Pharmacologic management of pain in patients with Chikungunya: a guideline

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Abstract

From the arrival of Chikungunya virus in the Americas in 2013 until March 2016, approximately two million cases of the disease have been reported. In Brazil, the virus was identified in 2014 and thousands of people have been affected. CHIKV is a single-stranded ribonucleic acid (RNA) virus of the Togaviridae family and the Alphavirus genus with three sub-types (two African and one Asian). The Aedes aegypti and Aedes albopictus mosquitoes are the main vectors involved in the transmission of CHIKV. Approximately 90% of individuals infected with CHIKV present with symptomatic infection. The disease may evolve in three phases: acute or febrile (lasting up to 10 days), subacute (11-90 days), and chronic (> 90 days). Approximately 50% of people who experience acute infection develop chronic joint pain that can last months to years. On Reunion Island, it was reported that 3 months after the acute infection, 80-93% of patients had chronic disease; after 15 months, 57% did, and after 2 years 47% of patients had chronic involvement[1,2].

The joint pain in the different phases of Chikungunya disease causes important physical incapacity that significantly impacts the quality of life of affected patients. In a study by

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symptoms remains unresolved. The inflammatory response associated with infection by alphaviruses, the cause of persistent failure/success of the drug administered. Given this need, a protocol for the pharmacologic treatment of acute and chronic group of specialists from different fields collaborated to produce a protocol for the pharmacologic treatment of acute and chronic according to the intensity of the pain and reassessment after also a lack of systematized practice of using staggered therapy such as dipyrone, often in sub-therapeutics doses. There is not familiar with how to approach the treatment of pain in the majority of published studies, and guidelines are limited to stating the drugs used in pain treatment. The majority of published studies and guidelines are limited to stating the drugs used in pain treatment, which include: dipyrone, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, codeine, and morphine. The use of methotrexate, chloroquine, and sulfasalazine has also been reported in patients with chronic pain(1) (6) (7) (8) (9) (10). A significant proportion of physicians are not familiar with how to approach the treatment of pain in Chikungunya, with frequent prescriptions limited to analgesics such as dipyrone, often in sub-therapeutics doses. There is also a lack of systematized practice of using staggered therapy according to the intensity of the pain and reassessment after failure/success of the drug administered. Given this need, a group of specialists from different fields collaborated to produce a protocol for the pharmacologic treatment of acute and chronic Chikungunya-associated joint pain; it is presented in this review.

THE PATHOPHYSIOLOGY OF THE PAIN OF CHIKUNGUNYA

Despite the improved understanding of joint damage associated with infection by alphaviruses, the cause of persistent symptoms remains unresolved. The inflammatory response of the host, the presence of viral products in macrophages and joint tissues, and auto-immune process may be involved in the pathogenesis. Different joint manifestations during different phases of Chikungunya fever have been described in the literature, including arthralgia, inflammatory arthritis, synovitis, enthesisis, tenosynovitis, and bursitis(11). Experimental models of arthritis induced by alphaviruses suggest that the pathogenesis is the result of a combination of direct tissue and cell damage caused by viral replication and indirect immune activation responses in the target tissues(12). Different cytokines, chemokines, and other inflammatory mediators are produced; these are related to the intensity of inflammation in the acute phase; are involved in the recruitment of macrophages, natural killer cells, and T lymphocytes to the site of viral replication; and cause dysregulation of inflammation in this stage, leading to the expression of other inflammatory proteins responsible for damaging the joint in the chronic phase(12)(13)(14)(15).

Viral persistence could also be a cause of chronic joint disease in a subgroup of patients. The presence of immunoglobulin M (IgM) antibodies detected months after the acute infection suggests persistence of the virus or its antigens; this may perpetuate the inflammatory process in the joints(16). In an outbreak in Italy, Moro et al. reported that IgM was detected in 52% (131/249) of patients within 5 months of the contracting disease and in 13.2% (30/227) with 12 months of disease evolution(17). Other risk factors associated with progression to a chronic form include age >35 years, marked joint impairment in the acute phase, and pre-existing prior joint disease(6) (9) (18). Some patients have polymorphisms of the human leukocyte antigens (HLA) that are associated with rheumatic diseases, such as HLA-27. These HLA polymorphisms may be involved in the pathogenesis of the disease(11)(12).

