National Guidelines
for Clinical Management of

Chikungunya Fever

National Center for Vector Borne Diseases Control
22-Shamnath Marg, Delhi-110054
Directorate General of Health Services
Ministry of Health & Family Welfare
2023

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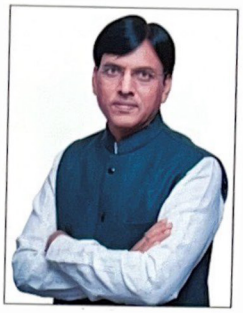

MESSAGE

Chikungunya, a mosquito-borne viral disease, is one of the public health problems in India. Once thought to have disappeared from the country, Chikungunya re-emerged in 2006 after quiescence of three decades in unprecedented magnitude. Although not a fatal disease, high morbidity rates and prolonged arthralgia lead to considerable disability in a proportion of the affected population, and can cause substantial socio- economic impact in affected areas. There is no specific drug or vaccine for Chikungunya infection, hence cases are treated symptomatically. Clinicians need to distinguish between Chikungunya, Dengue and other diseases for proper management of cases.

I feel very happy on the development of these National Guidelines for Clinical Management of Chikungunya Fever by incorporating the latest developments in the clinical field. I would like to congratulate the National Center for Vector Borne Diseases Control (NCVBDC, earlier NVBDCP) and the team of Experts for their efforts in framing this document.

I believe that these guidelines will be helpful to minimize morbidity associated with Chikungunya, and to serve as a source of reference for Clinicians working at different levels across the country.

(Dr. Mansukh Mandaviya)

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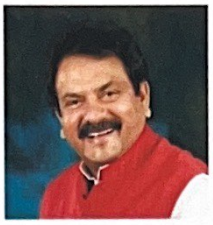

संदेश

चिकुनगुनिया एडीज मच्छर जनित वायरल बुखार है जो भारत में सार्वजनिक स्वास्थ्य के लिए एक चिंता का विषय है। हालांकि यह घातक रोग नहीं है, परन्तु पीड़ित व्यक्ति लंबे समय तक जोड़ों के दर्द से प्रभावित रहते हैं तथा इससे उन्हें कई सामाजिक-आर्थिक परेशानियों का सामना भी करना पड़ता है। चिकुनगुनिया से बचने के लिए किसी टीके के ना होने कि स्थिति में, इससे रोकथाम के लिए इसे फैलाने वाले एडीज मच्छरों का नियंत्रण महत्वपूर्ण प्रयासों में से एक है। साथ ही, चिकुनगुनिया के लिए कोई विशिष्ट दवा नहीं है, इसलिए लक्षणों के आधार पर इसका उपचार या प्रबंधन किया जाता है ताकि पीड़ित व्यक्ति को राहत मिल सके।

चिकुनगुनिया के लक्षण डेंगू और अन्य रोगों से मिलते-जुलते होने के कारण चिकुनगुनिया के मामलों के उचित प्रबंधन के लिए चिकित्सकों को दिशा-निर्देशों की आवश्यकता पड़ती है जिसके लिए राष्ट्रीय वैक्टर जनित रोग नियंत्रण कार्यक्रम (वर्तमान राष्ट्रीय वैक्टर जनित रोग नियंत्रण केंद्र-एन.सी.वी.बी.डी.सी.) ने 2016 में 'नेशनल गाईडलाईन फॉर क्लिनिकल मैनेजमेंट ऑफ़ चिकुनगुनिया' विकसित की और सभी राज्यों के साथ साझा की।

मुझे बहुत खुशी है कि चिकित्सा के क्षेत्र में हुए विकास को ध्यान में रखते हुए चिकुनगुनिया के प्रबंधन के लिए राष्ट्रीय दिशा-निर्देशों को नवीनतम रूप दिया गया है। मैं राष्ट्रीय दिशा-निर्देशों को तैयार करने में महत्वपूर्ण भूमिका के लिए राष्ट्रीय विशेषज्ञों और राष्ट्रीय वैक्टर जनित रोग नियंत्रण केंद्र को उनके अथक प्रयासों के लिए बधाई देना चाहता हूं। मुझे पूर्ण विश्वास है कि प्रस्तुत दिशा-निर्देश मेडिकल कॉलेजों में पढ़ाये जाने के साथ-साथ चिकुनगुनिया उपचार एवं प्रबंध में लिप्त सभी चिकित्सकों के लिए भी एक उपयोगी संदर्भ सामग्री सिद्ध होंगे। साथ ही, बेहतर नैदानिक प्रबंधन से चिकुनगुनिया पीड़ित व्यक्तियों को भी राहत प्राप्त होगी

