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REVIEW ARTICLE

Immunopathogenic mechanisms in chronic chikungunya arthritis

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ABSTRACT

This narrative review aims to analyze the immunopathogenic evidence explaining chronic chikungunya arthritis (CCA), integrating findings on the initial cytokine storm, the transition to chronicity, and the mechanisms of viral persistence versus autoimmunity. It concludes that CCA is primarily driven by CHIKV persistence in synovial macrophages, which maintains a chronic inflammatory state dominated by IL-6 and IL-1β, with a serological profile (anti-CCP negative) distinct from that of rheumatoid arthritis. The evidence supports a model in which persistent viral inflammation recruits local immunopathological mechanisms. These findings justify rethinking therapeutic strategies toward approaches that combine antiviral control with specific cytokine modulation, such as IL-6 blockade.

Keywords: Chikungunya Fever; Arthritis; Inflammation; Interleukin-6; Interleukin-1; Antivirals.

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INTRODUCTION

The Chikungunya virus (CHIKV) constitutes a global public health threat, characterized by explosive outbreaks and growing geographic expansion. Since its initial isolation in Tanzania in 1952, the virus, a reemerging alphavirus of the family Togaviridae, has protagonized epidemics in Africa, Asia, and, more recently, in the Americas and Europe. This dissemination has been facilitated by its adaptation to the vector Aedes albopictus through the E1-A226V mutation, which allows it to establish itself in temperate climate regions.[1]

According to recent epidemiological data, the chikungunya virus has shown significant expansion in the Region of the Americas, with explosive outbreaks that have strongly impacted public health. In Paraguay, during the first eight epidemiological weeks of 2023, 115,539 cases and 33 deaths were reported, registering the highest incidence rate in the region (1,128 cases per 100,000 inhabitants).[2] Brazil has consolidated as the regional epicenter, with more than 1.6 million cases reported since 2014 and continuous annual epidemics, mainly affecting states such as São Paulo, Pernambuco, and Paraíba. The geographic distribution also includes Argentina, which in 2023 reported more than 1,700 cases, and other countries such as Bolivia, Colombia, Peru, and Caribbean nations, where transmission remains active with recurrent outbreaks.[3]

The greatest socioeconomic burden of CHIKV infection does not lie in its acute phase—characterized by high fever and severe polyarthralgia—but in its chronic phase.[4,5] Rigorous epidemiological studies indicate that an alarming proportion of patients (up to 30 %) experience persistent or recurrent musculoskeletal symptoms months after the initial infection.[1]

A distinctive characteristic of CHIKV is its unique propensity among arboviruses to induce debilitating chronic polyarthritis (CCA). This condition can persist for months or years and presents a clinical phenotype that mimics that of Rheumatoid Arthritis (RA).

The transition to chronicity in CHIKV infection poses a fundamental immunological paradox. Whereas in most acute viral infections a robust humoral response and memory cellular immunity lead to pathogen elimination and resolution of inflammation, in CCA synovial inflammation persists despite such an effective immune response.

This phenomenon has led to the formulation of two competing, but not mutually exclusive, pathogenic hypotheses:

- Viral Persistence: The virus manages to evade complete eradication, establishing niches of low-level replication or RNA persistence in joint tissues (synovium, muscle, bone).
- Post-Infectious Autoimmunity: The acute infection triggers a breakdown of immunological tolerance through molecular mimicry or bystander activation, perpetuating inflammation in the absence of the virus.

Discerning between these mechanisms is not merely an academic exercise, but has direct implications for the development of rational therapeutic strategies, whether aimed at eliminating viral reservoirs or at modulating aberrant autoimmune responses. The objective of this review is to describe the immunological evidence, with a focus on cytokine profiles in synovial and peripheral fluids, that supports the hypotheses of viral persistence and autoimmunity in CCA.

