Rheumatology Advances in Practice, 2025, **9(2)**, rkaf029
https://doi.org/10.1093/rap/rkaf029
Review

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Review

Current and future advances in practice: arboviral arthritides

Ashish Sharma [1] **and Vinod Ravindran** [2,3,*]

[1]Dilshad Garden, Rheumatology Clinic, New Delhi, India
[2]Department of Rheumatology, Centre for Rheumatology, Calicut, Kerala, India
[3]Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

*Correspondence to: Vinod Ravindran, Department of Rheumatology, Centre for Rheumatology, On Chevarambalam-Paropady Road, Calicut, Kerala 673009, India. E-mail: drvinod12@gmail.com

Abstract

Arboviral arthritides are a group of viral infections affecting the musculoskeletal system. Mosquitoes are vectors for some of the arboviral febrile diseases such as due to chikungunya, dengue and Zika viruses, which constitute a major proportion of arboviral arthritide syndromes in humans. They have gained epidemiological importance as the natural habitats of these mosquitoes are in the vicinity of human dwellings. Chikungunya virus infection frequently leads to post-infectious chronic musculoskeletal syndromes including erosive inflammatory arthritis, which resembles RA. Clinical features of the chronic phase result from the chronic persistence of the virus in certain tissues after the acute infection has resolved. In addition, the triggering of autoimmunity has also been implicated in musculoskeletal syndromes. Due to the diversity of clinical presentations and overlapping features with other viral illnesses and inflammatory arthritides, diagnosis and management are challenging. Poor prognostic factors for predicting evolution to chronic arthritides are not well delineated. There is no universal agreement regarding when to start immunomodulatory agents and the duration of such therapy. The lack of specific antiviral agents adds to the complexity of the situation. A live-attenuated vaccine has been recently approved by the US Food and Drug Administration for the prevention of chikungunya virus infection. This review discusses the musculoskeletal syndromes related to arboviral infections, with a major focus on chikungunya virus–related arthritis to provide practical guidance to clinicians involved in managing patients with chikungunya and its sequelae.

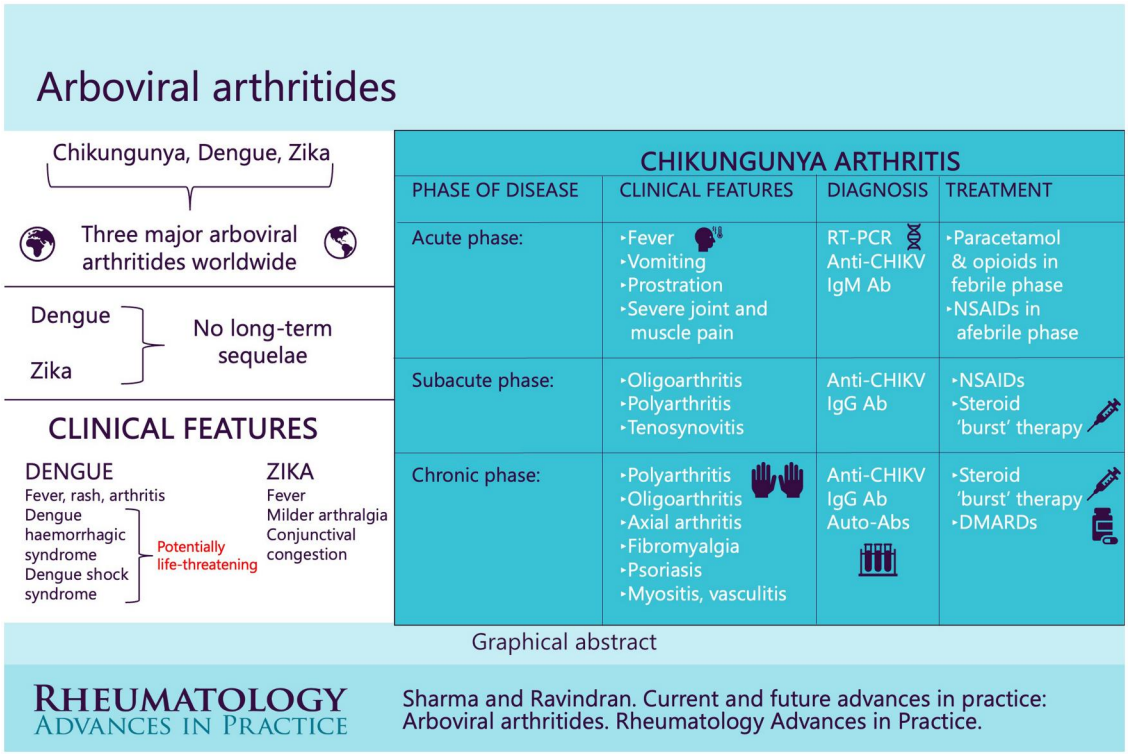
Lay Summary

What does this mean for patients?

Chikungunya virus (CHIKV) infection is the leading cause of immediate and long-term morbidity among all arboviral diseases. A significant proportion of patients develop chronic musculoskeletal problems, including inflammatory arthritis and fibromyalgia. No antiviral drug has been developed yet for the treatment of acute CHIKV infection. Therefore, the treatment is targeted toward symptoms of the disease, mainly the musculoskeletal manifestations. Acute and subacute phases are treated with anti-inflammatory agents such as acetaminophen, non-steroidal anti-inflammatory drugs and glucocorticoids. Patients who develop chronic inflammatory arthritis are treated with immunomodulatory drugs in a similar way as in the management of inflammatory arthritis such as rheumatoid arthritis. As there are no guidelines on the duration of treatment of chronic CHIKV arthritis, a gradual tapering of disease-modifying anti-rheumatic drugs in patients who remain in sustained remission is attempted.

Received: 14 September 2024. **Accepted:** 18 February 2025

Graphical abstract



Keywords: chikungunya arthritis, dengue virus, Zika virus, chronic arthritis, DMARDs, methotrexate, musculoskeletal.

Key messages

- Viral arthritis must be considered in any patient presenting with acute febrile illness with polyarthralgia.
- Detection of viral RNA or IgM antibodies aids in the diagnosis during the acute phase and IgG antibodies in the chronic phase of infection.
- The acute phase of CHIKV infection is treated with acetaminophen or NSAIDs along with supportive measures after ruling out coinfection with dengue to avoid haemorrhagic complications.
- Chronic post-chikungunya inflammatory rheumatism is treated with DMARDs. preferably as a combination therapy.
- Fibromyalgia and neuropathic pain syndromes, which frequently complicate subacute and chronic phases of CHIKV infection, are underrecognized and often treated suboptimally.

Introduction

Arboviruses are a subset of viruses that involve arthropods as a crucial part of their life cycle. They persist in nature between arthropods and vertebrate hosts. Humans are accidental hosts, and arboviral infection may cause a wide spectrum of diseases in humans, including of the musculoskeletal system, which is frequent and poses challenges in diagnosis and treatment. The acute phase of the infection causes constitutional and sometimes debilitating musculoskeletal pain that is often transient. In some, however, a myriad of musculoskeletal syndromes develop in the subacute and chronic phases. These arthritides can potentially cause chronic morbidity that may impact the quality of life and affect productivity. They also pose a healthcare-related economic burden worldwide. Due to increased travel, migration and resultant changes in vector distribution, hitherto unexposed places may see individuals with these infections and arthritides. In this review we discuss the musculoskeletal syndromes related to arboviral infections, with a major focus on chikungunya virus (CHIKV)-related rheumatism, which remains the main arboviral disease causing significant musculoskeletal issues. The role of immunomodulators, including biologic drugs, for treatment, emerging therapies and vaccines are also discussed.