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Message

Chikungunya fever is a mosquito borne viral disease that has emerged as a public health problem globally, including India. Although, it is a self-limiting disease, the morbidity can be high during outbreaks resulting in heavy tolls on human life & economy. Due to non-availability of any specific drug for treatment of Chikungunya till date, symptomatic treatment is the only option to minimize the morbidity. The development of National Guidelines for Clinical Management of Chikungunya by the National Center for Vector Borne Diseases Control (NCVBDC, earlier NVBDCP) and the team of subject Experts, incorporating recent developments in the field, is a welcome step towards further improvement of existing knowledge in case management.

I hope this will provide the needed guidance in minimizing the complications in managing the Chikungunya cases.

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MESSAGE

Chikungunya, a mosquito-borne viral disease re-appeared in the country in 2006 and since then cases are reported from various States and Union Territories every year. In absence of specific anti-viral treatment or vaccine, Chikungunya cases are managed symptomatically. In view of this, the Government of India developed guidelines for clinical management of Chikungunya in 2016, which helped the Clinicians in management of the cases effectively.

There are new development in the medical fields, hence, timely updation of the technical documents are needed to guide all those who are involved in disease management at various levels. It is a pleasure to share that the National guidelines have now been updated by National Centre for Vector Borne Diseases Control (NCVBDC), MoHFW, Govt. of India involving the team of National Experts incorporating the recent advances in the field.

I believe this document will be beneficial for all those who are involved in management of Chikungunya cases. Also, it will provide new insight to facilitate clarification of doubts regarding the diagnosis and clinical management of Chikungunya.

I look forward to the States for wide circulation of the updated guidelines and capacity building of Clinicians to prevent severity of the disease and provide relief to the patients from this disease.

(Rajiv Manjhi)

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FOREWORD

Chikungunya, a self-limiting mosquito-borne viral disease transmitted by *Aedes* mosquito has emerged as a major health concern in the last two decades. It has been reported from countries of South and East Africa, South Asia, South-East Asia and from Italy in Europe. In South-East Asia Region, outbreaks have been reported from India, Indonesia, Maldives, Myanmar, Sri Lanka and Thailand.

In India, Chikungunya outbreaks were first recorded during 60's and 70's. After this, the disease mysteriously disappeared and again re-appeared after a quiescence of almost 3 decades in 2006 affecting millions of people in 16 States/UTs. Since 2007, cases of clinically suspected cases of Chikungunya are being reported from various parts of the country. Currently, 34 States/UTs are endemic for Chikungunya in the Country.

The factors leading to re-emergence of Chikungunya are not entirely clear. These may be due to a combination of social, environmental, behavioral and biological factors including increasing human intrusion into forest areas. Although not fatal, high morbidity rates and prolonged residual arthralgia leads to considerable disability in a proportion of the affected population that can cause substantial socio-economic impact in the affected areas. In absence of any specific treatment and vaccine for prevention, appropriate management of patients based on clinical experience and scientific evidence becomes imperative. These guidelines are intended to provide support to the clinicians in planning and implementing appropriate care to patients suffering from Chikungunya fever.

I would congratulate the team of Experts under the umbrella of NCVBDC (Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India) for development of these guidelines. I hope, these guidelines will be helpful to the medical practitioners serving at all levels of health care in different parts of the Country for management of Chikungunya cases.

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Preface

Chikungunya is an arbo-viral illness transmitted by *Aedes* mosquito. Globally, large outbreaks of Chikungunya infections have been reported in last few decades. Chikungunya virus was isolated for first time in India from Calcutta (now Kolkata) in 1963. Outbreaks were reported during 1960's and 70's. After a gap of almost three decades, Chikungunya re-emerged in 2006 with 13.9 lakh cases from 15 States. Since then, cases are reported from various parts of country. At present, 34 States are reporting Chikungunya cases. Various socio-economic factors facilitated the rapid spread of infection and its continuation in endemic areas.