A sub-group of patients present with neuropathic-type pain(9). Neuropathic pain syndromes are caused by lesions in or dysfunction of the nervous system; they do not directly depend on an inflammatory processes, but involve specific changes in central and peripheral nociceptive processes(19). Therefore, it seems that the mechanisms are multifactorial and may different between patients. A clear understanding of the pathophysiologic mechanisms in patients with Chikungunya will have a direct bearing on the choice of ideal therapeutic agent to relieve the pain.

CLINICAL AND LABORATORY DIAGNOSIS OF CHIKUNGUNYA-ASSOCIATED ARTHRITIS/ARTHRALGIA

A suspected case of Chikungunya is defined as a fever of sudden onset, higher than 38.5°C, and intense arthralgia or arthritis not explained by other conditions in a person resident of or having visited an endemic or epidemic area up to two weeks before the beginning of the symptoms, or with an epidemiologic link to a confirmed case. The differential diagnosis includes infections caused by other virus or bacteria, as well as rheumatologic diseases that have fever as a symptom. Other arbovirus that are frequent and may circle at the same time and in the same epidemic areas, mainly dengue and Zika, must be borne in mind. In areas where it circulates, Mayaro virus,
an alphavirus that has arthralgia as symptom of infection, must also be considered\(^{(1)}\).

The laboratory diagnosis of Chikungunya in the first 5-7 days includes techniques for the detection of CHIKV genome [reverse transcription polymerase chain reaction (RT-PCR) and/or real-time RT-PCR] and viral isolation in cell cultures. Specific anti-CHIKV IgM antibodies are formed during the first week of the disease and may be detected from the seventh day on\(^{(1)}\). Specific examination and testing are only routinely performed in the periods between epidemics in order to detect the first cases and identify the start of an epidemic. However, once sustained transmission has been established, not all patients require laboratory confirmation. In this context, laboratory investigation is reserved for patients with alarm signs, severe cases, those with atypical manifestations, or in cases of difficult differential diagnosis. The diagnosis may be confirmed based on clinical-epidemiological criteria\(^{(1)}\). In the sub-acute and chronic phases of arthralgia, a history of having had an episode of acute fever with associated edema and joint pain during an epidemic period (clinical-epidemiologic criteria) dispenses with the need to perform serologic tests in patients that seek assistance for the treatment of pain. For patients not responding to initial analgesic therapy, serologic tests for Chikungunya [IgM, immunoglobulin G (IgG)] and tests in search of other etiologies must be performed, at the discretion of the specialist. Non-specific tests, such as a complete blood count, may be requested in the acute phase and biochemical tests such as transaminases, creatinine, and electrolytes may be necessary in at-risk patients or those who are severely ill\(^{(1)}\).

In the chronic phase, for patients that do not respond to treatment, autoantibodies (rheumatoid factor; anti-citrullinated protein antibody; and anti-nuclear antibodies) and molecular markers (HLA-B27) must be requested, according to the disease suspected, as the differential diagnosis includes chronic inflammatory arthritides\(^{(20)}\).

**STAGGERED APPROACH TO MANAGEMENT OF ACUTE AND CHRONIC PAIN**

Treatment involves all phases of the disease and cannot focus only on the sub-acute and chronic stages; it should be effective even during the first few days of experiencing symptoms. Neuroscientific studies have established that inadequately treated acute pain is one of the main causes of chronic pain, which then triggers other symptoms such as depression, fatigue, and sleeping disorders. This natural history is no different when it comes to Chikungunya. Therefore, an effective approach to control the pain is needed. This will also serve to decrease the duration of this clinical disease. The flowcharts contained in this document address the management of pain in different stages of the disease, aiming to increase the effectiveness of the available pharmacologic therapies (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7 and Figure 8).

**Pain measurement**

To institute a pain management protocol, it is essential to have a tool that allows the measurement of pain, and that can transform subjective data into objective data; this enables proper assessment and management. Without this, it becomes difficult to determine if a treatment is necessary, if the prescription is effective, or if it should be interrupted or substituted\(^{(21)}\).

