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Original article

Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. Part 2 – Treatment

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ABSTRACT

Chikungunya fever has become an important public health problem in countries where epidemics occur because half of the cases progress to chronic, persistent and debilitating arthritis. Literature data on specific therapies at the various phases of arthropathy caused by chikungunya virus (CHIKV) infection are limited, lacking quality randomized trials assessing the efficacies of different therapies. There are a few studies on the treatment of musculoskeletal manifestations of chikungunya fever, but these studies have important methodological limitations. The data currently available preclude conclusions favorable or contrary to specific therapies, or an adequate comparison between the different drugs used.

The objective of this study was to develop recommendations for the treatment of chikungunya fever in Brazil. A literature review was performed *via* evidence-based selection of articles in the databases Medline, SciELO, PubMed and Embase and conference proceedings abstracts, in addition to expert opinions to support decision-making in defining recommendations. The Delphi method was used to define the degrees of agreement in 2 face-to-face meetings and several online voting rounds. This study is part 2 of the Recommendations of the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia – SBR) for the Diagnosis and Treatment of chikungunya fever and specifically addresses treatment.

Recomendações da Sociedade Brasileira de Reumatologia para diagnóstico e tratamento da febre chikungunya. Parte 2 – Tratamento

Palavras chave:
Febre chikungunya
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RESUMEN

A febre chikungunya tem se tornado um importante problema de saúde pública nos países onde ocorrem as epidemias, visto que metade dos casos evolui com artrite crônica, persistente e incapacitante. Os dados na literatura sobre terapêuticas específicas nas diversas fases da artropatia ocasionada pela infecção pelo vírus chikungunya (CHIKV) são limitados, não existem estudos randomizados de qualidade que avaliem a eficácia das diferentes terapias. Há algumas poucas publicações sobre o tratamento das manifestações musculoesqueléticas da febre chikungunya, porém com importantes limitações metodológicas. Os dados atualmente disponíveis não permitem conclusões favoráveis ou contrárias a terapêuticas específicas, bem como uma adequada avaliação quanto à superioridade entre as diferentes medicações empregadas.

O objetivo deste trabalho foi elaborar recomendações para o tratamento da febre chikungunya no Brasil. Foi feita uma revisão da literatura com seleção de artigos baseados em evidência, nas bases de dados Medline, SciELO, PubMed e Embase e de resumos de anais de congressos, além da opinião dos especialistas para dar apoio às decisões tomadas para definir as recomendações. Para a definição do grau de concordância foi feita

uma metodologia Delphi, em duas reuniões presenciais e várias rodadas de votação *on line*. Este artigo refere-se à parte 2 das Recomendações da Sociedade Brasileira de Reumatologia para Diagnóstico e Tratamento da Febre Chikungunya, que trata especificamente do tratamento.

Introduction

The data on specific therapies in arthropathy following chikungunya fever are limited because the studies published have small samples, heterogeneous comparison groups, dosage variability, short follow-up time and methodological differences. There are no quality randomized trials enabling robust conclusions on the different drugs used; only open studies, case series and reports of experiences in pain and arthritis management during epidemics are available.

In April 2016, the multicenter cohort study CHIKBRASIL was started, aimed at assessing the behavior of chikungunya fever with chronic joint manifestations and collecting data to support future therapeutic decisions in Brazil. Thus far, 6 centers in the states Pernambuco (3), Paraíba (1), Ceará (1) and Sergipe (1) have collected data from 431 patients, whose analyses have not yet been published.

Method

Three study groups were created to develop the recommendations: a central group, a literature review group and a voting panel. The central group consisted of 5 rheumatologists and was responsible for defining and sending the leading questions used as the basis for preparing the recommendations, coordinating and supervising the members of the other 2 groups, conducting online voting rounds and writing the manuscript. The group that conducted the literature review consisted of 20 rheumatologists and 3 physiotherapists. The search for evidence was conducted in the databases MEDLINE, SciELO, PubMed and EMBASE, and articles related to the diagnosis and treatment of chikungunya fever, along with conference proceedings abstracts, published in Portuguese, English, French and Spanish until October 2016 were selected. This group was responsible for reviewing the evidence found, providing a theoretical basis for the final recommendations.

The critical evaluation of the methodological quality of the studies found was performed using the risk of bias for clinical trials. We used the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for the critical analysis of observational studies regarding the presence or absence of the necessary items to conduct an observational study[1] and the Newcastle-Ottawa Scale (NOS) for the methodological quality.[2] Because the methodological diversity of the studies found precluded performing the meta-analysis, the evaluation was performed based on the level of evidence and degree of recommendation according to the 2011 Oxford classification (Levels of Evidence),[3] considering Grading of Recommendations Assessment, Developing and Evaluation (GRADE)[4] aspects, in which an evaluation is performed, for each evidence, through 5 domains: risk of bias, consistency, precision, indirect results and reporting bias. This evaluation results in 4 degrees of quality of evidence (high, moderate, low and very low).

Due to the poor quality of the evidence found, and even the lack of evidence in some situations, we also used the results from the preliminary analyses of the CHIKBRASIL cohort data and the expert opinion of the group supporting the decision-making in defining the recommendations.

All members of the other 2 groups, in addition to 3 general practitioners, 1 Infectious disease specialist and 1 public health manager, were included in the voting panel. Two face-to-face meetings were held in the city of Recife, Pernambuco, (PE) to vote on the recommendations (October and November), with more than 90% attendance. In addition to face-to-face voting, several rounds of questions, voting and corrections were conducted online. The members of the voting panels gave scores from 0 (totally disagree) to 10 (totally agree) to define the degrees of agreement. The mean and standard deviation of each recommendation were calculated based on those scores.

Twenty-five recommendations, split into 3 thematic groups, were generated: A. Clinical, laboratory and imaging diagnosis; B. Special situations and C. Treatment. The first 2 themes are published in part 1 of the recommendations. The treatment-related recommendations included in the present study are outlined in Table 1.

Recommendations

C. Treatment

C.1. In the acute phase of chikungunya fever, common analgesics and/or weak opioids should be used (in cases of severe or refractory pain), and nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates should be avoided. Corticosteroids (CS) are not recommended for musculoskeletal manifestations in this phase. Agreement: 9.31 (SD ± 0.8906). GRADE: very low quality of evidence

In the acute phase, the main goal is the relief of musculoskeletal pain, which is intense and disabling in most cases. A verbal numerical or visual analogue scale (VAS) of pain from 0 to 10 can be used. In these recommendations, we consider pain to be intense when VAS ≥7.

In other countries where chikungunya fever epidemics occur, paracetamol was the analgesic of choice.[5] Dipyrone may also be used in this phase, with no preference for one analgesic over another in Brazil. These analgesics may be used alone or in combination at their usual doses (Table 2), according to

Table 1 – Summary of recommendations for the treatment of chikungunya fever.