Chikungunya outbreaks typically result in large number of cases. Till date, no death directly attributable to Chikungunya has been reported from any State/UT in the Country. However, prolonged and severe incapacitating arthralgia induced by Chikungunya virus in affected people makes it a concern. As specific treatment of Chikungunya is not available and there is no vaccine for prevention, therefore, cases are managed symptomatically. The National Guidelines for management of Chikungunya were developed by National Vector Borne Disease Control Programme (now National Center for Vector Borne Diseases Control- NCVBDC), Government of India in 2016 based on clinical experiences for appropriate management of patients. For wiser circulation, the guidelines were shared with the States.

The present guidelines have pooled the experience and knowledge of the experts and a standard protocol for management of Chikungunya addressing various issues including Epidemiology, Laboratory diagnosis, differential diagnosis, Clinical manifestations, pathogenesis, Clinical management has been developed.

I congratulate the team of Experts and Dengue & Chikungunya Division, NCVBDC for bringing out this updated version. I hope that these guidelines will be helpful in the area of case management and provide relief to patients suffering from Chikungunya.

(Dr. Tanu Jain)

Contents

Chapter	Name of the Chapter	Page No.
	Foreword	i
	Preface	ii
	Acknowledgements	iii
	List of Experts	iv
	Abbreviations	v
1	**Introduction**	**1-3**
1.1	Global scenario	1
1.2	National scenario	2
2	**Epidemiology**	**4-6**
2.1	Chikungunya virus	4
2.2	Genotype of Chikungunya virus	5
2.3	Vector	5
2.4	Environmental factors	5
2.5	Transmission cycle	6
3	**Laboratory diagnosis of Chikungunya**	**7-9**
3.1	Types of tests available and specimens required	7
3.2	Interpretation of results	8
3.3	NCVBDC laboratory network	9
4	**Case definition and differential diagnosis**	**10-12**
4.1	Case definition	10
4.2	Differential diagnosis	11
5	**Clinical manifestations and pathogenesis of Chikungunya**	**13-24**
5.1	Incubation period	13
5.2	Clinical features	13
5.3	High risk group	17
5.4	Mortality	21
5.5	Pathogenesis	21
6	**Clinical management of Chikungunya**	**25-30**
6.1	Management of acute phase	25
6.2	Management of sub-acute phase	28
6.3	Management of chronic phase	29
Annexure 1	Countries from where Chikungunya cases have been reported	31
References		**32-34**

Acknowledgements

Chikungunya fever, an arbovirus infection, is a serious public health problem globally. It is a self-limiting disease and the morbidity can be very high during outbreaks resulting in a heavy social and economic toll. The disease was re-emerged in 2006, which may be attributable to a variety of social, environmental, behavioral and biological factors. Currently, Chikungunya is endemic in 34 States/UTs of the Country. Like Dengue, there is no specific anti-viral drug for Chikungunya, hence, proper management of cases is utmost important. In view of this, the available guidelines on clinical management of Chikungunya have been revisited and updated.

National Center for Vector Borne Diseases Control (NCVBDC) is grateful to Prof. (Dr.) Ashutosh Biswas, Director, AIIMS, Bhubaneswar and former Professor of Medicine, AIIMS, New Delhi who has taken lead while updating these guidelines. The updated version is intended to provide guidance for Clinicians for management of Chikungunya Fever.

NCVBDC sincerely acknowledges its gratitude to Prof. (Dr.) Atul Goel, Director General of Health Services, Govt. of India for his valuable technical suggestions and guidance.

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NCVBDC appreciates the constant encouragement given by Dr. Tanu Jain, Director, NCVBDC in developing the updated guidelines. Also, acknowledges the endless efforts of Dr. Kalpana Baruah, Former Additional Director & Sr. Consultant, NCVBDC for taking the lead and coordination with the Experts throughout the process of development of the guidelines. The technical inputs provided by Dr. Pranab Jyoti Bhuyan, Joint Director, NCVBDC are also duly acknowledged.