There are several validated tools to use; however, the VAS is one of the simplest and can be applied by any health professional (Figure 1 and Table 1). Another scale used widely in Brazil is the face scale. It can be used with small children and elderly people with cognitive deficits. However, despite the simplicity of the tool, it is important to remember that pain is a subjective perception and therefore, has a relationship with social, cognitive, and psychological aspects. It is necessary that while measuring pain, the patient should be informed of the importance of being truthful, and that there is an approach for each type of pain and numbering in order to avoid methodologic failures; patients often report a very high level of pain (9-10 in VAS) in fear of not receiving analgesics if the numbers are too low.

**PHARMACOLOGIC TREATMENT**

**Analgesics**

*Dipyrone and paracetamol:* these are good analgesics when administered in appropriate doses and at regular intervals (Figures 2, 3, 7 and Figure 8). Dipyrone can be prescribed at 30-50mg/kg/dose, 6 hourly. Paracetamol can be prescribed at 500-750mg, 6 hourly, but the total daily dose should not exceed at 4g because of possible hepatotoxicity. If the patient’s pain is perceived as mild (VAS 1-3) one of these two drugs should be prescribed, always in fixed, regular doses and never when necessary. In cases of moderate pain (VAS 4-6) both drugs should be prescribed together, at fixed times, and in an alternating fashion (i.e., the patient will take an analgesic dose every three hours).

**Opioids:** the opioid drugs are potent and safe analgesics, especially in cases of acute pain. Adverse effect monitoring is required, and the patient should be warned about adverse effects. In the doses usually prescribed by non-specialists in pain management, the risk of respiratory depression is very low; drowsiness and lethargy are the preceding warning signs (Figures 2, 3, 7, and Figure 8). Tramadol is a good choice when suspicious of a neuropathic component of intense pain as, besides its action on opioid receptors, it acts as an antagonist of NMDA (N-methyl-D-aspartate) receptor that are involved in chronic pain. Tramadol should be used in a dose of 50-100mg, 6 hourly. Codeine is an opioid that should be prescribed in a dose of 30mg every 6 hours and can be used with other analgesics.
Flowchart 1-A
Acute phase (0-14 days)

Always ask about any history of allergy to dipyrone

Do not use NSAID (Non-steroidal anti-inflammatory) and acetylsalicylic acid at acute phase, due to the risks of complications associated to severe forms of Chikungunya (hemorrhage and renal failure).

Corticoid in the acute phase of viremia may be associated to risks and complications

TABLE 1
FLACC scale, for children aged two months to seven years.

<table>
<thead>
<tr>
<th>Points</th>
<th>Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>No special expression or smile</td>
<td>Grinace or occasional frowning eyebrows, introversion, disinterest</td>
<td>Frequent chin trembling, tight jaw</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>Normal or relaxed</td>
<td>Agitated, restless, tense</td>
<td>Kicking or stretched legs</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>Quiet, in a normal position, moving easily</td>
<td>Stirs and contorts, moving back and forth, tense</td>
<td>Curved, stiff or sudden movements</td>
<td></td>
</tr>
<tr>
<td>Cry</td>
<td>No crying (awake or asleep)</td>
<td>Moans or whines; occasional complaining</td>
<td>Continuous cry, screaming or with the hiccups; complaining frequently</td>
<td></td>
</tr>
<tr>
<td>Console</td>
<td>Satisfied, relaxed</td>
<td>Calmed by touch, hugs, or occasional talks; can be distracted</td>
<td>Difficult to console or comfort</td>
<td></td>
</tr>
</tbody>
</table>

Observe children for 5 minutes, points 0-2 are assigned up to the maximum total of 10 points (intense pain). FLACC: Face, Legs, Activity, Cry, Consolability scale.

Flowchart 1-B
Assess intensity of the arthralgia using the VAS

Mild VAS = 1 to 3

Moderate VAS = 4 to 6

Severe VAS = 7 to 10

Apply questionnaire for neuropathic pain (DN4) [4], If the result is ≥ 4, use the protocol for neuropathic pain (Flowchart 1 B)

Dipyrone 1g every 6h or paracetamol 750mg every 6h, orally [1]

Dipyrone 1g and paracetamol 750mg, alternating every 3h, orally [2]

Dipyrone or paracetamol combined with an opioid: Tramadol 50mg every 6h or codeine 30mg every 6h or oxycodone 10mg every 12h, orally [3]

Reassess after 7 days

Pain persists?

