Chapter

# Clinical Features and Management of Chronic Chikungunya Arthritis

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## Abstract

Chikungunya virus is a single-stranded RNA alphavirus transmitted to humans by *Aedes* species mosquitos, causing an acute illness known as chikungunya fever with maculopapular rash, headache, polyarthritis/arthralgias, and gastrointestinal symptoms. Up to half of affected patients develop a chronic disabling arthritis following resolution of the acute infection, which can last for months or even years. The pathophysiology of chronic chikungunya arthritis remains controversial; it may result from a dysregulated immune response or be caused by persistent viral infection. Treatment for patients with chronic chikungunya arthritis remains investigational. Limited data suggests that immunosuppressive therapies such as methotrexate and TNF alpha inhibitors may be beneficial, though randomized clinical trials are needed.

**Keywords:** chikungunya, alphavirus, arthritis, disability, DMARDs

## 1. Introduction

Chikungunya virus (CHIKV) is a small, single-stranded RNA alphavirus transmitted to humans by *Aedes* species mosquitoes, including *Aedes aegypti* and *Aedes albopictus*. CHIKV was initially isolated in Tanzania in 1952–1953 [1]. The word "chikungunya" means "that which bends up" or "to become contorted" in the Makonde language, referring to the prostrated appearance of affected patients [2].

Prior to its isolation, chikungunya (CHIK) was often misdiagnosed as dengue [3]. During the twentieth century, chikungunya fever (CHIKF) epidemics occurred sporadically and were limited to Africa and Asia, but in the twenty-first century CHIK has become a global disease. There was a major outbreak in coastal Kenya in 2004, which subsequently spread to Réunion in 2005 and throughout the Indian Ocean region [4]. Cases among travelers returning from endemic regions were reported in Italy in 2007 [5].

CHIKV reached the Western Hemisphere in 2013 with an outbreak on the island of Saint Martin. Since then, the virus has spread throughout the region with more than 2 million cases documented in the Americas by the end of 2016, though the actual number is likely much higher [3]. In the United States, cases involving travelers to endemic regions have been documented in 49 states, and locally-acquired cases have occurred in Florida and Texas [6].

Factors contributing to the spread of CHIK include increasing urbanization, overstrained health care infrastructures in developing countries, ease of international travel, and climate change with expansion of mosquito vectors [7].

There are three known genotypes of CHIKV: Asia, East/Central/South Africa, and West Africa. The 2004–2005 pandemic that originated in Kenya and subsequently spread throughout the Indian Ocean region involved the East/Central/South Africa genotype. The pandemic that emerged in the Americas in 2013 originally involved the Asia genotype, although more recently the East/Central/South Africa lineage has been reported in the Western Hemisphere [8, 9].

## 2. Clinical manifestations

### 2.1 Acute chikungunya fever

CHIKV infection results from transmission by the mosquito vector. Following an incubation period of 5–7 days, patients develop an acute febrile illness, chikungunya fever (CHIKF), characterized by high fevers, maculopapular rash, headaches, polyarthritis/arthralgias, myalgias, nausea, vomiting, and diarrhea [1]. Joint pain is often severe, and most often involves the metacarpal-phalangeal and interphalangeal joints of the hands, the wrists, the ankles, and the metatarsal-phalangeal joints of the feet. Less commonly involved but described joints include the shoulders, elbows, hips, knees, and inter-vertebral joints [10]. Acute CHIKF causes significant physical disability. For example, during the 2005 Comoros epidemic, an estimated 80% of affected patients were hospitalized or bed-bound due to severity of their symptoms [11].

More severely affected patients can develop neurological disease including meningoencephalitis, myelitis, radiculitis, and/or peripheral neuropathy, including reports of Guillain-Barré syndrome [12]. Rare ophthalmological manifestations reported include keratitis, episcleritis, optic neuritis, uveitis, and retinal detachment [13]. Uncommon but serious cardiac manifestations include arrhythmias, vasculopathy, myocarditis, and/or dilated cardiomyopathy [14, 15]. Patients with acute infection can have laboratory abnormalities including thrombocytopenia and leukopenia (lymphopenia is more common than neutropenia) [4].

