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Original article

Recommendations of the Brazilian Society of Rheumatology for diagnosis and treatment of Chikungunya fever. Part 1 – Diagnosis and special situations

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ABSTRACT

Chikungunya fever has become a relevant public health problem in countries where epidemics occur. Until 2013, only imported cases occurred in the Americas, but in October of that year, the first cases were reported in Saint Marin island in the Caribbean. The first autochthonous cases were confirmed in Brazil in September 2014; until epidemiological week 37 of 2016, 236,287 probable cases of infection with Chikungunya virus had been registered, 116,523 of which had serological confirmation. Environmental changes caused by humans, disorderly urban growth and an ever-increasing number of international travelers were described as the factors responsible for the emergence of large-scale epidemics. Clinically characterized by fever and joint pain in the acute stage, approximately half of patients progress to the chronic stage (beyond 3 months), which is accompanied by persistent and disabling pain. The aim of the present study was to formulate recommendations for the diagnosis and treatment of Chikungunya fever in Brazil. A literature review was performed in the MEDLINE, SciELO and PubMed databases to ground the decisions for recommendations. The degree of concordance among experts was established through the Delphi method, involving 2 in-person meetings and several online voting rounds. In total, 25 recommendations were formulated and divided into 3 thematic groups: (1) clinical, laboratory and imaging diagnosis; (2) special situations; and (3) treatment. The first 2 themes are presented in part 1, and treatment is presented in part 2.

Recomendações da Sociedade Brasileira de Reumatologia para diagnóstico e tratamento da febre Chikungunya. Parte 1 – Diagnóstico e situações especiais

Palavras-chave:
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RESUMO

A febre chikungunya tem se tornado um importante problema de saúde pública nos países onde ocorrem as epidemias. Até 2013, as Américas haviam registrado apenas casos importados quando, em outubro desse mesmo ano, foram notificados os primeiros casos na Ilha de Saint Martin, no Caribe. No Brasil, os primeiros relatos autóctones foram confirmados em setembro de 2014 e até a semana epidemiológica 37 de 2016 já haviam sido registrados 236.287 casos prováveis de infecção pelo chikungunya vírus (CHIKV), 116.523 confirmados sorologicamente. As mudanças ambientais causadas pelo homem, o crescimento urbano desordenado e o número cada vez maior de viagens internacionais têm sido apontados como os fatores responsáveis pela reemergência de epidemias em grande escala.

Caracterizada clinicamente por febre e dor articular na fase aguda, em cerca de metade dos casos existe evolução para a fase crônica (além de três meses), com dor persistente e incapacitante. O objetivo deste trabalho foi elaborar recomendações para diagnóstico e tratamento da febre chikungunya no Brasil. Para isso, foi feita revisão da literatura nas bases de dados Medline, SciELO e PubMed, 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*. Foram geradas 25 recomendações, divididas em três grupos temáticos: (1) diagnóstico clínico, laboratorial e por imagem; (2) situações especiais e (3) tratamento. Na primeira parte estão os dois primeiros temas e o tratamento na segunda.

General considerations

Epidemiology

The Chikungunya virus (CHIKV), a member of the Togaviridae family, Alphavirus genus, was first isolated from humans in 1952 during the first urban outbreak identified in the modern scientific age, causing an epidemic that affected the coastal area of Muawiya, Makondo and Rondo, present-day Tanzania.[1] The virus name is in the Makonde language, a dialect spoken in Southeastern Tanzania, and means "to bend forward or become contorted," an allusion to the posture adopted by patients as a function of the joint pain caused by infection.[1] While the disease is transmitted by a large number of mosquitos of the genus Aedes in Africa, the main vectors in Brazil are *Aedes aegypti* and *Aedeas albopictus*, the females of which are able to infect humans through biting.[2]

After the first outbreak of Chikungunya fever in Tanzania in the 1950s, several minor epidemics occurred periodically until 2004, when a major outbreak was identified in Kenya, which then spread to many islands in the Indian Ocean, India and Southeastern Asia.[3] Until 2013, all the cases in the Americas were imported, mostly into the United States; however, in October of that year, the first cases were documented in Saint Martin island in the Caribbean. By the end of 2015, 1.6 million people had been infected with CHIKV, resulting in 71 deaths.[4–6] In Brazil, the first autochthonous cases were almost simultaneously reported in Oiapoque (Amapa state – AP) and Feira de Santana (Bahia state – BA) in September 2014.[7] A total of 38,332 possible cases of Chikungunya fever were registered in 2015, of which 13,236 were confirmed. Until epidemiological week (EW) 37 of 2016 (up to September 17th, 2016), 236,287 probable cases of infection with CHIKV were registered, of which 116,523 had serological confirmation.[8]

Pathophysiology

During the inoculation of CHIKV through the skin by mosquito bites, mosquito saliva enters the body together with the virus; the saliva contains several molecules with anti-hemostatic and immunomodulating properties, which induce early cell infiltration and increased cytokine secretion. Then follows a stage characterized by intense replication of the virus in skin fibroblasts and macrophages and spread to lymph nodes, where replication intensifies before the virus is released into the bloodstream, with spread to and consequent infection of target organs, such as the joints and muscles. The virus might also be directly inoculated into the bloodstream through mosquito bites. Of particular relevance is the induction of the innate immune response, followed by the cell-mediated immune response, involving the release of several proinflammatory cytokines, such as interferon alpha, interleukins, chemokines and growth factors.[9–11]

Experimental models of alphavirus-induced arthritis suggest that progression to the chronic stage of Chikungunya fever results from the combination of direct cell and tissue damage caused by viral replication and, indirectly, by activation of the immune response in the target tissues.[12] Nevertheless, the main hypothesis involves dysregulated inflammation caused by persistent infection of tissue macrophages – or the presence of viral RNA within these cells.[13] The synovial histopathological changes after infection with CHIKV are similar to those found among patients with rheumatoid arthritis (RA) or other chronic inflammatory joint diseases, including synovial hyperplasia, vascular proliferation and perivascular macrophage infiltration.[14] In animal models of CHIKV infection, periosteal necrosis, bone proliferation and multifocal bone marrow ischemia were identified starting 5 days after infection.[15]

Clinical manifestations

The incubation period lasts 3 to 7 days, on average, varying from 1 to 12 days.[16] The disease evolves in 3 stages: acute, lasting 7 to 14 days; subacute, which might last up to 3 months; and chronic, namely, persistence of symptoms for more than 3 months.[17]

Acute infection is symptomatic in 80% to 97% of patients.[18,19] The most common symptoms are fever of sudden onset and joint pain and/or arthritis (nearly 100% of cases), which is usually symmetric and polyarticular. The joint complaints mainly involve the hands, wrists, ankles and feet, being disabling in most cases. Less frequent manifestations include asthenia, muscle pain (60–93%), headache (40–81%), nausea/vomiting, diarrhea, photophobia, retro-orbital pain, conjunctivitis, axial pain, macular/maculopapular exanthema (34–50%) with or without skin itch, face and limb swelling and cervical or generalized lymphadenopathy.[19–24]

Table 1 – Case definition of Chikungunya fever.[17,45]

Clinical criteria: fever of sudden onset > 38.5 °C and intense joint pain/arthritis of acute onset not explained by other medical conditions
Epidemiological criteria: individual residing at or visiting an endemic or epidemic area 15 days before the onset of symptoms or has epidemiological connection to a confirmed case
Laboratory criteria
- ◯ Isolation of CHIKV in culture
- ◯ CHIKV RNA by real-time PCR
- ◯ Specific anti-CHIKV IgM antibodies
- ◯ Four-fold increase of anti-CHIKV IgG antibodies in samples collected with at least
- ◯ a 10–14-day interval
- ◯ Detection of anti-CHIKV neutralizing antibodies in serum by means of PRNT

Classification
Suspected case: patient meets the clinical and epidemiological criteria
Confirmed case: a suspected case that meets any of the laboratory criteria
Atypical case: laboratory confirmation in a patient with other clinical manifestations (neurologic, cutaneous, involving the heart, eyes or kidneys, respiratory, etc.)