C. Treatment

C.1. In the acute phase of chikungunya fever, common analgesics and/or weak opioids should be used (in cases of severe or refractory pain), and NSAIDs and salicylates should be avoided. Corticosteroids (CSs) are not recommended for musculoskeletal manifestations in this phase. *Agreement: 9.31 (SD ± 0.8906). GRADE: very low quality of evidence.*

C.2. In the subacute phase of chikungunya fever, NSAIDs and/or adjuvant drugs may be used for pain management (anticonvulsants or antidepressants) in cases refractory to analgesics/opioids. In patients with moderate to severe musculoskeletal pain or in those with contraindications to the use of these drugs, the use of prednisone or prednisolone at a dose of up to 20 mg/day is recommended, and withdrawal should be performed slowly and gradually, according to patient response. *Agreement: 9.24 (SD ± 1.057). GRADE: low to very low quality of evidence.*

C.3. In the chronic phase of chikungunya fever, the use of analgesics is recommended for symptom relief. Weak opioids (codeine and tramadol) may be used for refractory or severe pain symptoms (VAS ≥7). *Agreement: 9.57 (SD ± 0.741). GRADE: low to very low quality of evidence.*

C.4. In the chronic phase of chikungunya fever, NSAIDs are recommended, taking into consideration the clinical context, contraindications and therapeutic response. *Agreement: 8.97 (SD ± 1.679). GRADE: low to very low quality of evidence.*

C.5. In the chronic phase of chikungunya fever, oral corticosteroids may be used for musculoskeletal and neuropathic complaints, and low doses are recommended (5–20 mg/day prednisone or prednisolone). The time of use may range from six to eight weeks, and withdrawal should be slow and gradual due to the risk of recurrence of joint symptoms. *Agreement: 9.24 (SD ± 1.154). GRADE: low to very low quality of evidence.*

C.6. In the chronic phase of chikungunya fever, antimalarials, preferably hydroxychloroquine, may be used for the treatment of joint symptoms, alone or in combination with MTX or SSZ. *Agreement: 9.21 (SD ± 1.166). GRADE: low quality of evidence.*

C.7. In patients with chikungunya fever progressing to the chronic phase and with inflammatory joint disease, with difficulties in CS withdrawal, we preferentially suggest MTX at doses of 10–25 mg/week. *Agreement: 9.43 (SD ± 0.858). GRADE: low to very low quality of evidence.*

C.8. In the chronic phase of chikungunya fever, sulfasalazine may be used at a dose of 2 to 3 g/day, alone or in combination, especially in patients with contraindication to or failure with MTX. *Agreement: 8.77 (SD ± 1.794). GRADE: low to very low quality of evidence.*

C.9. Biological therapy may be prescribed after rheumatologist evaluation of patients with chronic inflammatory joint disease after infection with CHIKV, refractory to the use of CS and DMARDs, following the recommendations used to treat RA or SpA. *Agreement: 8.97 (SD ± 1.267). GRADE: low to very low quality of evidence.*

C.10. During the acute phase, in patients undergoing biological therapy for their underlying disease, drug therapy discontinuation is recommended. However, treatment can be maintained in the subacute and chronic phases. *Agreement: 8.97 (SD ± 1.884). GRADE: low to very low quality of evidence.*

C.11. Rehabilitation interventions in all phases of chikungunya fever are recommended as a complementary non-pharmacological measure. In the acute phase, analgesic and anti-inflammatory therapies are indicated, and the use of heat should be avoided; furthermore, patient education, posture guidelines and manual therapy should be recommended, in addition to light-intensity exercise. In the subacute and chronic phases, the previous recommendations should be followed, which may also include heat, in addition to free, resisted, proprioceptive and active aerobic exercises, stretching, manual therapy and aquatic physical therapy. *Agreement: 9.43 (SD ± 0.935). GRADE: very low quality of evidence.*

the intensity of symptoms and the clinical response.[6,7] In the cases of severe pain or pain refractory to the use of common analgesics, weak opioids may be used, including tramadol and codeine[6,7] (Table 2).

Given the difficulty of differential diagnosis between chikungunya fever and Dengue fever in the acute phase, NSAIDs should be avoided in the first weeks of the disease because of the risk of bleeding. Furthermore, salicylates should also be avoided in this phase because their use in acute viral infections may lead to Reye syndrome.[6,7]

When the pain has neuropathic characteristics (burning and/or throbbing pain, pinching or feeling of shock, pins and needles, cold or tingling), tricyclic antidepressants (amitriptyline or nortriptyline) or anticonvulsants (gabapentin, pregabalin or carbamazepine) may be used at the recommended doses (Table 2).[8,9]

It should be noted that the stratification into disease phases is mostly didactic. Decisions should be made on a case-by-case basis. Although NSAIDs are not recommended for the acute phase of chikungunya fever due to the risk of hemorrhagic complications, if necessary, they may be used after the seventh day, as long as the diagnosis of Dengue is excluded. In these cases, the presence of comorbidities and possible adverse events from using NSAIDs must be considered, especially in the population older than 60 years (expert opinion).

Although inhibition of CHIKV cell infection with chloroquine was shown *in vitro*,[10] antimalarials were not able to improve the pain or to reduce the viral load in the acute phase[11] and, therefore, are not recommended in this phase.

The use of CS in this phase is not recommended due to the lack of evidence of long-term benefits, in addition to the risk of arthritis and tenosynovitis rebound after withdrawal.[5]

There is insufficient evidence on the safety or efficacy of the treatment of severe manifestations of chikungunya fever (neurological, cardiac, ocular or cutaneous vasculitis) in the acute phase. These cases may benefit from the use of CS at higher doses, albeit under careful evaluation by a specialist.

Patients with typical forms of chikungunya fever during the acute phase, with no signs of severity, can be followed-up as outpatients in primary care units (PCUs). In these cases, there is no need for daily follow-up, and the patients may be advised to return to the PCU if their fever persists for longer than 5 days or if signs of severity of complications appear.[6]

Table 2 – Drugs used for the treatment of chikungunya fever: doses, monitoring and precautions.