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Abbreviations

Ae	Aedes
ASO	Anti-streptolysin-O
C	Capsid
CAD	Coronary artery disease
CHC	Community Health Centre
CHIKV	Chikungunya Virus
CIR	Chronic inflammatory rheumatisms
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DMARDs	Disease-modifying antirheumatic drugs
E	Envelope
ECSA	East/Central/South African
GBS	Guillain–Barré syndrome
GoI	Government of India
IFNAR	Interferon α/β receptors
MAC-ELISA	IgM-capture enzyme-linked immunosorbent assay
MAP	Mean arterial pressure
MSD	Musculoskeletal disorders
NCVBDC	National Center for Vector Borne Diseases Control
NIV	National Institute of Virology
NK	Natural killer
NSAIDs	Non steroidal anti-inflammatory drugs
pCHIK	Post-Chikungunya
PHC	Primary Health Centre
PPI	Proton pump inhibitor
RNA	Ribonucleic acid
RT- PCR	Reverse transcription-polymerase chain reaction
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
TLR	Toll-like receptors
VAS	Visual analog scale
WHO	World Health Organization

Chapter 1

INTRODUCTION

Chikungunya fever is a viral disease transmitted to human beings by infected *Aedes aegypti* mosquitoes. Chikungunya virus (CHIKV) belongs to genus Alphavirus and family Togaviridae. CHIKV was first isolated from the blood of a febrile patient in Tanzania in 1953. Since then, it has been repeatedly identified in west, central, and southern Africa and many areas of Asia and appeared as the cause of numerous human epidemics. The virus is circulating throughout Africa, mainly between mosquitoes and monkeys. In the 'Swahili language, Chikungunya means "which contorts or bends up." It refers to the contorted (or stooped) posture of patients afflicted with severe joint pain (arthritis), a most common feature of the disease. It is a debilitating and a non-fatal viral illness.

In the South-East Asia Region, the Chikungunya virus is maintained in the human population by a human-mosquito-human transmission cycle. Human beings serve as the Chikungunya virus reservoir during the epidemic period. Outbreaks are most likely to occur post-monsoon when the vector density is very high and accentuates the transmission.

During inter- epidemic periods, several vertebrates have been implicated as reservoirs in the African region. These include monkeys, rodents, and birds. However, the reservoir status in the South-East Asian Region has not been documented yet.

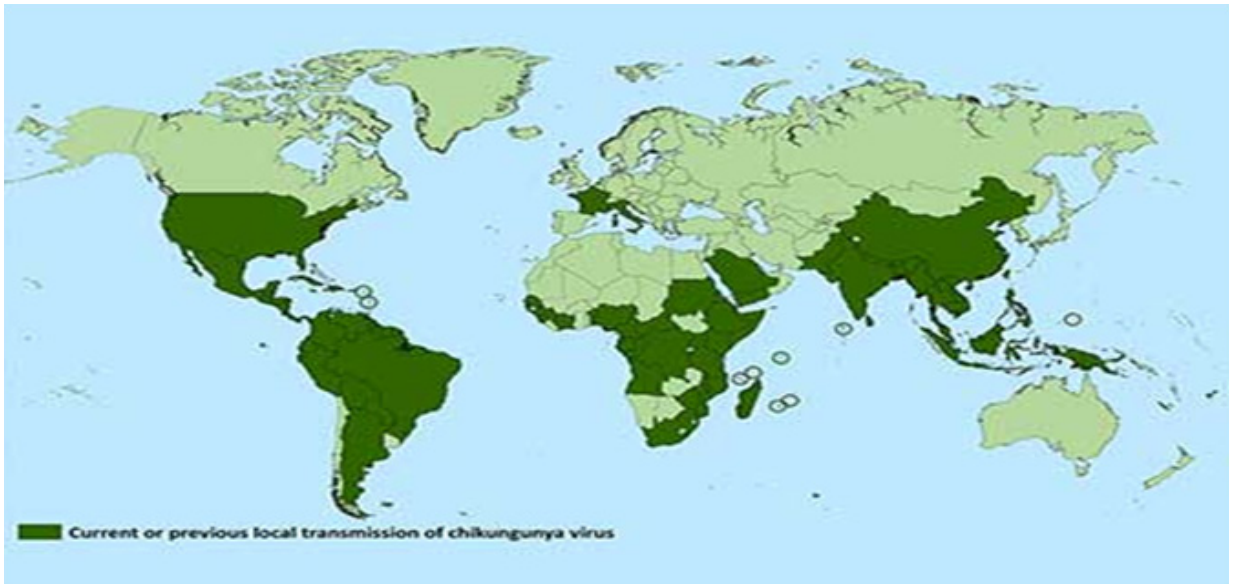
Since 1960, disease outbreaks in South East Asia have been reported in India, Sri Lanka, Myanmar, Thailand, Indonesia, the Philippines, and Malaysia. Chikungunya outbreaks typically result in many cases, but deaths are rarely encountered. Chikungunya cases start to increase in the post-monsoon season, with a peak between September and October, as during this period, vector density remains very high.