RNA, ribonucleic acid; real-time PCR, real-time polymerase chain reaction; PRNT, plaque reduction neutralization test; CHIKV, Chikungunya virus.

During the subacute stage, joint symptoms predominate, occurring in up to 50% of patients infected with CHIKV. The clinical manifestations include persistence of joint pain/arthritis, bursitis, tenosynovitis, morning stiffness and asthenia, which might exhibit continuous or intermittent progression.[21,24,25]

The prevalence of chronic joint disorders following infection with CHIKV varies from 14.4% to 87.2%.[14,19,21,23,26–30] Such a wide range of variation might be partially explained by methodological issues: variable sample size, duration of follow up, measures to assess chronic joint affection and methods for data collection. A statistical model developed with data from observational studies estimated that 47.6% of individuals with Chikungunya fever in Latin America will develop chronic joint manifestations.[31] A recent meta-analysis[32] analyzed the prevalence of chronic inflammatory joint disease (CIJD) after Chikungunya infection (post-CHIK) in 18 selected studies (9 prospective and 9 retrospective cohort studies) with a total of 5702 patients. The average length of follow up was 17.5 months; the prevalence of post-CHIK CIJD varied from 25.3% to 40.2% as a function of the stratification of the studies.

Chronic joint symptoms might translate into persistent (20–40%) or relapsing (60–80%) complaints.[33,34] They may include oligo- or polyarthralgia of variable intensity, usually symmetric, mainly in wrists, hands, ankles and knees, and are associated with morning stiffness and joint swelling.[33] Up to 72% of patients with early significant improvement might relapse, the interval lasting from 1 week to several years, presenting with variable symptoms and affecting the same joints that had previously been involved.[29,35]

Although the persistence of musculoskeletal complaints is the main characteristic of Chikungunya fever, the factors associated with chronic progression and poorer prognosis have scarcely been investigated. The results of the published case series indicate that some factors are more strongly associated with chronic progression, such as female gender,[34,36–38] age over 40 years old, prominent joint involvement in the acute stage (joint swelling and stiffness, polyarthritis, tenosynovitis),[32,34,36–39] presence of previous joint disease, such as osteoarthritis (OA),[39,40] and presence of comorbidities, such as diabetes mellitus (DM).[33,35] In turn, joint pain without swelling or stiffness was associated with higher odds of recovery.[34]

Relative to laboratory testing, high levels of C-reactive protein (CRP) and positive CHIKV IgG serology are considered to be predictors of chronic progression.[28,41] Persistence of positive CHIKV IgM beyond the acute stage is associated with erosive arthritis and chronic progression of the joint symptoms.[42,43]

The diagnosis of Chikungunya fever is typically clinical; the combination of acute fever with intense joint pain and/or arthritis of acute onset are highly suggestive of disease, with high sensitivity and positive predictive value in areas where disease is endemic and epidemics occur.[17,44] The current recommendation of the Brazilian Health Ministry is to apply clinical-epidemiological criteria for the definition of suspected cases of Chikungunya fever. Similar criteria were suggested at the last expert meeting in Nicaragua in 2015[17,45] (Table 1).

Some cases might exhibit atypical progression, characterized by less frequent clinical manifestations (Table 2) or signs of severity.[46] The frequency of severe cases is 0.3% and is associated with older age (>65 years old) and the presence of comorbidities. There are reports of occurrence of sepsis and septic shock in Chikungunya fever patients admitted to intensive care units, with no other identified etiological agent likely to account for these conditions.[21,25,46–49] Use of nonsteroidal anti-inflammatory drugs (NSAIDs) before hospitalization and cardiovascular disease are factors independently associated with increased mortality.[46,47] Bleeding is rare; the risk increases in the case of coinfection with dengue virus, but it is not associated with coagulation disorders or severe thrombocytopenia.[25] Similarly to other viral diseases, such as hepatitis C, Chikungunya fever is associated with a high prevalence of mixed cryoglobulinemia.[50]

A recent study assessed the concordance between CHIKV IgM serology and clinical diagnosis. Any combination of joint pain with fever, muscle pain or exanthema had 85% concordance with positive IgM testing (kappa = 0.289, $p < 0.001$). The authors suggested that as a function of the difficulty in performing the serology tests, these symptoms might be useful to define a case of Chikungunya fever when CHIKV is the predominant circulating virus.[51]

Table 2 – Main atypical clinical manifestations of Chikungunya fever.[55,136,137]

Organ/system	Clinical manifestations
Skin	Hyperpigmentation, aphthous ulcers, transient nose erythema, generalized erythema, vesicular-bullous lesions, palm desquamation, lip depigmentation, vasculitis lesions, lichenoid eruptions
Kidneys	Kidney failure (may be triggered or worsened by use of NSAIDs) Nephritis
Lungs	Pneumonia Respiratory failure
Gastrointestinal	Diarrhea, vomiting, acute hepatitis (associated with CHIKV, previous alcoholism and use of paracetamol)
Heart	Heart failure, arrhythmia, perimyocarditis, ischemic coronary artery disease
Neurological	Encephalitis, meningoencephalitis, meningeal irritation, Guillain-Barré syndrome, cerebellar syndrome, stroke, mental confusion, seizures
Eye	Conjunctivitis, optic neuritis, iridocyclitis, episcleritis, retinitis, anterior uveitis
Hematological	Thrombocytopenia, lymphadenopathy

Some evidence has indicated that chronic rheumatic diseases might develop after infection with CHIKV.[26,31,32,38,40,52,53] The pathogenesis of arthropathy following infection with CHIKV has not yet been well elucidated; however, based on studies conducted with other arthritogenic viruses, arthritis possibly occurs due to the virus' ability to replicate and mediate the production of tissue damage in joints, which in turn depends on the host immune response.[54] In the published case series, some patients met the criteria for RA[23,29] and spondyloarthritis (SpA).[19,20,29,52] during the chronic stage of disease. There are also reports of exacerbation of cutaneous psoriasis and of onset of psoriasis after an episode of Chikungunya fever.[55,56]

During the epidemic that occurred in Reunion Island, Javelle et al.[29] formulated criteria for undifferentiated inflammatory arthritis (non-validated) (Table 3) to classify the patients who did not meet the criteria for RA or SpA and thus distinguish those with inflammatory disease from those with joint pain only. According to such criteria, polyarticular inflammation lasting more than 3 months after the acute stage of Chikungunya fever suggests a potential diagnosis of post-CHIK CIJD. Morning stiffness was considered to be the clinical manifestation with the lowest diagnostic power due to its high prevalence in the post-CHIK period, when synovitis and tenosynovitis were highly indicative of CIJD. This was confirmed by ultrasonography to distinguish CIJD from soft tissue edema, which is also characteristic of disease.[29] These criteria are rather unspecific and were not validated with other populations; their accuracy in clinical practice cannot be asserted with precision. Thus, we recommend caution when they are applied because patients with other chronic inflammatory diseases might be easily misclassified as Chikungunya fever.