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DEVELOPMENT

Immunobiology of the Acute Phase: The Cytokine Storm The innate immune response triggered during the first days of CHIKV infection is a critical determinant of the long-term clinical course, setting the stage for resolution or transition to chronicity. Following viral entry into dermal fibroblasts and its systemic dissemination, viral RNA is detected by pattern recognition receptors (PRRs), such as TLR3, TLR7, TLR8, and the cytosolic sensors RIG-I and MDA5. This detection induces massive production of type I interferon (IFN-α/β) and triggers a broad cascade of proinflammatory cytokines, a phenomenon often termed "cytokine storm".[6]

Serum profiles during this acute phase reveal significant elevations of classic proinflammatory cytokines (IL-6, IL-1β, TNF-α), cytokines associated with Th1/Th17 responses (IFN-γ, IL-12, IL-17A), chemokines such as MCP-1 (CCL2), RANTES (CCL5), IP-10 (CXCL10), and IL-8 (CXCL8), and growth factors such as G-CSF and GM-CSF.[7]

There is scientific debate regarding whether this intense cytokine response in the acute phase is predominantly beneficial or detrimental, with evidence pointing to a delicate balance. On one hand, a robust and early response appears essential for effective viral control and prevention of chronic sequelae. A key study observed that elevated levels of IL-6, IL-1β, and TNF-α during acute infection correlated with a lower incidence of long-term chronic joint pain.[8,9]

It is proposed that intense and effective acute inflammation, mediated by a Th1/proinflammatory profile, achieves complete tissue sterilization, thereby eliminating potential viral reservoirs. Conversely, attenuated responses or those biased toward a tolerance/Th2 profile (with low levels of effector cytokines or presence of IL-4, IL-13) during the acute phase have been predictive of the development of chronic arthritis, suggesting that an insufficient immune response may facilitate viral persistence.[8]

On the other hand, various studies associate excessively high levels of IL-6 and IL-1β in the acute phase with greater initial clinical severity and markers of poor prognosis. Ng et al.,[10] demonstrated that acute disease severity correlates with increased IL-1β and IL-6 and, crucially, with a decrease in RANTES (CCL5). This reduction in RANTES could reflect a failure in the recruitment of effector T cells necessary for final viral control or massive consumption of the chemokine in inflamed tissues. Likewise, Roques P, et al.,[11] found that a high viral load is associated with elevated levels of proinflammatory cytokines, and that this "storm" contributes directly to tissue damage through immunopathology.

The resolution of this apparent contradiction likely resides in the kinetics and specificity of the response. An early and robust activation of type I IFN and Th1 cytokines is clearly protective. However, if the virus is not rapidly eliminated, the persistence of elevated levels of mediators such as IL-6 and IL-1β beyond the immediate acute phase ceases to be beneficial and becomes a driver of joint damage and chronicity.

Cytokine Dynamics in the Transition to Chronicity

The transition period between acute infection (weeks 1-2) and established chronic phase (>3 months) constitutes a critical phase in which the patient's joint fate is defined. During this interval, the cytokine profile undergoes significant evolution, transitioning from a generalized systemic inflammatory response toward the configuration of a specific and localized inflammatory microenvironment within the joint space.

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Interleukin-6 (IL-6)

Among the implicated cytokines, IL-6 emerges from multiple longitudinal studies as the most consistent and relevant biomarker in progression toward chronic chikungunya arthritis (CCA). Unlike other mediators that return to baseline levels, IL-6 shows selective persistence, remaining elevated in serum and synovial fluid of patients with arthralgias months after the initial infection.[11] This elevation strongly correlates in the subacute phase with the intensity of joint pain, morning stiffness, and persistence of symptoms.[12] Beyond its value as a marker, IL-6 acts as a central pathogenic effector: it stimulates the synthesis of C-reactive protein and fibrinogen, promotes the differentiation of B cells toward plasmablasts—which explains hypergammaglobulinemia and persistence of IgM—, induces polarization of T lymphocytes toward the Th17 lineage, thereby perpetuating inflammation of autoimmune characteristics, and activates osteoclasts, establishing a direct link between inflammation and bone erosion.[13]

IL-1β

Interleukin-1β (IL-1β), a product of NLRP3 inflammasome activation, plays a critical role in chronicity, despite the fact that its systemic levels may show greater fluctuation compared to those of IL-6. The persistence of this cytokine suggests continuous activation of the innate immune system within the joint, likely in response to endogenous danger signals (DAMPs) derived from tissue damage or pathogen-associated molecular patterns (PAMPs) originating from persistent viral RNA.[1] Furthermore, IL-1β acts as a potent mediator of pain, by sensitizing peripheral nociceptors and contributing significantly to the hyperalgesia and allodynia characteristic of patients in the chronic phase.

