Pan-American League of Associations for Rheumatology–Central American, Caribbean and Andean Rheumatology Association Consensus-Conference Endorsements and Recommendations on the Diagnosis and Treatment of Chikungunya-Related Inflammatory Arthropathies in Latin America

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Background/Objective: Although mortality rates related with chikungunya (CHIK) outbreaks in Latin America's (LA's) dengue-endemic rural and new urban regions are low, dealing with symptoms and sequelae can both produce a significant burden of disease and diminish quality of life—from many months to years—after the acute phase of the infection, with a significant impact on public and individual health.

The aim of this work was to establish Pan-American League of Associations for Rheumatology–Central American, Caribbean and Andean Rheumatology Association (ACCAR) consensus-conference endorsements and recommendations on the diagnosis and treatment of CHIK-related inflammatory arthropathies transmitted by *Aedes aegypti* and *Aedes albopictus* in LA.

Methods: Based on the Consensus Development Conference format, a panel of ACCAR rheumatologist voting members (n = 10) took part in this Pan-American League of Associations for Rheumatology initiative. Experts voted from a previous content analysis of the medical literature on CHIK, 4 subsequent topic conferences, and a workshop. Consensus represents the majority agreement (≥80%) achieved for each recommendation.

Results: The experts' panel reached 4 overarching principles: (1) CHIK virus (CHIKV) is a re-emergent virus transmitted by 2 species of mosquitoes: *A. aegypti* and *A. albopictus*; (2) CHIKV caused massive outbreaks in LA; (3) chronic CHIKV infection produces an inflammatory joint disease that, in some cases, can last for several months to years, and (4) currently, there are no vaccines or antivirals licensed for CHIKV infections.

Recommendations: Pan-American League of Associations for Rheumatology–ACCAR achieved 13 endorsements and recommendations on CHIK categorized in 3 groups: (1) epidemiology and clinical manifestations, (2) diagnosis, and (3) treatment, representing the consensus agreement from the panel's members.

Key Words: arthropathies, chikungunya (CHIK), chikungunya virus (CHIKV), Consensus Development Conference, mosquito vectors

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Infectious diseases are differentiated from other human diseases because of their unpredictable and explosive global nature, their transmissibility, the close relationship between the environment and human behavior, and their capacity to be prevented, controlled, and even eradicated.[1] In recent years, we have noted the occurrence of some arboviral diseases transmitted by mosquitoes in various countries and territories of the Americas, most notably chikungunya (CHIK).[2] Chikungunya has become a relevant public health problem in countries where epidemics occur. In 2013, the CHIK virus (CHIKV) arrived in the Western hemisphere, spreading across Caribbean islands, Central America, and South America, resulting in approximately 3 million infections.[3]

Transmission of CHIKV in Latin America (LA) dengue-endemic countries led to epidemics and generated a considerable burden of disease, challenging national health care systems.[4–6] Considering that CHIK outbreaks in LA rise with the absence of efficient garbage-collection services, unplanned urban growth, lack of complete public piped-water supply network systems, the absence of entomological surveillance, insecticide resistance, deficiencies in vector-control services, and an ever-increasing

number of international travelers,[7] the need for advancing health policy in this field represents a continental priority.[8]

Chikungunya is an emerging biphasic disease composed of an acute infection phase that may be followed by chronic rheumatism in the form of persistent joint signs and symptoms that can last for months or even years.[9,10] The relative insufficiency of harmonized clinical literature on the diagnosis of CHIK, its management, and consensus recommendations[9–15] motivated the Pan-American League of Associations for Rheumatology (PANLAR), in collaboration with the Central American, Caribbean and Andean Rheumatology Association (ACCAR, its Spanish-language acronym) to organize a consensus conference on the diagnosis and treatment of CHIK-related inflammatory arthropathies in LA.

Our aim was to provide LA rheumatologists, allied health professionals in rheumatology, and primary care physicians with practical clinical guidance on the diagnosis and treatment of patients with CHIK.

METHODS

For elaborating these recommendations, PANLAR-ACCAR selected the Consensus Development Panels (also denominated Consensus Development Conferences [CDCs]) methodology, organizing 4 sessions of ACCAR rheumatologists around this topic, and finally a face-to-face workshop.

