.^{1–3,7,8,11,22–24} Subclinical infection does occur, but the exact occurrence is unknown, with ranges from 3% to 25%,^{11,25} but most patients are expected to have acute symptoms, that can last up to 2 weeks. Not unlike the symptoms of other tropical arthritogenic alphaviruses, CHIKV can cause very severe joint pain, not unlike “break bone fever” of dengue, also requiring narcotics, and has a variable duration.^{1,7–9,22–25} These alphaviruses have a special tropism for bone and joint tissue.²⁶ After the acute phase, CHIKF is not infrequently followed by chronic, episodic, and often debilitating joint pain, swelling, myalgia, fatigue, even depression, and cognitive issues. Patients can develop chronic rheumatic disorders that are not dissimilar to rheumatoid arthritis and ankylosing spondylitis.¹¹

Table 1

<http://www.chikungunya.in/dengue-chikungunya-differences.shtml>.

| Type | Chikungunya | Dengue |
|----------------------------|---|---|
| Duration of disease | Incubation period of 1–12 days and disease duration varies from 1 to 2 weeks. However symptoms such as joint pain may persist for a long time | Incubation period of 3–7 days and disease duration varies from 4 to 7 weeks |
| Initial symptoms | Fever, joint pain, muscle pain, headache, eye infection, rashes | Fever, joint pain, headache, rashes |
| Joint pain and muscle pain | Joint pains on hands and feet. Swelling is present and the pain is high in the morning | Muscle pain on the back, arms and legs. Joint pain on knees and shoulders |
| Skin rashes | Rashes on trunk, limbs, face, palms, and feet | Rashes usually limited to face and limbs |
| Possible complications | Up to 10% of patients develop chronic joint pain. Neurological damage is possible, but rare | Life threatening complications such as shock, breathing difficulty and heavy bleeding can occur |

Table 2Abstracted from CDC and <http://www.denguevirusnet.com/compare-dengue-zika-and-chikungunya.html>.

NB—These are for general guidance. Some overlap with these and other pathologies is possible. Moreover severity of these signs and symptoms can be influenced by multiple factors—host immunity, comorbidities, strain of virus, etc.

| Associated findings/symptoms | Dengue (DENV) | Zika | Chikungunya |
|----------------------------------|---|-------------------------------|---|
| Onset post-infection | ~4–7 days | ~3–14 days | ~3–7 days |
| Fever | 38°C or higher—duration ~4–7 days | Minimal to no fever, 1–2 days | Typically high fever (> 38°C), ~2–3 days |
| Headache | ++ | + | + |
| Rash | + to ++ NB bruising/petechia also possible | ++ to +++ | + to ++ |
| Pruritus | + to ++ | ++ to +++ | + |
| Arthralgia | + to +++ | + | ++ to +++*, may persist for several months |
| Myalgia | ++ to +++ | + | + to ++ |
| Conjunctivitis | +/- | ++ | +/- |
| Neutropenia/ thrombocytopenia | +++ | +/- | + |
| Bleeding risk | + to ++++ | - | +/- |
| Shock | Variable: -to +++ depending upon type of DENV illness | - | - |
| Recovery | Varies; DF 6–7 days | 4–7 days | Usually < 7 days; NB arthralgias may persist or recur |

*Highlights the fact that the symptoms may persist.

The mechanism of CHIKV-induced arthritis may be related to cytokines, innate (monocytes, natural killer cells) and adaptive immune response (B and T cells), along with viral and possibly vector factors.^{4,11} CHIKV arthritis involves joints and likely a common pattern of leukocyte infiltrate, cytokine production, and complement activation, not unlike arthritis. Joint damage may be related to viral ability to cause host cellular processes, such as inflammatory response (macrophages, T cells, and antibodies). Chikungunya can be considered a fever, rash, arthralgia syndrome. These chronic arthralgias can persist for months, even years. Risk factors such as older age have been identified.^{5,11}

An index of suspicion is important, especially in treating patients returning from endemic areas. Other less publicized viruses including, but not limited to Ross River, and Barmah Forest viruses can also cause such symptoms.²²

Chikungunya shares a common vector, as well as clinical features with dengue, posing a risk for both co-infection, and misdiagnosis (Table 1).