TNF-α

Unlike what is observed in rheumatoid arthritis (RA), where tumor necrosis factor alpha (TNF-α) acts as the dominant cytokine, its profile in chronic chikungunya arthritis (CCA) is more variable. While some studies report normal or only slightly elevated serum levels of TNF-α during the chronic phase—a marked contrast to the sustained elevation of IL-6—,[11] its pathogenic importance should not be underestimated. Even low concentrations of TNF-α can exert synergistic effects with IL-6 and IL-1β, thereby contributing to maintaining activation of synoviocytes and the consequent degradation of the cartilaginous matrix.[14]

Chemokines

Chemokines contribute fundamentally to persistent joint inflammation in CCA through the continuous recruitment of leukocytes. The chemokine MCP-1 (CCL2) remains elevated in chronic patients, facilitating the sustained recruitment of inflammatory monocytes (CD14+CD16+) to the synovium. These cells not only perpetuate the inflammatory cycle but also act as precursors of osteoclasts, directly linking cellular recruitment with bone destruction.[15] In parallel, the persistent elevation of IL-8 (CXCL8) ensures neutrophil infiltration into the joint space. Once recruited, neutrophils release proteolytic enzymes, such as elastases and metalloproteinases, which contribute directly to articular cartilage damage.[7]

Viral Persistence

The understanding of CHIKV pathogenesis has undergone a fundamental paradigm shift in the last decade, transitioning from the model of a "hit-and-run" virus toward recognition of its capacity to establish long-term tissue persistence. The evidence supporting this new paradigm is multidimensional.

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Histopathological and molecular studies provide conclusive evidence. In non-human primate models, seminal investigations have demonstrated that CHIKV can persist for months in lymphoid tissues, liver, and, crucially, in joints, with detection of viral RNA and antigens in splenic macrophages up to three months after acute infection.[16] In humans, although more difficult to obtain, the evidence is equally compelling; viral antigens and CHIKV RNA have been identified in synovial macrophages of a patient 18 months after initial infection, and in muscle and synovial tissue of patients with chronic relapses.[17] Advanced single-cell RNA sequencing technologies (scRNA-seq) have specified that infiltrating macrophages in joint tissue constitute the main reservoir, harboring positive- and negative-strand viral RNA—indicative of active replication—and exhibiting a markedly proinflammatory transcriptomic profile.[18]

In this context, the synovial macrophage plays a fundamental dual role. On one hand, it acts as a viral refuge where CHIKV can establish a state of slow replication or latency, thereby evading the circulating neutralizing antibody response. On the other hand, it functions as a cytokine factory; the persistent intracellular presence of viral RNA chronically activates endosomal TLRs, inducing sustained secretion of IL-6, TNF-α, and IL-1β. This generates a positive feedback loop in which the resulting inflammation recruits new monocytes and macrophages to the joint, which in turn become new targets of infection, perpetuating the cycle.[18]

A distinctive serological finding supporting this notion of continuous antigenic persistence is the prolonged detection of CHIKV-specific IgM antibodies in CCA. In cohorts of patients with chronic arthritis, IgM has been detected up to 18-24 months after infection.[19] Given the short half-life of IgM, its sustained presence necessarily implies continuous antigenic stimulation, firmly supporting the hypothesis that foci of persistent viral replication periodically release antigens, keeping the B lymphocyte response active.

The Autoimmune Hypothesis

The clinical phenotype of chronic chikungunya arthritis (CCA), notably similar to that of rheumatoid arthritis (RA), justifies rigorous analysis of the possible involvement of autoimmune mechanisms, despite solid evidence pointing to viral persistence. To explain this similarity, several mechanisms of virus-induced autoimmunity have been proposed. One of these is molecular mimicry, whereby it is postulated that the E1 protein of CHIKV shares sequence homology with host autoantigens (such as heat shock proteins or cartilage components), potentially triggering a cross-reactive T cell response against these tissues.[20] Another mechanism is bystander activation, where the proinflammatory cytokine-rich microenvironment (IL-6, IL-12) generated during infection lowers the activation threshold of preexisting autoreactive T lymphocytes.[21] Finally, initial tissue destruction could induce epitope spreading, releasing cryptic neoantigens from cartilage and initiating a secondary autoimmune response independent of the virus.