No

Stop the medication

Yes

Reapply the pain scale (VAS) and DN4 questionnaire

Consider the use of corticosteroids according to the protocol (Sub-acute phase) in selected cases

[1] Analgesics: take in fixed, regular doses and never use when necessary.
[3] Opioids: in usual doses, the risk of respiratory depression is low. For intense pain not responsive to both drugs, combine two analgesics plus one opioid.
[4] DN4 Questionnaire annexed

Assess intensity of the arthralgia using the VAS

Moderate VAS = 4 to 6

Intense VAS = 7 to 10

Apply the neuropathic pain questionnaire of (DN4) [4]

Add amitriptyline 25 to 50mg once a day or gabapentin 300mg, every 12h (maximum daily dose 200mg) [5]

Reassess after 15 days

Yes No

Reapply the pain scale (VAS) and DN4 questionnaire

Consider using corticosteroids according to protocol (Sub-acute phase) in selected cases

Dipyrone or paracetamol combined with an opioid: Tramadol 50mg every 6 h or codeine 30mg every 6 h or oxycodone 10mg every 12h, orally [3]

Yes

No

Follow flowchart for non-neuropathic pain (Flowchart 1A)

DN4 ≥ 4 points?

Yes

Stop the medication

No

Pain persists?

Reassess after 15 days

Flowchart 1-B

If questionnaire is suggestive of neuropathic pain

Always ask about any history of allergy to dipyrone

In elderly people, avoid use of amitriptyline due to sedation risk. Use gabapentin instead, starting at low doses and increasing gradually. Do not use amitriptyline in patients with history of arrhythmia.

[5] The anti-depressants and anti-convulsants may need up to 2 weeks to show an effect.


Oxycodone is a synthetic opioid that has an extended-release formulation, allowing its prescription at intervals of 12 hours. The recommended dose is 10-20mg, 12 hourly (Figure 2).

NSAIDs and acetylsalicylic acid: despite the inflammatory component in the physiopathogenesis of the disease, NSAIDs should not be used due to the risk of complications associated with severe forms of Chikungunya (hemorrhage and renal insufficiency). Similarly, acetylsalicylic acid should not be used due to the risk of bleeding. In the acute phase, the differential diagnosis includes infection with other arbovirosis, such as Dengue, that are associated with thrombocytopenia; in such situations the use of these drugs is also contraindicated[11].

Corticosteroids: in the acute phase of viremia, corticosteroids can be associated with increased risks and complications.

Anti-convulsant and anti-depressant drugs

Neuropathic pain may be present if joint pain does not respond to the usual analgesics, making it necessary to add these therapeutic classes to treatment, after clinical confirmation (Figure 4 and Figure 7). In patients who experience severe and prolonged pain, it is recommended that the signs and symptoms of neuropathic pain be screened for using the Douleur Neuropathique 4 (DN4) questionnaire (Table 2). This is composed of two oral questions and two questions requiring a physical examination, totaling ten answers. If four or more answers are positive, the patient probably has a neuropathic component to their pain[22].

For these patients, the use of drugs that modulate the excitatory activity of the nervous system, such as amitriptyline and gabapentin, are indicated. Studies suggest that these drugs act by modulation of the lesion or dysfunction of the nervous system, reducing the nervous activity responsible for the maintenance of neuropathic pain. In elderly people, amitriptyline may lead to sedation, making it preferable to take gabapentin, starting in low doses. Patients with a medical history of arrhythmias should not take amitriptyline (opt for gabapentin). The use of gabapentin should be carefully considered and the dose should be optimized if the individual presents with sedation and drowsiness.

The role of corticosteroids (drugs of sub-acute phase)

The use of corticosteroids is indicated for the disease in its sub-acute phase in patients with moderate to severe pain...
### TABLE 2
DN4- Questionnaire used to diagnose neuropathic pain.