1.1 Global Scenario

After an extensive outbreak during the beginning of the current millennium in the French territory of Reunion Islands in the Indian Ocean, the disease has been reported in almost 40 countries from various WHO regions, including South-East Asia. The disease continues to cause epidemics in many countries in the region. The history of this disease epidemic has been known since 1952, with its first ravage in East Africa followed by numerous epidemics in Asia, including the Philippines (1954, 1956, and 1968), Thailand, Cambodia, Vietnam, India, Burma, and Sri Lanka. In India, the first Chikungunya outbreak was recorded during 1963-65 and later in 1973, and again the disease re-appeared in 2006 after a gap of almost three decades. A distinctive feature of the Chikungunya virus is that it causes explosive outbreaks before apparently disappearing for a period of several years to decades.

Re-emergence of the disease was documented in Kinshasa, the Democratic Republic of the Congo, 1999-2000, after more than 39 years with an estimated infection of 50,000 persons. Since then, frequent epidemics were noticed in Java (2001-2003), the islands of the South Western Indian Ocean (during the end of 2004), and Comoros islands (January-March 2005) involving 5,000 persons. Later, the virus circulated in other islands of the Indian Ocean, i.e., Mayotte, Seychelles, Reunion, and Mauritius. Of all the islands in the Indian Ocean, Réunion, with a total population of 770,000, was the most affected, with an estimated 258,000 cases by May 2006. The infection was thought to be imported from the Comoros islands. According to the Euro surveillance 2006, imported cases from these countries are nearly 307 in France, 197 in Italy, 17 in Germany, 9 in the United Kingdom, 12 in Belgium, and one in the Czech Republic and Norway (Source: Euro surveillance 2008). The global distribution of Chikungunya till 2020 is shown in **Fig 1.** Countries affected by Chikungunya on various continents are placed in **Annexure 1.**

Figure 1: Countries and territories from where indigenous Chikungunya cases have been reported(as of 2020)



Source: https://www.cdc.gov/chikungunya/images/index/Chik-World-Map-Index.jpg

1.2 National Scenario

In the Indian sub-continent, the virus was first isolated in Calcutta (present Kolkata) in 1963. A major epidemic of Chikungunya fever was reported during the last millennium, viz.; 1963 (Kolkata), 1965 (Puducherry and Chennai in Tamil Nadu, Rajahmundry, Vishakhapatnam and Kakinada in Andhra Pradesh; Sagar in Madhya Pradesh; and Nagpur in Maharashtra). After the outbreak of Chikungunya infection in India in 1971, sporadic cases continued to be recorded during 1973 in Barsi, Solapur district, Maharashtra state. The last outbreak of Chikungunya infection in the 20th century occurred in India in 1973.

The Chikungunya Virus (CHIKV) activity appeared to decline, and no outbreak was reported in India until 2005. A study in Calcutta (Kolkata) in 1994 showed a 4.3% seroprevalence of the Chikungunya virus out of 389 sera tested. The highest seropositivity was observed in

the age group of 51-55 years, and no Chikungunya antibodies were detected in young and adults.In 2006, after an inactivity of 2-3 decades, the disease re-appeared in the country in unprecedented magnitude, affecting millions of people in 16 States/UTs and incapacitating many with crippling disabilities for a varied period. Initially, when the disease was observed in some parts of Karnataka and Andhra Pradesh, it was thought to be Dengue, but the incapacitating arthralgia raised the doubt. In January 2006, the outbreak was confirmed as Chikungunya with laboratory findings with 13.9 million clinically suspected and 2001 laboratory-confirmed cases (https://ncvbdc.mohfw.gov.in). Subsequently, World Health Organization confirmed the re-occurrence of Chikungunya fever in India. The outbreak had an attack rate of 4-45%.