For this narrative review, articles on arboviral arthritides published in the English language were retrieved from the MEDLINE, Google Scholar, Scopus and EMBASE databases. We focused on the diagnosis and treatment of various phases of the illness, patterns of rheumatological manifestations, the role of small molecules and biologic drugs in treatment and appropriate timing of their use, newer treatment modalities and prevention of infection, including vaccination. Where relevant, evidence in the published literature and personal

experience were synthesized to propose a practical approach for all stakeholders.

CHIKV, dengue virus and Zika virus constitute the major proportion of arboviruses causing arthritide syndromes in humans [1, 2]. CHIKV belongs to the alphavirus genus of the Togaviridae family, whereas dengue and Zika viruses are members of the Flaviviridae family [3]. Unlike CHIKV, there is no published evidence regarding any specific management of these arthritides and treatment remains symptomatic.

Dengue virus

Dengue differs from CHIKV in two major aspects (Table 1). First, unlike CHIKV, there are no chronic sequelae of dengue infection. Second, its complications, such as haemorrhagic fever and shock syndrome, may prove fatal; although CHIKV can cause significant morbidity, it is seldom fatal [4]. The mosquito species *Aedes aegypti* is the principal vector for dengue [1]. *Aedes albopictus*, *Aedes polynesiensis* and *Aedes cooki* are other species responsible in some geographic areas [5, 6]. High-grade fever, pain in the muscles and joints, rash and gastritis are the most common symptoms in the acute phase. Joints and muscles may appear puffy due to inflammation extending beyond the anatomical boundaries of joints. However, there is no frank synovitis on examination. Most of the symptoms of the acute phase are self-limiting and start resolving in 7–10 days [7]. There is no specific antiviral therapy and treatment is aimed at controlling fever and pain with acetaminophen, gastritis with proton-pump inhibitors and adequate fluid replacement therapy to compensate for fluid loss. The acute phase is followed by either recovery or complications. Renal and hepatic failure, meningitis, encephalitis and respiratory distress are other potential complications besides haemorrhage and shock, which require specialized treatment in critical care settings. Musculoskeletal symptoms usually resolve within 10 days and may extend longer in some patients, manifesting as fatigue, muscle cramps and non-specific pain. Typically the symptoms are the same throughout the day and there is no worsened stiffness in the morning, unlike inflammatory arthritides. However, if frank synovitis is present on examination of the joints or there are features of myositis, such as tenderness in the muscles and reduced muscle power, then alternative diagnoses should be considered and appropriate investigations obtained.

Zika virus

Infection with Zika virus causes milder fever and musculoskeletal symptoms with prominent conjunctival injection (Table 1). It causes a self-limited illness typically lasting ≈1 week. Rarely, neurological complications may arise, including Guillain-Barré syndrome, meningitis and encephalitis [8]. *A. aegypti* and *A. albopictus* are the predominant vectors worldwide [9]. However, mosquitoes of other species, such as *Anopheles* and *Mansonia*, are increasingly being recognized as vectors. There is no specific antiviral agent for its treatment. Management includes supportive care with analgesics, maintaining adequate hydration and timely detection of possible neurological complications [10]. Differentiation from mild dengue may be difficult due to similar clinical features. Just like dengue, if musculoskeletal symptoms persist for a longer duration or if there is clinical evidence of ongoing inflammation in the joints, alternative diagnoses should be considered, including inflammatory arthritides. Persistent elevation of inflammatory markers is unusual and suggests other aetiologies.

Miscellaneous arboviruses

Some of the other arboviral diseases causing musculoskeletal manifestations are predominantly restricted to certain geographical areas, hence the names of the diseases. Ross River virus, O'nyong-nyong virus, Mayaro virus and Barmah Forest virus are examples. Sindbis virus is more widespread in distribution due to the intercontinental spread of the causative virus. Ross River virus may cause chronic inflammatory arthritis in ≈50% of patients. Large and small joints in a symmetrical pattern may be involved. However, involvement

Table 1. Clinical features of common arboviral diseases having musculoskeletal involvement and genus and vector of the virus

Arboviral disease	Clinical features	Genus	Vector
CHIKV	Arthralgia Myalgia High-grade fever with chills Severe prostration Nausea Vomiting Rash	Alphavirus	*Aedes aegypti*, *Aedes albopictus*
Dengue	High-grade fever with chills Rash: very prominent · Maculopapular rash · Petechial rash Gastritis Vomiting Arthralgia Myalgia Haemorrhagic manifestations (dengue haemorrhagic syndrome) Multi-organ failure (dengue shock syndrome)	Flavivirus	*Aedes aegypti*, *Aedes scutellaris hebrideus*, *Aedes polynesiensis*, *Aedes cooki*
Zika virus infection	Fever Milder arthralgia and myalgia Conjunctival congestion	Flavivirus	*Aedes aegypti*, *Aedes albopictus*, *Anopheles*, *Mansonia*

of a single joint, development of joint erosions and persistently elevated levels of inflammatory markers are unusual and alternative causes must be assessed in such cases [11, 12]. NSAIDs and glucocorticoids are the mainstay of treatment. Refractory cases are rare but have a clinical phenotype similar to seronegative RA. Whether such patients have Ross River virus–related chronic arthritis or inflammatory arthritis triggered by the infection remains to be understood. These patients have to be treated with immunomodulatory therapy. Barmah Forest virus causes a more widespread rash [12]. Symptoms are usually self-limiting and the rash resolves earlier than musculoskeletal symptoms. Typically the rash disappears within 2 weeks and arthralgias persist for ≈1 month. Persistence of the rash for >1 month should prompt a search for alternative diagnoses. There is no published evidence regarding any specific management of these arthritides and the treatment remains symptomatic.

CHIKV

Organism

CHIKV is a single-stranded RNA virus that is the leading cause of arboviral arthritide syndromes worldwide. Three different strains of CHIKV have been identified that cause significant human disease: Asian, West African and East/Central/South African [13]. The virus has an affinity towards the tissues of the musculoskeletal system involving the synovium of the joints and muscle fibres. This results in significant musculoskeletal symptoms during the acute infection.

Epidemiology

Chikungunya is predominantly a disease of tropical and subtropical countries. However, due to global changes in climate and increasing intercontinental travel, it no longer respects these geographic boundaries. Several epidemics of CHIKV infection have occurred in many parts of the world, predominantly African, South American and Asian countries [14] (Fig. 1). In addition, sporadic outbreaks are frequent in endemic areas, especially in overcrowded localities. Various long-term sequelae of this infection cause significant societal impact due to disability and poor quality of life [15, 16].

Vector and transmission

Two species of mosquitoes—*A. aegypti* and *A. albopictus*—are the major vectors for CHIKV. Natural habitats of mosquitoes are in the vicinity of human dwellings and they breed in areas where fresh water is collected. Ticks and sandflies are other arthropod vectors involved in relatively rarer diseases.

Arboviruses reach human blood circulation from the salivary glands of the infected mosquito during a blood meal. The virus is engulfed by local macrophages, fibroblasts and dendritic cells in the dermis along with endothelial cells. Subsequently it reaches the regional lymph nodes, where it undergoes replication [17]. Arboviruses have tropism for the synovial tissues, where they undergo replication in synoviocytes and fibroblasts.

Pathogenesis

Chikungunya infection can be classified into acute, subacute and chronic phases based on differences in pathogenesis. Musculoskeletal symptoms are common in all three phases [18, 19]. It causes significant morbidity and deterioration in the quality of life without causing mortality, unlike dengue fever.

