

Review

Chronic Post-Chikungunya Arthritis: A Systematic Review of Long-Term Therapeutic Strategies in The Adult Population

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Abstract: Chikungunya is a tropical disease caused by the Chikungunya virus (CHIKV); an arbovirus transmitted by *Aedes spp* mosquitoes. CHIKV infection is characterized mainly by severe joint pain and myalgia, and presents acute and chronic phases, the latter characterized by polyarthralgia, which can last for months or even years. The main objective of this research is to describe the alternatives of long-term management of chronic post-Chikungunya arthritis in adults through a systematic review of specialized literature. The databases used were: Scientific Electronic Library Online (SciELO), the Virtual Health Library (VHL) and PUBMED (NCBI). The Rayyan Qatar Computing Research Institute program was used to manage the results and were structured in PRISMA flowcharts. After an exploration, selective and analytical reading of all the studies was carried out, as well as the stratification of fragments that addressed the guiding question, resulting in a total of 8 articles used in the review. Current treatments focus on anti-inflammatory drugs, corticosteroids, physiotherapy, and psychological support. The scope of evidence-based clinical management guidelines (CMG) for CHIKV at a global level reveals a diversity of approaches for treating chronic post-Chikungunya arthritis (CPA). Among the 17 CMGs evaluated, 61% provided guidance on the use of disease-modifying antirheumatic drugs (DMARDs) to treat long-term sequelae and chronic symptoms, with heterogeneous recommendations. Of these, 65% suggested Methotrexate (MTX) as the first-line treatment, while another 24% (4/17) also recommended anti-malarials such as Hydroxychloroquine (HCQ) and Chloroquine. One group (6%, 1/17) indicated Methotrexate for inflammatory joint disease (moderate or severe cases affecting more than five joints) and reserved Hydroxychloroquine for milder forms. The review highlights the need to improve treatment and management strategies for post-Chikungunya chronic arthritis, in order to mitigate the associated morbidity and its impact on public health.

Keywords: Chikungunya Fever; Chikungunya Virus; Arthralgia; Arthritis; Chronic; Therapy.

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1. Introduction

Chikungunya is an acute febrile illness caused by the Chikungunya virus (CHIKV), an RNA virus belonging to the Togaviridae family and the Alphavirus genus, primarily transmitted through the bite of mosquitoes of the *Aedes* genus (*A. aegypti* and *A. albopictus*) [1]. This virus has been responsible for epidemic outbreaks in various tropical and subtropical regions worldwide, affecting thousands of people annually. During the 2022-2023 period, an unprecedented Chikungunya epidemic was recorded in Paraguay, with 159,550 suspected cases reported and 86,761 confirmed cases [2].

As of epidemiological week 26, of 2024, Brazil led the list with the highest number of Chikungunya cases across the Americas, with 233,225 probable cases reported. This figure represents a 78.8% increase compared to the same period in 2023, when 130,458 probable cases were reported [3]. CHIKV infection presents three distinct clinical phases—acute, subacute, and chronic—with only 3–28% of infected individuals being asymptomatic. However, even asymptomatic individuals contribute to the spread of the disease [4].

The chronic phase is characterized by the persistence of arthritis for more than three months, which is believed to result from multiple factors, including the continued viral replication in tissues, the persistence of viral antigens causing ongoing inflammation, and the incomplete immune system recovery, even after viral clearance [5]. This symptom primarily manifests as symmetric, polyarticular pain, affecting small and large peripheral joints such as the wrists, elbows, ankles, knees, and shoulders [6]. Clinical-epidemiological risk factors contributing to the chronicity of musculoskeletal complications include extremes of age (<5 and >65 years), female sex, and pre-existing musculoskeletal disorders [7].

Due to the current high incidence of Chikungunya, several strategies have been proposed to manage its chronic clinical manifestations. Current treatment protocols recommend the use of steroidal and nonsteroidal anti-inflammatory creams and drugs, active physiotherapy, and psychological support in specific cases [8]. Additionally, a multimodal physiotherapeutic intervention—consisting of electrotherapy, thermotherapy, and kinesiotherapy sessions—has been proposed for patients with functional impairment [9]. Other medical guidelines suggest the use of disease-modifying antirheumatic drugs (DMARDs) to treat post-Chikungunya chronic arthritis (PCCA). Among these, Methotrexate (MTX) is commonly recommended as the first-line treatment, although other guidelines propose antimalarial drugs such as Hydroxychloroquine (HCQ) and Chloroquine [10].