Since then, transmission has been ongoing in various parts of the country. The re-emergence of Chikungunya may be attributable to various social, environmental, behavioral, and biological factors. Lack of herd immunity might have probably led to its rapid spread across several states of India. Chikungunya cases have been reported from various parts of the country since 2006, but cases gradually declined until 2014. However, the disease showed an upward trend in 2018 (57,813 clinically suspected cases), 2019 (81,914 clinically suspected cases), 2020 (43,424 clinically suspected cases), 2021 (1,19,070 clinically suspected cases) and 2022 (1,48,587 clinically suspected cases). Presently, Chikungunya is endemic in 34 States/ UTs in the country. To date, no report of mortality directly attributable to Chikungunya has been received from any part of the country.

Chapter 2

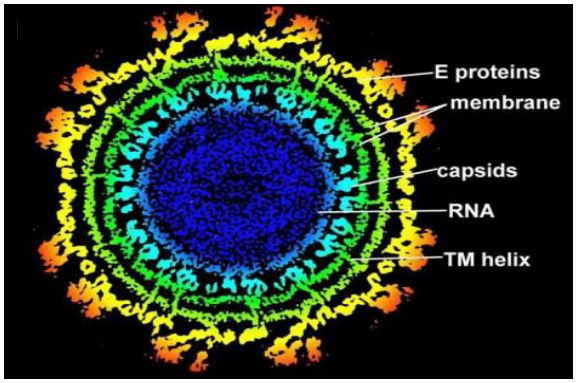
EPIDEMIOLOGY

Chikungunya fever is an emerging viral disease of global importance. It is caused by the Chikungunya virus (CHIKV), transmitted by infected mosquitoes from the genus Aedes. The recent outbreaks of Chikungunya fever in various continents have drawn global attention due to its explosive onset, rapid spread, and high morbidity. Imported cases were also reported from many countries in patients with recent travel history. Chikungunya fever epidemics display cyclical and seasonal trends, characterized by explosive outbreaks interspersed by periods of disappearance ranging from several years to a few decades. The exact reason for this behavior is still not known. Epidemiology of Chikungunya is a complex interaction between various factors, viz. virus, vector, and susceptible host.

2.1 Chikungunya Virus

Chikungunya is caused by an arbovirus that belongs to the genus Alphavirus under the Togaviridae family. It has a single-stranded RNA genome, a 60-70nm diameter capsid, and a phospholipids envelope **(Fig.2)**. It is sensitive to temperatures above 58°C and also to desiccation. Believed to be enzootic throughout much of Africa, the CHIKV virus probably spread to other parts of the world from this origin. African and Asian strains are reported to

Figure 2.Electron microscopic view of Chikungunya Virus



differ biologically with distinct lineages. Three lineages with distinct genotypic and antigenic characteristics have been identified: East-Central Southern, West African groups from Africa, and Asian phylogroup. Isolates from the recent outbreak in the Indian Ocean Islands belong to a distinct clad within the large east-central-southern Africanphylogenetic group. The isolates from the ongoing outbreaks in India are closely related to this. The different geographical genotypes inhibit differences in their transmission cycles. In Asia, the virus appears to be

maintained in an urban human-mosquito-human transmission cycle with vectors, namely, *Aedes aegypti* and *Aedes albopictus*. Analysis of the recent outbreak has suggested that the increased severity of the disease may be due to a change in the genetic sequence, altering the virus' coat protein, potentially allowing it to multiply more quickly in mosquito cells.

2.2 Genotype of Chikungunya virus

The definition of chikungunya genotype is based on the identification of well-defined phylogenetic clusters whose origin has been associated with a given geographic region. CHIK epidemics have been described in Africa, the Middle East, Europe, India and Southeast Asia. CHIKV, a RNA virus, is susceptible to high mutation rates, which may help the virus evade the immune response and thus adapt efficiently. Three phylogenetically distinct groups of CHIKV with distinct antigenic properties have been identified: the Asian genotype, the West African genotype, and the East/Central/South African (ECSA) genotype.

CHIKV strains with an Asian genotype of the E1 gene were reportedly detected during the 1963–73 outbreaks in India. It was prevalent in Thailand, Malaysia and Indonesia during the period. In the 2006 outbreak, the East Central South African genotype was isolated. The same genotype was isolated from samples collected from 2010 to 2014. The East Central South African genotype circulated in the Delhi region during 2010–2014 (Singh P et al. 2016).