Maternal-to-child transmission has also been reported, with up to 50% of neonates acquiring infection during childbirth if born within 5 days of maternal infection. Musculoskeletal manifestations are less prominent in newborns, with CHIKF being more notable for fevers, rash, cytopenias, hepatitis, and/or encephalitis [16].

Acute CHIKF typically resolves in 10–14 days, and has an overall reported case fatality rate of <1% based on epidemics in the Indian Ocean region and the Americas. However, the case fatality rate is higher among newborns, the elderly, and patients with underlying cardiovascular and pulmonary conditions [7, 17, 18]. Economopoulou and colleagues studied the case fatality rate among atypical cases of CHIKF in Réunion (defined as patients presenting with symptoms other than fevers and arthralgias); 65/610 patients from this group died for a case fatality rate of 10.6% [19].

During the widespread Indian Ocean region pandemic, a point mutation (A226V) in the E1 surface glycoprotein of CHIKV may have allowed better adaptation in *Aedes albopictus*, which had previously been a minor vector [20]. Along with low background immunity among populations residing in regions not historically affected, this may account for the rapid spread and high rates of infectivity seen for CHIKV in the twenty-first century.

### 2.2 Chronic chikungunya arthritis

Arthritis/arthralgia is a principal feature of CHIKF. Many patients recover within several weeks, but up to 50% develop chronic joint pain and swelling. When rheumatic disease persists for more than 12 weeks, we refer to these symptoms as

chronic chikungunya arthritis (CCA). Arthritic manifestations can last for weeks, months, or even years [21]. Rodriguez-Morales and colleagues retrospectively studied 283 patients from the 2015 epidemic in Risaralda Department, Colombia. At 26 weeks post-infection, 53.7% of the patients reported chronic musculoskeletal symptoms, including 49.5% with morning stiffness, 40.6% with joint swelling, and 16.6% with joint erythema [22]. Another large observational study from Kerala, India found that 57% of patients had chronic polyarthralgias, 22% chronic polyarthritis, and 19.5% chronic tenosynovitis 15 months after CHIKF [23].

The classical pattern of arthritis involves the small-to-medium sized joints in a peripheral and symmetric distribution [24]. This pattern can resemble rheumatoid arthritis (RA). Joint pain with/without synovitis can persist following acute CHIKF, or joint symptoms may remit and then recur at a later time [21].

A prospective Mexican cohort study showed that greater severity of acute infection predicted development of chronic arthritis, as measured by the disease activity index 28 (DAS28), World Health Organization Disablement Assessment Schedule II (WHODAS-II), and serum IL-6 level [25]. Other risk factors for chronic disease include patient age >45 years and high viral load (>$10^9$ per ml) during acute infection [26].

During acute CHIK infection, serum cytokines IL-1Ra, IL-1β, IL-6, IL-7, IL-8, IL-12, IL-15, and IFN-α increase, while RANTES (CCL5) decreases [27, 28]. With the transition to CCA, elevated levels of IL-6, GM-CSF, and IL-17 become predominant [28]. The IL-17 signature in particular may drive chronic joint inflammation, stimulating the upregulation of other pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, matrix metalloproteinases, and RANK-RANKL leading to osteoclastogenesis and bone erosions [29]. Alphavirus infection of osteoblasts has been shown to perturb the RANKL-osteoprotegerin ratio, contributing to bone loss. This imbalance may also provide a mechanism for joint erosions in chronic disease [30].