Acute phase

The initial acute febrile phase involves active viral replication. The resulting viraemia induces a type I interferon response [20]. Initially, activation of the innate immune system occurs, resulting in the stimulation of macrophages, natural killer cells and dendritic cells. Chemokines are then released, resulting in an influx of other inflammatory cells with activation of the adaptive immune response. Activation of cluster of differentiation (CD)-8 cytotoxic T cells and effector B cells results in the release of pro-inflammatory cytokines, propagating the

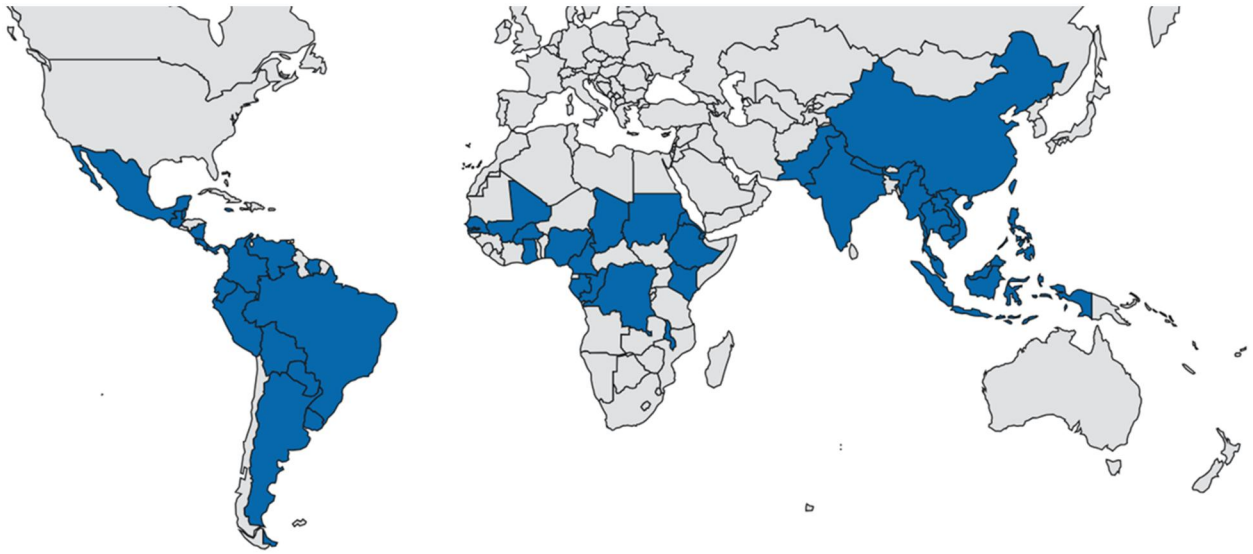


Figure 1. Countries with outbreaks or evidence of CHIKV transmission to humans during the last 5 years (as of 8 November 2024). Almost all of South America, Mexico and Africa (Congo, Nigeria, Sudan, Ethiopia, Cameroon, Gabon, Kenya and the others), and Asia (India, Pakistan, China, Indonesia, Thailand, Vietnam, Malaysia, and the Philippines) are among the most affected. Source: Chikungunya Virus | CDC, accessed 5 March 2025

immune response [21]. IL-6, GM-CSF and many other cytokines predominate in the acute phase [20].

Subacute phase

The robust immune response generated in the acute phase results in clearing of the virus and virus-infected cells. However, the inflammatory infiltrates and cytokines (IL-6 and GM-CSF) from the acute phase persist. In addition, IL-17 also contributes to a pro-inflammatory milieu [20]. Pathogen-associated molecular patterns (PAMPs) expressed on the cell surface are the molecular structures possessed by pathogenic organisms. These are recognized by toll-like receptors (TLRs) on the immune cells. Activation of TLRs by PAMPs results in the stimulation of macrophages, which leads to the propagation of immune response and clearing of virus-infected cells.

Chronic phase

Clearance of the virus by the host immune response after the acute phase may not be complete in some instances and low levels of the virus persisting in the synovial tissues may contribute to chronic CHIKV rheumatism [22, 23]. However, this hypothesis has not been confirmed and there are several reports of the absence of a viral genome in patients with chronic CHIKV rheumatism [24]. Molecular mimicry is another plausible mechanism [21]. The sharing of common epitopes of viral antigens and host cells gives rise to an inappropriate immune response to the self-antigens. In addition, infection of the host cells by the virus results in the expression of certain hidden antigens on the host cell surface, which have not developed anergy during the early stages of development. Because of this, the self-antigens are recognized as non-self by the immune system, resulting in an immune response. Epitope spreading also occurs, with resultant widespread autoimmunity [25]. The ultimate result is the release of pro-inflammatory cytokines and impaired function of natural killer cells [26]. Imbalance in the activity of T helper cells 1 and 2 occurs, giving rise to an aberrant immune response. In addition, bone resorption occurs as a net result of upregulation of receptor activation of nuclear factor κB ligand and downregulation of osteoprotegrin [27]. Elevated levels of monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein-1 are also observed [28]. Mesenchymal stem cells differentiate into fibroblast-like synoviocytes (FLSs) in response to the cytokines. FLSs are the effector cells that give rise to synovial inflammation and joint damage [29].

Immunologic similarities between chronic chikungunya arthritis and RA

The profile of inflammatory cytokines (IL-1, IL-6, IL-17 and TNF-α) and immunological phenotypes of inflammatory cells seen in patients with chronic musculoskeletal manifestations related to CHIKV are similar to what is seen in RA [24, 30–32]. This is the probable reason for similarities in the pattern of joint involvement seen in patients with chronic CHIKV-related polyarthritis and RA. People who are genetically predisposed to the development of inflammatory arthritis may develop acute joint inflammation after infection with certain viruses, including CHIKV [33]. Viral infection results in the activation of B and T cells. An aberrant response of these inflammatory cells in genetically predisposed individuals results in the development of autoimmunity, thereby giving rise to arthritis [34].

Clinical features

The clinical features of CHIKV infection may also be classified into three phases based on differences in clinical manifestations: acute (initial 3 weeks), subacute (3–12 weeks) and chronic (>12 weeks) [35]. (Table 2)

Acute phase

Acute CHIKV infection can be classified into a febrile phase, which is followed by an afebrile phase. High-grade fever with chills, severe prostration, anorexia, nausea, vomiting and rash predominates the febrile phase. Pain in the joints and muscles is the most prominent symptom and is incapacitating, hence the name chikungunya, which means 'that which bends up' [39]. Fever disappears in ≈7–10 days. However, fatigue and joint pain persist in the afebrile phase. Patients with pre-existing comorbidities such as inflammatory or degenerative arthritis, diabetes mellitus, chronic kidney or cardiac diseases are more likely to develop severe musculoskeletal symptoms during the acute phase [40]. Rarely, extra-articular manifestations may occur during this phase, including Bell's palsy, optic neuritis, viral encephalitis, Guillain–Barré syndrome and myocarditis [36].

Subacute phase

The subacute phase extends from 21 days to 3 months after infection. Two patterns of arthritis are observed in clinical practice in the subacute phase. One is self-limiting and resembles reactive arthritis. In the other, joint inflammation persists longer. In the former, the most common clinical manifestation is symmetrical polyarthritis. It is usually self-limiting. In the latter, the joint inflammation does not resolve and progresses to frank post-CHIKV arthritis resembling RA. In both forms, synovitis of the joints can be appreciated clinically. In addition, bursitis, tenosynovitis, carpal tunnel syndrome and tender points in the muscular planes may also be observed [41, 42]. Monoarthritis and oligoarthritis (four and less than four joints, respectively) are other relatively uncommon clinical phenotypes.