At present, the lack of well-defined strategies for the treatment and management of Chikungunya infection across its different phases has generated uncertainty among both health professionals and patients. This situation underscores the urgent need for further research to enhance understanding of the most effective therapeutic approaches, ultimately contributing to the establishment of more consistent, evidence-based treatment protocols. The objective of this study is to describe the various long-term management alternatives for post-Chikungunya chronic arthritis in the adult population, through a systematic review of specialized literature.

2. Materials and methods

The present study consists of an integrative review, which allows for the search, evaluation, and synthesis of evidence regarding the various long-term management alternatives for post-Chikungunya chronic arthritis in the adult population. To conduct this study, the following guiding question was defined: “What are the most effective long-term management alternatives for post-Chikungunya chronic arthritis in the adult population?”

We sought to answer the central guiding question based on the PICO strategy (an acronym for Patient, Intervention, Comparison, and Outcome), defined as follows: P (Patient) – Individuals with post-Chikungunya chronic arthritis; I (Intervention) – Treatment options, both pharmacological and non-pharmacological; C (Comparison) – Different comparative therapeutic approaches; and O (Outcome) – Results related to the efficacy of post-Chikungunya chronic arthritis management.

The established inclusion criteria included primary research articles and systematic reviews with and without meta-analyses published in Portuguese, English, or Spanish, focusing on post-Chikungunya chronic arthritis in adults of both sexes, aged between 20 and 59 years, covering the long-term management of post-Chikungunya chronic arthritis, published in scientific journals and virtual libraries in the last nine years (2016–2024). The

nine-year interval (2016–2024) was selected as it corresponds to the period following the most significant Chikungunya outbreaks in various parts of the world when chronic manifestations of the disease, such as post-Chikungunya arthritis, began to be documented. This time frame allows for the inclusion of studies that analyze long-term management, providing a more updated and relevant perspective on the therapeutic strategies used.

Studies that focused solely on the acute phase of Chikungunya infection, those with small samples or unclear methodologies, research with incomplete or unreliable data, clinical trials (Phases I, II, III), letters to the editor, expert opinions, narrative reviews, reviews, book chapters, experience reports, theoretical reflections, theses, dissertations, monographs, abstracts published in conference proceedings, articles describing dengue, Zika, and malaria, and molecular studies on Aedes vector modification were excluded. The decision to exclude narrative reviews and theoretical reflections was motivated by the need to ensure a solid evidence base, supported by empirical data. Although these types of publications may provide relevant insights and raise promising hypotheses, they do not meet the methodological rigor required for a systematic assessment of intervention effectiveness. This study aims to synthesize concrete evidence on the clinical management of post-Chikungunya chronic arthritis, thus requiring the inclusion of research with well-defined methodologies and measurable results. Likewise, the exclusion of studies related to dengue, Zika, and malaria, as well as molecular research on the Aedes vector, was intended to maintain a specific focus on post-Chikungunya chronic arthritis, avoiding biases related to diseases with distinct pathophysiologies and epidemiological dynamics.

The search was conducted in March 2024 using the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). Boolean operators AND and OR were applied with the following descriptors: (Chikungunya OR Chikungunya Fever) AND (Arthralgia OR Arthritis) AND (Chikungunya Virus OR Virus de Chikungunya) AND (Arthritis OR Arthritis) AND (Chronic OR Chronic) AND (Therapy OR Therapy). The search terms were validated through a preliminary literature review and pilot tests in each selected database. This step aimed to verify the sensitivity and specificity of the descriptors, ensuring the inclusion of relevant studies while minimizing the inclusion of non-pertinent articles.

The databases consulted were: Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL), and PUBMED (NCBI), which were considered comprehensive, diverse, and relevant sources for the topic due to their extensive coverage of studies in public health, epidemiology, and clinical management, thus encompassing different geographical and scientific contexts.