Drug	Dose	Monitoring and precautions
Paracetamol	60 mg/kg/day, without exceeding 4 g/day, orally, 4 times a day	The increased risk of hepatitis resulting from the association of viremia, drug interactions and comorbidities (liver or kidney disease or alcoholism) with high doses of paracetamol should be carefully monitored.
Dipyrone	1 g, orally, 4 times a day	Evaluate kidney and liver function, especially in the elderly.
Tramadol	50 mg to 100 mg, orally, 2–4 times a day	In patients over 65 years of age, start with the lowest dose; in patients older than 75 years, do not exceed 300 mg/day. Risk of respiratory depression in the elderly.
Paracetamol + Codeine	500 mg + 30 mg, orally, 2–4 times a day	Evaluate hepatotoxicity.
NSAIDs	Depending on the compound chosen	Use the lowest dose for the shortest possible time. Never use two NSAIDs in combination. Evaluate the risk factors: age >65 years, previous history of ulcer, SAH, kidney disease, use of CS, anticoagulants, asthma and smoking. Monitor blood pressure, peripheral edema and kidney function.
Amitriptyline	25–50 mg/day, orally	Use with caution in patients with cardiovascular disease, diabetes mellitus, mania, kidney or liver failure, thyroid dysfunction or epilepsy. Withdrawal should be gradual.
Gabapentin	300 mg, 2–3 times a day, orally	In children aged 3–12 years, there is a risk of neuropsychiatric adverse events (emotional lability, hostility, thought disorders and hyperkinesia). Withdrawal should be in phases.
Pregabalin	50–150 mg, 2–4 times a day, orally	Use with caution in patients with heart and kidney failure. Monitor thrombocytopenia and symptoms of dependence. Withdrawal should be gradual.
Prednisone/Prednisolone	5–20 mg/day, preferably a single dose in the morning Higher doses may be used in severe cases	Assess the presence of risk factors for osteoporosis, glaucoma (family history) and diabetes mellitus. Monitor blood pressure and fasting blood glucose.
Antimalarials	5.0 mg/kg HCQ and 3 mg/kg chloroquine, orally, 1 time a day	With risk factors for retinal toxicity[a]: previous ophthalmologic evaluation; annual re-evaluation. Without risk factors: there is no need for prior evaluation; re-evaluation after 5 years of treatment.
Methotrexate	10–25 mg/week, orally or SC	Hemogram, transaminases, and kidney function prior to initiation of treatment and every 3 months. Potentially teratogenic. The use of folic acid (5 mg, orally, weekly, the day after MTX) reduces the risk of adverse events. Risk of pulmonary toxicity.
Sulfasalazine	1–2 g/day, orally	Hemogram, transaminases and kidney function prior to initiation of treatment and every three months. May cause orange urine or skin.
Anti-TNFs	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab	Screening – the same recommendations as the current protocols for RA and SpA. Respiratory symptoms must be carefully monitored – risk of reactivation of latent tuberculosis.

NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous; IV, intravenous; SAH, systemic arterial hypertension; AR, rheumatoid arthritis; SpA, spondyloarthritis.

[a] Dose >5 mg/kg/day; treatment length; previous ocular disease; kidney disease; liver disease; use of tamoxifen; advanced age (risk of age-related ocular diseases complicating toxicity assessment).

In addition to drug treatment for pain relief, proper hydration and the use of cold compresses to reduce joint pain (avoiding hot compresses) should be recommended. At-risk patients (pregnant women, patients with comorbidities, elderly people and infants younger than 2 years of age, except newborns) may also be followed-up at PCUs during the acute phase, but they require differentiated observation due to the risk of developing severe forms of the disease; they should be followed up daily until their temperature drops and no signs of severity are detected.

The cases with signs of severity (neurological impairment, hemodynamic instability, dyspnea, chest pain, persistent vomiting, mucosal bleeding and underlying disease decompensation) or meeting admission criteria (newborns) should be followed up in wards.

Suspected cases must be advised to adopt individual antivectorial protection measures (mosquito netting, repellent, long-sleeved shirts and pants) to break the transmission chain, in addition to measures that should be implemented at home to prevent mosquito proliferation.[5]

In cases where the fever persists for longer than 5 days, there is diagnostic doubt or the disease progresses to the subacute/chronic form, the patients should be referred to the secondary level.

C.2. In the subacute phase of chikungunya fever, NSAIDs and/or adjuvant drugs may be used for pain management (anticonvulsants or antidepressants) in cases refractory to analgesics/opioids. In patients with moderate to severe musculoskeletal pain or in those with contraindications to the use of these drugs, the use of prednisone or prednisolone at a dose of up to 20 mg/day is recommended, and withdrawal should be performed slowly and gradually, according to patient response. Agreement: 9.24 (SD ± 1057). GRADE: low to very low quality of evidence

In the subacute phase, NSAIDs may be used to treat symptoms refractory to analgesics, with no differences in effectiveness between classes, and the choice should be based on the physician's experience and the patient's clinical status. Rosario et al.[12] evaluated 514 patients with a mean disease time of 2.5 months, and most (89%) showed a good response to the use of NSAIDs (naproxen, celecoxib or etoricoxib). The effectiveness of NSAID therapy should be reevaluated after 7–10 days of use. In cases of inadequate responses after the tenth day of use, the NSAID class should be changed. If well tolerated and effective, the NSAID can be maintained for several weeks, and the withdrawal should be slow and gradual, depending on the clinical response.[5]

Although several studies agree on the efficacy of CS for the treatment of pain in chikungunya fever after the failure of analgesics and NSAIDs, there is still no consensus regarding the optimal dose and time of use. The French guideline recommends the use of 10 mg/day prednisone for 5 days and withdrawal over 10 days for moderate cases and 0.5 mg/kg/day for severe cases for 5 days and dose reduction in 10 days.[5] In Brazil, the Ministry of Health (MH) recommends 0.5 mg/kg/day (40 mg/day maximum dose) until resolution of symptoms, with gradual withdrawal, but without exceeding 3 weeks of treatment.[6,7]

Preliminary results from the CHIKBRASIL cohort show that the use of CS in the subacute phase led to considerable clinical improvement, which was most significant at doses higher than 10 mg/day; however, there was no additional benefit from using more than 20 mg/day prednisone. Thus, we recommend using lower doses (5–20 mg/day) of prednisone or prednisolone, with a slow and gradual reduction, according to the resolution of joint symptoms (unpublished data). It is important to highlight the need to advise patients on the risks of indiscriminate use of CS for long periods of time, especially in the cases of chronic diseases, including systemic arterial hypertension (SAH), diabetes mellitus (DM), glaucoma and obesity (expert opinion).

Infiltrations in joint and periarticular conditions and compression syndromes can be performed in this phase.[5]

The evidence on the use of antimalarials in the subacute phase of symptoms refractory to analgesics is scarce and indicates poor clinical response. An Indian study compared a group of patients with a minimum disease time of 30 days (mean time: 9 weeks) using chloroquine (250 mg/day) with a group using meloxicam (7.5 mg/day) for 24 weeks. Although the response was numerically better in the chloroquine group, there was no significant difference in the improvement in the pain VAS score or number of painful joints.[13]

Another study, also conducted in India, compared 4 treatment groups in patients followed during the subacute phase for 6 weeks: Group A (200 mg/day aceclofenac); Group B (400 mg/day aceclofenac + hydroxychloroquine); Group C (10 mg/day aceclofenac + prednisolone) and Group D (aceclofenac + hydroxychloroquine + prednisolone). All groups showed improvement in the analogue pain scale, but with a greater difference favoring the groups that used CS (groups C and D).[14]

Interestingly, although it was not the primary objective of the study, the authors concluded that adding hydroxychloroquine (HCQ) produced no benefit to the treatment, and both groups using corticoids had better results in the first weeks. Preliminary data from the CHIKBRASIL cohort showed similar results regarding the use of HCQ in the subacute phase, and its response was more satisfactory in the groups that used CS in combination (unpublished data).