Not uncommonly, acute infection is relatively less symptomatic but chronic sequelae are significant. In such cases, it might be difficult to make an appropriate diagnosis, as minor symptoms in the acute phase might go unnoticed [43].

Table 2. Clinical features of different phases of chikungunya infection

Phase	Clinical features (estimated frequency, where available)
Acute phase (0–21 days) [36]	Fever (96%), arthralgia (93%) and myalgia (81%), puffy hands and feet (7–8%), severe prostration (91%), anorexia, nausea, vomiting (33%) and rash (33%)
Febrile phase (initial 7 to 10 days)	Arthralgia and myalgia, fatigue (43%)
Afebrile phase	Mono-/oligo-/polyarticular arthritis
Subacute phase (21 days–3 months)	
Chronic phase (>3 months) [37, 38]	Mono-/oligo-/polyarticular arthritis (20%), symmetrical polyarthritis (20%), inflammatory lower back pain (23%), enthesitis (13%), psoriasis, muscle pain and tenderness along with reduced muscle strength (myositis), widespread pain and fatigue (FM, 6.1%)

Chronic phase

Various musculoskeletal manifestations occur in the chronic phase of CHIKV infection [2, 43, 44]. The most common is arthritis involving the appendicular or axial skeleton with significant early morning stiffness [37]. Other autoimmune and non-autoimmune manifestations may also occur, giving rise to musculoskeletal symptoms.

Chronic inflammatory arthritis develops in 25–34% of patients infected with CHIKV [45, 46]. A majority of patients will have clinically appreciable synovitis and some may also develop radiographic erosions resembling those of RA. However, some patients with post-CHIKV chronic arthritis may not have synovitis on clinical examination. Such patients may be misdiagnosed as FM, as they may also have prominent fatigue. Ultrasonographic examination of joints is valuable in such patients. Demonstration of synovitis/tenosynovitis or positive colour Doppler signals confirms subclinical inflammation.

Recognition of the pattern of joint involvement is an important step towards classifying arthritis into a particular category. Symmetrical polyarthritis involving large and small joints resembling RA is the most common variant. Peripheral monoarticular or oligoarticular involvement and enthesitis resemble undifferentiated SpA, while axial symptoms occur in some patients, mimicking axial SpA (Table 3). Psoriasis is triggered by CHIKV infection along with its typical musculoskeletal symptoms [38]. Rarely, myositis or vasculitis may be the predominant clinical manifestation. FM occurs in a significant number of patients. Pain in 'widespread' distribution beyond the anatomical boundaries of joints, 'tender points', prominent fatigue and dysthymia are the pointers towards FM. As a significant number of patients will have a negative result of the autoantibodies corresponding to the clinical pattern observed, pattern recognition is even more important for post-CHIKV arthritis.

Risk factors for the development of chronic post-CHIKV arthritides are female gender (female:male ratio 3:1), older age, comorbidities at the time of acute infection and severe clinical manifestations during the acute phase [18, 43] (Table 4). In addition, long-term persistence of anti-CHIKV IgM antibody in serum is associated with chronic CHIKV arthritis [47, 48]. Patients with pre-existing inflammatory arthritis may develop an arthritic flare after infection with CHIKV [38]. A recent meta-analysis reported a relatively low rate of mortality (0.3%), with age >65 years as the single major risk factor [4].

An important difference between post-CHIKV arthritis syndromes and the corresponding inflammatory arthritis is the absence of extra-articular manifestations in the former. Rheumatoid subcutaneous and lung nodules, interstitial lung disease, uveitis and circinate balanitis are not seen in post-CHIKV-related arthritis.

Of the patients with chronic musculoskeletal symptoms, 6.1% have no signs of inflammation on clinical or ultrasonographic examination [49]. This group of patients has FM as a sequelae of CHIKV infection. In practice, it is a significant problem that poses a challenge in diagnosis and treatment. Given the history of preceding CHIKV infection, such patients with musculoskeletal symptoms are treated with serial NSAIDs and corticosteroids, without benefit. Inadequate relief contributes to anxiety in patients, which further exacerbates FM. Therefore, a high index of clinical suspicion and focused evaluation is necessary to diagnose FM. Unfortunately, there is a paucity of data on FM in patients with preceding CHIKV infection.

Table 3. CHIKV-related chronic musculoskeletal syndromes and their corresponding diseases [37, 38]

CHIKV-related chronic syndrome	Corresponding disease (estimated frequency in percentages, where available)
Symmetrical polyarthritis	RA (20%)
Peripheral mono-/ oligoarticular arthritis	Undifferentiated SpA (20%)
Inflammatory lower back pain	Axial SpA (23%)
Muscle pain and weakness	Inflammatory myositis
Widespread pain	FM (6.1%)

Table 4. Predictive factors for the development of chronic CHIKV-related arthritis

Age >45 years
Female
Severe clinical manifestations during the acute phase
Symmetric pattern of joint involvement during the acute and subacute phases
Joint pains persisting >4 months
High 28-joint DAS score
High viral load during the acute phase
Elevated levels of IL-6 and ferritin

Rare cases of inflammatory myositis and cutaneous vasculitis have been reported following CHIKV infection [38, 50, 51]. Also, pre-existing psoriasis can flare up in response to CHIKV, along with psoriatic arthritis [38].

Investigations

Diagnostic workup is challenging and differs with the phase of the disease. In the acute phase, the investigations aim to confirm the diagnosis of CHIKV infection. In the subacute and chronic phases, the investigations serve two purposes. First, a temporal sequence of CHIKV infection before the development of current musculoskeletal features has to be established. Second, the type of arthritis has to be classified and the degree of involvement of articular and periarticular structures has to be assessed. Most importantly, autoimmune inflammatory problems have to be differentiated from FM, for which there is no specific investigation.

Investigations to diagnose CHIKV infection

Diagnosis of acute CHIKV infection is made by detecting anti-CHIKV antibodies or viral RNA in serum by RT-PCR. Epidemiological definition of acute CHIKV infection requires clinical and laboratory evidence—acute fever with joint pains of at least 48-h duration and detection of either anti-CHIKV IgM and IgG antibodies or viral RNA by RT-PCR [52] (Table 5). Anti-CHIKV IgM antibodies are detectable in serum from day 5 of infection until day 21. IgG antibodies appear in serum by day 7 of infection and are detectable long term [30, 35] (Fig. 2). The presence of IgM in serum is suggestive of a recent infection. However, this distinction may not be possible in endemic areas due to the persistence of low-grade infection in the population [15, 40, 53]. Demonstration of a increasing trend of antibody titres points to a recent infection. Viral RNA is detectable in serum in the initial 7 days of infection. Clearance of virus-infected cells by the host immune response results in non-detectability of viral RNA after 1 week [30].

Detection of dengue or parvovirus infection

Dengue infection frequently coexists with CHIKV in the community, as the habitats, vectors and hosts are similar for both. Clinical features of both diseases mimic each other (Table 1). Detection of dengue by serology or non-structural protein-1 antigen helps in diagnosing dengue. Parvovirus B-19 is a common cause of viral arthritis, mimicking CHIKV arthritis, and can be diagnosed with ELISA for IgM antibodies [3].