The National Library of Medicine's Medical Subject Headings (MeSH) define CDC as "official statements of the findings or recommendations expressing the outcome of a meeting convened to evaluate current thought and research on a subject of interest."[16] This method—introduced in 1988—presents summary statements representing the majority agreement of a panel of experts convening for the purpose of reaching a consensus on a subject of interest.[17]

The CDC methodology's most well-established form is applied by the National Institutes of Health to assess the current scientific literature surrounding pertinent biomedical issues, with more than 160 consensus statements.[18] Recent examples of this method are widely available.[19–27]

We selected CDC to draw up these consensus recommendations because this method permits the synthesis of information to define agreement within the panel of elected experts; in addition, it allows for establishing a level of agreement, identifying nonconsensual positions. In addition, group members deal with the literature reviews and presentations that are more likely to generate evidence-based opinions, allowing the synthesis of the best possible information in the field; ACCAR delegates took care with the topic because it impacts their countries, thus adding to the validity of this consensus method.[17] Finally, this consensus method delivers rapid results.[27]

Course Objectives

The First PANLAR-ACCAR Regional Course held in San José, Costa Rica, from May 3 to 5, 2017, included the participation of ACCAR countries to promote, strengthen, and foster Pan-American, especially regional Central American, Caribbean, and Andean rheumatology.

Taking into account that continuing medical education is one of PANLAR's priorities and given the shortage of rheumatologists in the LA region,[28] the course aims were 2-fold:

(1) to bring top information to internists, orthopedists, physical medicine and rehabilitation specialists, family physicians, general practitioners, and other health care providers who require updated information on how to arrive at a CHIK diagnosis and on how to manage referrals and counter-referrals more efficiently and how to treat this arboviral disease and
(2) to establish a PANLAR-ACCAR consensus on the diagnosis and treatment of CHIK-related inflammatory arthropathies.

The consensus-conference meeting was sponsored entirely by PANLAR—with no participation of the pharmaceutical industry—with the support of ACCAR national rheumatology societies and associations.

We expect that this document will reduce gaps and strengthen patient-centered care on the subject for the entire LA rheumatology community, allied clinicians, health care providers, authorities, and governments of the region.

Delegates

With the approval of the PANLAR Executive Committee, the consensus-conference convener (P.M.) worked together with the steering committee composed of a representative of the PANLAR Education and Scientific Committee, local scientific committee, and the organizing committee members.

Each ACCAR national rheumatology society or association designated delegates based on the following profile: (1) being a certified rheumatologist, (2) university professor with clinical experience in the diagnosis and treatment of arboviral diseases, (3) having participated in scientific publications in national and/or international journals or being a national or international lecturer on arboviral diseases, and (4) with no conflict of interest.

The panel of voting delegates consisted of 10 ACCAR members. This number complies with the recommendations (between 8 and 12 members) for the development and conduct of CDC.[27]

Procedures

The proceedings of PANLAR-ACCAR consensus comprised the procedures listed in the Figure 1.

During the first scientific committee meeting, several questions were proposed, and those clinically relevant were selected by consensus to guide a comprehensive literature review. The review of the literature included CHIK epidemiology and clinical manifestations,[1,29–43] diagnosis, and treatment,[44–51] according to evidence-based medicine to retrieve best evidence in making decisions about the care of patients.

During the second meeting, the results of the literature review were presented, and the steering committee developed "overarching" statements to preface the recommendations.

The face-to-face phase began with the attendance and participation of the task force delegates to the scientific program activities, which began with 4 conferences: (1) arthropods, CHIKV, and other arboviral diseases; (2) update on CHIK; (3) update on arthropathies related to other tropical alphaviruses (O'nyong-nyong, Mayaro, Ross River) and (4) arthropod-transmitted diseases in LA with emphasis on CHIK coordinated by the convener.

After these 4 scientific sessions, a workshop on arthropod-transmitted diseases with an emphasis on CHIK was held. During the consensus meeting, only delegates appointed by the PANLAR-ACCAR participated in the voting.