Pathogenesis

Fibroblasts, macrophages, epithelial cells, and endothelial cells are susceptible to CHIKV. The progression from acute infection to persistent arthralgias/arthritis may involve macrophage virus tropism, local virus persistence, and inflammatory responses. CHIKV has been associated with varying degrees of cytokine responses, involving interleukins, and INF alpha. There has been a difference in the cytokine profile during acute and chronic phases of CHIKV.^{11,22,27–30} CHIKV is tropic to fibroblasts of joints, muscles, and skin, as well as central nervous system (CNS) cells. Of note, some of it has been shown that CHIKV RNA has not been detected in the joint tissue of during the chronic disease phase, suggesting CHIK arthritis may be the result of a post-infectious inflammatory disorder, and an autoimmune response is triggered.^{11,31} Some research suggests arthralgias induced by Chikungunya virus infection are associated with interleukin 6 and granulocyte macrophage colony stimulating factor.^{28,29}

Symptoms

CHIKF begins, often dramatically, with high fever, arthralgias, rash, fatigue, headache, and back pain within 2–7 days of viral transmission from a mosquito bite. Other symptoms including a variety of gastrointestinal can occur. The acute phase can last approximately 10 days. Polyarthralgia is not uncommon, involving hands, feet, ankles, knees. Of note, any joint can become involved, including the temporomandibular.

The rash is present in most patients, and is usually maculopapular. It can be pruritic. Some men have reported aphthous ulcers in the groin region. In the majority of cases skin problems developed in the very early stages of the illness, usually within 7 days. These can be accompanied by high fever and severe muscle and joint pain. About a third of patients developed skin lesions after the fever abated, albeit muscle and joint pain likely remain.

Neurological complications have been reported, and should be watched for. These include optic neuritis, encephalitis, facial paralysis, sensorineural deafness, and Guillain Barre Syndrome (GBS)—these can be mistaken for other infectious or non-infectious etiologies, so a good history and exam are needed.^{11,32,33} Myocarditis, cardiac dysrhythmia, sepsis including shock have on occasion been reported.³² Of note, Zika has been associated with GBS.

Almost all patients infected with CHIKV will develop some symptoms according to the CDC and reports of illness from various regions.^{7,8,10,11,27–33}

Symptoms associated with Chikungunya appear between 3 and 7 days after the patient has been bitten by the infected mosquito and these include:

- High fever (40 °C/104 °F)
- Joint pain (lower back, ankle, knees, wrists, or phalanges)
 - Often severe
- Joint swelling (Fig. 1)
- Rash (Fig. 3)
- Headache
- Muscle pain
- Nausea
- Fatigue
 - Can be moderate to severe

Symptoms usually are self-limiting, usually lasting 2–3 days, although chronic illness may develop. It is rarely a fatal infection,¹⁰ although in certain subpopulations, including persons over 65 the risk of fatality increases. Bleeding is uncommon, but meningoencephalitis may occur. Typically,



Fig. 3. Chikungunya viral rash.



Fig. 4. Dengue virus rash (www.cdc.gov).

the fever lasts for 2 days and then ends abruptly. However, other symptoms like joint pain, intense headache, insomnia and an extreme degree of prostration, can last for about 5–7 days. In some cases, arthralgias and myalgias may persist for longer periods of time.

Patients at increased risk include newborns infected around the time of birth, older adults (≥ 65 years), and people with medical conditions such as high blood pressure, diabetes, or heart disease. Chikungunya virus remains in the patient's system approximately 5–7 days during which time if a mosquito feeds on an infected person, it can also become infected.

For some patients a chronic phase exists; characterized by polyarthralgia that can last from weeks to years. A significant percent of infected adults are symptomatic after infection. There is a risk of disability associated with decreased dexterity (Fig. 1), loss of mobility, and delayed reaction that can last weeks to months.¹¹ Approximately 30–40% of those infected experience recurrent joint pain. Myocarditis, meningoencephalitis, and mild hemorrhage, as well as uveitis and retinitis, have been noted in outbreaks.

In patients who suddenly develop arthralgia, a good travel, exercise (hiking in the woods), and occupational history are important, as such symptoms may result from vector-borne illnesses that range from Lyme and other tick-borne infections to arboviral arthralgias.

The time course to develop CHIKV arthritis varies—at times during the acute phase and remains unremitting over time. The illness can also present biphasic—acute illness followed by relief of symptoms, only to then have them return as a form of persistent arthritis.

A Colombian study from 2015 noted that at 26 weeks post-infection, 53.7% of patients continued to have rheumatologic symptoms.³⁴ Other studies yielded similar results of post-viral polyarthralgia, inflammatory arthritis, tenosynovitis, which lasted at least 15 months.³⁵ Of note, various studies described symptoms consistent with seronegative RA, with swelling, and pain noted (Fig. 1).