Investigations to classify post-CHIKV chronic arthritis

Testing for autoantibodies helps in classifying post-CHIKV chronic arthritide syndromes. Patients with symmetrical polyarthritis can have RF and anti-CCP antibodies tested [18, 19, 35]. A total of 57% of patients with symmetric polyarthritis resembling classical RA had significant titres of RF and 28% had positive anti-CCP in a study from Reunion Island [54].

Table 5. Investigations of chikungunya infection

Parameters	Derangements observed
Specific investigations	
RT-PCR for viral RNA	Viral RNA detected during the acute febrile phase of infection
Anti-CHIKV serology	IgM antibodies detected in the acute and subacute phases IgG antibodies detected in the chronic phase
Supportive investigations	
Complete blood count	Anaemia, leucocytopenia, thrombocytopenia
Acute phase reactants	Elevated ESR, CRP, IL-6
Liver function tests	Elevated SGPT and SGOT
Musculoskeletal ultrasound	Synovitis, tenosynovitis, bursitis
Plain radiographs	Joint erosion in chronic disease

SGPT: serum glutamic pyruvic transaminase; SGPT: serum glutamic oxaloacetic transaminase.

Whether such patients already have positive antibodies and CHIKV infection triggered their arthritis or the positive antibody response is the result of immune aberration caused by the infection is unclear. Patients with axial symptoms, psoriasis, enthesitis or dactylitis may test positive for HLA-B27 [18, 19]. Those with suspected myositis and connective tissue disease require testing for ANA.

Other investigations to support the diagnosis of CHIKV

Acute CHIKV infection gives rise to several abnormalities in haematological and biochemical parameters. Mild anaemia, leucocytopenia, thrombocytopenia, transaminitis and elevated levels of serum IL-6 are commonly observed. ESR and CRP are invariably elevated during the acute phase of the infection. Patients with active arthritis in the chronic phase also have elevated levels of ESR and CRP (Table 5).

Treatment

Treatment varies according to the phase of the disease [55] (Tables 6–8). French and Brazilian guidelines have been published for the management of acute CHIKV infection and its chronic sequelae [18, 19].

Acute phase

The alleviation of fever and pain is the primary objective of treatment in this phase (Table 6). The risk of drug-related adverse effects is higher in the initial febrile phase of the disease. A very careful approach in treating the symptoms and preventing iatrogenic complications is necessary. Therefore, a limited number of drugs may be used with extreme caution. Once the fever has abated, drugs may be used more generously for the control of musculoskeletal signs and symptoms.

Fever, nausea and vomiting are treated with acetaminophen, proton-pump inhibitors and antiemetic agents like dopamine antagonists or serotonin receptor antagonists. The effect of acetaminophen on pain control is modest. Tramadol

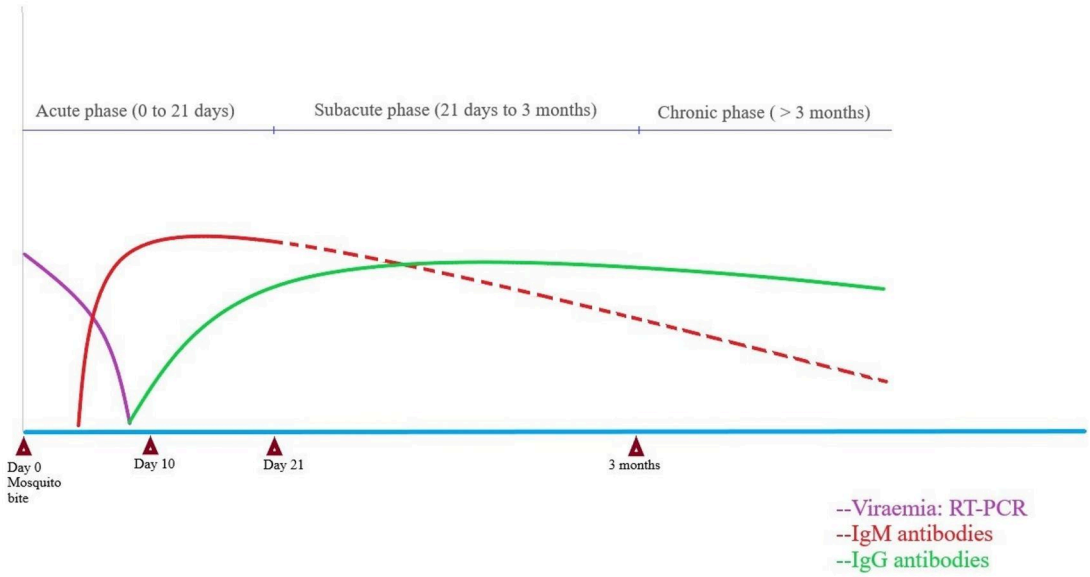


Figure 2. Diagnosis of CHIKV infection during different phases of the disease. Viraemia occurs in the initial febrile phase of 7 days, in which the diagnosis is made by detecting viral RNA by RT-PCR (purple curve). Anti-CHIKV IgM antibodies are detectable in serum by day 5 of infection until day 21, suggestive of acute infection (red curve). However, the persistence of low-grade infection in endemic areas may result in long-term detection of IgM antibodies (breached red curve). IgG antibodies appear in serum by day 7 of infection and are detectable long-term (green curve)

Table 6. Medications used for musculoskeletal manifestations of the acute phase of CHIKV infection

Drug	Usage
Acetaminophen	In the febrile phase: for pain and fever. Up to 4 g/day
Opioids	In the febrile phase: for pain refractory to acetaminophen. Tramadol up to 200 mg/day
NSAIDs	In the afebrile phase: for pain. Doses as per the NSAID index [56]

may be used in these patients [55]. However, the use of NSAIDs should be restricted until dengue is ruled out. This is because Reye's syndrome (acute toxic hepatitis) may result when NSAIDs are administered in the presence of dengue infection. In addition, life-threatening haemorrhagic manifestations may result from the use of NSAIDs in dengue [18]. It is not always possible to rule out dengue coinfection, which is not an uncommon occurrence in endemic areas. Therefore, NSAIDs should be used very carefully during the acute febrile phase of CHIKV infection.

NSAIDs can be readily used after the disappearance of fever. The use of glucocorticoids should be restricted during both the febrile and afebrile stages of the acute phase, as it may increase the chances of viral persistence. Moreover, a significant rebound of arthralgia and frank arthritis occurs after cessation of a short course of glucocorticoids. DMARDs are not recommended in the acute phase [19].

Subacute phase

If the musculoskeletal symptoms persist during the subacute phase, NSAIDs or a short course of glucocorticoids may be used (Table 7). Oral prednisolone equivalent in a dose of 0.3–0.5 mg/kg body weight with rapid tapering over a maximum of 4 weeks may be used [18, 30]. A depot preparation of injectable methylprednisolone, 1–1.5 mg/kg body weight administered as a weekly intramuscular injection for 4 consecutive weeks, is an alternative that allows a lower cumulative dose of the steroid, and due to dependence on healthcare professionals for administering the injection, reducing the potential for abuse. A glucocorticoid burst may have to be followed by a short course of NSAIDs to prevent the rebound of arthritis [18]. The majority of patients recover with these regimens and go into drug-free remission.

Chronic phase

Objectives of treatment in this phase are providing relief in pain and inflammation; preventing stiffness, joint damage and loss of muscle tone; and limiting the long-term consequences of the inflammatory process (Table 8). Treatment varies according to the type of musculoskeletal syndrome.