To investigate the behavior of Chikungunya fever in Brazil and collect data to ground future therapeutic decision-making, a multicenter cohort study – CHIKBRAZIL COHORT – was launched in April 2016. The sample is composed of Brazilian patients with CHIKV infection and joint symptoms. In its initial stage, 6 centers from 4 Brazilian states (Pernambuco, Paraíba, Ceará and Sergipe) participated in the study, and patients were included when they had a clinical-epidemiological diagnosis of Chikungunya fever[17] and chronic joint symptoms. Up to the present time, 431 patients have been included, and the corresponding data are periodically collected and analyzed (these analyses have not yet been published).

Methods

To elaborate the present recommendations, 3 working groups were established: a core group, a literature review group and a voting panel. The core group was composed of 5 rheumatologists (CDLM, ALBPD, VMT, JTSV, GC) and was charged with formulating and sending the leading questions that served as the basis for formulation of the recommendations, coordinating and supervising the other 2 groups, conducting the voting panels and writing the manuscript. The group that performed the literature review included 20 rheumatologists and 3 physical therapists. The search was conducted in several databases (MEDLINE, SciELO, PubMed, EMBASE), and articles on the diagnosis and treatment of Chikungunya fever were selected in addition to abstracts published in conference proceedings in Portuguese, English, French or Spanish through October 2016.

Table 3 – Criteria for the classification of post-Chikungunya chronic inflammatory joint disease (CIJD).[29]

>4 joints with arthritis + symptom duration ≥6 weeks + no alternative diagnosis

A. Arthritis = 1 inflammation criterion
- Synovitis[a]
- Heat and/or erythema on the joint
- Morning stiffness >30 min
- Inflammatory pain – improves with exercise and worsens with rest or during the night

B. Patient does not meet the criteria for rheumatoid arthritis or spondyloarthritis, in addition to ruling out other causes of polyarthritis: gout, autoimmune diseases, thyroid dysfunction, chronic viral hepatitis, and sarcoidosis

[a] Must be distinguished from joint swelling without synovitis.

This group was charged with reviewing the evidence to provide theoretical grounds for the final recommendations.

The methodological quality of the identified studies was subjected to critical assessment based on the risk of bias in clinical intervention studies and STROBE (Strengthening the Reporting of Observational studies in Epidemiology).[57] As the methodological diversity of the studies did not allow performing a meta-analysis, the assessment was based on the levels of evidence and grades of recommendation formulated by the *Oxford Centre for Evidence-Based Medicine*, 2011 (*Levels of Evidence*).[58] Here, the studies are classified into levels of evidence 1–5 based on their type and ability to respond to the corresponding question and to produce the best evidence to ground decision-making. As in the present recommendations, we used studies with different levels of evidence, and we chose to indicate the various levels of evidence that grounded the final recommendations in 2 ways: sequentially, i.e., separated by a comma, or as an interval, as indicated by a hyphen.

Due to the low quality of the located evidence, or a complete lack of evidence in some cases, we also employed the preliminary analyses of the CHIKBRAZIL cohort data (described along the text, especially as concerns treatment) and the opinions of the participating experts to ground decision-making vis-à-vis the recommendations.

The Delphi method was used to establish the degree of expert concordance at 2 in-person meetings and in various online voting rounds. The voting group included all the members of the other 2 groups in addition to 3 general practitioners, 1 specialist in infectious diseases and 1 representative of public health management. The 2 in-person meetings were conducted in Recife, Pernambuco state, Brazil (October and November 2016); the rate of attendance was over 90%. In addition to in-person voting, several rounds of questioning, voting and amendments were conducted via the internet. To assess the degree of expert concordance, the participants in the voting panel were requested to attribute scores from 0 to 10 on a continuous scale, zero representing "I fully disagree" and 10 "I fully agree." The mean and standard deviation (SD) corresponding to each recommendation were calculated from the individual scores.

A total of 25 recommendations were formulated and classified into 3 thematic groups: A. Clinical, laboratory and imaging diagnosis; B. Special situations; and C. Treatment.

The present article includes the first 2 themes (Table 4), comprising 14 recommendations; the recommendations for treatment are described in part 2.

To facilitate the reading of the text, the levels of evidence of the studies used to ground the recommendations are indicated in the list of references. References corresponding to guidelines, treatment protocols, abstracts published in conference proceedings and those not directly related to Chikungunya fever were not classified.

Recommendations

A. Clinical, laboratory and imaging diagnosis

A.1 Possible occurrence of Chikungunya fever should be strongly considered in cases with acute fever, severe joint pain/arthritis and with or without exanthema within the context of an epidemic. However, other acute febrile diseases ought to be considered in the differential diagnosis, especially as concerns the severe or atypical cases. *Concordance: 9.31 (SD ± 1.168); level of evidence (2–4)*

The symptoms typical of the acute stage of Chikungunya fever (fever, exanthema and joint pain) might also occur in other viral diseases, dengue fever (DENV) in particular.[59,60] While many symptoms and signs are similar, some manifestations are more characteristic, which might help in the differential diagnosis between both conditions. Odynophagia, cough, nausea, vomiting, diarrhea, abdominal pain, anorexia and tachycardia are more common in dengue fever than in CHIKV infection.[61] In addition, in dengue fever, the fever is usually lower; the skin rash appears later (from days 5 to 7); and retro-orbital pain, thrombocytopenia and neutropenia are more frequent.[62,63] As the Zika virus (ZIKV) in Brazil coexists within one and the same epidemic, it should also be considered in the differential diagnosis. In the case of ZIKV, the fever is milder or might even be absent, the joint and muscle pain is not debilitating, and hyperemia of the conjunctiva is common; manifestations might include skin rash, which is also itchy.[64] Coinfection with CHIKV and ZIKV and/or DENV might occur in epidemics of arboviral diseases.[62–64]