However, if CCA were a classic autoimmune disease triggered by the virus, the presence of characteristic autoantibodies would be expected, an assumption that laboratory findings contradict for the majority of patients. The most specific marker of RA, the anti-cyclic citrullinated peptide antibody (anti-CCP), shows very low or null prevalence (<1-5 %) in CCA, as reported by the vast majority of studies.[19] This absence constitutes a key differentiator, indicating that CCA is not pathogenically a classic seropositive RA. Regarding rheumatoid factor (RF) positivity, it is variable among studies (reported in up to 25-50 % in some series, but <10 % in others).[22] Nevertheless, RF is a nonspecific marker that can be elevated in various chronic viral infections due to polyclonal activation of B lymphocytes, without necessarily denoting a specific autoimmune joint pathology.[19]

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There is an exception in a small subgroup of patients who develop classic RA de novo (with positive anti-CCP) following CHIKV infection. It is hypothesized that in these genetically susceptible individuals (for example, carriers of the shared epitope HLA-DRB1), the virus would act as an environmental trigger that reveals latent autoimmunity.[8]

In conclusion, the available evidence favors the concept that CCA is, in most cases, a persistent inflammatory arthritis of viral etiology that clinically mimics RA, rather than a bona fide classic autoimmune disease. The lack of specific autoantibodies, particularly anti-CCP, represents the strongest argument against a purely autoimmune hypothesis.

Synthesis and Integrated
Model The immunological evidence reviewed dispels the apparent dichotomy between the hypotheses of viral persistence and autoimmunity in chronic Chikungunya arthritis (CCA). Instead, an integrated and dynamic pathogenic model emerges in which viral persistence acts as the primary inflammatory driver, and phenomena of local autoimmunity or immunopathology are amplifying consequences, not initial causes. This synthesis reconciles seemingly contradictory findings and has profound implications.

The axis of the model is the capacity of CHIKV to establish foci of low-level persistent replication in synovial macrophages and (possibly) osteoblasts. This reservoir is not inert. The continuous presence of viral RNA in endosomes chronically activates TLRs (TLR3/7/8), transforming these cells into "sustained factories" of proinflammatory cytokines, mainly IL-6 and IL-1β. This joint microenvironment, chronically enriched in these cytokines, creates a state of "sterile inflammation"—persistent and tissually destructive, but driven by a remnant viral antigenic stimulus, not by classic autoantigens. The prolonged detection of anti-CHIKV IgM is the serological hallmark of this process.

In this context of virus-driven chronic inflammation, classic autoimmune mechanisms may be recruited as pathological amplifiers, but they are not necessarily initiators:

- Bystander activation: the environment rich in IL-6, IL-1β, and IL-23 favors the differentiation of T lymphocytes toward a Th17 profile and lowers the activation threshold of autoreactive T lymphocytes, which may attack damaged joint tissues.
- Limited Molecular Mimicry: although it has been postulated, the lack of specific autoantibodies (anti-CCP) suggests that any mimicry is epitope-specific, weak, or transient, insufficient to generate a classic systemic autoimmune response. It may contribute to chronicity in a small subgroup of genetically susceptible individuals (e.g., carriers of HLA-DRB1), who may progress to true RA.
- Immunopathology Vs. Autoimmunity: much of the joint damage (bone erosion, synovitis) can be explained by direct cytokine-mediated immunopathology (IL-6→RANKL→osteoclasts; IL-1β→pain; chemokines→cellular recruitment) without the need for autoantibodies. CCA thus resembles more a chronic post-infectious inflammatory arthropathy than a de novo autoimmune disease.