Glucocorticoids in moderate doses with rapid tapering according to the clinical response along with DMARDs are effective in the majority of patients. We have previously shown that treatment with triple therapy of MTX, SSZ and HCQ is effective for polyarthritis resembling RA [57]. MTX and HCQ have been a preferred initial DMARD combination [57, 58]. LEF and tofacitinib may be used in those with inadequate response or drug intolerance. Some patients have refractory disease and may need biologic DMARDs, with TNF-α inhibitors being the first-line agents [18, 19]. Intra-articular or soft-tissue injection of a glucocorticoid can be used for refractory arthritis, enthesitis or carpal tunnel syndrome. SSZ and TNF-α inhibitors are used for axial SpA variants of post-CHIKV arthritis.

Table 7. Medications used for musculoskeletal manifestations of the subacute phase of CHIKV infection

Drug	Usage
Glucocorticoids	For severe inflammation in joints: a short glucocorticoid 'burst' therapy Oral glucocorticoids: prednisolone equivalent 0.3–0.5 mg/kg body weight with rapid tapering over a maximum of 4 weeks Injectable glucocorticoids: depot preparation of methylprednisolone 1–1.5 mg/kg body weight administered as a weekly intramuscular injection for 4 consecutive weeks

Table 8. Medications used for musculoskeletal manifestations of the chronic phase of CHIKV infection

Drug	Usage
NSAIDs	For pain as a rescue therapy in patients on DMARDs Doses as per the NSAID index [56]
Glucocorticoids	For severe inflammation in joints: a short glucocorticoid 'burst' therapy may be used as a 'bridging' therapy until the onset of action of DMARDs is seen Oral glucocorticoids: prednisolone equivalent 0.3–0.5 mg/kg body weight with rapid tapering over a maximum of 4 weeks Injectable glucocorticoids: depot preparation of methylprednisolone 1–1.5 mg/kg body weight administered as a weekly intramuscular injection for 4 consecutive weeks
MTX	15–25 mg once a week
HCQ	400 mg/day
LEF	10–20 mg once daily
SSZ	Up to 3 g/day
Tofacitinib	5 mg twice daily
Biologic DMARDs	TNF-α inhibitors
Antiepileptics, TCAs, SNRIs	Pregabalin, duloxetine, fluoxetine, amitriptyline, gabapentin

TCAs: tricyclic antidepressants; SNRIs: serotonin norepinephrine reuptake inhibitors.

A retrospective study reported significant improvement in arthritis with a combination of MTX and/or LEF, and dexamethasone, administered for 4 weeks. Clinical improvement was persistent 5 months after discontinuation of the treatment. This appears to be the effect of the short dexamethasone therapy alone, as MTX and LEF show their immunomodulatory effects only after several weeks of treatment [59].

For post-CHIKV FM, pregabalin and duloxetine are the preferred therapeutic agents. Fluoxetine and amitriptyline may be used in patients with refractory neuropathic symptoms [55].

Many patients with chronic arthritis may require long-term treatment. Data on the tapering of treatment is insufficient; it may be attempted in those with sustained remission [30]. In the absence of specific tools for chronic CHIKV arthritis, standard tools for assessing disease activity for RA, such as the 28-joint DAS with ESR or CRP, can be used to

classify a patient in remission. If CHIKV infection develops in a patient with pre-existing rheumatological disease, there is no need to discontinue the ongoing DMARDs during the acute viral infection [60].

On the whole, management of CHIKV infection and its complications remains far from optimum. As yet, no antiviral drugs are available that control the infection in the initial stage, thereby preventing long-term immune-mediated complications. Moreover, the clinical and laboratory parameters used for predicting evolution into chronic musculoskeletal syndromes have low specificity. This uncertainty results in either overtreatment of patients with potentially self-limiting disease or undertreatment of those progressing to chronic arthritis. With a lack of specific guidelines and treatment protocols, many such patients are initiated on DMARDs, without achieving any relevant benefit. Moreover, there is no clarity on the duration of treatment with DMARDs in patients with chronic sequelae and treatment tapering and withdrawal remain at the discretion of the treating clinician. Therefore, there is an urgent need for relevant guidelines addressing the aforementioned areas.

Prevention

Control of vector reproduction is an important aspect of controlling the disease at an epidemiological level before it reaches the human host. Elimination of areas of fresh water collection is an indispensable step, as these are the sites of mosquito breeding. In addition, the development of larvae through the stages of pupa and adult also occurs in collected fresh water. Application of insecticides/larvicides in areas of collected water can kill the developing larvae. Insecticides are also directed against the adult mosquitoes. In addition, prevention of mosquito bites as a self-defence mechanism can be used to prevent acquiring the infection. The use of clothing and local application of mosquito-repelling agents like diethyl toluamide on exposed body parts are some of the measures [1].

Future directions

A live-attenuated single-dose vaccine (IXCHIQ) was approved by the US Food and Drug Administration in November 2023 for the prevention of CHIKV infection for adult (≥18 years of age) travellers who are at higher risk of exposure or increased risk of severe disease. It was found to be efficacious and safe in a randomized prospective trial [61, 62]. Various therapeutic agents for the treatment of acute CHIKV infection have been tried in preclinical and animal studies. However, none of them has demonstrated sufficient evidence of efficacy and safety in humans. Based on the immunological mechanisms of chronic arthritis related to CHIKV, various targeted treatment modalities might have important treatment implications. Fingolimod is a sphingosine-1-phosphate receptor agonist that is found on CD-4$^+$ T lymphocytes. Animal studies have shown that it inhibits the influx of CD-4$^+$ T cells to the joints, thereby reducing inflammation [63]. Targeting monocyte chemotactic protein or C-C chemokine receptor type 2 by bindarit inhibits CHIKV-induced loss of bone in mice [64]. Pentosan polysulphate sodium (PPS) is a glycosaminoglycan that helps in reducing the circulating levels of pro-inflammatory cytokines like IL-6, IL-9, GM-CSF and MCP-1. Reduced joint inflammation was histologically demonstrated in mice infected with CHIKV upon administration of PPS [65]. Treatment with a combination of abatacept (a T cell co-stimulation inhibitor) and an anti-CHIKV neutralizing antibody has shown promising results in animal studies [66]. HCQ's efficacy has been tested and attempts have been made to extrapolate it against other viruses such as coronavirus [67]. Suramin, an anti-trypanosomiasis drug, and its derivatives have been shown to inhibit the replication of CHIKV [68]. Ribavirin (a nucleoside analogue) has shown some benefit in underpowered studies in human subjects [69, 70]. Micafungin is an antifungal drug that has been shown to inhibit CHIKV replication [71]. Ivermectin, an antiparasitic drug, has been postulated to have antiviral activity in addition to its well-known insecticidal properties against mosquitoes [72]. Non-structural proteins 1 and 2 (nsP1 and nsP2, respectively) are important in the virulence and replication of CHIKV. Development of inhibitors of nsP1 and nsP2 appears to be an attractive area of study [73, 74].

Conclusion

While other arboviral arthritides leave no sequelae and require only symptomatic treatment, CHIKV infection poses a significant epidemiological concern worldwide due to its chronic post-infectious musculoskeletal consequences. Inflammatory burden in the chronic phase can be significant enough to require long-term treatment with immunomodulatory agents. Diagnosis and treatment in the chronic phase are challenging due to the diversity of clinical features and negative results for autoimmune markers in several patients. Future research is desirable to address various unmet needs in CHIKV-related musculoskeletal syndromes. The development of biomarkers that can predict development of the chronic inflammatory phase is much needed, as it will identify patients who should be treated with immunomodulatory therapy. Second, studies evaluating the role of biologic DMARDs and small molecules such as Janus kinase inhibitors in patients with refractory chronic disease would be most helpful. Third, evidence-based standardized guidelines addressing all aspects of management, including diagnosis and treatment, are needed. Fourth, research to develop effective antiviral agents against CHIKV with the potential to control the disease and its long-term immune-mediated consequences is needed. Lastly, as the only effective way to prevent long-term chronic complications of the disease is to prevent getting infected by CHIKV, control of the vector and vaccination against CHIKV are promising strategies but have a long way to go.