CHIKV primarily infects human epithelial and endothelial cells, fibroblasts, and macrophages. Replication has not been observed in lymphocytes, monocytes, or monocyte-derived dendritic cells [31]. Viral tropism to the highly-vascularized synovial tissues of the joints may be responsible for the prominence of arthritis following acute infection. Whether CHIKV persists in synovial tissue during the chronic phase remains unclear, however, and there is ongoing debate about whether CCA arises secondary to immunological dysregulation or is due to persistent alphavirus infection of the synovial tissue.

Hoarau and colleagues demonstrated the presence of CHIKV RNA and viral proteins within perivascular synovial macrophages from one patient with CCA 18 months following acute infection [32]. This finding has not been replicated in other patients with chronic joint disease, however. Viral RNA has been isolated from knee synovial tissue of patients infected with a related alphavirus, Ross River virus [33]. In non-human primates, CHIKV can be recovered from muscle, synovial, lymphoid, and hepatic tissues following resolution of acute infection. Macrophages have also been identified as viral reservoirs [34].

In a cohort from the Réunion epidemic, 16 CCA patients were evaluated for persistence of viral infection. Synovial fluid (10 patients) and biopsied tissue (6 patients) was evaluated with reverse transcriptase polymerase chain reaction (RT-PCR) for CHIKV. All samples were negative, suggesting active viral replication is not the cause of chronic articular disease [35].

These findings were replicated in a Colombian cohort with CCA, evaluated during the 2014–2015 epidemic. In all patients, synovial fluid was aspirated from inflamed joints. CHIKV DNA was not recovered by RT-PCR, viral proteins were not detected by mass spectrometry, and viral cultures were also negative for all patients. The authors concluded that CCA is probably a post-infectious autoimmune process [36].

Evidence for molecular mimicry between host tissues and CHIKV E1 glycoprotein has been postulated [37]. However, the specific mechanisms by which CHIK infection might lead to immunological dysregulation and autoimmunity are unknown.

### 2.3 Diagnosis of chronic chikungunya arthritis

The diagnosis of CHIK depends on epidemiologic information, characteristic clinical features, the time course of the infection, and laboratory confirmation. Many patients live in or have had recent travel to an area with endemic transmission of *Aedes* mosquitos. Laboratory testing depends on the time course of infection. During acute disease, CHIK viremia lasts for 5–7 days. At this time, RT-PCR of serum can be diagnostic. Anti-CHIKV IgM antibodies appear at 3–8 days and remain positive for 1–3 months. Anti-CHIKV IgG antibodies are detectable at 4–10 days and remain positive for months to years [1].

CCA patients present with chronic debilitating joint symptoms ranging from morning stiffness and arthralgias to frank inflammatory synovitis. A classical pattern of small-and-medium joint peripheral involvement has been described, but mono- and oligoarthritis can also occur (**Figure 1**). In some patients, CCA presents clinically as an RA "mimic," but most patients have negative tests for rheumatoid factor and anti-cyclic citrullinated peptide antibodies [38]. Patients with CCA often meet diagnostic and/or clinical criteria for RA or spondyloarthritis [39]. The distinguishing clinical feature is a previous history of acute CHIKF, with laboratory confirmation of serum positivity for IgM and/or IgG anti-CHIK antibodies.

Radiographic imaging of involved joints may be normal, especially early in the disease, with progression to bone erosions in some patients over time. Magnetic resonance imaging has greater sensitivity for the detection of inflammatory changes, and can show synovial thickening, bone marrow edema, effusions, and/or tenosynovitis [38].