In addition to DENV and ZIKV, other arboviruses might cause symptoms similar to those of the acute stage of Chikungunya fever, such as Ross River virus, Barmah Forest virus, O'nyong-nyong virus, Sindbis group and Mayaro virus.[60] From these, the only one found in Brazil is Mayaro virus (MAYV), which causes Mayaro fever that, in addition to acute symptoms similar to those of CHIKV, also exhibits arthritogenic characteristics with possible chronic progression. However, Mayaro fever predominantly occurs in wild areas and is generally limited to small epidemics.[65] In Brazil, MAYV transmission is restricted to the Northern area,[66] although it has already been detected in states from other regions.[67,68]

Other causes of acute febrile viral diseases, such as those caused by adenoviruses, enteroviruses, parvovirus B19, measles and rubella, should be considered in the differential diagnosis of Chikungunya fever, for which purpose data, such as history of exposure, recent travels and geographical area of residence, should be taken into account.[69]

In addition to viral diseases, acute bacterial infections, such as leptospirosis, and parasitic diseases, such as malaria, might be attended with clinical manifestations similar to those of the early stage of Chikungunya fever, such as high fever, muscle pain, joint pain, headache, fatigue, diarrhea and, in some cases, abdominal pain, for which reason should be considered in the differential diagnosis, especially as concerns the atypical cases.[70,71]

Some autoimmune diseases, such as Still's disease and systematic lupus erythematosus (SLE), might exhibit symptoms similar to those of infection with CHIKV, even in its acute stage. Still's disease, which presents with high fever, exanthema, joint pain/arthritis, leukocytosis and elevated transaminase levels, might be confounded with viral infections. Fever, joint and skin manifestations; kidney, lung and neurological involvement; and lymphopenia are characteristic of SLE and might be confounded with complicated CHIKV infection (expert's opinion).

Table 4 – Summary of recommendations for diagnosis of and special situations for Chikungunya fever.

Recommendations

A. Clinical, laboratory and imaging diagnosis

A.1. Possible occurrence of Chikungunya fever should be strongly considered in cases with acute fever, severe joint pain/arthritis with or without exanthema within the context of an epidemic. However, other acute febrile diseases ought to be considered in the differential diagnosis, especially as concerns severe or atypical cases. *Concordance: 9.31 (SD ± 1.168); level of evidence (2–4)*

A.2. In patients with clinical suspicion of acute Chikungunya fever, laboratory assessment (complete blood count, liver enzymes, creatinine, fasting glycemia, erythrocyte sedimentation rate (ESR)/CRP) should be decided on a case-by-case basis according to comorbidities and signs of severity. *Concordance: 7.12(SD ± 3.5); level of evidence (3,4)*

A.3. CHIKV should only be investigated in cases for which diagnostic confirmation at the acute stage is needed: atypical cases, differential diagnosis in the case of severe presentation or to establish public health policies (suspicion of new foci or post-epidemic cases), in which case the first-choice method is real-time PCR that should be performed within the first week of the appearance of symptoms. *Concordance: 9.19 (SD ± 0.839); level of evidence (2,3)*

A.4. Relative to acute cases of Chikungunya fever, serology (ELISA) for CHIKV (IgM and IgG) should only be performed in cases with atypical presentation or when differential diagnosis is needed; in such cases, it should be performed after the tenth day since the onset of symptoms. Relative to chronic cases, serology is recommended for the purpose of confirmatory diagnosis, but not to start treatment. *Concordance: 9.29 (SD ± 1.510); level of evidence (2–4)*

A.5. During the chronic stage of Chikungunya fever, autoantibodies should only be investigated when differential diagnosis with specific rheumatologic diseases is necessary with compliance with the available consensuses/guidelines. *Concordance: 8.55 (SD ± 2.593); level of evidence (3,4)*

A.6. In the acute and subacute stages of Chikungunya fever, most patients do not need imaging tests. In the chronic stage of disease, plain radiography should be requested by the rheumatologist on the first visit for initial structural and preexisting damage assessment. *Concordance: 9.70 (SD ± 0.651); level of evidence (3,4)*

A.7. Musculoskeletal ultrasound might contribute to the assessment of joint and periarticular abnormalities at any stage of Chikungunya fever. In the acute stage of disease, it is the only imaging test that might be performed according to the doctor's opinion, being particularly useful for the differential diagnosis of lower limb swelling. *Concordance: 9.29 (SD ± 1.510); level of evidence (3,4)*

B. Special situations

B.1. In the treatment of pregnant women with Chikungunya fever, the risk posed by medicines to the fetus should be taken into account; when indicated, analgesics, prednisone/prednisolone and hydroxychloroquine may be used. *Concordance: 9.71 (SD ± 0.534); level of evidence (3,4)*

B.2. By itself, Chikungunya fever is not an indication of cesarean section, the need of which should be established on obstetrical grounds only. Breastfeeding is allowed. *Concordance: 9.67 (SD ± 0.547); level of evidence (3–4)*

B.3. Relative to the elderly (>60 years old) with Chikungunya fever, strict clinical monitoring of medications, comorbidities and higher risk of complications is recommended at all stages of disease, the acute stage in particular. *Concordance: 9.61 (SD ± 0.737); level of evidence (3,4)*

B.4. Children under 2 years old should receive special attention due to their higher risk of severe and atypical manifestations, involvement of the central nervous system (CNS) in particular. *Concordance: 9.30 (SD ± 1.179); level of evidence (3,4)*

B.5. Newborn infants from mothers with clinical manifestations suggestive of Chikungunya fever close to labor should be subjected to close observation along the first 5 days of life. Rational use of medications should be performed for cases that develop disease; complex cases should be managed at the intensive care unit. *Concordance: 9.54 (SD ± 0.838); level of evidence (3,4)*

B.6. Treatment for the acute stage of Chikungunya fever in children consists of hydration, analgesics and antipyretic agents; salicylates should be avoided. For the chronic stage, we suggest following the recommendations for adults, while taking the particularities inherent to this age range into account. *Concordance: 9.48 (SD ± 0.785); level of evidence (3,4)*

B.7. We recommend paying special attention to patients with previous diagnosis of rheumatoid arthritis, spondyloarthritis or systemic lupus erythematosus, as these conditions might become reactivated or exacerbated. *Concordance: 9.42 (SD ± 1.840); level of evidence (3,4)*

In its subacute and chronic stages, the clinical manifestations of CHIKV infection might be similar to those of several chronic rheumatic diseases. Symmetrical arthritis involving the hands, wrists, knees and ankles, combined with morning stiffness, are found in RA and also in arthropathy secondary to CHIKV infection. Enthesis and fascia involvement and the presence of inflammatory lumbar pain in patients with CHIKV infection might simulate SpA, especially among young male patients.[20,29] Notably, the onset of specific treatment of such cases might be delayed due to mistaken diagnosis as Chikungunya fever, a mistake induced by the epidemiological situation.[72]

A.2. In patients with clinical suspicion of the acute stage of Chikungunya fever, laboratory assessment (complete blood count, liver enzymes, creatinine, fasting glycemia, erythrocyte sedimentation rate (ESR)/C-reactive Protein (CRP)) should be decided on a case-by-case basis according to comorbidities and signs of severity. *Concordance: 7.12(SD ± 3.5); level of evidence (3,4)*