Chikungunya shares some clinical signs with dengue and can be misdiagnosed in areas where dengue, another vector-borne illness, is common (Figs. 3 and 4).

Given Zika, as well as Chikungunya and DENV share common mosquito vectors, it is important to recognize the symptoms associated with each illness, based on similar epidemiology, and co-infection. Each has a biodrome—cascade of clinical findings; while there is overlap, there are also some notable differences, such as bleeding accompanied by significant CBC alterations is strongly associated with Dengue, whereas a moderate-to-severe pruritic rash is mostly associated with Zika, as seen Tables 1 and 2.

Diagnosis

The initial diagnosis and management of Chikungunya should be based on a strong index of suspicion. Infectious disease specialty care, university hospital laboratorian, and state public health

laboratories should be able to guide in testing. The Centers for Disease Control and Prevention (CDC) can also provide guidance. The CDC 1.800-232-4636

The presumptive diagnosis is made by a careful history, and clinical information. Testing should take into consideration other co-circulating arboviruses, especially if the patient has returned from an area endemic for DENV or Zika.

CHIKV infection should be considered in patients presenting with an acute onset of fever and polyarthralgia, especially those who have recently returned from areas with known virus transmission. A good travel and occupational history is important in any encounter with potential infectious disease diagnosis.

Most public health laboratories and many health care facilities can test for CHIKV.

Laboratory diagnosis is generally accomplished by testing serum or plasma to detect virus, viral nucleic acid, or virus-specific immunoglobulin (IgM) M and neutralizing antibodies. Viral culture may detect virus in the first 3 days of illness.

Biosafety lab (BSL) safety precaution

Of note, according to the CDC, Chikungunya virus should be handled under biosafety level (BSL) 3 conditions. During the first 8 days of illness, Chikungunya viral RNA can often be identified in serum. Chikungunya virus antibodies normally develop toward the end of the first week of illness. Therefore, to definitively rule out the diagnosis, convalescent-phase samples should be obtained from patients whose acute-phase samples test negative.

Samples can be sent to CDC but contact with local health care facility, public health department beforehand may provide for specific, up to date guidance. The following is a link for information concerning sending samples to the CDC <https://www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html>

For additional information, the clinician or laboratorian can contact the Division for Vector-Borne Diseases (DVBD):

The DVBD Arbovirus Diagnostic and Reference Laboratory at 1-970-221-6400.

Testing

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The best type of tube is serum separator (typically tiger/speckled-top). The blood should be allowed to coagulate and tubes should be spun to separate the serum from the clot prior to shipping.

If a red-top is used (no additive), the blood must be allowed to coagulate, the tube centrifuged, and the serum drawn off into a clean tube prior to shipping. Heparin (green top) and EDTA (purple top) are unsuitable for CHIK testing

Where and how should I send the samples to CDC?

Please refer to the *instructions for sending diagnostic specimens to CDC*, which also includes detailed instructions for completing the *on-line CDC specimen submission form 50.34*[PDF—2.5 MB].

Please note: because Chikungunya virus testing is not listed in the drop-down menu for the Test Order Name field of form 50.34 (located on 1st page, top left), you will need to select “ARBOVIRUS SEROLOGY” and then type “CHIK testing” in the Brief Clinical Summary field located at the top of the second page of the form

When will results be available?

Test results are normally available 4–14 days after specimen receipt. Reporting times for test results may be longer during summer months when arbovirus activity increases. Receipt of a hard copy of the results will take at least 2 weeks after testing is completed. Initial serological testing will be performed using IgM-capture ELISA and IgG ELISA. If the initial results are positive, further confirmatory testing will be performed and it may delay the reporting of final results. ALL RESULTS WILL BE SENT TO THE APPROPRIATE STATE HEALTH DEPARTMENT. Notify your state health department of any direct submissions to CDC.

Prevention

Unfortunately to date there are no FDA approved vaccines to prevent CHIKV. The National Institutes of Health (NIH) are studying various candidate vaccines, as are research centers internationally. Although some early phase trials show promise, none to date are licensed.

Also significant research is ongoing to identify preventive and therapeutic approaches to this and other emerging or reemerging pathogens that threaten significant global populations. Not surprisingly, viruses with keen adaptation capabilities have made controlling them somewhat elusive.