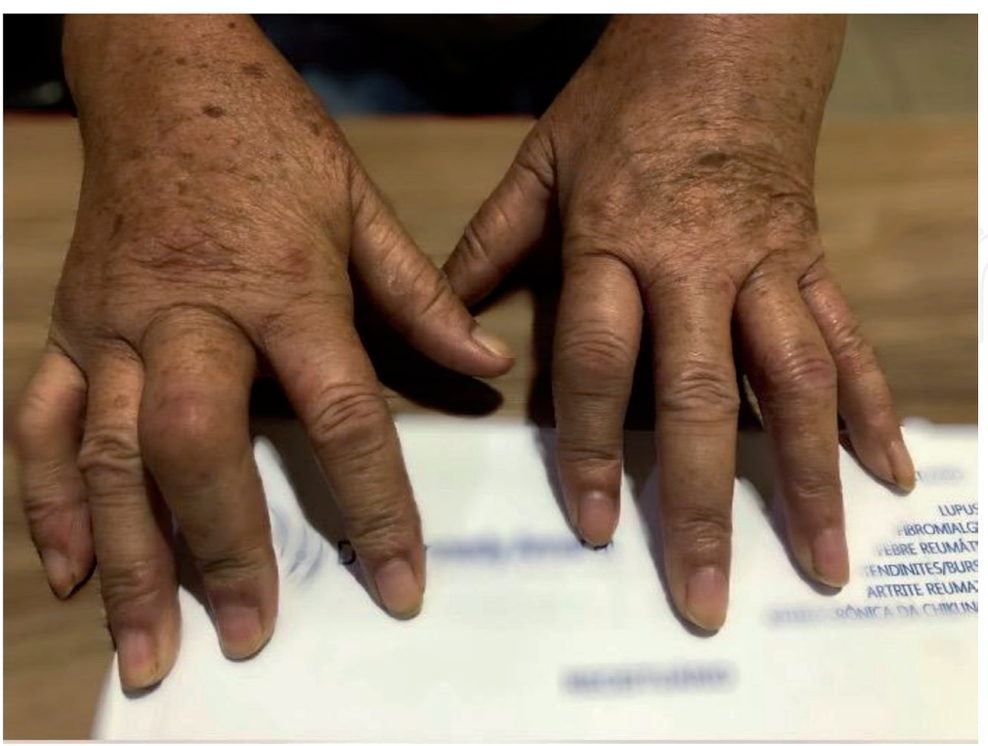

**Figure 1.**
*Patient with chronic chikungunya arthritis (CCA). A 50-year-old woman with CCA and synovitis of the right third PIP and left second PIP joints. She had acute CHIKF 3 years prior and subsequently developed CCA of the hand joints. Image courtesy of José Kennedy Amaral, M.D., Pernambuco, Brazil.*

## 3. Treatment of chronic chikungunya arthritis

Guidelines for the management of CCA emphasize symptomatic pain control with acetaminophen/paracetamol, codeine, and/or neuropathic medications such as gabapentin. Adjunctive treatment includes physical therapy, thermotherapy, and/or cryotherapy [16]. These approaches can relieve pain and improve function, but are not disease-modifying.

### 3.1 Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs)

In an uncontrolled case series during the 2005–2006 Indian Ocean pandemic, short-term corticosteroid treatment improved arthritis and tenosynovitis, and reduced disability in patients with CCA [40]. Corticosteroid treatment led to greater pain relief and patient satisfaction compared to paracetamol, NSAIDs, medicinal herbs, and physical exercise [41].

Padmakumar and colleagues performed a randomized-controlled trial evaluating the efficacy of single and combination NSAID and corticosteroid treatment regimens for CCA. Functional and pain assessments improved with corticosteroids (prednisolone 10 mg daily) in addition to the NSAID aceclofenac 200 mg daily, compared to those who received aceclofenac alone. The addition of hydroxychloroquine (HCQ) did not provide added benefit [42].

Despite positive results, long-term use of corticosteroids is not advised due to well-known risks of infection, cataracts, glaucoma, hyperglycemia and diabetes mellitus, and osteopenia/osteoporosis associated with chronic corticosteroid use.

### 3.2 Chloroquine and hydroxychloroquine

An open-label pilot study of chloroquine (CQ) treatment for CCA in South Africa showed improvement in patient and physician disease activity assessments, though this trial was not blinded [43]. Brito and colleagues recommended HCQ at a dose of 6 mg/kg daily as first-line treatment for CCA, as part of a regimen potentially escalating to triple therapy with sulfasalazine (SSZ) and methotrexate (MTX) [44].