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient interview</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 1: Does the pain have one or more of the following characteristics?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Burning</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2. Painful cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Electric shocks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 2: Is the pain associated with one or more of the following symptoms in the same area?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Tingling</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. Pins and needles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Numbness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Itching</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Examination of the patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 3: Is the pain located in an area where the physical exam may reveal one or more of the following characteristics?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Hypoesthesia to touch</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9. Hypoesthesia to prick</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 4: In the painful area, can the pain be caused or increased by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Brushing</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Score

**Zero (0):** For each negative item. **One (1):** For each positive item.

The total score is calculated as the sum of the 10 items. The cut-off value for the diagnosis of neuropathic pain is a total score ≥4/10.
Venous access with administration of physiologic solution

Administer 30mg/kg of dipyrone in distilled water IV over 5 min

Reassess within 90 min

Hospital discharge with symptomatic orientation for home according to flowchart 1A-B

Patient feeling better, VAS < 4

Administer 50 mg of tramadol IV in 100mL of physiological solution over 20 min

Plus

Administer 10mg of bromopride IV in 8mL of distilled water [6]

No

Yes

Hospital discharge with symptomatic orientation for home according to flowchart 1A-B

Assess for another diagnosis, the other drugs available at the service, and the need for in-patient, hospital care.

[6] Nausea may be present, due to tramadol or the infection; thus, administer 10mg of bromopride with the tramadol.

FIGURE 4. Flowchart 1-C. Treatment of arthralgia in the acute phase of Chikungunya in adults in urgency/emergency units. VAS: visual analog scale; DN4: Douleur Neuropathique 4; NSAIDs: non-steroidal anti-inflammatories.

based on the VAS scale (FIGURE 5 and FIGURE 7). The standard medication for oral use is prednisone, that has anti-inflammatory effects when taken in low doses; its anti-inflammatory effects predominate at a dose ≤0.5mg/kg per day. Given at intermediate doses (>0.5 to <1mg/kg per day), its effect lies between anti-inflammatory and immunosuppressive actions, whereas in higher doses (≥1mg/kg per day) its immunosuppressive action predominates, independent of its anti-inflammatory action. For the treatment of pain, the dose is 0.5mg/kg per day as a single dose taken in the morning. An adequate response to the treatment is best assessed by improvement in the ability to walk without assistance and satisfactory pain control. If the treatment response is adequate, continue at the recommended dose until the full resolution of the joint pain.

In the event of complete remission of pain, continue taking the recommended dose for 3-5 more days. If there is no relapse, start weaning by decreasing the dose by 5mg/day every 7 days.

The initial dose may be maintained for up to 21 days, the average time during which there is usually no risk of inducing adrenal insufficiency.

During the weaning phase, if pain recurs, return to the previous dose and try to repeat weaning only five days after
Assess intensity of the arthralgia using the VAS

Mild VAS = 1 to 3
Moderate VAS = 4 to 6
Intense VAS = 7 to 10

Non-steroidal anti-inflammatories [7]
Ibuprofen 600mg every 8h, orally
Continue until resolution of the symptoms, maximum 7-10 days

Prednisone [8]
0.5mg/kg/day, orally (maximum dose: 40mg)
Continue until resolution of symptoms, maximum 3 weeks

After resolution of the symptoms, maintain dose for 3-5 days and begin weaning by 5mg/day every 7 days
If relapse occurs, during weaning, take the previous dose until the symptoms resolve, maintaining that dose for no longer than 3 weeks. After improvement, continue for 3-5 days and begin weaning by 2.5mg/day every 7 days
If relapse occurs, refer to a referral unit

[7] NSAIDs: only to be used after the acute phase (>10-14 days). Be attentive to side effects. Renal function must be assessed in elderly people and in those with comorbidities, prior to starting treatment. Be alert for the higher risk for chronic degenerative diseases in patients such as the elderly, those with diabetes, peptic ulcer disease, nephropathy, liver disease, and cardiopathy, among others.

[8] Until the onset of corticosteroid action, prescribe analgesics according to protocol (Flowchart 1A-B)
- Anti-inflammatory dose of corticosteroid is ≤ 0.5mg/kg per day
- Exclusion criteria for the use of corticosteroids: Patients with diabetes, difficult to control hypertension, history of fracture due to documented osteoporosis, bipolar mood disorder, chronic renal failure on dialysis, Cushing’s syndrome, obesity grade III, arrhythmias, and coronary artery disease.
- There is no risk of inducing adrenal insufficiency if used for ≤21 days.
- Corticosteroids may be prescribed for patients in the chronic phase if not yet used.