We defined consensus as a majority of 80% of the votes required for the approval of a particular endorsement and recommendation. If clear-cut approval or rejection was not achieved, the wording of the recommendation was changed until the predetermined level of approval was found. Levels of evidence and grades of recommendation were based on Evidence Based Health Care—the practice guidelines levels of evidence and grades of recommendations used by the National Guideline Clearinghouse.[52] The consensus resulting from the delegates' voting will comprise the official position of PANLAR-ACCAR.

RESULTS

The PANLAR-ACCAR delegates' panel concurred on the following four overarching statements:

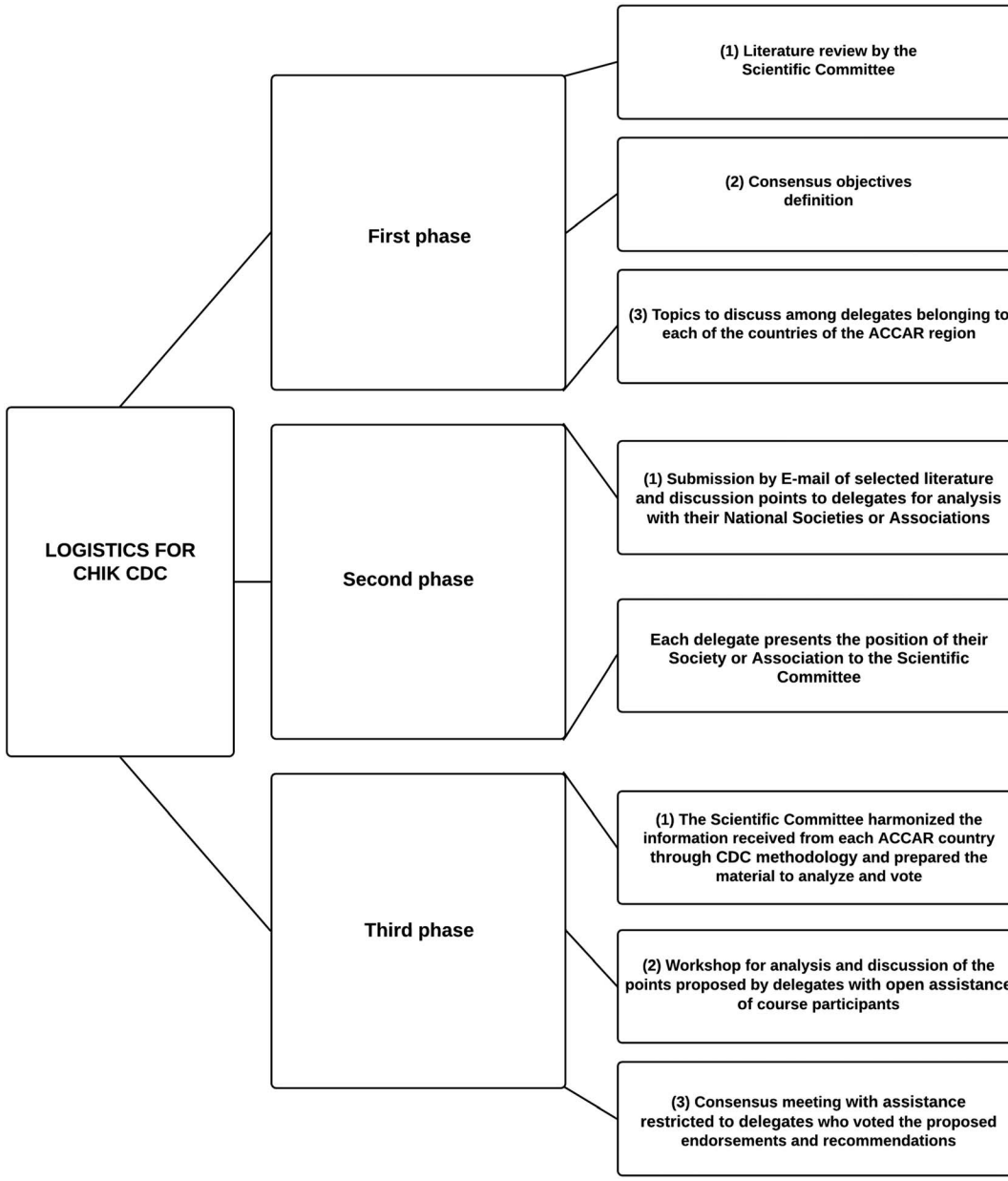

FIGURE 1. Procedures for the Consensus Development Conference (CDC) on Chikungunya.

