

Technical Report

Classification of chikungunya cases: a proposal

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Abstract

Since 2005, chikungunya virus (CHIKV) has caused large outbreaks, with reports of more than 10 million cases worldwide over the course of a decade. Since 2013, almost three million cases have been reported in the Americas. Although musculoskeletal involvement is the most prevalent symptom in the disease spectrum, systemic manifestations with involvement of important organs have also been described. Currently, case classifications of chikungunya based on the intensity and duration of articular symptoms have been used to guide the clinical management of the joint manifestations, with little or no emphasis on the severe clinical forms associated with systemic disease and target organ involvement. Thus, these classifications have failed to aid health professionals in the detection and early management of severe cases, which can lead to fatal outcomes and sequelae. Based on data from international literature and the opinions of clinical professionals, epidemiologists, and arbovirologists with extensive experience gained from the Brazilian chikungunya outbreak, a group of specialists proposed a revised classification for chikungunya cases. In this proposed classification, the specialists highlight the different patterns of the disease, including systemic manifestations, with the aim of sensitizing health professionals for the prompt detection and early management of severe conditions, which can contribute to reducing fatal outcomes.

Keywords: Chikungunya. Classification. Alarm signs. Severe.

INTRODUCTION


Since 2005, chikungunya virus (CHIKV) has caused large outbreaks, with reports of more than 10 million cases worldwide over the course of a decade¹. Although musculoskeletal involvement

is the most prevalent symptom in the disease spectrum, systemic manifestations with involvement of important organs have also been described²⁻⁴.

Currently, case classifications of chikungunya based on the intensity and duration of articular symptoms have been used to guide the clinical management of the joint manifestations, with little or no emphasis on the severe clinical forms associated with systemic disease and target organ involvement. Thus, these classifications have failed to aid health professionals in the detection and early management of severe cases, which can lead to fatal outcomes and sequelae⁵.

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A group of experts decided to review the classification of chikungunya fever cases to raise awareness to the severe forms of chikungunya with the aim of reducing mortality, which is aligned with the World Health Organization (WHO)'s goals of decreasing fatal outcomes of vector-borne diseases by 50% and 75% by 2025 and 2030, respectively. The proposed classification system will be incorporated into the new guidelines for the diagnosis and treatment of chikungunya fever of the Brazilian Ministry of Health, which are already under development.

The findings from chikungunya clinical studies and the accumulated experience of specialists during epidemics in India, the Caribbean, and, most recently, Brazil support the need for adjustments to the current classifications⁶. We believe that a revised classification system should be based on an expanded description of the different clinical presentations of the disease, expressing the various biological gradients, which should range from mild to severe, as would be expected for an infectious disease (Evans' Fifth Postulate). A classification system encompassing the full disease spectrum will help increase health professionals' awareness of the severity and complications associated with each category, similar to the systems that have been developed for countless other epidemic infectious diseases. A structured classification system allows the standardization of treatment according to clinical complexity and severity, guiding actions such as the definition of the treatment setting based on disease complexity, ordering of complementary exams, and initiation of therapies.

DISCUSSION

In 2015, a panel of experts revised the classification of chikungunya cases and proposed four disease categories: acute, atypical, severe acute, and chronic⁷. Although this proposed classification system represents an important improvement, it still has limitations, as the main symptom used to categorize the patients is joint impairment, without focusing on systemic symptoms that can occur. A study performed in a university hospital in Martinique showed that the current chikungunya fever classification system produced by the WHO is especially ineffective for elderly patients. Of the 257 patients older than 65 years with laboratory confirmation of CHIKV infection with positive reverse transcriptase polymerase chain reaction results, 42.7% could not be classified in any category of the current system, and in the group of 109 younger patients (<65 years), 17.4% could not be classified, showing that this model has limitations. Additionally, in the group aged 65 years and older, only 8.2% were classified as having the typical form as defined by the WHO⁸.

Furthermore, the pathophysiological mechanisms of the main arbovirus infections, including chikungunya, reinforce the concept that the disease is dynamic and that the impairment of systemic organs (classified as atypical forms) can evolve into severe forms and become the main cause of death related to CHIKV infections. Therefore, at any stage, systemic manifestations should represent an important sign of severity. The atypical and acute severe groups suggested in the 2015 modification of the classification system represent the same group with different biological levels of intensity.