Nevertheless, among one of the promising approaches is vectored immunoprophylaxis (VIP)—tailored antibodies derived from non-hematopoietic cells, thus bypassing the humoral immune system. By using genes encoded for neutralizing antibodies—these have shown effectiveness in preventing and treating certain viral infectious disease in animal models.³⁷ These include HIV, dengue, Hepatitis C, Chikungunya, and influenza, as well as the bacterium *bacillus anthracis*.

Other areas of pursuit include passive immunization using monoclonal antibodies. These have had some positive findings against MERS-CoV and Ebola. Problematic of course is the need for high antibody concentrations, multiple injections since this intervention has a short half-life, are the logistics given many of these pathogens infect persons living in resource limited, often remote regions.

Travelers can protect themselves by reviewing recommendations by the CDC available at: <https://www.cdc.gov/chikungunya/prevention/index.html>. Of critical importance is avoiding mosquito bites. When traveling to countries with Chikungunya virus, use insect repellent, wear long sleeves and pants; some clothing is treated with insect repellent.¹⁶ Wherever possible, stay in places with air conditioning, but make certain if it is not centralized, instead using window units that there are no gaps between the air conditioner and window area. Also make certain if using window and door screens that you check for breaks in those screens. Bear in mind, some mosquitoes are house-dwellers, and may already be in the lodging, under beds and other areas where urban vectors may rest.

In mosquito, and malaria-infected areas, use DEET insect repellent. Wear long pants and long-sleeved shirts, especially from dusk to dawn. Some sporting goods stores sell outdoor wear that is impregnated with approved mosquito repellent. Use mosquito netting around your bed can protect from bites while you sleep.

According to the CDC, persons infected with CHIKV are likely to be protected from future infections. However the duration and extent of protection, and influence of immune status, remain unknown.⁸

Treatment—Chikungunya

To date there are no FDA approved antivirals for the treatment of CHIKV infection according to CDC, although much research is being conducted to develop new and/or repurpose existing antimicrobial therapies. A variety of novel agents and antiviral medications are being studied and are in various stages of development.^{38,39} Ribavirin, an antiviral agent was used to treat CHIKV-induced arthritis in a small cohort of patients and was found to be beneficial in resolving joint and soft tissue swelling.^{39,40} That notwithstanding, Ribavirin use in CHIKV is not an FDA approved indication as antiviral for this arbovirus. Risk and clinical benefit must be taken into consideration.

Small molecule inhibitors of viral polymerase and specific nonstructural proteins, also host factor interventions are being investigated.⁴⁰

As with other vector-borne infections that can co-circulate with Dengue, it is important to rule out DENV before utilizing medications such as aspirin and non-steroidal anti-inflammatory agents (NSAIDs) that can influence coagulation. Acetaminophen containing products may be used. Fluids are recommended to prevent dehydration, along with rest. Until a consistently effective antiviral is identified or developed, aggressive symptomatic and supportive care remain the mainstays of therapy.

Treatment—Chikungunya arthritis/pain

To relieve pain, acetaminophen (500–750 mg every 6 h, not exceeding 4 g/day), tramadol (50–100 mg every 6 h) and codeine (30 mg each 6 h), or oxycodone (10–20 mg every 12 h), are recommended.^{11,41–44}

As mentioned earlier, owing to the risk of co-infection because of co-circulating viruses that share vectors, such as DENV and Zika, along with other arboviruses sharing mosquito vectors, unless and until Dengue is ruled out, use of aspirin and NSAIDs is not recommended, in order to reduce bleeding risk.

Fluids are recommended to prevent dehydration, along with rest.

Acetaminophen can be used for both fever and pain, as fever is common in CHIKV, along with other arboviruses.

During the acute phase of CHIKF, when patients have high levels of viremia, corticosteroids, although effective at controlling symptoms, should be avoided—outcomes have been suboptimal in several cases.¹¹ Cold compresses may reduce joint pain.^{11,43,45} Maintaining mobility and preventing functional impairment are important.^{11,41} Patients with neuropathic pain may benefit from amitriptyline or gabapentin.^{11,43} Close follow up is also recommended to ensure worsening

infection or co-infection are not missed, and to address any early neurological or arthritic sequelae.²³ Persons who are pregnant should be closely monitored for co-infection and possible fetal distress.