For laboratory testing decisions in cases of Chikungunya fever, the clinical manifestations and stage of disease should be taken into consideration. As diagnosis in the acute stage is established based on clinical-epidemiological criteria and the specificity of tests is low in this stage, no laboratory test is needed for non-complicated typical cases. Relative to high-risk patients (elderly, pregnant women, children under 2 years old, presence of complications), only complete blood count (CBC) is recommended. More thorough laboratory investigation might be needed as a function of the overall condition of the patients, comorbidities and medications used, especially in the case of elderly patients.[17,24]

The most frequent laboratory finding in Chikungunya fever is lymphopenia, which is most intense during the viremic stage.[4] Unlike dengue fever, thrombocytopenia is less frequent and less accentuated. Other possible findings include leukopenia, neutropenia, abnormalities of liver and kidney function, hypocalcemia and elevated creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels, especially among patients

who require hospital admission.[25,26,49,73,74] Relative to inflammatory activity tests, ESR was found to be elevated in most patients during the first 10 months of disease in a study conducted in India.[23] Elevated CRP levels were detected in more than 70% of patients.[20,26]

In the chronic stage, in addition to routine testes (CBC, ESR, CRP), investigation of autoantibodies should be considered when the clinical presentation is suggestive of CIJD and according to the existing comorbidities. Synovial fluid analysis might be necessary to confirm the inflammatory nature of joint involvement and help in differential diagnosis (i.e., gout or septic arthritis).

A.3. CHIKV should only be investigated in cases for which diagnostic confirmation in the acute stage is needed: atypical cases, differential diagnosis in the case of severe presentation or to establish public health policies (suspicion of new foci or post-epidemic cases), in which case the first-choice method is real-time PCR that should be performed within the first week of the appearance of symptoms. *Concordance: 9.19 (SD ± 0.839); level of evidence (2,3)*

Confirmatory diagnosis of infection with CHIKV might be established by means of 3 main laboratory tests: virus isolation, molecular techniques for viral genomic RNA detection (real-time PCR) and serology.[75]

Virus isolation through the detection of viral RNA might be performed on serum samples during the acute stage of disease (≤8 days)[76]; however, this method is not used in clinical practice.

Real-time PCR for the detection of viral genomic RNA has several advantages compared to conventional PCR: faster to perform, quantitative, low contamination risk, simple standardization and high sensitivity/specificity. By means of this technique, the presence of viral RNA can be detected during the early stage of viremia (0–7 days).[77]

Considering that the symptoms associated with arbovirus infection (CHIKV, DENV and ZIKV) might be quite similar, especially in the early stages of disease when differential diagnosis is necessary, triple real-time PCR is the most advantageous technique because it simultaneously identifies RNA from all 3 viruses.[78–80]

As a function of the known difficulty in performing real-time PCR in clinical practice, including high cost and no access to most of the population, we recommend performing confirmatory diagnosis of acute cases only for atypical or severe cases during epidemics or for special situations (children under 2 years old, pregnant women, suspect of new foci, post-epidemic cases). In such cases, sample collection should be performed within the first 6 days of the onset of symptoms.

A.4. Relative to acute cases of Chikungunya fever, serology (ELISA) for CHIKV (IgM and IgG) should only be performed in cases with atypical presentation or when differential diagnosis is needed; in such cases, it should be performed after the tenth day since the onset of symptoms. Relative to chronic cases, serology is recommended for the purpose of confirmatory diagnosis, but not to start treatment. *Concordance: 9.29 (SD ± 1.510); level of evidence (2–4)*

According to the current recommendations by the Brazilian Ministry of Health, in the face of an epidemic, specific serology for CHIKV during the acute stage of infection should only be performed for atypical cases and complicated clinical situations.[17] However, in areas where arboviruses are endemic, accurate identification of the specific type of infection is highly relevant for the purpose of patient management, especially for cases that progress to the chronic stage, in order to implement adequate public health measures and guide health managers.[66]

In practice, serology is the most widely used method for confirmatory diagnosis of CHIKV infection. ELISA (enzyme-linked immunosorbent assay) and the plaque reduction neutralization test (PRNT) might be used for this purpose.[17]

IgM antibodies are detected in 4% to 20% of cases from day 3 onward, reaching 80% positivity after the first week.[81,82] Higher levels are detected from week 3 to 5, and the antibodies might remain elevated for 1 to 3 months or longer in some cases. IgG antibodies are also detected starting week 1 after infection, usually 1 or 2 days after the elevation of IgM antibodies, and might remain detectable for several years.[81–83]

Serology for CHIKV can be performed starting 5 days after the onset of symptoms. However, to obtain a better operational performance of this test, it should be performed 7 to 10 days after the onset of symptoms for IgM antibodies and 10 to 14 days for IgG antibodies for ELISA, especially in areas where other alphaviruses do not circulate. The sensitivity of the test varies from 85% to 98%, with specificity above 90%.[14,65,81–88] Persistence of a specific IgM response several months after the initial infection was found in some patients with chronic musculoskeletal symptoms.[84] The meaning of this phenomenon is not yet clear; according to the most widely accepted hypothesis, it denotes persistence of the virus in some tissues through still poorly understood mechanisms.[84,88]

Coinfection with other arboviruses is an occurrence in areas endemic for Chikungunya fever, dengue fever and Zika. CHIKV is an alphavirus; as such, it might exhibit cross-reactivity with other viruses from this family.[65,88] In Brazil, the most frequent of such viruses is Mayaro virus, which also causes fever and (limited) joint pain; its circulation is limited to the Northern region of the country,[66] although it has already been detected in states from other regions.[67,68]

A study group from Federal University of Rio de Janeiro (Universidade Federal do Rio de Janeiro – UFRJ) reported a case series with 30 patients from areas endemic for ZIKV, CHIKV and DENV coinfection. DENV RNA was not detected in any of the clinical samples, while ZIKV RNA was detected in 17 samples (56.7%). ZIKV and CHIKV coinfection was documented in 1 case. From the 17 ZIKV-positive individuals, 8 exhibited reactivity for anti-DENV IgM, which is suggestive of recent infection with DENV, cross-reactivity or coinfection. These findings reinforce the relevance of laboratory testing for confirmatory diagnosis, especially for cases originating in areas endemic for all 3 arboviruses.[75]

PRNT, developed in 1959 by Henderson and Taylor,[89] identifies and quantifies neutralizing antibodies in serum samples by calculating the percent viral activity reduction. PRNT is widely accepted as the most specific test for the diagnosis of diseases by arboviruses. In samples from patients with specific anti-CHIKV neutralizing antibodies, the number of plaques was lower compared to the controls due to the presence of neutralizing antibodies in the infected host cells.[90] Diagnosis

Table 5 – Prevalence of autoantibodies in Chikungunya fever according to various studies.