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Immunological Bases of Manifestations

Bone erosion, one of the most severe consequences of CCA observable radiographically, is an active process driven by the direct interaction between the virus, cytokines, and bone cells. CHIKV possesses the unique capacity to directly infect human osteoblasts, the cells responsible for bone formation. This infection not only induces apoptosis and alters osteoblastic function—decreasing bone mineralization and alkaline phosphatase levels—,[23] but also transforms infected osteoblasts into potent sources of pro-osteoclastogenic cytokines, leading them to secrete elevated levels of IL-6 and receptor activator of nuclear factor kappa-B ligand (RANKL).[24]

Bone remodeling critically depends on the balance between RANKL (a potent promoter of osteoclast differentiation and activation) and its natural inhibitor, osteoprotegerin (OPG). In CCA, this balance is profoundly altered. Key cytokines such as IL-6 and TNF-α massively stimulate RANKL expression in osteoblasts and synovial fibroblasts, while simultaneously suppressing OPG production.[25] The resulting increase in the RANKL/OPG ratio induces the differentiation of monocytes—previously recruited by chemokines such as MCP-1—into mature and active osteoclasts, which degrade the bone matrix and generate characteristic erosions. This process is further potentiated by IL-17, whose elevation in the chronic phase synergizes with TNF-α to induce greater RANKL expression, thus closing a vicious cycle of inflammation and bone destruction.[13]

On the other hand, pain in CCA is often disproportionate to visible joint inflammation and frequently presents neuropathic characteristics, such as burning sensation, electric shocks, and paresthesias. This phenomenon has immunological bases both peripheral and central. In the periphery, cytokines such as IL-6, IL-1β, and TNF-α can bind directly to receptors on sensory nerve endings (nociceptors), lowering their activation threshold and causing hyperalgesia.[1]

Furthermore, the virus or inflammatory signals may induce neuroinflammation in the dorsal root ganglia, where upregulation of pain receptors such as TRPV1 and TLR4 in sensory neurons has been observed. Finally, central sensitization is established: the massive influx of painful signals and cytokines to the spinal cord activates microglia and astrocytes. These glial cells, in turn, release more cytokines and neurotrophic factors (such as BDNF), establishing a state of persistent neuronal hyperexcitability that maintains the sensation of pain even when the peripheral inflammatory stimulus diminishes.[1]

Differentiation is crucial for clinical management. Below, a detailed comparison based on the reviewed evidence is presented (Table 1).

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Table 1. Immunopathogenic and Clinical Comparison between Chronic Chikungunya Arthritis and Rheumatoid Arthritis.

Characteristic	Chronic Chikungunya Arthritis (CCA)	Rheumatoid Arthritis (RA)
Clinical Onset	Abrupt, febrile, explosive ("strike").	Insidious, progressive (weeks/months).
Joint Pattern	Distal symmetric polyarthritis (hands, feet, knees).	Distal symmetric polyarthritis.
Viral Persistence	Yes (Macrophages, Synovium, Muscle).	No (Multifactorial/autoimmune etiology).
Serology (Anti-CCP)	Negative (<5% positive).	Positive (High specificity).
Serology (RF)	Variable (nonspecific, polyclonal activation).	Positive (frequent).
Viral Serology	Persistent anti-CHIKV IgM (+) (months/years).	Negative (unless coincidental).
Dominant Cytokine	IL-6 (+++), IFN-α, IL-1β.	TNF-α (+++), IL-6, IL-1.
Bone Mechanism	Osteoblast infection + IL-6-induced RANKL.	Synovial pannus + Autoantibodies + RANKL.
Response to Steroids	Moderate/Good (but risk of viral rebound).	Excellent.
Response to MTX	Variable/Controversial (see therapeutic section).	Gold Standard (High efficacy).

Therapeutic Implications

The understanding of chronic chikungunya arthritis (CCA) as a disease driven by viral persistence and an inflammatory signature dominated by IL-6, rather than by classic autoimmunity, carries direct implications for the therapeutic approach.

Methotrexate (MTX)

Methotrexate (MTX) is commonly used in CCA by analogy with its use in rheumatoid arthritis (RA), although evidence regarding its efficacy is mixed. Studies such as the randomized clinical trial MARCH and others have suggested benefit in terms of pain and function, especially in combination with hydroxychloroquine or sulfasalazine,[26] while other investigations show limited efficacy as monotherapy.[27] Although MTX reduces cellular inflammation and the production of cytokines such as IL-6 and IL-1—potentially beneficial effects—its immunosuppressive action generates a theoretical concern: it could compromise immunological control of the virus and facilitate its persistence.