Several of the terms used in the classification system may need to be revised in the process of creating a categorization system that can ultimately enable professionals to detect cases. The term "atypical"

refers to that which does not correspond to the predominant clinical features of chikungunya but rather to a situation that is unexpected, which minimizes the relevance; however, it is clear that the impairment of systemic organs is part of the spectrum of the disease, even if it is less common. Similar patterns have been observed in numerous other epidemic viral diseases (dengue, yellow fever, and influenza).

Expanded clinical spectrum of the disease

Musculoskeletal manifestations are the most common, and their management is related to different phases⁹⁻¹⁰. Chronologically, the spectrum of the disease involves three phases (acute, postacute, and chronic). Clinically, there are different patterns of joint manifestations that may be predominantly noninflammatory/musculoskeletal (mechanical) or inflammatory with arthritis and periarticular manifestations. Approximately 50% of patients develop chronic joint disease, with important impairment of their quality of life, and, in many cases, mimicking clinical patterns of rheumatic diseases such as rheumatoid arthritis (RA), seronegative spondylarthritis (SpA), fibromyalgia (FM), and undifferentiated polyarthritis¹⁰⁻¹³.

In addition to musculoskeletal involvement, there are relevant systemic manifestations with the involvement of important organs. Systemic manifestations that can evolve with exacerbation mainly affect the nervous, cardiac, pulmonary, renal, hepatic, endocrine, and vascular systems²⁻⁴.

In 2016 on Reunion Island, among the 123 cases of severe chikungunya fever, the main reasons for hospitalization were respiratory failure (19 cases), cardiovascular decompensation (18), meningoencephalitis (16), severe hepatitis (11), severe skin lesions (10), and renal failure (7)⁴.

Among the 96 nonpregnant adults enrolled in a study by Bonifay et al. in French Guiana during the 2014/2015 CHIKV outbreak, 29% of the patients were classified as having atypical or severe forms, with the most common symptoms being neurological symptoms (Guillain-Barret syndrome, encephalitis, seizure, confusion, and stroke), followed by cardiorespiratory failure, hepatitis, pancreatitis, renal failure, and muscular impairment².

Severe forms of the disease and fatal outcomes have been described as more often affecting those at the extreme ends of the age spectrum, predominantly elderly patients, and the presence of comorbidities may contribute to the development of complications⁴. However, severe forms have also been described in different age groups in the absence of associated diseases¹⁴⁻¹⁶. In a study of 44 patients with arrhythmia conducted by Economopoulo et al., 63% had no history of cardiovascular disease, and in 131 patients with blood glucose level alterations, 20% were diagnosed with diabetes mellitus for the first time³.

The signs and symptoms described in the systemic form of chikungunya fever are related to the injury of target organs by the disease¹⁷⁻¹⁸. In a systematic review of the systemic manifestations associated with chikungunya, cardiac involvement was reported in 54% of the articles, and the predominant symptoms were chest pain, fatigue, dyspnea, palpitations, vagal symptoms (diaphoresis, pallor, and coughing), nausea, dizziness, and lipothymia/syncope.

On physical examination, the findings included tachycardia, atrial and ventricular premature ectopic beats, crepitation or rhonchi in the lungs, and tachypnea¹⁷.

Mehta R et al., in a systematic review of neurological impairment due to chikungunya, found encephalitis to be the most common complication, followed by myelopathy, myelitis, and Guillain-Barré syndrome¹⁸. The most common symptoms included headaches, altered sensorium, lethargy, seizures, weakness, and paresthesia¹⁸.

Studies conducted first in India and more recently in Brazil reported significantly higher mortality rates in the months coinciding with chikungunya outbreaks than in the same period in previous years and the expected rates after the outbreak. Retrospective analyses in different Latin American countries have produced similar results, demonstrating a strong temporal association and potential causality between this surplus mortality and the outbreak^{19,20}.

It is possible that the failure to accurately identify the mortality rate associated with chikungunya is related not only to flaws in the surveillance system but also, and perhaps mainly, to the lack of an awareness of the possibility of CHIKV infection as a cause of death on the part of doctors. In part, this can be justified by the limited knowledge of serious systemic manifestations and possible complications related to CHIKV infection and the lack of a case classification system that contributes to increasing the awareness of health professionals about the spectrum of this disease.