Although the evidence on HCQ is insufficient to recommend formal use in the subacute phase, the experience of the specialists included in the Brazilian group suggests that a beneficial effect may occur, particularly when it is used as a corticoid-sparing drug. Therefore, we recommend using antimalarials in this phase, according to clinical criteria (expert opinion).

Tricyclic antidepressants and anticonvulsants are options for cases with neuropathic pain characteristics[9] and may be combined with common analgesics if more effective analgesia is required. The therapeutic regimen of choice should be the one with the lowest dose and the shortest time possible to obtain the best cost-benefit and to reduce the risk of possible adverse events[5] (Table 2). There are no controlled studies evaluating the responses to the use of these drugs in neuropathic pain during chikungunya fever.

C.3. In the chronic phase of chikungunya fever, the use of analgesics is recommended for symptom relief

Weak opioids (codeine and tramadol) may be used in refractory or severe pain symptoms. Agreement: 9.57 (SD ± 0.741). GRADE: low to very low quality of evidence

C.4. In the chronic phase of chikungunya fever, NSAIDs are recommended, taking into consideration the clinical context, contraindications and therapeutic response. Agreement: 8.97 (SD ± 1.679). GRADE: low to very low quality of evidence

In patients with persistent localized or diffuse musculoskeletal pain, without inflammatory signs and with more than 3 months of illness, simple analgesics or weak opioids should be used, depending on the pain intensity,[15] at the same doses recommended for the acute or subacute phases.

Longitudinal studies have shown high use of analgesics in the chronic phase: 72% after 36 months[16] and 93% after 15 months of chikungunya fever.[17] However, only 34% patients were satisfied with this pharmacological approach.[17] The treatment may be optimized by combining analgesics with NSAIDs, local anti-inflammatory therapies (joint or peritendinous infiltration) and physical therapy; the therapeutic effectiveness is maintained in the medium-term (weeks).[5]

Although some studies show good clinical response using NSAIDs alone,[9,12] they are retrospective studies and were not designed to evaluate this outcome. However, in clinical

practice, NSAIDs may be used in any patient with chikungunya fever showing refractory pain or intolerance to the use of simple analgesics and opioids, whether or not the symptoms are related to inflammatory manifestations.

In the study by Rosario et al.,[12] although 89% of patients reported a satisfactory response in pain improvement using an NSAID, 72% of them subsequently required the use of CS.[12] Sissoko et al. reported that only 1/3 patients using a combination of analgesics and NSAIDs after 15 months of treatment of chikungunya fever reported satisfactory responses.[17]

Cases progressing to the subacute and chronic forms require a more careful evaluation from the musculoskeletal standpoint, which must be performed by the rheumatologist; the follow-up may be performed by the general practitioner. The physical examination should be focused on the articular and periarticular involvement; tendon involvement should be thoroughly researched. Other associated manifestations should be assessed: lack of appetite, non-restorative sleep, impairment of work and daily activities, urinary urgency and incontinence, mood changes and depression.

C.5. In the chronic phase of chikungunya fever, oral corticosteroids may be used for musculoskeletal and neuropathic complaints, and low doses are recommended (5–20 mg/day prednisone or prednisolone). The time of use may range from 6 to 8 weeks, and withdrawal should be slow and gradual due to the risk of recurrence of joint symptoms. Agreement: 9.24 (SD ± 1.154). GRADE: low to very low quality of evidence.

Most patients (approximately 70%) with chronic symptoms associated with chikungunya fever use oral CS, with good clinical response rates[12,16–18] and high levels of satisfaction.[17] However, although the efficacy of using CS in this phase is well established, the existing evidence on the optimal dose and time of use is controversial.

In a cohort study from the Dominican Republic, very low doses of prednisone/prednisolone (5–7.5 mg/day) or deflazacort (6 mg/day) were used, with excellent clinical response after 6–8 weeks.[12]

The French guideline recommends using a low CS dose (10 mg/day) for up to 5 days and gradually reducing it until the tenth day; the CS should be used in moderation after the failure of the initial treatment of musculoskeletal symptoms (tenosynovitis/distal edematous polyarthralgia and compressive neuropathy); NSAIDs should be used after CS withdrawal to avoid clinical worsening.[5,18]

In Brazil, the MH's clinical management protocol of chikungunya fever recommends using 0.5 mg/kg/day prednisone (40 mg/day maximum dose), for a maximum period of 3 weeks; longer than this time, in the absence of a response, and combining opioids with the discontinuation or not of the CS should be considered, depending on the clinical response and on the absence of adverse events.[6,7]

The patients participating in the CHIKBRASIL cohort study were prescribed prednisone in 64% cases, with a mean dose of 15 mg/day. At the first return visit (on average, 4 weeks after the initial visit), patients treated with CS showed a more significant improvement in the overall assessment, number of painful and swollen joints; as observed in the subacute phase analysis, patients who used a dose higher than or equal to 10 mg/day showed a better response. However, when the improvement of these same parameters was analyzed, comparing the dose of 10 mg with higher doses, no significant difference was observed (unpublished data).

An important issue raised in the discussion was the recurrence of joint symptoms in patients for whom the CS was withdrawn rapidly after clinical improvement (expert opinion). Thus, we recommend using doses ranging from 5 to 20 mg/day, for 6–8 weeks, with a slow and gradual withdrawal, depending on the clinical response. In cases precluding withdrawing the CS after this period, the patients should be moved to the second stage of treatment of the chronic phase, with introduction of methotrexate and/or HCQ (recommendations C6 and C7). An improvement in the symptoms of neuropathic pain was also observed by the specialists when using oral CS, which may be used alone or in combination with antidepressants or anticonvulsants.

The risk/benefit ratio of using CS should be considered in patients with DM, poorly controlled SAH, documented history of fracture due to osteoporosis, bipolar mood disorder, chronic renal failure on dialysis, Cushing's syndrome, grade III obesity, arrhythmias and coronary diseases. When choosing to prescribe CS, the lowest dose should be used for the shortest time possible, with strict clinical and laboratory surveillance (expert opinion).

Intra-articular or peritendinous infiltration can also be used as a therapeutic approach in this phase, with good results.[5]

C.6. In the chronic phase of chikungunya fever, antimalarials, preferably hydroxychloroquine, may be used for the treatment of joint symptoms, alone or in combination with MTX or SSZ. Agreement: 9.21 (SD ± 1.166). GRADE: low quality of evidence

Similar to the acute and subacute phases, treatment with antimalarials in the chronic phase lacks consistent evidence and may be the most controversial therapeutic issue.