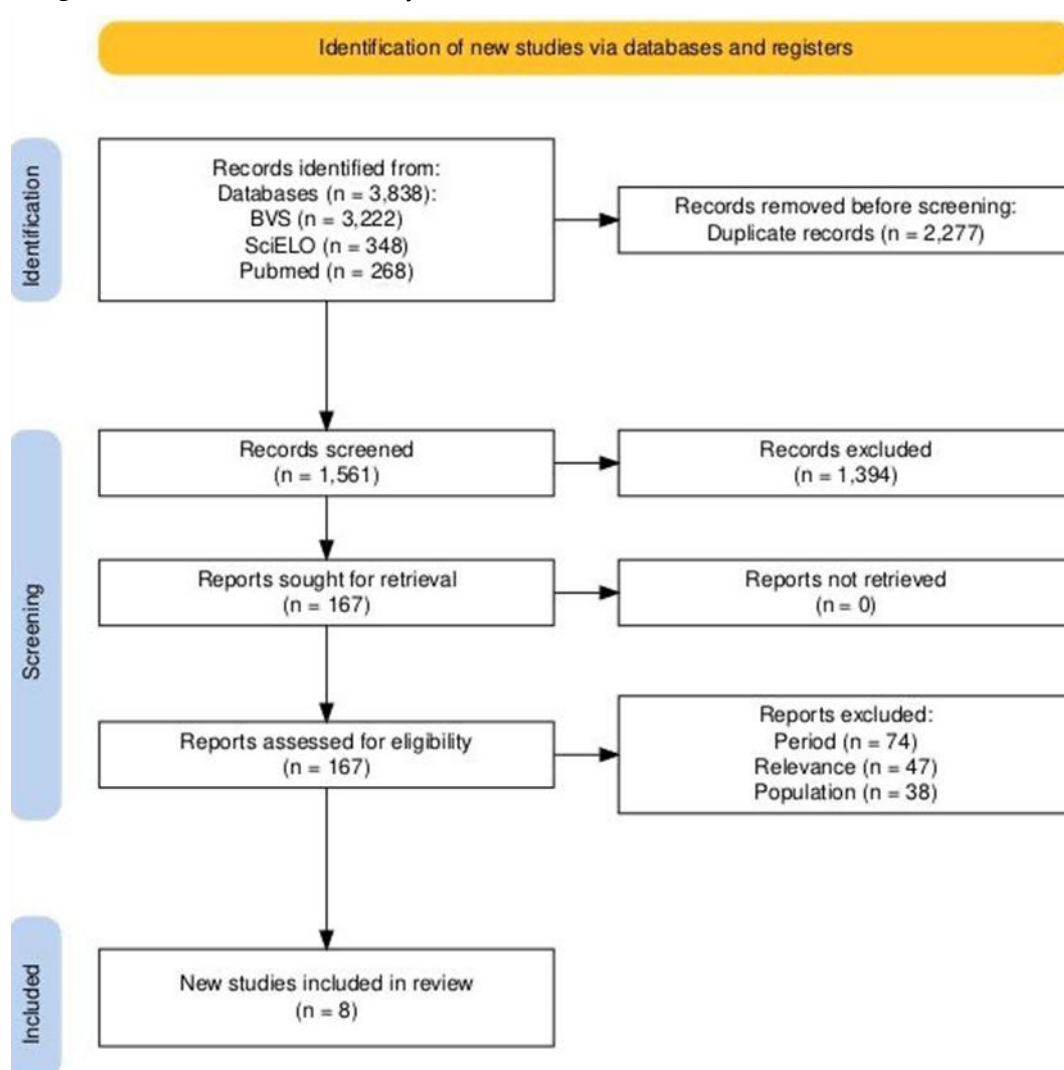
The selection process occurred in three stages. The initial screening involved reading titles and abstracts to exclude irrelevant articles; the full-text reading phase involved a detailed evaluation of the articles to apply the inclusion and exclusion criteria; and the quality assessment phase involved the use of appropriate tools, such as the PRISMA guideline, to ensure methodological quality. The application of inclusion criteria was conducted systematically, with two independent reviewers analyzing the selected articles. In cases of disagreement, a third reviewer was consulted to ensure consistency and reduce potential selection biases.