2.3 Vector

Aedes aegypti is the main vector of transmission of Chikungunya in India. However, *Ae. albopictus* has posed serious threats of Chikungunya transmission in certain geographical regions endowed with a sylvatic environment, particularly in southern and NE states. Aedes mosquitoes are principally day biters. Eggs of these vectors can withstand desiccation for more than a year. This could result in the virus to remain in nature for long periods and cause outbreaks. The flight range of these mosquitoes is less, making the outbreaks occur in clusters, especially in congested localities. It has recently been shown that viremia is relatively high, and infected mosquitoes could transmit the disease to more than one person. Aedes mosquitoes take multiple feeds perfeed, and it would also result in small focal outbreaks. In the initial part of the outbreak, the individual population is not protected, which could result in larger outbreaks.

2.4 Environmental factors

The vector of Chikungunya has spread throughout the country. Vector density rises and falls during pre-monsoon, monsoon, and post-monsoon periods which is correlated with rainfall, temperature, and humidity. The peak population density of Aedes is found during temperatures between 16o C and 30oC and relative humidity between 60%-80%. It is mainly anthropophilic (preferring a human over another animal) and rests in cool, shady, dark, and hard-to-find areas. Due to lifestyle changes and population movement, the disease has spread from urban to rural areas. Rapid urbanization, poor living conditions, and scarcity of water leading to water storage contribute to the establishment and spread of Chikungunya.

2.5 Transmission Cycle

Human infections are acquired by the bite of infected Ae.aegypti mosquitoes, and epidemics are sustained by human-mosquito-human transmission. Man is the natural host and reservoir of infection in Asia, while a sylvatic reservoir (monkeys) exists in the African region. Both genders and all ages are susceptible to virus infection. Mother-to-child transmission has been reported to lead to neonatal infection.

Chapter 3

LABORATORY DIAGNOSIS OF CHIKUNGUNYA

As the clinical manifestations of Chikungunya (CHIK) fever resemble those of Dengue and other fevers caused by arthropod-borne viruses of the *Alphavirus* genus, laboratory diagnosis is essential to establish the cause of fever for individual case management and initiate specific public health response.

3.1 Types of tests available and specimens required

The laboratory tests available for the diagnosis of Chikungunya fever are discussed below. The specimen is usually blood or serum, but in patients with neurological manifestations like meningoencephalitis, cerebrospinal fluid (CSF) may also be sent for analysis.

3.1.1. Virus isolation

Virus isolation provides the most definitive diagnosis but takes one to two weeks for completion and must be carried out in bio-safety level III laboratories to reduce the risk of viral transmission. The technique involves exposing specific cell lines to whole blood/serum/CSF samples and identifying chikungunya virus-specific responses. The isolation process is time-consuming, and the degree of success is dependent on several factors, for example, time of collection, transportation, maintenance of cold chain, storage, and processing of samples. Virus isolation is usually advised during the first week of illness. Demonstrations of all diagnostic markers of Chikungunya virus (CHIKV) are depicted in **Fig. 3.**

3.1.2. Serological diagnosis

The serological diagnosis uses an ELISA assay to measure Chikungunya-specific IgM levels in the serum. CHIK IgM antibody tests are generally appropriate after the first week of onset of symptoms. An acute-phase serum must be collected immediately after the onset of illness, and the convalescent-phase serum 2-3 weeks later. The blood specimen should be transported at 4°C and not frozen for immediate transfer to the laboratory. If the testing cannot be done immediately, the serum specimen should be separated, stored, and shipped

frozen. ELISA test is quite specific with minimal cross-reactivity with related alphaviruses. Serological diagnosis can be made by demonstrating a four-fold rise in antibody titer in acute and convalescent sera or IgM antibodies specific to the CHIK virus. IgM antibody that captures enzyme-linked immunosorbent assay (MAC-ELISA) is used for diagnosis in the serum. Results of MAC- ELISA can be available within the same day. Demonstrating IgG antibodies by ELISA test during the acute and convalescent phases is also important to diagnose recent or past Chikungunya virus infection.