Ravindran et al.[19] evaluated patients using HCQ 200 mg/day and with active disease, defined by at least 3 swollen joints, 6 painful joints and erythrocyte sedimentation rate (ESR) >28 mm/1st hour. The patients were randomized into 2 groups: 37 patients continued using HCQ in monotherapy (dose optimized to 400 mg/day), and 35 began a combined scheme of HCQ, methotrexate (MTX, 15 mg/week) and sulfasalazine (SSZ, 1 g/day). After 24 weeks, the group using the combined therapy showed significant improvements in all parameters of disease activity. It should be noted that the sample of this study was small and the patients were randomized to compare the use of HCQ alone and the combined HCQ-MTX-SSZ therapy in a group that had already shown therapeutic failure with HCQ.

Chopra et al.[13] conducted a randomized study lasting 24 weeks in which the patients were allocated for treatment with meloxicam (7.5 mg/day) or chloroquine (250 mg/day). At the end of the follow-up time, the patients showed a significant improvement in pain based on the VAS, number of painful and swollen joints, joint function and ESR in both groups. Although the difference was numerically

higher in the chloroquine group, there was no significant difference in efficacy between the groups. These results suggest that using antimalarials in patients with contraindications to the use of NSAIDs could be an effective option for the treatment of chronic joint pain in chikungunya fever.

Another randomized study[20] assessed the efficacy of chloroquine (150 mg/day) compared with paracetamol (500 mg/day) in improving pain in 86 patients with chikungunya fever. A benefit in pain relief in favor of chloroquine was observed, with a significant difference for pain classified as mild to moderate. However, the follow-up was limited to 8 days, and both groups used low doses.

Published case series report controversial results. The first, published in 1984,[21] evaluated ten patients with arthritis following chikungunya fever treated with chloroquine for 20 weeks and observed improvements in the Ritchie articular index, morning stiffness and general physician and patient assessments. In the cohort from Reunion Island, only 18% of patients were treated with HCQ and failed to show an adequate response for diffuse joint symptoms; no information on the time of use was reported.[18]

The existing treatment protocols for chikungunya fever also lack uniformity regarding the use of antimalarials. The World Health Organization (WHO) recommends the use of HCQ (200 mg/day) or chloroquine (300 mg/day) for a period of 4 weeks, when arthralgia is refractory to other medications.[8] The French guideline did not validate the use of HCQ in patients with chikungunya fever and chronic symptoms, considering it an indication restricted to isolated cases when the use of MTX or SSZ is contraindicated.[5] The Brazilian MH recommends HCQ in the chronic phase of chikungunya fever, at the maximum dose of 600 mg/day for a 6-week period, which may be combined with analgesics in cases of persistent mild to moderate pain.[6,7]

In the CHIKBRASIL cohort, HCQ (400 mg/day) was prescribed in 47.1% cases. In the first follow-up visit, after 4 weeks on average, a clearer improvement in the number of painful and swollen joints was observed compared with patients not treated with HCQ, although the difference was not statistically significant (unpublished data). Thus, we recommend using antimalarials, particularly HCQ, for the treatment of the chronic phase of chikungunya fever in mild to moderate cases. In addition to its known effects in pain control and joint inflammation[22] and its potential antiviral activity,[23] HCQ is a more easily used drug than MTX for general practitioners.

Classically, the recommended daily dose of HCQ is 6.5 mg/kg/day, considering the ideal weight and not the actual weight of the patient, to reduce the risk of toxicity.[24] However, a more recent study, which calculated the dose using the actual weight, showed that doses higher than 5 mg/kg/day increase the risk of retinal toxicity by 10% after 10 years, reaching 40% in 20 years.[25] Therefore, the new recommendations from the American Academy of Ophthalmology (2016) indicate lower doses (5 mg/kg/day, 400 mg/day maximum) and using the actual weight to reduce the risk of ocular toxicity (Table 2).[26]

C.7. In patients with chikungunya fever progressing to the chronic phase and with inflammatory joint disease, with difficulties in CS withdrawal, we preferentially suggest MTX at doses ranging from 10 to 25 mg/week. Agreement: 9.43 (SD ± 0.858). GRADE: low to very low quality of evidence.

Many longitudinal follow-up studies of patients in the chronic phase of chikungunya fever include MTX in the management of joint symptoms, although most of them are uncontrolled open studies or case series.

Ravindran et al.[19] conducted an uncontrolled, open study that included patients with more than 1 year of arthritis post-infection with CHIKV who failed to respond to the use of HCQ alone. After 24 months of follow-up, the group in which MTX (15 mg/week) and SSZ (1 g/day) were combined with HCQ obtained a better clinical response than those who continued using HCQ alone. Another uncontrolled study evaluated for 16 weeks the combination of MTX (15 mg/week) with HCQ in 149 patients with more than 3 months of joint symptoms post-infection with CHIKV. After this period, 48.9% of patients showed improvements of at least 20% in the number of painful and swollen joints, combined with improvements in at least 3–5 parameters: (1) patient's evaluation, (2) physician's evaluation, (3) pain scale, (4) disability questionnaire and (5) acute-phase reactants.[27]

In Reunion Island, of 159 patients who developed rheumatic disease established post-infection with CHIKV, 77% were treated with MTX (15 mg weekly mean dose). After a mean period of 25 months, 75% of cases showed a positive response to MTX.[18]

In the Dominican Republic cohort, 5 patients (0.97%) required the use of MTX (12.5–15 mg/week), which was included in the treatment when reducing the CS was difficult and was used for a maximum of 3 months.[12]

In Martinique, 27 patients with chronic arthropathy caused by chikungunya fever (without previous rheumatologic diagnosis) were treated with MTX (21 mg/week mean dose), with good responses in 21 cases (77.7%) and a mean follow-up time of 6 months.[15]

In Brazil, the MH's protocol recommends using MTX only after therapeutic failure with HCQ and SSZ (2 g/day), for at least 6 weeks, with persistent moderate and severe pain (VAS ≥4).[6,7] Conversely, the French consensus recommends MTX as the first-choice drug for the treatment of chronic inflammatory joint disease (CIJD) post-infection with CHIKV, following the same recommendations used for the treatment of rheumatoid arthritis (RA) or undifferentiated arthritis.[5,28]

In the CHIKBRASIL cohort, 5.8% of the 431 patients were prescribed MTX in the study inclusion visit at a 13 mg/week mean dose. In this group, all patients presented arthritis and arthralgia after an average of 13 weeks of disease, with a VAS for pain ranging from moderate to severe in 88% of cases. It is interesting to note that MTX was initiated in 56% patients who had not previously used HCQ or CS, and the decision was made based on the severity of the joint manifestations.

The first evaluation performed after an average of 4 weeks of prescription showed improvements in both the general VAS and the number of painful and swollen joints. However,

the follow-up time of these patients was still short, which precludes further conclusions on the long-term efficacy of MTX in patients with chikungunya fever.