RESULTS: A structured classification system based on the clinical spectrum of the disease

The clinical spectrum of the disease chronologically involves three phases: an acute phase (up to 14 days), a postacute phase (15 to 90 days), and a chronic phase (after 3 months). The disease should be classified according to the clinical spectrum and level of intensity as follows:

- “Classic chikungunya”, divided into 3 phases according to the duration of symptoms: “acute”, “postacute”, and “chronic”; and
- “Systemic chikungunya”, divided by severity into “chikungunya with alarm signs” and “severe chikungunya” (**Figure 1**).

1. Classic chikungunya: The classic form of chikungunya is characterized by musculoskeletal impairment, which is the most common clinical manifestation of the disease with an inflammatory component predominantly in the acute phase. The postacute and chronic phases have different patterns of manifestations that can involve: (a) localized or diffuse noninflammatory musculoskeletal pain; (b) arthritis/tenosynovitis (articular or periarticular disease associated with edema); and (c) neuropathic pain. It is important to emphasize that a patient can present with a combination of patterns such as arthritis or noninflammatory musculoskeletal pain associated with neuropathic pain.

2. Systemic chikungunya: These forms are characterized by systemic manifestations resulting from organ impairment that

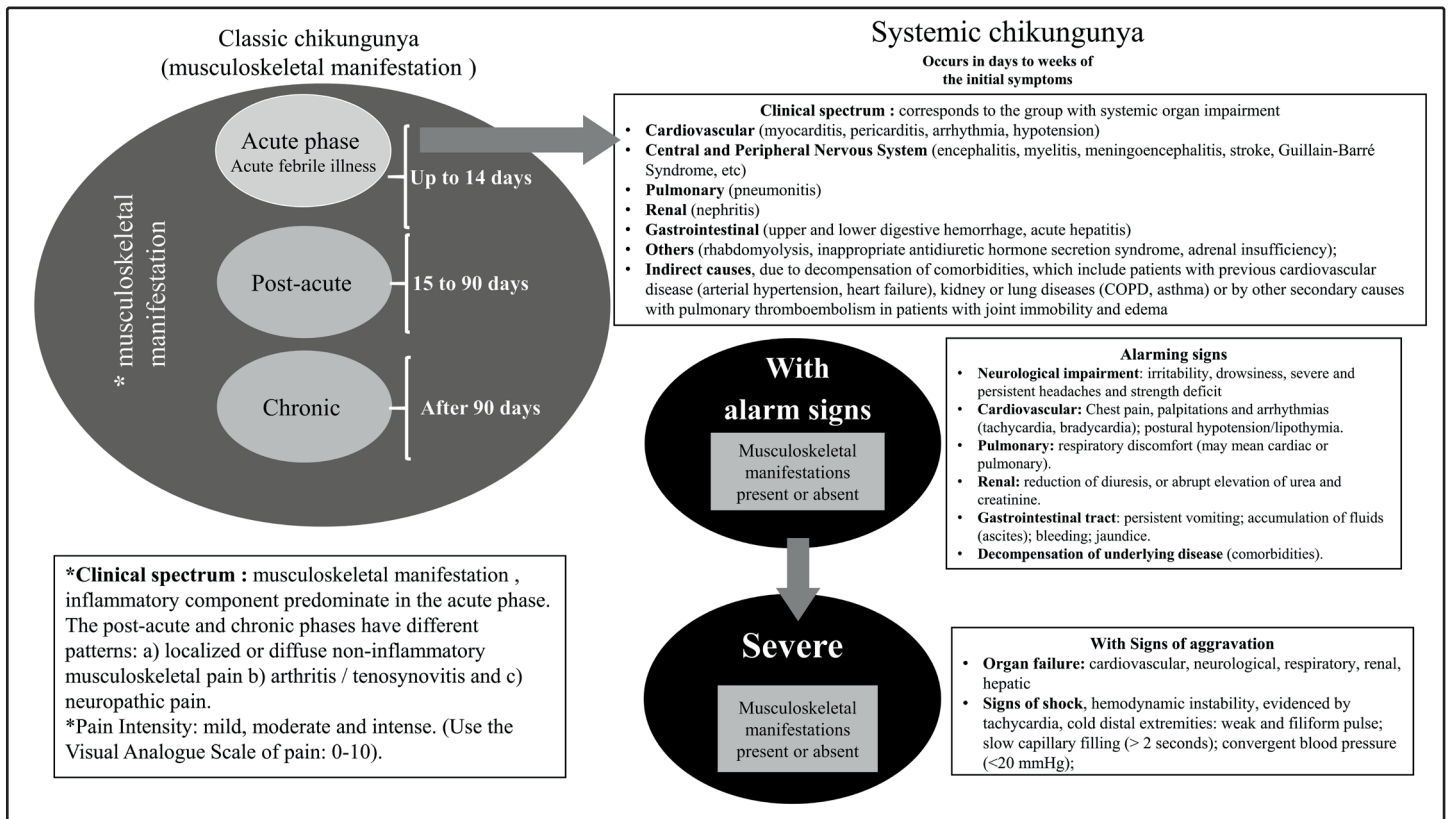


FIGURE 1: Proposal of new classification system for chikungunya cases.

may or may not present simultaneously with or be preceded by musculoskeletal manifestations. The clinical spectrum involves systemic organ impairment due to the direct effects of the virus, systemic inflammatory response, or indirect causes (as a consequence of decompensating underlying disease). The systemic impairment of organs can involve the following: cardiovascular (myocarditis, pericarditis, arrhythmia, and hemodynamic instability); central and peripheral nervous system (encephalitis, myelitis, meningoencephalitis, stroke, Guillain-Barré syndrome, optic neuritis, cerebellitis, and rhombencephalitis); pulmonary (pneumonitis); renal (nephritis); gastrointestinal (upper- and lower-digestive