(1) CHIKV is an emergent virus transmitted by 2 species of mosquitoes: *Aedes aegypti* and *Aedes albopictus.*
(2) CHIKV caused massive outbreaks in LA.
(3) CHIKV infection produces an inflammatory joint disease that can last several months to years.
(4) To date, there are neither licensed vaccines nor effective antiviral therapy licensed for CHIKV infections.

Endorsements and Recommendations

Table 1 summarizes 13 endorsements and recommendations with their corresponding level of evidence, grade of recommendation, and level of agreement. Each recommendation is presented in detail below.

Epidemiology and Clinical Manifestations

(1) What is the most prevalent strain of CHIKV in LA?

Asian strain is the most prevalent in LA. This strain (1) does not require an animal reservoir and (2) is the most prevalent in all regional cases reported, and (3) transmission occurs among humans, facilitating its greater diffusion in urban environments.

(2) What is the main transmission agent?

Although both *Aedes aegypti* and *Aedes albopictus* are the usual transmission agents, in the cases of the American continent, *Aedes aegypti* is the main transmitter. It is necessary to recognize that, by means of the adaptability of *Aedes albopictus* in subtropical environments and in the urban environment, it is an excellent transmitting agent. Given the distribution of *Aedes albopictus*, this agent can become an important agent for transmission in LA.

TABLE 1. PANLAR-ACCAR Endorsements and Recommendations, Levels of Evidence, and Level of Agreement

Endorsements and Recommendations on Epidemiology and Clinical Manifestations	Levels of Evidence[a]	Level of Agreement[b]	Grade of Recommendation[c]
Asian strain of the CHIKV is the most prevalent of all regional cases reported. Vector transmission facilitating its greater diffusion in urban environments.	II	100	B
Despite that *Aedes aegypti* is the main transmitter, it is necessary to recognize that *Aedes albopictus* is an excellent transmission agent in new urban environments.	II	90	B
Some cases of intrapartum transmission through high maternal viremia have been reported. Also, there are cases of transmission by transplantation or even by transfusion.	III	100	C
There are no significant differences reported between the Asian and African strains.	III	100	C
More severe behaviors of the disease have been registered in populations of older adults and children.	III	100	C
Fifteen percent to 30% of cases can progress to a chronic arthropathy that can take months or years to remit.	IIb	90	B
It is feasible that, in patients with a genetic predisposition, this viral agent can trigger a condition such as rheumatoid arthritis, spondyloarthropathies, reactive arthritis, and others.	III	100	C
Endorsements and Recommendations on Diagnosis	**Levels of Evidence[a]**	**Level of Agreement[b]**	**Grade of Recommendation**
VHIK diagnosis must consider: (A) Patient coming from an epidemic area (WHO Epidemiological Criterion); (B) Abrupt onset of a clinical profile of (B1) Symmetrical arthritis of any of the following joints: hands, wrists, shoulders, knees, ankles, or feet; (B2) Presence of any of the following systemic symptoms: fever; rash; fatigue, or myalgia; (B3) Positive serology by ELISA or RT-PCR for CHIKV Sensitivity 74.2%, specificity 88.4%.[50]	IIb	100	B
Stages of CHIKV infection: acute: up 9 d; subacute: from 10 d to <3 mo; chronic: ≥3 mo	II	100	B
Risk factors for chronicity must consider the following: high viral load; persistence of inflammatory cytokines (such as IL-6, IFN-α, IL-2, IL-1β); presence of reservoirs of the virus in target tissues such as macrophages, fibroblasts, and synovial tissue, and genetic predisposition.	III	90	C
According to the experience obtained from epidemics on Reunion Island, India, the Dominican Republic, and Colombia, 15%–30% can evolve into a chronic course, in which case an autoimmune disease should be ruled out due to more substantial grounds.	III	100	C
Endorsements and Recommendations on Treatment	**Levels of Evidence[a]**	**Level of Agreement[b]**	**Grade of Recommendation**
Treatment is symptomatic. Rest, maintain adequate hydration. Initial treatment for management of musculoskeletal fever and pain should be carried out with acetaminophen up to a maximal dose of 3 g/d. In case an adequate response is not obtained, we can use NSAIDs. It is not convenient to use these in the presumptive-diagnosis phase until dengue has been ruled out. In cases that do not respond to the above, low-dose glucocorticoids may be used, usually no more than 15 mg/d of prednisone or its equivalent (adults).	IV	90	D
Most appropriate treatment in the chronic phase where polyarthritis and high acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein) persist for >3 months, the use of DMARDs should be considered when the patient does not respond favorably to the use of NSAID and/or steroids at a recommended dose. Regarding DMARDs, first option would be METHOTREXATE at a dose of 7.5–25 mg weekly or sulfasalazine at a dose of 1–3 g/d. These drugs can be used in combination with antimalarials (chloroquine or hydroxychloroquine), making the observation not to use the latter group as monotherapy. Faced with the failure of these DMARDs, the use of biological therapy would be indicated, where first option would be anti–TNF-α.	IV	80	D