Flowchart 2
Sub-acute phase (after 10-14 days)

Always ask about a history of allergy to anti-inflammatories

Assess intensity of the arthralgia using the VAS

Mild VAS = 1 to 3
Moderate VAS = 4 to 6
Intense VAS = 7 to 10

Non-steroidal anti-inflammatories [7]
Ibuprofen 600mg every 8h, orally
Continue until resolution of the symptoms, maximum 7-10 days

Prednisone [8]
0.5mg/kg/day, orally (maximum dose: 40mg)
Continue until resolution of symptoms, maximum 3 weeks

After resolution of the symptoms, maintain dose for 3-5 days and begin weaning by 5mg/day every 7 days
If relapse occurs, during weaning, take the previous dose until the symptoms resolve, maintaining that dose for no longer than 3 weeks. After improvement, continue for 3-5 days and begin weaning by 2.5mg/day every 7 days
If relapse occurs, refer to a referral unit


symptom resolution. The weaning must be slower, with a decrease of 2.5mg/day every seven days.

**Exclusion criteria for the use of corticosteroids:** the use of corticosteroids is contraindicated in patients with diabetes, difficult to control hypertension, previous documented osteoporotic fracture, bipolar mood disorder, chronic renal failure on dialysis, Cushing’s syndrome, obesity grade III, arrhythmias, and coronary artery disease.

**Hydroxychloroquine, sulphasalazine, methotrexate (chronic phase drugs)**

The medical care of patients with chronic Chikungunya must take place in referral units with professionals qualified to assist these patients. The medications used in this phase of treatment – hydroxychloroquine, sulphasalazine, and methotrexate – have adverse effects related to their therapeutic classes and require clinical and laboratory monitoring before and during use. They must be prescribed by qualified professionals (Figure 6 and Figure 8). There are a limited number of publications regarding the use of these drugs in the chronic phase of Chikungunya. Most studies involved a small number of patients, and different methodologies were used; thus, it is currently impossible to draw conclusions regarding the efficacy of these drugs, or to assess the superiority of different therapies in patients with chronic Chikungunya(23) (24) (25) (26) (27) (28). The use of these drugs is based on extrapolation from their use in the treatment of chronic rheumatic diseases(29) (30).

The chronic phase of Chikungunya is defined as continuity of symptoms for more than three months after the onset of the disease; it may last for many years. Usually, the disease progresses to the cure without sequelae, either spontaneously or after treatment. However, the patient may present with persist
Hydroxychloroquine, 6mg/kg once a day (maximum 600mg daily), orally, for 6 weeks [9]

Use the VAS to assess pain

No pain

Persistent pain with VAS < 4

Stop the medication

Pain persists?

No

Yes

Stop the medication

Refer to a rheumatologist to widen the investigation

Persistent pain with VAS ≥ 4

Return for assessment within 6 weeks.

Pain persists?

No

Yes

Stop the medication

Refer to a rheumatologist to widen the investigation

Add sulfasalazine 2 x 500mg tablets (1g) every 12h (2 g/day), orally

Change to methotrexate 15 to 25mg, once a week, orally, for 6 weeks


Flowchart 4
Pediatrics

Acute phase

Always ask about a history of allergy to dipyrone

Do not use NSAIDs (nonsteroidal anti-inflammatory) or acetylsalicylic acid in the acute phase, due to the risk of complications associated with severe forms of Chikungunya (hemorrhage and renal failure).

Assess intensity
Apply pain scale for appropriate age

Mild = 1 to 3

Dipyrone or paracetamol: 10 to 15mg/kg/dose every 6h, orally

Reassess after 5 days

Face scale < 4 points.

No

Yes

Stop the medication

Pain persists?

Maintain medication for five days more. Ambulatory follow up

Severe = 7 to 10

Admit for in-patient dipyrone and paracetamol, alternating every 3h (10 to 15mg/kg/dose), orally, and combined with codeine (10 to 15mg/kg/dose) or tramadol (>1 year)

Reassess after 24 hours

Apply appropriate pain scale for each group age

Face scale > 4 points.

No

Yes

Add amitriptyline or carbamezapine or gabapentin (>6 years). Investigate for another diagnosis.