Thus, we recommend initiating treatment with MTX in patients with chikungunya fever in the chronic phase and persistence of joint symptoms or when facing difficulties in CS withdrawal (after 6–8 weeks of use), at the minimum initial dose of 10 mg/week. Treatment should be reassessed every 4 weeks, with a gradual dose increase up to a maximum of 25 mg/week in cases of partial response. Table 2 outlines the initial assessment for prescription and monitoring of adverse events with MTX.

The various studies lack a consensus on the ideal time when MTX should be used in the chronic phase of chikungunya fever or when it should be discontinued. In our experience, we observed that a minimum use time of 3 months may lead to complete symptom remission, without relapses after withdrawal (expert opinion).

There are no studies involving leflunomide for the treatment of chronic arthropathy following chikungunya fever. The French guidelines indicate their use according to the recommendations for treatment of RA, after MTX treatment failure; however, there is no evidence supporting this recommendation.[5] There is only 1 case report describing improvements in subacute and chronic joint symptoms when using colchicine 0.6 mg 2 x day (for 6 months) after celecoxib failure.[29]

Patients with disease time longer than 6 weeks, with persistent arthritis/tenosynovitis symptoms or the onset of bone erosions requiring immunosuppressive treatment should be monitored by the rheumatologist.

C.8. In the chronic phase of chikungunya fever, sulfasalazine may be used at a dose of 2–3 g/day, alone or in combination, especially in patients with contraindication to or failure with MTX. Agreement: 8.77 (SD ± 1.794). GRADE: low to very low quality of evidence.

There are few studies evaluating the use of SSZ in the chronic phase of chikungunya fever, and they were all case series without a detailed description of efficacy.

The study by Ravindran et al.[19] showed good response in only 12.5% of 16 patients who used SSZ as monotherapy in the chronic phase of chikungunya fever. When combined with MTX, the response increased to 71.4%. It should be noted that all cases included had already used HCQ (200 mg/day) and NSAIDs.

Bouquillard et al.[30] reported the use of SSZ in 3 of 21 patients who progressed to RA (according to the American College of Rheumatology (ACR) criteria) after infection with CHIKV. Although no detailed description of the response was reported, radiographic progression was observed in most patients, despite the use of disease-modifying antirheumatic drugs (DMARDs), including HCQ, MTX and SSZ.

The French guideline suggests using SSZ as a second-line drug treatment for chikungunya fever.[5] Conversely, the Brazilian MH protocol recommends using SSZ as a first-line DMARD, before MTX.[6,7]

In the CHIKBRASIL cohort, SSZ was prescribed to only 4 patients (0.9% of cases). Three of them showed inflammatory neck and low back pain, which may have influenced the choice of SSZ over MTX, although we lack sufficient data to state that, in these cases, SSZ may be the best option (expert opinion).

Our recommendation is that SSZ be used as an alternative in cases of therapeutic failure or contraindication to the use of MTX, at doses of 1–2 g/day, or according to the opinion and clinical experience of the prescribing physician. Prescription precautions and monitoring recommendations for SSZ are outlined in Table 2.

C.9. Biological therapy may be prescribed after rheumatologist evaluation of patients with chronic inflammatory joint disease post-infection with CHIKV, refractory to the use of CS and DMARDs, following the recommendations used to treat rheumatoid arthritis or spondyloarthritis. Agreement: 8.97 (SD ± 1.267). GRADE: low to very low quality of evidence.

Biological therapy, also known as biological DMARDs (bDMARDs), is considered the breakthrough of the last decade in the treatment of chronic inflammatory diseases, including RA, spondyloarthritis (SpAs) and inflammatory bowel disease (IBD). Tumor necrosis factor inhibitors (anti-TNF), the first class of bDMARDs to be used in rheumatologic clinical practice, has been a safe and effective therapeutic option for the control of disease activity, radiographic progression and functional impairment in both RA and ankylosing spondylitis (AS) and psoriatic arthritis (PsA).[31–33]

There are some reports of anti-TNF use in patients with chronic joint symptoms of chikungunya fever. In the Martinique cohort, 6 patients (23.3%) had to use anti-TNF after failure with MTX, HCQ and CS, with good joint response and no adverse events. The efficacy was as expected according to the symptoms for which they were used.[15] In the Reunion Island cohort, after 6 years of follow-up, anti-TNF was prescribed in 12 (12.8%) of the 94 patients who developed rheumatic disease following chikungunya fever after MTX failure.[18] The French guideline recommends using biological therapy in cases that progress to RA or SpA, after treatment failure with DMARDs, and the same prescription precautions and recommendations indicated for each particular disease should be followed.[5]

It should be noted that although CHIKV infection has behavior similar to that of RA or AS, chikungunya fever is a different disease. The rationale for using immunobiologicals for chikungunya fever was extrapolated from the experience in RA and SpAs, and similarly to MTX and SSZ, these drugs were not evaluated in clinical trials for use in patients with chronic infection with CHIKV.

We recommend that when inflammatory joint activity persists even after using CS, HCQ, MTX and SSZ, anti-TNFs should be prescribed, exclusively by the rheumatologist, after careful clinical evaluation, considering the cost of and patient access to the medication. Thus far, anti-TNFs are only prescribed in the public health network for RA, SpA, PsA, IBD and juvenile idiopathic arthritis.

Table 3 – Physical therapy treatment modalities recommended for the acute, subacute and chronic phases of chikungunya fever.

Objectives	Acute phase	Subacute and chronic phases
Pain and swelling reduction	Cryotherapy TENS Manual therapy Compression bandages	Electrothermal therapy and phototherapy (ultrasound, low-power laser) Manual therapy Aquatic physical therapy
Maintenance of joint function	Light, active exercise (caution) Orthoses	Manual therapy Therapeutic exercises: passive and free and resisted active exercises – progressive Stretching Proprioceptive training Aquatic physical therapy
Physical fitness improvement		Aerobic exercise
Posture	Avoid painful postures Adoption of decubitus positions favoring venous return	Stretching
Avoid	Use of heat – may worsen the inflammatory response	Prolonged joint immobilization
Patient education	Advice about the disease Strategies supporting treatment Adjustment of environmental and individual factors that may affect the course of the disease	

TENS, transcutaneous electrical nerve stimulation.