[a]Categories of evidence: Ia, evidence for meta-analysis of randomized controlled trials; Ib, evidence from at least 1 randomized controlled trial; IIa, evidence from at least 1 controlled study without randomization; IIb, evidence from at least 1 other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

[b]0% To 100% agreement.

[c]According to Shekelle et al.[52]

(3) Are there other forms of transmission?

The most frequent form of transmission is through the bite of the mosquito. However, some cases of intrapartum transmission through high maternal viremia have been reported. Also, there are cases of transmission by transplantation of cornea and other tissues. There is even the possibility of transmission through transfusions.

(4) Are there differences in the clinical manifestations among the different strains?

There are no clinically significant differences reported between the Asian and African strains.

(5) Is the disease more severe in some population groups?

There are severe cases reported in children, with dermal and neurological manifestations, such as encephalitis. More severe behaviors and poor disease outcomes have also been registered in populations of older adults.

(6) What is the percentage of CHIK cases that progress to chronic arthropathy?

The disease evolves in a few days; however, 15% to 30% of cases can progress to a chronic stage in which arthropathy can take months or years to remit. It can cause structural joint changes and mortality, as shown in the epidemics of Colombia and Reunion Island. Older populations with comorbidities, especially metabolic syndrome features and preexisting arthropathy, are those most at risk.

(7) Can viral infection trigger rheumatic disease?

It is feasible that in patients with a genetic predisposition this viral agent can trigger a condition such as rheumatoid arthritis, spondyloarthritis, reactive arthritis, and others.

Diagnosis

(8) What could be the diagnostic criteria for CHIKV infection?

The definitive diagnosis should consider epidemiological, clinical, and laboratory criteria; however, it is not always possible to perform serological tests that confirm the disease with full certainty.

That is why international organizations have proposed epidemiological criteria (living in an endemic area of vectors and the characteristic clinical triad that includes fever, rash, and joint involvement). However, these criteria are nonspecific and would allow us to establish only a presumptive diagnosis.

It should be emphasized that our own proposal—from the ACCAR voting group—based on the work of Colombian colleagues—is fundamental and exerts a great clinical and epidemiological impact. The diagnosis must consider the following:

(A) patient coming from an epidemic area (World Health Organization [WHO] Epidemiological Criterion) and
(B) abrupt onset of
(B1) symmetrical arthritis of any of the following joints: hands, wrists, shoulders, knees, ankles, or feet;
(B2) presence of any of the following systemic symptoms: fever, rash, headache, fatigue, or myalgia; and
(B3) positive serology by enzyme-linked immunosorbent assay (ELISA) or reverse transcriptase–polymerase chain reaction (RT-PCR) for CHIKV.
Sensitivity 74.2%, specificity 88.4%.[51]

(9) What are the stages of CHIKV infection?

The WHO defines 3 phases:

- acute: up to 9 days,
- subacute: from 10 days to less than 3 months, and
- chronic: 3 months or more.

(10) What is the reason for chronification of the disease?