hemorrhage, and acute hepatitis); others (rhabdomyolysis, inappropriate antidiuretic hormone secretion syndrome, and adrenal insufficiency); indirect causes due to decompensation of comorbidities, including preexisting cardiovascular (arterial hypertension and heart failure), kidney, or lung (COPD and asthma) diseases, or other secondary causes like pulmonary thromboembolism in patients with joint immobility and edema (**Figure 1**).

With regard to chronology, these manifestations may occur days or weeks after the initial symptoms appear. The timing of the event depends on the causes and organs affected, while the gradient of intensity is classified as chikungunya with alarm signs or severe chikungunya, which can be identified by the presence of alarm signs or their aggravation, respectively (**Figure 1**). Alarm signs manifest when target organs are affected. The presence of alarm signs should be defined as a separate group, since it indicates the presence of clinical conditions that can progress with aggravation and carries the risk of a fatal outcome, necessitating careful medical care and specialized treatment.

In the severe form, the patient experiences aggravation of the clinical features, with worsening of alarm signs due to organ failure that may be cardiovascular, neurological, respiratory, renal, and/or hepatic. Signs of shock represent one of the manifestations of aggravation related to systemic cardiovascular impairment.

CONCLUSION

We believe that the proposed classification system takes into consideration the different clinical manifestations of CHIKV infection, thus facilitating the construction of flowcharts and guiding the development of future clinical guidelines for addressing the complete spectrum of the disease and increasing awareness of this spectrum, enabling health care professionals to identify and treat systemic chikungunya before the development of worse outcomes.

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AUTHORS' CONTRIBUTION

All contributing authors have participated in the study to the conception or design of the work, or the acquisition, analysis or interpretation of cases; and subsequent revisions of the manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interests.