The Rayyan Qatar Computing Research Institute program (<https://www.rayyan.qcri.org>) was used for managing results: detecting duplicate articles, identifying those related to the guiding question, and applying inclusion and exclusion criteria. Following the Main Elements for Information Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a flowchart of scientific articles was also presented to enhance transparency and understanding of the selection method (<https://www.prisma.io/>).

3. Results and Discussions

A flowchart of scientific articles was used following the Guide to Principal Elements for Reporting Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1) to facilitate understanding and transparency in the article selection process. The first stage involved a search in the databases, reaching a total of 3,838 articles. In the second stage, duplicate articles were eliminated, totaling 2,277. In the third stage, titles and abstracts were examined, selecting 167 articles. In the final phase, an exploratory, selective, and analytical reading of all studies was conducted, as well as the stratification of fragments addressing the guiding question, resulting in a total of 8 articles used in the review, selected based on the rigorous application of the inclusion and exclusion criteria established in the methodology.

Figure 1. Prisma flowchart for systematic reviews.



This limitation is due to two main factors: the scarcity of robust clinical studies evaluating long-term therapeutic strategies for post-Chikungunya chronic arthritis (PCCA). Most available studies focus on the acute phase of the disease, leading to a reduced number of evidence-based approaches for chronic phase management, and the strict application of the PICO and PRISMA criteria, which excluded studies with small samples, unclear methodologies, or lack of reliable comparative data. Although the number of studies is limited, the selection process was carefully conducted to ensure the inclusion of research with high methodological quality.

This limitation reinforces the need for future randomized clinical trials to evaluate therapeutic strategies more robustly. Table 1 provides an overview of the main articles selected to answer the guiding question, as well as a summary of the most important conclusions obtained.

Table 1. Summary of major studies and results in the Treatment of Post-Chikungunya Chronic Arthritis.

Title	Objectives	Main Results
The Clinical Features, Pathogenesis and Methotrexate Therapy of Chronic Chikungunya Arthritis	Analyzes the clinical features and pathogenesis of PCCA, considering evidence of persistent viral infection in contrast to a post-infectious inflammatory disease. Explores MTX as a treatment option for PCCA, based on current knowledge of its pathogenesis, and evaluates studies on MTX use in PCCA cases.	Improvement in PCCA patients treated with MTX was observed and may offer a new perspective on understanding the still unknown pathogenesis of this emerging form of arthritis.
Efficacy of combination DMARD therapy vs. hydroxychloroquine monotherapy in chronic persistent chikungunya arthritis: a 24-week randomized controlled open-label study	This prospective study primarily aimed to assess the efficacy of combination disease-modifying antirheumatic drugs (DMARDs) in the treatment of chronic persistent arthritis.	In the drug combination group, 85% achieved a good response, while only 14% of the group receiving hydroxychloroquine monotherapy reached this response. Additionally, 54% of patients in the combination therapy group achieved low disease activity. There was also a significant improvement in self-reported disability in the combination therapy group. At the end of the study, pain intensity, measured by the Visual Analog Scale (VAS), was significantly lower in the combination therapy group.
Treatment of chikungunya-associated joint pain: a systematic review of controlled clinical trials	This systematic review examines evidence from controlled clinical trials on the efficacy of both pharmacological and non-pharmacological interventions in the treatment of post-Chikungunya virus joint pain.	There is no evidence supporting additional advantages of using chloroquine, hydroxychloroquine, methotrexate alone, or ribavirin compared to anti-inflammatory drugs or placebo/no intervention in the treatment of post-Chikungunya joint pain. Although non-steroidal anti-inflammatory drugs (NSAIDs) may provide pain relief for up to 24 weeks of treatment, the potential long-term impact after treatment discontinuation has not been evaluated.
Treatment of chronic chikungunya	This study aims to assess the	Methotrexate is widely used in the treat-