Data availability

No new data were generated or analysed in support of this article.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors declare no conflicts of interest.

References

1. Barrett ADT, Weaver SC. Arboviruses: alphaviruses, flaviviruses and bunyaviruses: encephalitis; yellow fever; dengue; haemorrhagic fever; miscellaneous tropical fevers; undifferentiated fever.

In: D Greenwood, M Barer, R Slack, W Irving, eds. Medical microbiology. 18th edn. Edinburgh: Churchill Livingstone, 2012:520–36.
2. Bartholomeeusen K, Daniel M, LaBeaud DA *et al.* Chikungunya fever. Nat Rev Dis Primers 2023;9:17.
3. Mathew AJ, Ravindran V. Infections and arthritis. Best Pract Res Clin Rheumatol 2014;28:935–59.
4. Rama K, de Roo AM, Louwsma T *et al.* Clinical outcomes of chikungunya: a systematic literature review and meta-analysis. PLoS Negl Trop Dis 2024;18:e0012254.
5. Monge S, García-Ortúzar V, López Hernández B *et al.* Characterization of the first autochthonous dengue outbreak in Spain (August–September 2018). Acta Trop 2020;205:105402.
6. Calvez E, Pocquet N, Malau A *et al.* Assessing entomological risk factors for arboviral disease transmission in the French Territory of the Wallis and Futuna Islands. PLoS Negl Trop Dis 2020; 14:e0008250.
7. Ng DH, Wong JG, Thein TL, Leo YS, Lye DC. The significance of prolonged and saddleback fever in hospitalised adult dengue. PLoS One 2016;11:e0167025.
8. Davies, Alexander J, Lleixà, Cinta, Siles, Ana M, *et al.* Guillain–Barré syndrome following Zika virus infection is associated with a diverse spectrum of peripheral nerve reactive antibodies. Neurol Neuroimmunol Neuroinflamm2023;10:e200047.
9. Pielnaa P, Al-Saadawe M, Saro A *et al.* Zika virus-spread, epidemiology, genome, transmission cycle, clinical manifestation, associated challenges, vaccine and antiviral drug development. Virology 2020;543:34–42.
10. Falcao MB, Cimerman S, Luz KG *et al.* Management of infection by the Zika virus. Ann Clin Microbiol Antimicrob 2016;15:57.
11. Russell RC. Ross River virus: ecology and distribution. Annu Rev Entomol 2002;47:1–31.
12. Suhrbier A, La Linn M. Clinical and pathologic aspects of arthritis due to Ross River virus and other alphaviruses. Curr Opin Rheumatol 2004;16:374–9.
13. Khongwichit S, Chansaenroj J, Chirathaworn C, Poovorawan Y. Chikungunya virus infection: molecular biology, clinical characteristics, and epidemiology in Asian countries. J Biomed Sci 2021; 28:84.
14. Li Z, Wang J, Cheng X *et al.* The worldwide seroprevalence of DENV, CHIKV and ZIKV infection: a systematic review and meta-analysis. PLoS Negl Trop Dis 2021;15:e0009337.
15. Kang H, Auzenbergs M, Clapham H *et al.* Chikungunya seroprevalence, force of infection, and prevalence of chronic disability after infection in endemic and epidemic settings: a systematic review, meta-analysis, and modelling study. Lancet Infect Dis 2024; 24:488–503.
16. Costa LB, Barreto FKdA, Barreto MCA *et al.* Epidemiology and economic burden of chikungunya: a systematic literature review. Trop Med Infect Dis 2023;8:301.
17. van Duijl-Richter MK, Hoornweg TE, Rodenhuis-Zybert IA, Smit JM. Early events in chikungunya virus infection-from virus cell binding to membrane fusion. Viruses 2015;7:3647–74.
18. Simon F, Javelle E, Cabie A *et al.* French guidelines for the management of chikungunya (acute and persistent presentations). Med Mal Infect 2014; 2015;45:243–63.
19. Marques CDL, Duarte ALBP, Ranzolin A *et al.* Recommendations of the Brazilian Society of Rheumatology for diagnosis and treatment of chikungunya fever. Part 1 – diagnosis and special situations. Rev Bras Reumatol (Engl Ed) 2017;57(Suppl 2):421–37.
20. Wauquier N, Becquart P, Nkoghe D *et al.* The acute phase of chikungunya virus infection in humans is associated with strong innate immunity and T CD8 cell activation. J Infect Dis 2011; 204:115–23.
21. Albert LJ, Inman RD. Molecular mimicry and autoimmunity. N Engl J Med 1999;341:2068–74.
22. Hoarau J-J, Jaffar Bandjee M-C, Krejbich Trotot P *et al.* Persistent chronic inflammation and infection by chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 2010;184:5914–27.
23. Berthelot JM, Sibilia J. Rampant infections of bone marrow stem cell niches as triggers for spondyloarthropathies and rheumatoid arthritis. Clin Exp Rheumatol 2016;34:329–36.
24. Chang AY, Martins KAO, Encinales L *et al.* Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. Arthritis Rheumatol 2018;70:585–93.
25. de Aguiar GPCG, Leite CMGdS, Dias B *et al.* Evidence for host epigenetic signatures arising from arbovirus infections: a systematic review. Front Immunol 2019;10:1207.
26. Thanapati S, Ganu M, Giri P *et al.* Impaired NK cell functionality and increased TNF-α production as biomarkers of chronic chikungunya arthritis and rheumatoid arthritis. Hum Immunol 2017;78:370–4.
27. Phuklia W, Kasisith J, Modhiran N *et al.* Osteoclastogenesis induced by CHIKV-infected fibroblast-like synoviocytes: a possible interplay between synoviocytes and monocytes/macrophages in CHIKV-induced arthralgia/arthritis. Virus Res 2013;177:179–88.
28. Roosenhoff R, Anfasa F, Martina B. The pathogenesis of chronic chikungunya: evolving concepts. Future Virol 2016;11:61–77.
29. El-Jawhari JJ, El-Sherbiny YM, Jones EA, McGonagle D. Mesenchymal stem cells, autoimmunity and rheumatoid arthritis. QJM 2014;107:505–14.
30. Zaid A, Gérardin P, Taylor A *et al.* Chikungunya arthritis: implications of acute and chronic inflammation mechanisms on disease management. Arthritis Rheumatol 2018;70:484–95.
31. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.
32. Taneja V. Cytokines pre-determined by genetic factors are involved in pathogenesis of Rheumatoid arthritis. Cytokine 2015; 75:216–21.
33. Getts MT, Miller SD. 99th Dahlem Conference on Infection, Inflammation and Chronic Inflammatory Disorders: triggering of autoimmune diseases by infections. Clin Exp Immunol 2010; 160:15–21.
34. Perl A. Mechanisms of viral pathogenesis in rheumatic disease. Ann Rheum Dis 1999;58:454–61.
35. Pathak H, Mohan MC, Ravindran V. Chikungunya arthritis. Clin Med (Lond) 2019;19:381–5.
36. Pinheiro TJ, Guimarães LF, Silva MT, Soares CN. Neurological manifestations of chikungunya and Zika infections. Arq Neuropsiquiatr 2016;74:937–43.
37. Manimunda SP, Vijayachari P, Uppoor R *et al.* Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging. Trans R Soc Trop Med Hyg 2010;104:392–9.
38. Chopra A, Anuradha V, Lagoo-Joshi V *et al.* Chikungunya virus aches and pains: an emerging challenge. Arthritis Rheum 2008; 58:2921–2.
39. Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. I. Clinical features. Trans R Soc Trop Med Hyg 1955;49:28–32.
40. Staikowsky F, Talarmin F, Grivard P *et al.* Prospective study of chikungunya virus acute infection in the Island of La Réunion during the 2005–2006 outbreak. PLoS One 2009;4:e7603.
41. Amaral JK, Bilsborrow JB, Schoen RT. Chronic chikungunya arthritis and rheumatoid arthritis: what they have in common. Am J Med 2020;133:e91–7.
42. Kularatne SAM, Weerasinghe SC, Gihan C *et al.* Epidemiology, clinical manifestations, and long-term outcomes of a major outbreak of chikungunya in a hamlet in Sri Lanka, in 2007: a longitudinal cohort study. J Trop Med 2012;2012:639178.
43. Chopra A, Anuradha V, Ghorpade R, Saluja M. Acute chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. Epidemiol Infect 2012;140:842–50.
44. Tritsch SR, Encinales L, Pacheco N *et al.* Chronic joint pain 3 years after chikungunya virus infection largely characterized by relapsing-remitting symptoms. J Rheumatol 2020;47:1267–74.