REFERENCES

1. Pan American Health Organization (PAHO). Number of Reported Cases of Chikungunya Fever in the Americas, by Country or Territory 2017 (to week noted). Cumulative cases. *Epidemiological Week / EW 27* [Internet]. Washington, DC: Pan American Health Organization; 2017 [updated 2017 July 7; cited 2020 July 27] Available from: <https://www.paho.org/hq/dmdocuments/2017/2017-jul-7-phe-CHIKV-cases-ew-27.pdf>.
2. Bonifay T, Prince C, Neyra C, Demar M, Rousset D, Kallel H, et al. Atypical and severe manifestations of chikungunya virus infection in French Guiana: A hospital-based study. *PLoS ONE*. 2018;13(12):e0207406. doi:10.1371/journal.pone.0207406.
3. Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quene P, et al. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion. *Epidemiol Infect*. 2009;137(4):534-1. doi:10.1017/S0950268808001167. Epub 2008 Aug 11.
4. Renault P, Solet JL, Sissoko D, Balleydier E, Larrieu S, Filleul L, et al. A major epidemic of chikungunya virus infection on Réunion Island, France, 2005-2006. *Am J Trop Med Hyg*. 2007;77(4):727-31.
5. Pan American Health Organization (PAHO). Preparedness and Response for Chikungunya Virus Introduction in the Americas [Internet]. Washington, DC: Pan American Health Organization; 2011. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=3545:2010-preparedness-response-chikungunya-virus-introduction-americas&Itemid=39837&lang=en
6. Cavalcanti LPG, Gadelha B, Kalline FB, Siqueira AM, Ribeiro GS, Freitas ARR, et al. Chikungunya Case Classification after the Experience with Dengue Classification: How Much Time Will We Lose? *Am J Trop Med Hyg*. 2020;102(2):257-9. doi:10.4269/ajtmh.19-0608.
7. World Health Organization (WHO). Chikungunya: case definitions for acute, atypical and chronic cases. Conclusions of an expert consultation, Managua, Nicaragua, 20-21 May 2015. *Wkly Epidemiol Rec*. 2015;90(33):410-4.
8. Godaert L, Najioullah F, Bartholet S, Colas S, Yactayo S, Cabié A, et al. Atypical Clinical Presentations of Acute Phase Chikungunya Virus Infection in Older Adults. *J Am Geriatr Soc*. 2017;65(11):2510-5. doi:10.1111/jgs.15004.
9. Brito C, Marques C, Falcão M, Cunha R, Simon F, Valadares LDA, et al. Update on the treatment of musculoskeletal manifestations in chikungunya fever: a guideline. *Rev Soc Bras Med Trop*. 2020;53:(e20190517). doi:10.1590/0037-8682-0517-2019.
10. Amaral K, Taylor P, Teixeira M, Morrison T, Schoen R. The Clinical Features, Pathogenesis and Methotrexate Therapy of Chronic Chikungunya Arthritis. *Viruses*. 2019;11(3): 289. doi:10.3390/v11030289.
11. Dias J, Costa M, Campos G, Paixão E, Natividade M, Barreto F, et al. Seroprevalence of chikungunya virus after its emergence in Brazil. *Emerg Infect Dis*. 2018;24(9):1773. doi:10.3201/eid2404.171370
12. Paixão E, Rodrigues L, Costa M, Itaparica M, Barreto F, Gérardin P, et al. Chikungunya chronic disease: A systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2018;112(7):301-16. doi:10.1093/trstmh/try063
13. Amaral J, Bilborrow J, Schoen R. Brief report: the disability of chronic chikungunya arthritis. *Clin Rheumatol*. 2019;38(7):2011-2014. doi:10.1007/s10067-019-04529-x
14. Sharma PK, Kumar M, Aggarwal GK, Virender K, Srivastava RD, Sahani A, et al. Severe manifestations of chikungunya fever in children, India, 2016. *Emerg Infect Dis*. 2018;24:1737-9. doi:10.3201/eid2409.180330.

15. Rollé A, Schepers K, Cassadou S, Curlier E, Madeux B, Hermann-Storck C, et al. Severe sepsis and septic shock associated with chikungunya virus infection, Guadeloupe, 2014. *Emerg Infect Dis.* 2019;22:891-4. doi:10.3201/eid2205.151449.
16. Koeltz A, Lastere S, Jean-Baptiste S. Intensive Care Admissions for Severe Chikungunya Virus Infection, French Polynesia. *Emerg Infect Dis.* 2018;24:794-796. doi:10.3201/eid2404.161536.
17. Alvarez M, Bolívar-Mejía A, Rodríguez-Morales A, Ramírez-Vallejo E. Cardiovascular involvement and manifestations of systemic Chikungunya virus infection: A systematic review. *F1000Res.* 2017;6:390. doi:10.12688/f1000research.11078.2.
18. Mehta R, Gerardin P, Brito C, Soares C, Ferreira M, Solomon T. The neurological complications of chikungunya virus: A systematic review. *Rev Med Virol.* 2018;28(3):e1978. doi:10.1002/rmv.1978
19. Neto A, Sousa G, Nascimento O, Castro M. Chikungunya-attributable deaths: A neglected outcome of a neglected disease. *PLoS Negl Trop Dis.* 2019;13(9):e0007575. doi:10.1371/journal.pntd.0007575.
20. Beesoon S, Funkhouser E, Kotea N, Spielman A, Robich RM. Chikungunya Fever, Mauritius, 2006. *Emerg Infect Dis.* 2008;14(2):337-8. doi:10.3201/eid1402.071024.