Studies	*n*	RF+	ACPA+	ANF+	RF or ACPA+
Blettery et al., 2016[72]	147	0%	0%	0%	na
Bouquillard and Combe, 2009[92]	21	57.1%	28.6%	9.5%	66%
Chopra et al., 2008[20]	156	43.3%	3,3%	na	na
Ganu and Ganu, 2011[93]	16	12.5%	56.5%	na	na
Javelle et al., 2005[29]	159	na	na	na	30%
Lambourne et al., 2015[136]	54	15%	0%	na	na
Manimunda et al., 2010[23]	20	0%	5%	na	na
Minner et al., 2015[137]	8	0%	0%	30%	na
Zhukov et al., 2015[138]	234	25.2%	1.7%	na	na

n, number of patients; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; ANF, antinuclear factor; na, not assessed.

through PRNT is confirmed when the titer increases 4 times from the acute stage to convalescence.[76]

A recent study conducted in the Philippines found that PRNT might be useful for detecting cases of subclinical infection. The sample comprised 853 randomly selected individuals before the onset of symptoms suggestive of Chikungunya fever during an epidemic in 2012. Twelve months later, 19 symptomatic cases and 87 cases of subclinical infection were identified. Positive PRNT at inclusion was associated with 100% (95% confidence interval – CI: 46.1, 100.0) protection against symptomatic infection. These data might be relevant to assess the impact of disease, understand the virus' transmission and to help in the development of a vaccine against CHIKV.[91]

As PRNT has high cost, is difficult to perform and interpret and has limited access, the first-choice serological method must be based on immunoenzymatic assays (ELISA), which have low cost, are widely accessible and are simple to perform.[65,84] As in the case of CHIKV detection, we recommend performing serology during the acute stage of Chikungunya fever only when differential diagnosis is necessary or for atypical cases. For typical cases, diagnosis should be established based on the clinical-epidemiological criteria (Table 5).

A.5. During the chronic stage of Chikungunya fever, autoantibodies should only be investigated when differential diagnosis with specific rheumatologic diseases is necessary with compliance with the available consensuses/guidelines. *Concordance: 8.55 (SD ± 2.593); level of evidence (3,4)*

Data on the presence of autoantibodies in patients with Chikungunya fever are scarce and rather conflicting, likely as a result of differences among the population groups assessed and in the design of studies, most of them having a retrospective design and consisting of case series. Preliminary results of the CHIKBRAZIL cohort study, which thus far has included 430 patients with Chikungunya fever from 4 Brazilian state capitals, detected rheumatoid factor (RF) in 28.3% of 113 patients who performed the test, antinuclear factor (ANF) in 33.3% of 66 patients and anti-citrullinated protein antibody (ACPA) in a single patient (unpublished data).

Table 5 describes the results of autoantibody testing in several cohorts of patients with Chikungunya fever.

Considering the available data, RF and ACPA should only be investigated in cases with persistent synovitis in 1 or more joints in the chronic stage of disease despite adequate treatment. ANF should only be measured for the purpose of differential diagnosis relative to cases lasting more than 12 weeks and without a definitive diagnosis. In addition to these autoantibodies, investigation of HLA-B27 is relevant in cases with clinical manifestations suggestive of SpA.[24]

A.6. In the acute and subacute stages of Chikungunya fever, most patients do not need imaging tests. In the chronic stage of disease, plain radiography should be requested by the rheumatologist on the first visit for initial structural and pre-existing damage assessment. *Concordance: 9.70 (SD ± 0.651); level of evidence (3,4)*

A.7. Musculoskeletal ultrasound might contribute to the assessment of joint and periarticular abnormalities at any stage of Chikungunya fever. In the acute stage of disease, it is the only imaging test that might be performed according to the doctor's opinion, being particularly useful for differential diagnosis of lower limb swelling. *Concordance: 9.29 (SD ± 1.510); level of evidence (3,4)*

The studies conducted up to the present time did not establish a protocol defining when plain radiographs should be performed. Radiographs taken during the acute stage of disease did not evidence erosions, and the occurrence of the latter in the chronic stage diverges among published studies.[20,29,72,92] In the study conducted in Reunion Island, some patients exhibited partial or total recovery of the bone lesions after treatment, while the degree of bone destruction became worse in others even with treatment.[29]

Radiographic abnormalities associated with arthropathy secondary to CHIKV infection were found in images mainly taken after 3 months to 2 years of disease.[93] In a retrospective study, the average time to radiological diagnosis of joint lesions from the acute stage was 45 months.[29] As a result, radiographs are not suggested for patients in the acute stage of disease. Relative to patients with less than 3 months of disease, radiographs are recommended for select situations, such as the presence of complications, doubts about diagnosis and assessment of the indication of early treatment. As concerns patients in the chronic stage of disease and long-lasting symptoms, plain radiographs should be taken as a function of the pattern of involvement to assess the progression of joint damage as needed.[24,29]

Ultrasonography (USG) is a fast, low-cost and non-invasive method; however, its results are highly dependent on the physician who performs the tests. It is useful to investigate the presence of synovitis, the degree of inflammatory

Table 6 – Indications of and possible findings on imaging tests for Chikungunya fever.

Test	Indication	Possible findings
Plain radiograph	*Only at the chronic stage* • Assessment of previous joint lesions, especially in patients at high risk of progression into the chronic stage • Assessment of structural damage related to Chikungunya fever joint involvement	• Increase in soft tissue • Calcifications • Erosions • Subchondral sclerosis • Osteophytes • Periarticular osteopenia • Periosteal reaction • Joint space narrowing
Ultrasonography	*Acute, subacute and chronic stages* • Assessment of articular and periarticular inflammation • Assessment of the joint status in patients with suspicion of previous joint lesions • Assessment of structural damage related to Chikungunya fever joint involvement	• Calcifications • Crystal deposition (differential diagnosis with gout) • Joint effusion • Erosions • Osteophytes • Periarthritis/enthesitis • Synovitis • Tenosynovitis/tendinitis
Magnetic resonance imaging	*Only at the chronic stage* Assessment of structural damage related to Chikungunya fever joint involvement, suspicion of progression into rheumatologic disease (RA/SpA)	Joint effusion • Bone marrow edema (sacroiliac in particular) • Enthesopathy • Erosions • Periosteal inflammation • Synovitis (synovial thickening) • Tenosynovitis/tendinitis

RA, rheumatoid arthritis; SpA, spondyloarthritis.

activity, bone erosions and ligament and tendon lesions due to Chikungunya fever. It further helps to elucidate doubts about the diagnosis and detect previous lesions.[22,46,94] In the acute stage of Chikungunya fever, it enables assessing lower limb swelling and helps in the differentiation among articular and periarticular lesions and edema of vascular origin (expert's opinion).

In a USG study conducted in Martinique, which assessed articular manifestations during the acute stage of Chikungunya fever in 28 patients (average length of disease: 6.15 days), joint effusion was detected in 92.8% of the sample. Periarthritis of the ankle was less frequent (28%), only 2 patients exhibited tenosynovitis and no instances of erosions were found.[95]

The few studies that assessed the indication of magnetic resonance imaging (MRI) in chronic arthropathy secondary to CHIKV infection are descriptive, do not establish the superiority of this method over USG and do not define the need to include imaging methods in the follow up of patients. In addition, one needs to take into account the cost and availability of tests, as well as the examiner's experience in the selection of the most adequate method for imaging assessment on a case-by-case basis.[23,27] The MRI abnormalities that might be found in patients with Chikungunya fever are similar to those of inflammatory joint involvement, RA in particular.[23,24,27,42,72,93] Table 6 describes the indications and possible findings according to clinical stage and type of imaging method used.