The risk factors for chronicity reported must consider the following: a high viral load, the persistence of high levels of inflammatory cytokines (such as interleukin 6 [IL-6], interferon α [IFN-α], IL-2, and IL-1β), and the presence of reservoirs of the virus in target tissues such as macrophages, fibroblasts, and synovial tissue.

(11) What could be the differential diagnoses?

We must rule out other viral diseases such as dengue, Zika, Mayaro, malaria, or O'nyong-nyong; leptospirosis; measles; and rubella in endemic vector areas. In addition, we must conduct studies to rule out autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus, and even spondyloarthritis. According to the experience obtained from epidemics in Reunion Island, India, the Dominican Republic, and Colombia, 15% to 30% can evolve into a chronic course, in which case an autoimmune disease should be excluded.

Treatment

(12) What is the appropriate treatment in the acute and subacute phases?

We must start out from the fact that, as occurs in other viral nosological entities, there is no specific treatment. Treatment is symptomatic and includes rest and maintaining adequate hydration. Initial treatment for fever and musculoskeletal pain should be carried out with acetaminophen up to a maximal dose of 3 g/d. In case an adequate response is not obtained, nonsteroidal anti-inflammatory drugs (NSAIDs) should be used. It is not convenient to use these in the presumptive-diagnosis phase if dengue has not been ruled out. In cases that do not respond to the above, low-dose glucocorticoids may be used, usually no more than 15 mg/d of prednisone or its equivalent (adults).

These recommendations result from the practice and extrapolation of the schemes used in other viral diseases.

(13) What would be the most appropriate treatment in the chronic phase?

In cases in which polyarthritis and high acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein) persist for more than 3 months, the use of disease-modifying antirheumatic drugs (DMARDs) should be considered when the patient does not respond favorably to the use of NSAIDs and/or steroids at a recommended dose.

Regarding DMARDs, the first option would be methotrexate at a dose of 7.5 to 25 mg weekly or sulfasalazine at a dose of 1 to 3 g/d.

These drugs can be used in combination with antimalarials (chloroquine or hydroxychloroquine), with the observation not to use the latter group as monotherapy.

In case of failure of these DMARDs, the use of biological therapy would be indicated, in which the first option would be an anti–tumor necrosis factor α agent (anti–TNF-α) (Table 1).

DISCUSSION

These endorsements and recommendations for CHIK aim to assist and inform rheumatologists, allied professionals, hospital managers, representatives of social security agencies, regulatory agencies, and national health care systems. They also seek to reflect Central American, Caribbean, and Andean viewpoints, raising awareness and giving some new voices to replicate in other national rheumatology societies and associations outside these countries, as they constitute the first multinational effort to facilitate the diagnosis and treatment of this arboviral condition in LA.

This work has two main limitations to consider: (1) experts represented on the conference were only rheumatologists, so we did not include another kind of specialists, public health professionals, or government representatives to reduce professional bias,

and (2) we define consensus as a simple percentage of agreement; therefore, we did not include a rating scale.

This consensus, along with other two new studies[53,54] and a comprehensive review published recently,[55] stresses the importance of the CHIK outbreaks in the Americas by calling for more research—basic, clinical, and translational—able to prepare the continent for a new emergence or re-emergence epidemics of CHIKV and other arthritogenic alphaviruses,[3] such as Mayaro virus, which is endemic in some LA countries.

Finally, we wish to emphasize that adoption of therapeutic recommendations in clinical practice has proven to be very unrealistic, and in a previous analysis of the application of guidelines and recommendations in Europe, there was room for improvement.[56,57]

Therefore, it will be a challenge for PANLAR to monitor the extent to which these recommendations are put into practice, to know what their impact is, and to perform their periodic updating according to the advance of scientific knowledge, the availability of new diagnostic tools, and preventive and therapeutic resources in the future.

We consider improved dissemination or implementation of therapeutic guidelines or consensus through government policies is a top public health priority, which is an issue in itself, so we encourage LA national rheumatology societies and associations and rheumatologists to develop these strategies through additional scientific research in the short and medium term.

In conclusion, we developed 13 endorsements and recommendations covering different areas of the clinical practice of CHIK based on both available scientific evidence and expert opinion to provide a practical guide for health care providers in LA countries.

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