Pain scale specified according to age and pain measurement

- **Mild** = 1 to 3
- **Moderate** = 4 to 6
- **Severe** = 7 to 10

**Paracetamol or dipyrone (1)**
10 to 15mg/kg/dose every 6h, orally

**Naproxen:** 10 to 20mg/kg/day every 12h (maximum dose: 1,000mg/day) or
**Ibuprofen:** 30 to 40mg/kg/day in 3 to 4 divided doses (maximum dose: 2,400mg/day) or
**Indomethacin:** 1 to 3mg/kg/day in 3 to 4 divided doses (maximum dose: 200mg/day), orally [2]

**Prednisone or prednisolone**
0.5mg/kg/day every 24h (maximum dose: 40mg/day) for 2-4 weeks, followed by weaning [3]

**Stop the medication**

**Pain persists?**
- Yes: **Stop the medication after weaning (3)**
- No: **Refer to a referral unit**

**Prednisone or prednisolone**
0.5mg/kg/day every 24h (maximum dose: 40mg/day) for 2-4 weeks, followed by weaning [3]

**Pain persists?**
- Yes: **Hydroxychloroquine:** 6mg/kg/day for 6 weeks (Maximum dose: 400mg/day)  
  **Methotrexate:** 0.5mg/kg/week, oral or subcutaneous (Maximum dose: 25mg/week)
- No: **Stop the medication after weaning**

**Always ask about a history of allergy to dipyrone and anti-inflammatories**

**FIGURE 8.** Flowchart 5. Treatment of arthralgia in the sub-acute and chronic phases of Chikungunya in children. **NSAIDs:** non-steroidal anti-inflammatories.

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The patient should return for assessment after six weeks, when the VAS scale is applied again. If after this period the patient is without pain, the medication should be stopped. If the VAS is less than four, hydroxychloroquine and sulphasalazine should be continued for another six weeks. If the VAS is greater than or equal to four, the combination of hydroxychloroquine and sulphasalazine should be replaced by methotrexate (2.5mg tablet), at an initial dose of 10mg/week, orally; this dose may be increased to 25mg/week. Folic acid should always be given in combination with methotrexate, at a dose of 5mg/week, taken the day after methotrexate is taken [20][32].

If after six weeks there is persistence of pain, the patient should be referred to a rheumatologist to widen the diagnostic investigation and introduce other therapies. Be attentive to the main side effects of methotrexate, including hepatotoxicity, myelotoxicity, and gastrointestinal effects. The dose must be adjusted in patients with impaired renal function, and it is contraindicated in patients with a creatinine clearance <30mL/min.

The main side effects of hydroxychloroquine include visual disturbances, hematologic abnormalities, and alopecia. The risk of adverse events is higher in patients with glucose-6-phosphate dehydrogenase deficiency, liver failure, porphyria, psoriasis, myopathies, or cardiomyopathy.
Non-pharmacologic treatment

Physiotherapy should be considered, beginning in the acute phase of Chikungunya. It may be combined with cryotherapy as an analgesic measure. It should also be prescribed in the sub-acute and chronic phases, aiming to minimize the osteoarticular damage, consequently enabling rehabilitation. Physiotherapy should be requested equally in the three phases of disease; however, it should be a priority in the sub-acute and chronic phases. The manufacture and use of orthoses as an adjuvant measure may be required; this may achieve more rapid relief of pain and, above all, may help to prevent muscular atrophy consequent to the disuse of the compromised joint. Other therapies, such as acupuncture, may be used in the sub-acute and chronic phases. It is worth mentioning that psychological support is important in all phases of the disease, especially to relieve the sadness and suffering arising from the state of pain and chronic swelling during a long period of consequent illness.

CONCLUSION

Chikungunya epidemics, with the high attack rate of CHIKV, affect a large number of people in a short period of time, producing not only acute cases, but also a high number of chronic cases. Pain, the most frequent clinical manifestation of Chikungunya, is difficult to control, compromising the quality of life of affected patients. It may have immeasurable psychosocial and economic repercussions, constituting a serious public health problem that requires a targeted approach. There are few protocols for managing the pain caused by Chikungunya; hence, it was necessary to produce a guideline to diagnose and appropriately manage patients with Chikungunya. It is important to emphasize that in addition to medical treatment, the approach to the management of patients with Chikungunya requires the involvement of multidisciplinary teams. General physicians, specialists, nurses, pain specialists, physiotherapists, social workers, and healthcare managers are required to institute these guidelines and to organize services to manage patients with different levels of complexity.

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Conflict of interest

The author declares that there is no conflict of interest.

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