The majority of patients will experience resolution of acute symptoms within 2 weeks, but up to 50% of individuals remain symptomatic during a sub-acute phase that can last several months. In these individuals, the predominant symptoms are musculoskeletal—usually polyarthralgias: arthritis, bursitis, and tendonitis. They also experience fatigue. Hair loss, and sometimes endocrinopathy have been reported.^{11,44,45} Among different reports, a highly variable percentage (1.6–89.7%) of patients progress to develop chronic arthritis lasting up to 6 years following acute CHIKF.¹¹ Not surprisingly studies suggest risk factors associated with long-term disease include age greater than 45, diabetes mellitus, hypertension, dyslipidemia, and previous rheumatic disease.^{11,45} In patients with pre-existing arthritis, it may be difficult to distinguish recurrence from CHIKV disease.

There appear to be clinical similarities of CHIKV arthritis and rheumatoid arthritis and related disorders; some suggest disease-modifying anti-rheumatic drugs (DMARDs) should be considered for the treatment of what is now referred to as post-Chikungunya chronic inflammatory rheumatism (pCHIK-CIR).^{11,46}

Guidelines for the management of Chikungunya arthropathy (2014) have been proposed.^{11,44} These guidelines suggest patients with rheumatic symptoms of more than 3 months duration should be referred to rheumatologists for further evaluation, and disease categorization. Based upon these guidelines treatment options include methotrexate (MTX) sulfasalazine (SSZ), leflunomide, hydroxychloroquine (HCQ), NSAIDs, or immunobiologics.^{11,44}

Of note there have been several publications promoting the use of HCQ as first-line therapy for CHIKF arthritis. There is limited evidence of efficacy. Brito et al. recommend HCQ (6 mg/kg/day), with evaluation every 6 weeks using the visual pain scale (VAS) as the primary outcome measure as a decision point whether to discontinue therapy, or add another medication—SSZ (1000 mg/day).¹¹ They suggest after 36 weeks, initiate MTX therapy (at an initial oral dose of 10 mg/week).^{11,43} But a study comparing chloroquine (CQ) to placebo revealed there was no reduction in joint pain severity or duration.¹¹ In vitro, CQ and HCQ may inhibit CHIKV replication, but one study did not identify significant differences in the duration of febrile arthralgia or viremia in patients treated with CQ vs placebo.¹¹ Also noted CQ was compared to meloxicam in 70 patients, resulting in no differences in chronic symptoms (> 6 weeks). Other studies question HCQ and CQ in the treatment of CHIK arthritis.¹¹ CQ-treated patients were tested for and found to maintain persistently elevated levels of IL-6 and IL-13. This puts into question whether this antimalarial can confer immunomodulatory benefit.¹¹

Glucocorticosteroids have been tried as a treatment for CHIKV arthritis.¹¹ During the CHIKF outbreak on Reunion Island, Simon et al. described significant improvement in symptoms associated with tenosynovitis and polyarthritides. Also low dose prednisone provided months after the acute illness, enhanced ability to ambulate.¹¹ In another study, Sissoko et al. evaluated 147 patients who had had CHIKF. In that study, 57% had persistent or recurrent joint pain. They demonstrated better symptomatic improvement comparing glucocorticoids to NSAIDs and acetaminophen.¹¹

In a Dominican Republic outbreak, 370 of 514 (72%) CHIKV arthritis patients were treated with glucocorticoids with good clinical response.^{3,11} In another study 12-week study of 120 patients that evaluated treatment of early stage CHIKF musculoskeletal symptoms, Padmakumar et al.⁴³ compared NSAID monotherapy (aceclofenac 200 mg/day), NSAID in combination with HCQ (aceclofenac and HCQ 400 mg/day), NSAID in combination with corticosteroid (aceclofenac and prednisolone 10 mg/day), and triple therapy (aceclofenac, prednisolone, and HCQ). Improvement in pain reduction or improvement in quality of life was greatest in the NSAID plus glucocorticoid group. They report no greater benefit resulted from the addition of HCQ.^{3,11,43} Corticosteroids should be limited to short-term therapy referable to potential toxicity. Available reports do not suggest corticosteroid-induced exacerbation of CHIKV infection when glucocorticoid therapy is utilized during the chronic phase of infection.