Tocilizumab

Given the central role of Interleukin-6 (IL-6) in the pathogenesis of CCA, blockade of its receptor using antagonists such as tocilizumab represents a therapeutic strategy with a solid pathophysiological basis. Studies have suggested its utility in refractory patients, with possible reduction of inflammation and a potential halt to osteoclast-mediated bone erosion.[28]

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Tumor Necrosis Factor (TNF)

Inhibitors Although TNF inhibitors (such as etanercept and adalimumab) are highly effective in RA, their utility in CCA is less predictable because TNF-α does not always constitute the dominant cytokine in this disease. Nevertheless, successful experiences have been documented in severe cases with a clinical phenotype similar to seronegative RA.[14]

Janus Kinase (JAK)

Inhibitors JAK inhibitors (for example, baricitinib and tofacitinib), a class of oral drugs, block the JAK-STAT signaling pathway common to multiple cytokines implicated in CCA, such as IL-6, interferons, and GM-CSF. They offer a potent anti-inflammatory effect, but their mechanism of action poses a theoretical dilemma: by also blocking interferon signaling—key in the antiviral response—they could theoretically favor viral replication. Despite this consideration, recent studies suggest that they possess useful clinical potential, justifying their use under strict monitoring.[28]

CONCLUSIONS

The transition toward chronic Chikungunya arthritis (CCA) finds its main pathophysiological substrate in the capacity of the virus to persist in tissue reservoirs, particularly in synovial macrophages, which sustains a state of active chronic inflammation. In contrast, the hypothesis of classic systemic autoimmunity, similar to rheumatoid arthritis (RA), appears to be a secondary phenomenon that manifests predominantly in a minority of patients with genetic predisposition. The immunological profile of CCA is dominated by a distinctive cytokine signature. Interleukin-6 (IL-6) emerges as the master cytokine, orchestrating both local and systemic inflammation as well as associated bone destruction. Its persistence, together with that of IL-1β and variable—frequently low—levels of TNF-α, defines an inflammatory pattern clearly different from that observed in RA. These findings have direct implications for therapeutic management. The observed correlation between a robust innate immune response during the acute phase and a better long-term prognosis suggests that early interventions should avoid indiscriminate suppression of antiviral immunity. In the chronic phase, conventional treatment with methotrexate (MTX) is suboptimal for a significant number of patients. Therefore, the future of CCA management will likely reside in combined strategies that integrate antiviral agents aimed at eradicating tissue reservoirs with biological or synthetic drugs—such as IL-6 receptor antagonists (tocilizumab) or JAK inhibitors—designed to control immunopathology without critically compromising the host's global antiviral defenses.

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Conflict of Interest

The authors declare no conflicts of interest.

Authorship Contribution

MGM: Conceptualization, formal analysis, writing – original draft, Writing – review and editing.
GDB: Conceptualization, formal analysis, writing – original draft, Writing – review and editing.
CAMV: Conceptualization, formal analysis, writing – original draft, Writing – review and editing.

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BIBLIOGRAPHIC REFERENCES

1. Sun W, Shi S, Liao S, Zhai M. Chikungunya fever: pathogenesis and mechanisms underlying pain symptoms. Front Immunol [Internet]. 2025 [citado 22/11/2025]; 16: 1679385. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12643972/

2. Samudio JSG, González CMR. Caracterización clínico-epidemiológica del virus chikungunya en pacientes pediátricos de un Hospital Regional de Paraguay, 2023. Anales de la Facultad de Ciencias Médicas [Internet]. 20 de septiembre de 2024 [citado 22/11/2025]; 57(2): 33-9. Disponible en: https://revistascientificas.una.py/index.php/RP/article/view/4692

3. Menéndez MDJA, Solorzano NPA, Mendoza IAB, Peñafiel JJV. Chikungunya: Epidemiologia, Prevención y Abordaje Comunitario. Revista Veritas de Difusão Científica [Internet]. 12 de septiembre de 2025 [citado 22/11/2025]; 6(2): 4204-28. Disponible en: https://revistaveritas.org/index.php/veritas/article/view/834