B. Special situations

B.1. In the treatment of pregnant women with Chikungunya fever, the risk posed by medicines to the fetus should be taken into account; when indicated, analgesics, prednisone/prednisolone and hydroxychloroquine may be used. *Concordance: 9.71 (SD ± 0.534); level of evidence (3,4)*

B.2. By itself, Chikungunya fever is not an indication of cesarean section, the need of which should be established on obstetrical grounds only. Breastfeeding is allowed. *Concordance: 9.67 (SD ± 0.547); level of evidence (3–4)*

During an outbreak that took place in Thailand in 2009–2010, an epidemiological survey of dengue fever and Chikungunya fever was performed among women who delivered infants from November 2009 through May 2010. The mothers were subjected to serology testing; the umbilical cord blood was also tested for the CHIKV-positive cases. The seroprevalence of CHIKV was 71.2%; no instance of the most frequent obstetrical complications occurred, and specific IgM was not detected in the umbilical cord blood samples.[96]

In 2015, Dotters-Katz et al.[97] reviewed obstetrical aspects related to Chikungunya fever by searching English articles on the subject of interest based on the PRISMA criteria. In total, 25 articles were analyzed. The results showed that despite indications suggesting that disease is more severe in individuals with chronic diseases, elderly and children, it does not seem to be more severe among pregnant women, although there were no comparative studies with non-pregnant women.

Furthermore, the gestational outcomes did not seem to be influenced by CHIKV infection. In a prospective study conducted in Reunion Island, Fritel et al.[98] compared pregnant women with and without Chikungunya fever. The infected women had a larger number of admissions to the hospital during pregnancy, but there was no difference relative to

congenital defects, prematurity or other disorders. In another prospective study by Gérardin et al.,[99] also performed in Reunion Island, maternal viremia intrapartum was associated with a higher incidence of abnormalities of the fetal heart rate, which doubled the frequency of cesarean sections; this was the single difference found.

The pregnancy trimester in which infection with CHIKV occurs is the main predictor of fetal outcome. The virus can cross the placental barrier in the first and second trimesters and cause fetal infection and miscarriage, which are considered to be rare occurrences. However, maternal active infection up to 4 days after delivery increases the risk of vertical transmission, the incidence of which varies from 27% to 48% among the various published case series.[97,99–103] Vertical transmission should be suspected when the symptoms of disease manifest within the first week of life and there is no evidence of a mosquito bite.[103] As cesarean section does not prevent vertical transmission,[104,105] it is not mandatory for cases of Chikungunya fever; rather, it should be performed as per obstetrical indications. The transmission of CHIKV by mother's milk is still under discussion.[97]

The treatment of pregnant women with chronic Chikungunya fever should take into account the known effects of medicines on the fetus. It is recommended to start analgesic treatment in the acute stage of disease with paracetamol, with a maximum dose of 4 g/day. NSAIDs are contraindicated from gestational week 24 onward due to the risk of fetal kidney failure and premature closure of the ductus arteriosus.[24] The use of non-selective COX-2 inhibitors might be allowed over a short period of time from pregnancy week 16 to 30, but it is preferable to indicate prednisone in low doses, which might be used all across pregnancy and breastfeeding with no fetal risk.[106]

Hydroxychloroquine is an option for the treatment of chronic joint disorders during pregnancy and breastfeeding due its acknowledged safety during these periods[106,107] and the evidence indicating improvement of joint disorders in a case series from the overall population.[108,109]

A steroid sparing agent, azathioprine, might be used during pregnancy and breastfeeding, while methotrexate (MTX) should be avoided by the time of conception, pregnancy and breastfeeding.[106] In addition to paracetamol, ibuprofen and opioids might also be indicated in select cases.[110]

B.3. Relative to the elderly (>60 years old) with Chikungunya fever, strict clinical monitoring of medications, comorbidities and higher risk of complications is recommended in all the stages of disease, acute ones in particular. *Concordance: 9.61 (SD ± 0.737); level of evidence (3,4)*

Considering elderly individuals as those aged 60 years and older, few studies have approached this specific subpopulation. However, with a cutoff point of 40 years old, older patients exhibited higher odds of progression into the chronic stage, as found in the La Virginia, Colombia cohort, where the frequency was 52%,[38] and the Reunion Island cohort, in which 70% of the patients above 45 exhibited persistent joint pain 15 months after acute infection (odds ratio (OR) 4.2 (CI 1.9–9.3)).[39]

In a study conducted in India with 509 patients, the intensity of the acute stage of disease was higher among the elderly (above 65 years old) who were confined to bed on average for 4–6 days; 42% of them attained full recovery after 4 weeks, and no deaths occurred.[19] The particularities of disease among the elderly are not clear in the remainder of the analyzed cohorts; some of them reported a higher number of medical visits compared to other groups of patients.

The factors to be taken into account in the approach and treatment of the elderly are polypharmacy and the presence of comorbidities (arterial hypertension – AH – and DM), which are frequent in this age range. Concomitant use of several medications might result in complications derived from the interaction of the analgesics and steroids indicated for pain and arthritis. Many elderly use aspirin prophylactically, which is associated with Reye's syndrome, but there are no reports among patients with Chikungunya fever. Decompensation of DM is associated with dehydration, which might be a complication in cases with acute infection (6).

In Brazil, up to EW 27 of 2016, 38 deaths by Chikungunya fever were confirmed, corresponding to the following states: Pernambuco ($n = 25$), Rio Grande do Norte ($n = 5$), Paraíba ($n = 2$), Rio de Janeiro ($n = 2$), Ceará ($n = 2$), Maranhão ($n = 1$) and Alagoas ($n = 1$); the median age of the deceased was 71 years old.[111] Relative to Pernambuco, i.e., the state with the largest number of deaths in the country, more recent data (EW 37) showed that 7970 of 53,061 notified cases corresponded to individuals above 60 years old, with 53 confirmed deaths by Chikungunya fever.[112]

Although the elderly do not represent the group with the highest prevalence of disease, most deaths occurred within this age range. This shows that this population needs particular attention during the acute stage, more specifically, those who live alone and might have no assistance for feeding and personal care. Many elderly are confined to bed for up to 7 days, which increases the risk of urinary tract infection and pneumonia.[113]

B.4. Children under 2 years of age should receive special attention due to their higher risk of severe and atypical manifestations and involvement of the central nervous system (CNS). *Concordance: 9.30 (SD ± 1.179); level of evidence (3,4)*

Up to the present time, few observational studies have investigated clinical and laboratory manifestations of infection with CHIKV among children. Most such studies describe more severe forms of diseases occurring in newborn infants and emphasize the fact that the clinical presentation might be different in children compared to adults. The rate of asymptomatic infection seems to be higher among children, varying among the various reports of outbreaks (35–40%).[46,114–120] A recent study analyzed the seroprevalence among children on the occasion of the first CHIKV outbreak in Nicaragua. The results showed detectable antibody levels in 6.1% of children aged 2–14 years and 13.1% in those above 15 years of age.[121]