The use of biologics has been a significant advance toward reducing symptoms in inflammatory arthropathies. In terms of their use in arbovirus arthropathy, limited information exists

documenting the safe and effective use of biologic therapies for CHIK arthritis. Among 147 chronic arthritis patients treated during an outbreak on Martinique, most patients were treated with MTX (up to 25 mg/week) with good results; 12 patients received anti-TNF therapy. The mechanism of action associated with Methotrexate includes inhibiting cell proliferation by inhibiting purines and pyrimidines; it acts as an anti-folate agent.^{3,11,43} Although the precise mechanism of methotrexate associated anti-inflammatory action remains yet to be fully elucidated, it may be the result of induction release of adenosine. Adenosine is associated with the suppression of neutrophil, macrophages/monocytes, dendritic cell and lymphocyte inflammatory function.^{3,11,47,48} The anti-inflammatory effect of MTX on rheumatoid arthritis (RA) is thought to involve the inhibition of the following proinflammatory cytokines: IL-1, IL-2, IL-6, IL-8, and TNF- α . Methotrexate is also thought to affect neutrophil chemotaxis, the proliferation of synovial fibroblasts and lymphocytes, and increases the production of IL-4 and IL-10, and other cytokines.^{11,47} Over the years much clinical experience and benefit of MTX as a treatment of RA and related inflammatory arthropathies has been realized. Moreover ready availability and relative cost effectiveness make MTX attractive as a potential treatment for persistent CHIKV arthritis. Overall it is well tolerated.¹¹ During a Dominican Republic epidemic, 53 of 328 rheumatoid arthritis patients developed CHIKF while on biologic therapy. Their illness was similar to other patients treated for CHIKF during this outbreak. Of note, the use of biologic therapy did not appear to protect against or exacerbate their CHIK infection.³

Multiple studies have evaluated MTX in this setting. For example, a cohort treated initially with SSZ plus HCQ, which failed to achieve a clinical response at 3 months, was given MTX, which resulted in a significant benefit.⁴⁸ Other studies demonstrate patients experiencing complete resolution of chronic joint symptoms with the use of MTX without significant toxicity.^{3,11,41,48} Improvement in symptoms, radiological findings, and inflammatory markers after 4 months of MTX therapy was demonstrated.

In several other studies, elevated levels of cytokines that are proinflammatory and are associated with osteoclastogenesis—erosive disease in RA (examples IL-1, IL-6, IL17, and TNF- α) were shown to correlate with severity of CHIK arthritis.^{28,30,49} Such similarities in immune responses of RA and CHIK-CIR provide a rationale for considering MTX in the treatment of CHIK arthritis.^{11,43,44} As with RA, in addition to symptom control, the goal of therapy is to prevent further tissue damage.^{11,44}

It is important to consider the impact of chronic disease, including arboviral infections on overall patient well-being, and function. If functional limitations occur, referral to physical and occupational therapy may need to be considered.

As with other chronic, painful illnesses, the psychological burden of CHIKV chronic inflammatory arthritis—including anxiety and depression, should be addressed.⁵⁰

Conclusion

During a little more than the past 10 years the epidemiology of CHIKF has dramatically changed, with epidemics occurring throughout the tropic and subtropical regions, with millions at risk. With changing population movement, and expansion of vector regionality continue, the risk of more outbreaks increases. As greater numbers of persons become infected, the viral disease will be better characterized. To date CHIKV has a low case fatality rate, but increasingly being recognized for potential chronic, sometimes severe post-infectious arthritis.

To date there are no FDA approved vaccines or specific antiviral medications to prevent or treat CHIKV. Aggressive symptomatic and supportive care are critical; diagnosis should be made clinically with laboratory confirmation. Aggressive pain management should be provided in the acute stage, and close observation of patients in anticipation of potential chronic post CHIKV arthritis.

Vector control, and preventive measures to reduce the risk of mosquito bites, including selection of clothing (long sleeve, insect repellent impregnated cloths), use of insect repellents, and proper selection of and attention to characteristics of domiciles/hotels (air conditioning, intact screens, bed netting) along with avoiding endemic regions. Control of *Aedes* mosquito vectors is also a high priority.

CHIKV is an emerging arbovirus, and co-circulates in many regions where DENV and ZIKV are also endemic; many North Americans will travel to these regions on business, vacation, or military/humanitarian missions. The astute clinical will be mindful of these vector-borne illnesses in patients returning from travels, as well as the potential for co-infection. Recognizing the mosquitoes capable of transmitting arboviral infections are present in many parts of the United States and US territories, counseling about mosquito precautions, and encourage patients to seek travel guidance, available travel-related immunizations, as well as obtain early medical care if returning with fever, rash, joint pain, or other symptoms, making sure patients are quick to alert health care providers of recent travels and/or occupational risks.

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