45. Rodríguez-Morales AJ, Cardona-Ospina JA, Fernanda Urbano-Garzón S, Sebastian Hurtado-Zapata J. Prevalence of post-chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2016;68:1849–58.
46. Brighton SW, Prozesky OW, de la Harpe AL. Chikungunya virus infection. A retrospective study of 107 cases. S Afr Med J 1983; 63:313–5.
47. Malvy D, Ezzedine K, Mamani-Matsuda M *et al.* Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. BMC Infect Dis 2009;9:200.
48. Marques C, Cavalcanti N, Luna M *et al.* Chikungunya fever outbreak in Brazil: preliminary assessment in a cohort of patients with rheumatological manifestations. Arthritis Rheumatol 2016;68:abstract 1320.
49. Blettery M, Brunier L, Polomat K *et al.* Brief report: management of chronic post-chikungunya rheumatic disease: the Martinican experience. Arthritis Rheumatol 2016;68:2817–24.
50. Tuão RC, Macabú MdO, Athayde PDS *et al.* Antisynthetase syndrome after chikungunya infection: a case report. Clin Case Rep 2022;10:e05877.
51. Dev N, Kumar R, Gogna A, Sharma S. Chikungunya-induced inflammatory myositis: a case report in India. Trop Doct 2019; 49:241–3.
52. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med 2015;372:1231–9.
53. Costa DMdN, Coêlho MRCD, Gouveia PAdC *et al.* Long-term persistence of serum-specific anti-chikungunya IgM antibody—a case series of Brazilian patients. Rev Soc Bras Med Trop 2021;54:e0855.
54. Bouquillard E, Combe B. A report of 21 cases of rheumatoid arthritis following chikungunya fever. A mean follow-up of two years. Joint Bone Spine 2009;76:654–7.
55. Webb E, Michelen M, Rigby I *et al.* An evaluation of global chikungunya clinical management guidelines: a systematic review. EClinicalMedicine 2022;54:101672.
56. Dougados M, Simon P, Braun J *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis 2011;70:249–51.
57. Ravindran V, Alias G. Efficacy of combination DMARD therapy vs. hydroxychloroquine monotherapy in chronic persistent chikungunya arthritis: a 24-week randomized controlled open label study. Clin Rheumatol 2017;36:1335–40.
58. Pandya S. Methotrexate and hydroxychloroquine combination therapy in chronic chikungunya arthritis: a 16-week study. Indian J Rheumatol 2008;3:93–7.
59. Amaral JK, Bingham CO, Taylor PC *et al.* Therapy for chikungunya arthritis: a study of 133 Brazilian patients. Am J Trop Med Hyg 2023;109:542–7.
60. Rosario V, Munoz-Louis R, Valdez T *et al.* Chikungunya infection in the general population and in patients with rheumatoid arthritis on biological therapy. Clin Rheumatol 2015;34:1285–7.
61. Schneider M, Narciso-Abraham M, Hadl S *et al.* Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2023;401:2138–47.
62. US Food and Drug Administration. FDA approves first vaccine to prevent disease caused by chikungunya virus. https://www.fda.gov/ news-events/press-announcements/fda-approves-first-vaccineprevent- disease-caused-chikungunya-virus (16 November 2023, date last accessed).
63. Teo T-H, Chan Y-H, Lee WWL *et al.* Fingolimod treatment abrogates chikungunya virus-induced arthralgia. Sci Transl Med 2017; 9:eaal1333.
64. Chen W, Foo S-S, Taylor A *et al.* Bindarit, an inhibitor of monocyte chemotactic protein synthesis, protects against bone loss induced by chikungunya virus infection. J Virol 2015;89:581–93.
65. Rudd PA, Lim EXY, Stapledon CJM, Krishnan R, Herrero LJ. Pentosan polysulfate sodium prevents functional decline in chikungunya infected mice by modulating growth factor signalling and lymphocyte activation. PLoS One 2021;16:e0255125.
66. Miner JJ, Cook LE, Hong JP *et al.* Therapy with CTLA4-Ig and an antiviral monoclonal antibody controls chikungunya virus arthritis. Sci Transl Med 2017;9:eaah3438.
67. Khan M, Santhosh SR, Tiwari M, Lakshmana Rao PV, Parida M. Assessment of in vitro prophylactic and therapeutic efficacy of chloroquine against chikungunya virus in vitro cells. J Med Virol 2010;82:817–24.
68. Henß L, Beck S, Weidner T *et al.* Suramin is a potent inhibitor of chikungunya and Ebola virus cell entry. Virol J 2016;13:149.
69. Ravichandran R, Manian M. Ribavirin therapy for chikungunya arthritis. J Infect Dev Ctries 2008;2:140–2.
70. Mishra P, Kumar A, Mamidi P *et al.* Inhibition of chikungunya virus replication by 1-[(2-methylbenzimidazol-1-yl) methyl]-2-oxo-indolin-3-ylidene] amino] thiourea (MBZM-N-IBT). Sci Rep 2016;6:20122.
71. Ho Y-J, Liu F-C, Yeh C-T *et al.* Micafungin is a novel anti-viral agent of chikungunya virus through multiple mechanisms. Antiviral Res 2018;159:134–42.
72. Dong S, Kang S, Dimopoulos G. Identification of anti-flaviviral drugs with mosquitocidal and anti-Zika virus activity in *Aedes aegypti*. PLoS Negl Trop Dis 2019;13:e0007681.
73. Lampio A, Ahola T, Darzynkiewicz E *et al.* Guanosine nucleotide analogs as inhibitors of alphavirus mRNA capping enzyme. Antiviral Res 1999;42:35–46.
74. Gigante A, Gómez-SanJuan A, Delang L *et al.* Antiviral activity of [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones against chikungunya virus targeting the viral capping nsP1. Antiviral Res 2017;144:216–22.

Rheumatology Advances in Practice, 2025, 9, 1–11
https://doi.org/10.1093/rap/rkaf029
Review