However, a randomized-controlled trial comparing short-term treatment with CQ to placebo for acute CHIK arthritis found no differences between-group in the duration of arthralgias or viremia, but increased rates of chronic arthralgias in the treated group [45]. Chopra and colleagues performed a comparative effectiveness trial between CQ 250 mg daily and meloxicam 7.5 mg daily in patients with CCA and found no difference in efficacy [46].

In the open-label randomized trial by Ravindran and Alias, combination therapy (MTX 15 mg weekly, SSZ 1000 mg daily, and HCQ 400 mg daily) was superior to HCQ monotherapy [47]. The trial did not include a placebo group, precluding the possibility of determining the efficacy of HCQ.

Overall, most current evidence suggests that antimalarials such as CQ and HCQ are not effective for the treatment of CCA.

### 3.3 Sulfasalazine

The Ravindran and Alias trial included SSZ 1000 mg daily in combination with HCQ and MTX as part of triple therapy, compared to HCQ [47]. While combination therapy was more efficacious, the contribution of SSZ separate from MTX could not be established.

Ganu and Ganu evaluated a cohort of 16 patients with persistent arthritis following acute CHIKF, comparing treatment with SSZ and MTX to SSZ alone. Improvement was noted in 71.4% of patients receiving combination therapy compared to 12.5% of patients receiving SSZ monotherapy [48]. A significant limitation of this trial was the lack of a control group; it remains questionable whether SSZ was any more effective than a placebo response. In addition, a majority of the patients had anti-cyclic citrullinated peptide antibodies, suggesting they had RA rather than CCA.

Overall, there is very limited data suggesting efficacy of SSZ monotherapy for the treatment of CCA, but it may be efficacious in combination with other medications such as MTX.

### 3.4 Methotrexate

Pandya treated 149 Indian patients with CCA with MTX 15–20 mg weekly in combination with HCQ. At 16 weeks, ACR20 responses were achieved in 48.9%, ACR50 in 18.8%, and ACR70 in 4.0%. Clinical response was less robust as measured by DAS28-ESR, with just 1/149 patients achieving clinical remission (DAS28-ESR <2.6) and only 4/149 with a good clinical response (DAS28-ESR <3.2) [49]. One important limitation of the study was that the diagnosis of CCA was made entirely on clinical grounds, without serological confirmation of anti-CHIKV antibodies. As such, the patient population may have been heterogeneous, including non-CHIK inflammatory arthritis syndromes.

In the trial by Ravindran and Alias, the combination therapy regimen including MTX 15 mg weekly (along with SSZ 1000 mg daily and HCQ 400 mg daily) was superior to HCQ alone (DAS28-ESR <3.2 at 24 weeks, 84% versus 14% respectively). Both groups also received prednisolone 7.5 mg daily, but this was tapered off by 6 weeks [47]. In another trial by Ganu and Ganu, patients with an inadequate treatment response to combination SSZ and HCQ were escalated to treatment with MTX 15–20 mg weekly versus placebo. The MTX group achieved a superior clinical response versus SSZ/HCQ (71.4% versus 12.5%) [48].

Javelle and colleagues reported on treatment of a Réunion cohort with CCA following the 2005-2006 epidemic. Among patients treated with MTX 7.5–25 mg weekly, 54/72 (75%) achieved a good clinical response [39].

Bouquillard and Combe treated patients with acute CHIKF who were subsequently diagnosed with RA. Among 19 patients treated with MTX, 13 had a good clinical response (68.4%). Among these patients, 54.1% were positive for rheumatoid factor, and 28.6% had anti-cyclic citrullinated peptide antibodies [50]. As such, many of the patients were diagnosed with seronegative RA, which can closely mimic the signs and symptoms of CCA, and which might respond to similar treatments.