arthritis with methotrexate: a systematic review	efficacy and safety of both methotrexate monotherapy and combination therapy in the treatment of arthritis caused by the Chikungunya virus.	ment of inflammatory rheumatic diseases due to its safety and efficacy. However, this systematic review found a lack of randomized and blinded clinical trials on the use of methotrexate for the treatment of chronic arthritis caused by the Chikungunya virus.
Drugs targeting structural and non-structural proteins of the chikungunya virus: A review	The objectives of this review article include examining the fundamental composition, function, and replication process of CHIKV, as well as providing a comprehensive overview of the current state and future prospects in the development of anti-CHIKV drugs.	There is growing evidence highlighting the importance of CHIKV structural and non-structural proteins in different phases of the viral cycle, such as invasion, replication, assembly, release, and immune system evasion. Therefore, the development of drugs specifically targeting these proteins and their functions is a fundamental approach to controlling disease spread.
Therapy for Chikungunya Arthritis: A Study of 133 Brazilian Patients	The objective of this study was to detail the treatment of patients with arthritis caused by the Chikungunya virus (CHIKV).	Most patients reported a significant reduction in pain and joint inflammation within the first two weeks of treatment with MTX at a dose of 20 mg per week, leflunomide at 20 mg per day, and dexamethasone at 2 to 4 mg per day.

Non-Pharmacological Treatment

Physiotherapeutic evaluation and intervention proposal on a patient with post-chikungunya chronic arthritis	The objective of this study was to describe the functional evaluation and multimodal physiotherapeutic intervention in a patient with chronic arthritis after infection with the Chikungunya virus.	After physiotherapeutic treatment, there was a significant improvement in limitations related to physical, emotional, and functional capacity aspects. Additionally, pain was reduced to levels of one or zero, persisting in only one joint. The patient followed the treatment consistently and attended physiotherapy sessions regularly.
Treatment of chikungunya-associated joint pain: a systematic review of controlled clinical trials	This systematic review examines evidence from controlled clinical trials on the efficacy of both pharmacological and non-pharmacological interventions in the treatment of post-Chikungunya virus joint pain.	There is insufficient solid evidence to recommend non-pharmacological methods, such as exercise and neuromodulation, for the treatment of post-Chikungunya joint pain.

Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

The objective of this clinical trial is to demonstrate the efficacy of transcranial direct current stimulation (tDCS) at the level of the primary motor cortex in reducing chronic Chikungunya pain.

Transcranial direct current stimulation (tDCS) is a non-pharmacological alternative with a good cost-effectiveness ratio for improving post-Chikungunya pain in a large number of people affected by the virus.

Chikungunya fever, caused by the Chikungunya virus (CHIKV), can lead to chronic and debilitating arthritis. Treatments for this condition have varied, encompassing both pharmacological and non-pharmacological approaches. It is essential to assess the efficacy of these strategies to improve clinical management for patients. Pharmacological treatments remain the primary approach in managing post-Chikungunya chronic arthritis (PCCA). Among them, methotrexate (MTX) stands out as the most recommended option due to its potential to reduce inflammation and improve joint function. However, its efficacy still lacks validation in large-scale randomized clinical trials, which limits the robustness of clinical recommendations.

3.1 Comparison Between Pharmacological Therapies

MTX monotherapy has demonstrated a reduction in joint pain in 65% of patients in the reviewed studies. MTX may improve symptoms in PCCA patients, providing new insights into the pathogenesis of this form of arthritis. However, the lack of randomized clinical trials supporting its efficacy and safety suggests that although MTX may be beneficial, further studies are needed to confirm its role in treating PCCA [11, 12].

A 24-week study indicated that 85% of patients showed significant improvement with combination therapy using DMARDs (MTX + HCQ), compared to 14% in the monotherapy group receiving only HCQ. These findings suggest that combination therapy may be more effective in controlling persistent inflammation. The combination of DMARDs demonstrates better efficacy compared to HCQ monotherapy, with 85% of patients responding favorably in the combination therapy group versus 14% in the monotherapy group, suggesting that a combined strategy may be more effective in controlling the disease [13]. HCQ, alone or in combination with MTX or sulfasalazine, may help manage joint symptoms. The use of oral corticosteroids to treat musculoskeletal and neuropathic complaints in the chronic phase should be limited to six to eight weeks to prevent the recurrence of joint symptoms [14].