4. Dutra JIS, de Souza MC, Lins CAA, de Medeiros ACQ. Impact of chronic illness caused by chikungunya fever on quality of life and functionality. Einstein (Sao Paulo) [Internet]. 20 de septiembre de 2024 [citado 23/11/2025]; 22: eAO0562. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11461011/

5. Amaral JK, Taylor PC, Schoen RT. Bone erosions and joint damage caused by chikungunya virus: a systematic review. Rev Soc Bras Med Trop [Internet]. 2024 Apr 5 [citado 23/11/2025]; 57: e00404-2024. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11000508/

6. Pullen L. Cytokine Response Provides Clues to Chikungunya Sequelae [Internet]. The Rheumatologist; 2014 [citado 22/11/2025]. Disponible en: https://www.the-rheumatologist.org/article/cytokine-response-provides-clues-to-chikungunya-sequelae/

7. Chirathaworn C, Chansaenroj J, Poovorawan Y. Cytokines and Chemokines in Chikungunya Virus Infection: Protection or Induction of Pathology. Pathogens [Internet]. junio de 2020 [citado 22/11/2025]; 9(6): 415. Disponible en: https://www.mdpi.com/2076-0817/9/6/415

8. Chang AY, Tritsch S, Reid StP, Martins K, Encinales L, Pacheco N, et al. The Cytokine Profile in Acute Chikungunya Infection is Predictive of Chronic Arthritis 20 Months Post Infection. Diseases [Internet]. 20 de octubre de 2018 [citado 22/11/2025]; 6(4): 95. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313749/

9. dos Santos CF, Nunes PCG, Fiestas-Solorzano VE, Gandini M, dos Santos FB, Pinheiro RO, et al. Monocyte Dynamics in Chikungunya Fever: Sustained Activation and Vascular-Coagulation Pathway Involvement. Viruses [Internet]. 7 de septiembre de 2025 [citado 23/11/2025]; 17(9): 1224. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12474508/

10. Ng LFP, Chow A, Sun YJ, Kwek DJC, Lim PL, Dimatatac F, et al. IL-1β, IL-6, and RANTES as Biomarkers of Chikungunya Severity. PLOS ONE [Internet]. 21 de enero de 2009 [citado 22/11/2025]; 4(1): e4261. Disponible en: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0004261

11. Roques P, Gras G. Chikungunya Fever: Focus on Peripheral Markers of Pathogenesis. J Infect Dis [Internet]. 15 de enero de 2011 [citado 22/11/2025]; 203(2):141-3. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3071053/

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2026; 30(2026): e6870

12. Tritsch SR, Amdur R, Encinales L, Bonfanti AC, Fierbaugh P, Avendaño G, et al. Sleep Disturbances are a Significant Predictor of Chikungunya Arthritis Flare Severity. J Cell Immunol [Internet]. [citado 23/11/2025]; 3(3):191-7. Disponible en: https://www.scientificarchives.com/article/sleep-disturbances-are-a-significant-predictor-of-chikungunya-arthritis-flare-severity

13. Liu X, Poo YS, Alves JC, Almeida RP, Mostafavi H, Tang PCH, et al. Interleukin-17 Contributes to Chikungunya Virus-Induced Disease. mBio [Internet]. 7 de marzo de 2022 [citado 22/11/2025]; 13(2): e00289-22. Disponible en: https://journals.asm.org/doi/10.1128/mbio.00289-22

14. Amaral JK, Schoen RT, Weinblatt ME, Cândido EL. Chikungunya Fever and Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Trop Med Infect Dis [Internet]. 12 de febrero de 2025 [citado 22/11/2025]; 10(2): 54. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11861052/

15. Venugopalan A, Ghorpade RP, Chopra A. Cytokines in Acute Chikungunya. PLOS ONE [Internet]. 24 de octubre de 2014 [citado 22/11/2025]; 9(10): e111305. Disponible en: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111305

16. Gasque P, Bandjee MCJ, Reyes MM, Viasus D. Chikungunya Pathogenesis: From the Clinics to the Bench. The Journal of Infectious Diseases [Internet]. 15 de diciembre de 2016 [citado 22/11/2025]; 214(suppl_5): S446-8. Disponible en: https://doi.org/10.1093/infdis/jiw362