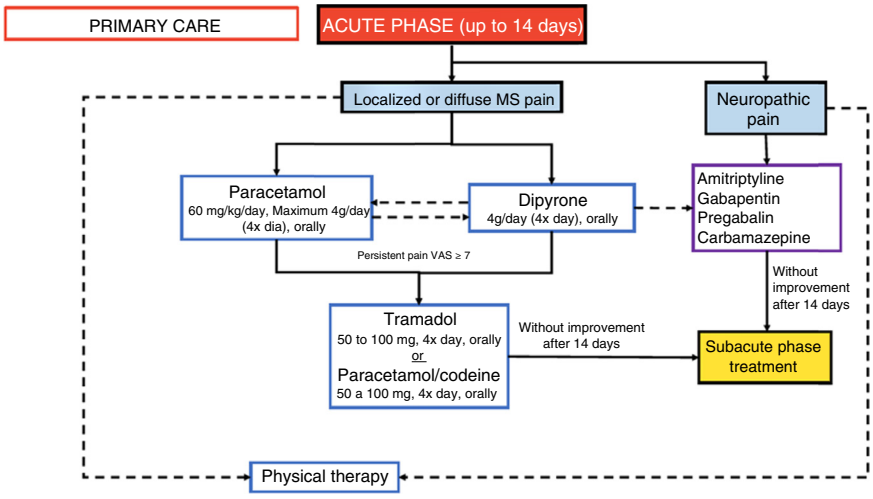

Figure 1 – Treatment flowchart of the acute phase of chikungunya fever according to the recommendations from the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia – SBR).
MS, musculoskeletal; VAS, visual analogue scale.

C.10. During the acute phase, in patients using DMARDs or biological therapy for the treatment of their underlying disease, the medication should be discontinued. However, the treatment may be maintained in the subacute and chronic phases. Agreement: 8.97 (SD ± 1.884). GRADE: low to very low quality of evidence.

The existing data on chikungunya fever in patients with prior rheumatologic diseases are scarce and derived from case series published during epidemics in other countries. However, all studies agree that there seems to be no risk of worsening of the viral condition or complications resulting from treatment with immunosuppressants or immunomodulators in this group of patients, in contrast to other types of viral infection.[12,15,34,35]

Rosario et al.[12] evaluated a group of 53 Colombian patients with RA treated with biologics who showed musculoskeletal manifestations of chikungunya fever: symmetric polyarthralgia (96.2%), arthritis (47.1%) and tendinopathy (24.5%). Most patients responded to NSAIDs (51/53), and 23 patients partly responded; a total of 25 patients (47.1%) required a low dose of steroids. There was no need to change the treatment with DMARDs, including biological therapy. Patients with RA were followed up for 10 months, responded well to symptomatic therapy and showed no serious complications.

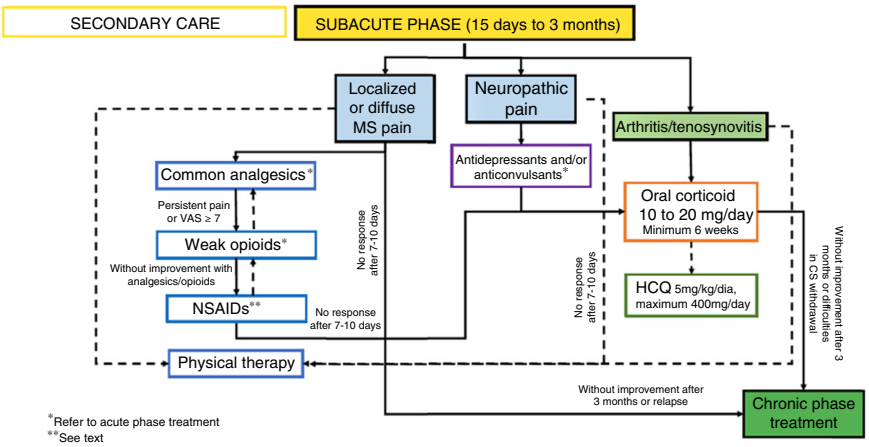

Figure 2 – Treatment flowchart for the subacute phase of chikungunya Fever according to the recommendations of the Brazilian Society of Rheumatology.
MS, musculoskeletal; VAS, visual analogue scale; NSAID, nonsteroidal anti-inflammatory drug; HCQ, hydroxychloroquine.

In the epidemic in Martinique,[36] 22 patients with infection with CHIKV using bDMARDs and synthetic DMARDs for the treatment of previous rheumatologic diseases were studied: 17 patients used MTX (21.6 mg/week mean dose), 3 used HCQ, 2 used azathioprine, 1 used mycophenolate mofetil (MMF) and 2 used cyclophosphamide. Of the 22 patients, 11 used corticoids (8.6 mg/day mean dose). There were no complications or hospitalizations due to infection with CHIKV. Treatment performed with analgesia alone (4/22), combined with a NSAIDs (17/22) or prednisone (1/22) and rest, sufficed to control the crisis. The basic treatment was maintained for all patients (except 1), with no complications (DMARDs, biologics and immunosuppressants) and with the same result as that observed in other studies.[15,35]

Studies conducted at other sites of epidemics have shown that, although there seemed to be no complications resulting from the use of DMARDs or bDMARDs, if the disease became active in some patients with previous rheumatologic disease, these patients required treatment intensification. In Reunion Island,[18] of 159 study patients, 18 had previous rheumatologic disease (6 RA, 8 SpA, 2 systemic lupus erythematosus (SLE) and 2 chronic hepatitis with joint manifestations), who worsened immediately after infection with CHIKV. Most of these patients required systemic CS therapy (70%), and complete withdrawal was only possible in half of the cases; 8 patients required MTX initiation, with treatment failure in 6, who were switched to biologics. Three patients with RA, previously controlled with MTX, required switching to biologics, and improvements were observed in the 3 cases. Similarly, Blettery et al.[15] observed a reactivation of the previous disease in patients with SpA and seronegative RA, which led to an intensification or initiation of treatment with DMARDs or bDMARDs. Tolerance was good, without any viral infection recurrence or complications.

Another study conducted in Martinique[37] described 56 patients with SLE and positive serology for CHIKV using immunosuppressants (33.9%), antimalarials (86.8%) and prednisone (64.8%); 3 patients used rituximab. Although the prognosis of SLE patients is more severe than that observed in RA, with the induction of disease activity and severe manifestations, the use of immunosuppressive drugs seems to have no effect on the clinical symptoms of chikungunya fever.

An active search for symptoms of chikungunya fever was performed in patients included in the Brazilian Registry of Biological Therapies (Registro Brasileiro de Medicamentos Biológicos – BIOBADABRASIL)[38] in 4 centers of the Brazilian Northeast. At the time of data collection (2016), 358 patients were included in the registry, and 112 patients were contacted by telephone. The other patients had outdated or deactivated telephone numbers. These contacted patients were asked about the presence of typical symptoms of CHIKV infection. Patients with compatible symptoms were evaluated in person through a structured interview in which disease characteristics were identified, and the diagnosis was performed using clinical-epidemiological criteria. Among the 112 patients interviewed, 30 cases of chikungunya fever (27%) were identified, according to the MH clinical-epidemiological criteria. Thirteen of these patients were using bDMARDs, and 17 were using DMARDs. No significant differences in clinical manifestations were observed when comparing the groups. Interestingly, at the onset of chikungunya fever symptoms, 76% of patients were in remission, and only 15% reported that their joint manifestations were similar to those of their underlying disease. The other patients reported much higher pain intensity, and its location was different from other exacerbations of their prior disease. No complications were observed in any of the treatment groups.