Relative to the acute stage of infection, the differences between children and adults concern the skin, hemorrhagic and neurological manifestations.[117] Maculopapular exanthema occurs in 35–50% of adults but is less frequent among children, especially those under 2 years old, with hyperpigmentation a more common finding. In addition, infants under 6 months old might exhibit extensive skin bullous lesions, affecting up to 35% of the body surface.[122] Hemorrhagic manifestations, including epistaxis, gum bleeding and purpura, occur in 10% of pediatric cases, while they are rare among adults.[117]

The main concern relative to the pediatric population is the involvement of the CNS. During the Chikungunya fever outbreak in Reunion Island, 25% of the children exhibited neurological symptoms. Among such children, a high proportion (40–50%) exhibited severe manifestations, including status epilepticus, complex seizures and encephalitis.[123,124] The neurological symptoms can last from several months to years.[123]

B.5. Newborn infants from mothers with clinical manifestations suggestive of Chikungunya fever close to labor should be subjected to close observation during the first 5 days of life. Rational use of medications should be performed for cases that develop disease; complex cases should be managed at the intensive care unit. *Concordance: 9.54 (SD ± 0.838); level of evidence (3,4)*

Perinatal infection was first described in the Reunion Island outbreak in 2005.[125] Although intrauterine CHIKV transmission is extraordinarily rare at the onset of pregnancy, its rate increases to almost 50% when maternal viremia occurs 1 week before birth.[126]

A recent Latin American multicentric study analyzed 169 newborn infants with symptomatic Chikungunya fever at 4 large maternity hospitals from 3 countries whose mothers had CHIKV infection confirmed by PCR. In these infants, the symptoms started around the fourth day of life, the most frequent ones being fever, irritability, hyperalgesia, diffuse limb swelling, meningoencephalitis, skin rash and bullous dermatitis and petechiae. Laboratory testing evidenced thrombocytopenia and lymphopenia in most cases. Complications included intracerebral hemorrhage, status epilepticus and multiple organ failure.[103]

The mortality rate is high, for which reason long-term outcomes and damage could not be assessed in studies. Among survivors, half of the children exhibited reduced cognitive development by 2 years of age.[99,105,126] These data clearly show that infection with CHIKV among children is not always benign; rather, it might result in permanent sequelae and death.

B.6. Treatment for the acute stage of Chikungunya fever in children consists of hydration, analgesics and antipyretic agents; salicylates should be avoided. For the chronic stage, we suggest following the recommendations for adults, while taking the particularities inherent to this age range into account. *Concordance: 9.48 (SD ± 0.785); level of evidence (3,4)*

No recommendations specific for the management and treatment of infection with CHIKV among children were located. In most case series published after outbreaks in Asia and the Americas, the recommendations are similar to those for adults: in the acute stage, hyper-hydration, analgesics and antipyretics, with avoidance of salicylates and NSAIDs due to the risk of triggering bleeding. When the joint symptoms persist, the recommendations do not differ from those for adults who progress to the chronic stage, treatment being based on the use of NSAIDs, steroids and MTX; however, the benefits for the pediatric population are still unknown.

The more specific available recommendations target newborn infants, in which morbidity and mortality are common. Rational use of medications and adequate monitoring are recommended, which seem to have a direct relationship with improved clinical progression. Abuse of medications, such as salicylates, NSAIDs, steroids and antibiotics, might contribute to worsening disease through development of bleeding, thrombocytopenia and gastrointestinal symptoms, leading to complications, including hydroelectrolytic disorders, dehydration and kidney failure, which might indirectly trigger death.[99–101,103]

B.7. We recommend paying special attention to patients with previous diagnosis of rheumatoid arthritis, spondyloarthritis or systemic lupus erythematosus, as these conditions might become reactivated or exacerbated. *Concordance: 9.42 (SD ± 1.840); level of evidence (3,4)*

Infection with CHIKV among patients with previous rheumatologic diseases is not well characterized in the literature. In the published case series and cohorts, the frequency of previous musculoskeletal disorders among patients with Chikungunya fever varies from 6.9% to 86%,[20,23,26,41,127] the highest prevalence rates being found in studies conducted at specialized services.

A history of rheumatologic disease was associated with persistence of joint symptoms after infection with CHIKV[40,41,127] and greater disability.[128] Exacerbation of pain complaints in the previously affected sites was described in patients with chronic diseases, such as OA, tendinopathy, lumbar pain and carpal tunnel syndrome.[23,29,74,127] Sissoko et al.[39] followed up 147 patients along 15 months; 28% of the sample had a previous diagnosis of OA, which behaved as a predictor of persistence of symptoms (OR 2.9 (95% CI 1.1–7.4; $p = 0.029$)).

The acute clinical manifestations of patients with previous musculoskeletal pain tend to be similar to those of previously healthy patients with Chikungunya fever; atypical or severe acute manifestations are not more frequent, not even among patients using immunosuppressants or immunobiological agents.[129–132] Interestingly, patients are able to distinguish the symptoms related to CHIKV infection from those of the underlying disease because the former are more intense or occur in sites different than the latter.[133]

Javelle et al.[29] assessed 18 patients with previous rheumatologic disease among 159 patients followed up over 6 years. In 6 patients with RA, 8 with SpA, 2 with SLE and 2 with chronic hepatitis, the joint symptoms worsened immediately after infection with CHIKV, requiring changes in treatment or onset of new treatments in half of them.

Patients with SpA might exhibit exacerbation characterized by greater peripheral involvement (arthritis and/or enthesitis),[20,29] and those with psoriatic arthritis experience exacerbation of the skin and/or joint disease.[20]

Patients with previously controlled RA might exhibit exacerbation of the joint symptoms in the acute stage of Chikungunya fever, eventually with the typical manifestations of RA involving the joints of the hands and feet.[19,129] However, assessment of patients with previous rheumatic disease in Martinique did not detect any cases of post-CHIK RA exacerbation, which suggests that previous treatment with disease-modifying antirheumatic drugs (DMARDs) and/or immunobiological agents might have a protective effect.[72]

Retrospective assessment of 167 patients with SLE in Martinique showed that, among the 56 patients with serology positive for CHIKV, 82.6% exhibited clinical symptoms compatible with Chikungunya fever, while only 10.7% exhibited exacerbation of SLE. Severe manifestations of Chikungunya

fever were detected in 4 patients, including encephalopathy in all 4, associated with bullous cutaneous lesions in 3, kidney involvement in 1 and multiple organ failure resulting in death in 1.[130] There is risk of severe complications – 1 case of antiphospholipid antibody syndrome (APS) was described in a patient with a previous diagnosis of SLE.[134,135] However, the available data are not sufficient to establish whether the risk of atypical manifestations/severe complications is higher in this specific population.

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Conflicts of interest

The authors declare no conflicts of interest.

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