Amaral and colleagues treated 48 patients with CCA with open-label MTX initiated at 7.5 mg weekly, with dose escalations for refractory symptoms at 4 weeks. The final mean MTX dose was 9.2 ± 3.2 mg per week. MTX therapy was combined with prednisone at a mean daily dose of 6.1 ± 2.2 mg for nine patients (18%). Two patients received HCQ (400 mg daily) with MTX, and one also received SSZ (1000 mg daily). At the first visit, the mean value for pain by visual analog scale was 7.7 ± 2.0. The mean values for pain at 4 and 8 weeks, compared to baseline, decreased to 3.0 and 2.6 respectively [24].

Overall, MTX has shown promise in the treatment of CCA, though previous trials have either combined MTX with HCQ and SSZ, or have been unblinded. Further randomized trials are needed to evaluate MTX monotherapy.

### 3.5 Biologics

No human trials have yet been conducted to evaluate the efficacy of biologic therapy with monoclonal antibodies for the treatment of CCA.

Ross River virus (RRV) is an alphavirus phylogenetically related to CHIKV. In RRV infected mice, treatment with the TNF-α inhibitor etanercept resulted in decreased weight gain, increased viral titers, and increased inflammatory cell recruitment and tissue damage [51]. This study suggests that etanercept treatment of human patients with acute CHIKF might be detrimental, though treatment of patients with CCA could have a different outcome.

Bouquillard and Combe treated patients with acute CHIKF followed by the diagnosis of RA (not categorized as CCA) with TNF-α inhibitors. These patients had been refractory to initial therapy with MTX. 6/6 patients had a good clinical response (four with etanercept, two with adalimumab) [50]. The majority of the patients had been diagnosed with seronegative RA, which was not distinguished from CCA.

Treatment of CHIKV acutely-infected mice with the anti-CTLA-4 monoclonal antibody abatacept showed decreased T cell infiltration of joint tissues without affecting viral replication [52]. There is currently no data for its use in humans, nor for its use in treating CCA.

### 3.6 Novel agents

Pentosan polysulfate is a novel glycosaminoglycan-like molecule developed for the treatment of alphavirus infections. Treatment of CHIKV-infected mice with pentosan polysulfate reduced cartilage thinning and immunological infiltration of joints [53]. Intra-articular levels of the pro-inflammatory cytokines IL-6, IL-9, CCL2, and G-CSF were decreased, and levels of the anti-inflammatory IL-10 were increased through unclear mechanisms [30]. While developed for the treatment of acute CHIK infection, it remains unclear if pentosan polysulfate could be used for the treatment of CCA, in particular to prevent joint erosions.

Fingolimod is a sphingosine 1-phosphate receptor agonist developed for the treatment of multiple sclerosis. In CHIKV-infected mice, fingolimod treatment decreased the migration of CD4+ T cells into joints without affecting viral replication [54]. While the utility of fingolimod for treatment of CCA remains unknown, decreasing T cell migration into joints might be beneficial.

## 4. Conclusions

CCA is an emerging chronic and disabling rheumatological syndrome which can persist for weeks, months, or years after acute CHIKF. With the global spread of CHIKV in past decades, increasing numbers of patients from developing countries in particular have acquired or are at risk for this chronic disabling rheumatic syndrome.

The pathophysiology of the disease remains uncertain, though the weight of evidence suggests that the syndrome is caused by a post-viral autoimmune process, which follows viral clearance.

There is limited clinical trial evidence for the use of disease modifying therapeutics for patients with CCA. Most previous trials have been open-label or of limited quality. Empiric treatment courses with corticosteroids, NSAIDs, antimalarials, and SSZ can be considered. However, given similarities between CCA and RA, it is our

opinion that management with MTX should be further evaluated. Over time, new treatments including biologics and novel agents (pentosan polysulfate, fingolimod) may also emerge as treatment options.

## Conflicts of interest

None of the authors have any conflicts of interest to report.

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