The experience gained with patients using bDMARDs treated in the CHIKBRASIL cohort identifies 3 types of chikungunya fever progression: (a) milder clinical manifestations and with shorter progression time than that of patients without prior disease; (b) possibility of disease reactivation requiring changing the DMARDs or bDMARDs and (c) patients without chikungunya fever symptoms (possibly subclinical infection), although all household contacts showed typical clinical symptoms.

Although there is no evidence of complications, even in cases that inadvertently used DMARDs, we recommend the discontinuation of drugs during the acute phase; these drugs

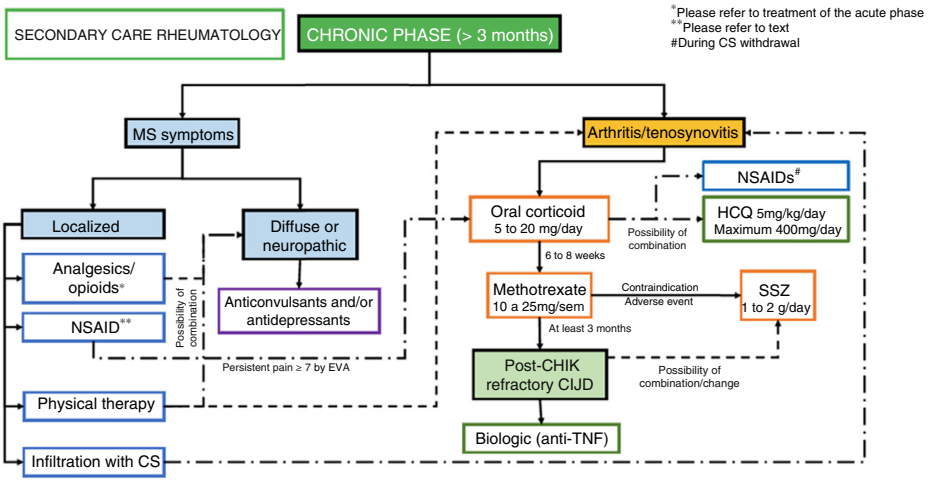

Figure 3 – Treatment flowchart of the chronic phase of chikungunya fever according to the recommendations of the Brazilian Society of Rheumatology.
MS, musculoskeletal; VAS, visual analogue scale; NSAID, nonsteroidal anti-inflammatory drug; CS, corticosteroid; HCQ, hydroxychloroquine; SSZ, sulfasalazine; CIJD, chronic inflammatory joint disease.

can be continued during the subacute and chronic phases. In the case of reactivation of the underlying disease, without response to the treatment in use, we recommend changing the drug treatment, as recommended for each disease.

C.11. Rehabilitation interventions are recommended at all phases of chikungunya fever as a complementary non-pharmacological measure. In the acute phase, analgesics and anti-inflammatory therapy are indicated, and the use of heat should be avoided; furthermore, patient education, posture guidelines and manual therapy should be recommended, in addition to light-intensity exercise. In the subacute and chronic phases, the previous recommendations should be followed, which may include heat and active free, resisted, proprioceptive and aerobic exercises, stretching, manual therapy and aquatic physical therapy. Agreement: 9.43 (SD ± 0.935). GRADE: very low quality of evidence.

In the acute phase, physical therapy includes the resources indicated for pain relief and swelling reduction[8] and may contribute to limiting the persistence of these symptoms and progression to the subacute and chronic phases of the disease (expert opinion). Among the resources, cryotherapy favors analgesia and helps reduce local swelling and joint inflammation.[5,8,39] Transcutaneous electrical nerve stimulation (TENS) is another useful resource for pain relief, as some studies have shown satisfactory results in patients with RA.[40–44] TENS is mainly indicated for patients with persistent pain, even when using analgesic and anti-inflammatory drugs, and for cases of neuropathic pain (Simon et al., 2015).[5]

Manual therapy methods may also be applied in this phase, including manual lymphatic drainage, which may be combined with the use of compression bandages.[5] This method is indicated because it improves lymphatic circulation[45,46] in cases of extra-articular swelling, especially in the presence of lymphedema. This complication has been frequently observed in cases of CHIKV infection.

Light-intensity, active exercise should be recommended to maintain joint function, with caution not to exacerbate inflammatory symptoms.[5,8,39] Relative rest must be indicated, avoiding pain-triggering movements[8,39]; accordingly, orthoses may be used.[5]

Posture guidelines are crucial in this phase. The adoption of antalgic postures should be avoided, and decubitus positions favoring the return circulation should be recommended[5] (expert opinion). In this phase, the use of heat should be avoided to prevent increasing the internal temperature of joints or exacerbating the inflammatory response.[8]

Patient education is a key resource to promote knowledge on the disease and strategies that might help the treatment, in addition to the adjustment of environmental and individual factors that may affect the course of the disease (expert opinion).

Several studies indicate the use of a physiotherapeutic approach in the subacute and chronic phases of chikungunya fever. However, most of these studies do not describe which therapies were used in their treatment protocols.[8,15,18,39,47,48] In these phases, when the initial inflammatory symptoms persist, the same resources used in the acute phase may be applied, and other therapies should be included in the treatment of musculoskeletal manifestations that occur as the disease progresses.[5]

Electrothermal and phototherapeutic resources, including low-power laser and ultrasound, may help to control symptoms in joint and tendon inflammatory processes, despite their low levels of evidence for the treatment of musculoskeletal diseases.[40,41,43,44]

Exercise therapy is the most mentioned in the literature[8,15,18,39,47,48] because dynamic methods have acquired a good level of evidence for the treatment of inflammatory injuries, as observed in persistent symptoms after CHIKV infection. Passive, free active and resisted active exercises may be progressively introduced (isometric followed by isotonic and isokinetic muscle contractions) aiming at

maintaining or gaining joint range of motion (ROM) and muscle strength and endurance.[5] Stretching exercises contribute to maintaining muscle-tendon flexibility and preventing postural changes.[49] Proprioceptive training also includes treatment, providing stimuli for movement reeducation and the recovery of functional skills. Aerobic exercises are indicated to improve the patient's general physical fitness and to reduce fatigue.[5]

Manual therapeutic resources, such as soft tissue mobilization and joint mobilization techniques, are indicated for muscle relaxation, reducing muscle tension and restoring painless ROM and are useful for recovery from tendonitis, tenosynovitis, arthritis and arthralgia.[5]

Aquatic physiotherapy may relieve pain, reduce swelling and improve joint mobility and functional skills in different phases of chikungunya fever, as occurs in other rheumatologic diseases[50–55] (Table 3).

Figs. 1–3 summarize the recommendations for the treatment of chikungunya fever in each phase (acute, subacute and chronic) based on level of care complexity.

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Conflicts of interest

The authors declare no conflicts of interest.

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