17. Pott F, Postmus D, Brown RJP, Wyler E, Neumann E, Landthaler M, et al. Single-cell analysis of arthritogenic alphavirus-infected human synovial fibroblasts links low abundance of viral RNA to induction of innate immunity and arthralgia-associated gene expression. Emerging Microbes & Infections [Internet]. 1 de enero de 2021 [citado 22/11/2025]; 10(1): 2151-68. Disponible en: https://doi.org/10.1080/22221751.2021.2000891

18. Zarrella KM, Sheridan RM, Ware BC, Davenport BJ, da Silva MOL, Vyshenska D, et al. Chikungunya virus persists in joint-associated macrophages and promotes chronic disease. Res Sq [Internet]. 25 de junio de 2025 [citado 22/11/2025]; rs.3.rs-6917990. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12270208/

19. Ansah-Dico S, Heckler I, Premazzi Papa M, Sucerquia Hernández A, Mejía JF, Tritsch SR, et al. The role of autoantibodies in post-chikungunya viral arthritis disease severity. Microbiology Spectrum [Internet]. 5 de marzo de 2025 [citado 22/11/2025]; 13(4):e02656-24. Disponible en: https://journals.asm.org/doi/10.1128/spectrum.02656-24

20. Reddy V, Desai A, Krishna SS, Vasanthapuram R. Molecular Mimicry between Chikungunya Virus and Host Components: A Possible Mechanism for the Arthritic Manifestations. PLoS Negl Trop Dis [Internet]. 26 de enero de 2017 [citado 22/11/2025]; 11(1): e0005238. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5268390/

21. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. Viruses [Internet]. 19 de agosto de 2019 [citado 22/11/2025]; 11(8): 762. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723519/

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2026; 30(2026): e6870

22. Abella J, Rojas Á, Rojas C, Rondón F, Medina Y, Peña M, et al. Clinical and immunological features of post-chikungunya virus chronic arthritis and its effect on functional ability and quality of life in a cohort of Colombian patients. Rev Colomb Reumatol [Internet]. 1 de octubre de 2019 [citado 23/11/2025]; 26(4): 223-294. Disponible en: http://www.elsevier.es/en-revista-revista-colombiana-reumatologia-english-edition--474-articulo-clinical-immunological-features-post-chikungunya-virus-S2444440519301244

23. Avila-Trejo AM, Rodríguez-Páez LI, Alcántara-Farfán V, Aguilar-Faisal JL. Multiple Factors Involved in Bone Damage Caused by Chikungunya Virus Infection. Int J Mol Sci [Internet]. 23 de agosto de 2023 [citado 23/11/2025]; 24(17): 13087. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10488091/

24. Urbanski AH, Maso VE, Martins FM, da Costa-Martins AG, do Nascimento Oliveira APB, Nakaya HI. Chikungunya-Driven Gene Expression Linked to Osteoclast Survival and Chronic Arthralgia. Infect Dis Rep [Internet]. 20 de septiembre de 2024 [citado 23/11/2025]; 16(5): 914-22. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11417755/

25. Srivastava P, Kumar A, Hasan A, Mehta D, Kumar R, Sharma C, et al. Disease Resolution in Chikungunya—What Decides the Outcome? Front Immunol [Internet]. 28 de abril de 2020 [citado 23/11/2025]; 11: 695. Disponible en: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.00695/full

26. 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 [Internet]. 1 de junio de 2017 [citado 23/11/2025]; 36(6):1335-40. Disponible en: https://doi.org/10.1007/s10067-016-3429-0

27. Adarsh MB, Sharma SK, Dwivedi P, Singh MP, Dhir V, Jain S. Methotrexate in Early Chikungunya Arthritis: A 6 Month Randomized Controlled Open-label Trial. Current Rheumatology Reviews [Internet]. 2020 [citado 23/11/2025]; 16(4): 319-23. Disponible en: https://www.eurekaselect.com/article/101010

28. Baker H, Amaral JK, Schoen RT. Management of postinfectious inflammatory arthritis. Current Opinion in Rheumatology [Internet]. mayo de 2024 [citado 23/11/2025]; 36(3):155-162. Disponible en: https://journals.lww.com/co-rheumatology/abstract/2024/05000/management_of_postinfectious_inflammatory.2.aspx?context=latestarticles