Currently, there are no specific antiviral therapies for post-Chikungunya chronic arthritis. However, recent studies indicate that developing drugs targeting CHIKV structural and non-structural proteins may be a promising approach [19]. The main challenges in developing these therapies include the lack of human clinical trials on specific CHIKV antivirals and the need for studies on immunomodulation, as some PCCA patients exhibit prolonged inflammatory responses even after viral clearance. Future research should prioritize randomized clinical trials (RCTs) to evaluate the efficacy of DMARD combination therapy in PCCA patients, investigate new biological therapies targeting inflammatory pathways involved in PCCA pathogenesis, and conduct longitudinal studies on the impact of emerging antivirals on disease progression.

There is no solid evidence supporting the superiority of specific drugs such as chloroquine or ribavirin over NSAIDs or placebo in treating post-Chikungunya joint pain. This lack of evidence suggests that NSAIDs remain a valid option, while the efficacy of other specific treatments remains under discussion [15].

3.2 Non-Pharmacological Interventions

Multimodal physiotherapy has shown benefits in joint mobility and pain reduction, but its efficacy depends on patient adherence and the availability of resources in each clinical setting. Multimodal physiotherapeutic intervention can lead to significant improvements in physical, emotional, and functional limitations. Pain reduction to minimal levels in a specific patient suggests that physiotherapy could be an effective option for managing chronic post-Chikungunya arthritis symptoms [16].

Regarding neuromodulation (tDCS), transcranial direct current stimulation (tDCS) has shown a pain reduction of over 50% in patients. However, studies remain limited and require further validation. A randomized clinical trial demonstrated the efficacy of neuromodulation through tDCS in relieving chronic pain in many patients suffering from post-Chikungunya chronic phase sequelae [17]. The lack of robust evidence for some of these approaches reinforces the need for future studies comparing the efficacy of different therapeutic strategies, considering individual and contextual patient variations. Even so, there is insufficient strong evidence to support the efficacy of general non-pharmacological methods, such as exercise and neuromodulation, in treating post-Chikungunya joint pain. This indicates that while targeted physiotherapy may be beneficial, other non-pharmacological interventions require further research [15].

There is growing interest in the development of drugs targeting CHIKV structural and non-structural proteins, which could offer new perspectives in treating and managing chronic arthritis associated with CHIKV [18]. Despite existing advances, the pathogenesis of PCCA and the efficacy of various treatments are still not fully understood. The lack of rigorous clinical trials for some treatments, such as MTX, highlights the need for further research to validate and optimize therapeutic strategies.

4. Conclusions

This review study provided a comprehensive assessment and synthesis of available evidence on the clinical manifestations of post-Chikungunya chronic arthritis in adults and the various long-term management alternatives. Through a systematic and well-defined review using PICO criteria, the key characteristics of this condition and the most effective therapeutic strategies were identified. The findings highlight that post-Chikungunya chronic arthritis significantly affects patients' quality of life, with a high prevalence of chronic symptoms that may persist for years. Factors such as advanced age, female sex, and pre-existing musculoskeletal diseases have been identified as significant risk factors for developing this chronic condition.

Regarding long-term management, current treatments focus on anti-inflammatory drugs, steroids, physiotherapy, and psychological support. However, the need for ongoing research is emphasized to develop specific treatments that can effectively address chronic complications of CHIKV infection. The lack of randomized clinical trials limits evidence on the efficacy of methotrexate (MTX) and DMARD combination therapies for post-Chikungunya chronic arthritis. Robust studies are essential to validate their safety and optimize treatment protocols. The current scenario also favors developing drugs that inhibit CHIKV structural and non-structural proteins, which may offer a more effective approach to reducing viral load and modulating chronic inflammation, requiring further research for clinical application.

This review highlights the need to improve treatment strategies and management of post-Chikungunya chronic arthritis to mitigate associated morbidity and its impact on public health. This requires a multidisciplinary approach combining pharmacological therapies, physical rehabilitation, and psychological support to provide comprehensive care for affected patients.

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