3.1.3. Reverse transcription-polymerase chain reaction

The **reverse transcription**-polymerase chain reaction (RT- PCR) detects CHIKV RNA from whole blood/ or serum. The CHIKV RT-PCR assay is appropriate in the early days of symptom onset since CHIKV RNA can be detected during the acute phase of illness (≤8 days after symptom onset). RT-PCR can also be used to quantify the viral load in the blood. Using real time RT-PCR, diagnostic results can be made available early (in one to two days). The technique is used for diagnosing the CHIK virus using primer pairs amplifying specific components of structural gene regions; Capsid (C), Envelope E-2 and part of Envelope E1. Heparinized whole blood can be used for PCR as well as virus isolation.

3.2. Interpretation of results

Sero-diagnosis rests on demonstrating a four-fold increase in CHIK IgG titer between the acute and convalescent-phase sera; however, getting paired sera is usually not practical. Alternatively, the demonstration of IgM antibodies specific for CHIK in acute-phase sera is used in instances where paired sera cannot be collected. Results and interpretation of IgM and IgG serological tests are tabulated in **Table 1.** A positive virus culture supplemented with neutralization is the definitive proof of the presence of the Chikungunya virus. Positive PCR result for E1 and C genome, either singly or together from the specimen, also constitutes positive evidence of CHIK infection. The tests are usually performed: RT PCR between days D0 and D7 and serology after D7.

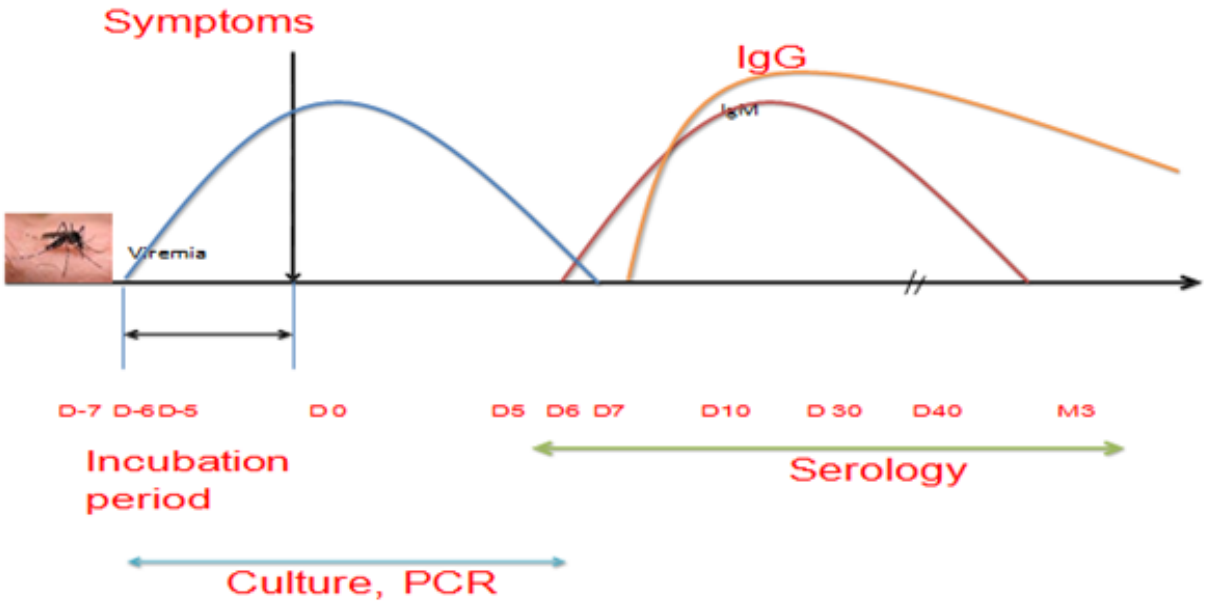
Table 1: Interpretation of IgM and IgG serological tests in Chikungunya

IgM	IgG	Interpretation
+	-	Recent infection
-	+	Past Infection
+	+	Recent or Recent past infection
-	-	Negative

*Repeat testing in 5 to 10 days is recommended if clinical suspicion persists

No significant pathognomonic hematological finding is seen. Leucopenia with lymphocyte predominance is the usual observation. Severe thrombocytopenia is rare. Erythrocyte sedimentation rate is usually elevated. C-reactive protein increases during the acute phase and may remain elevated for a few weeks.

Figure 3: Day-wise appearance of various markers of Chikungunya virus infection



Abbreviations: D, day; IgM, immunoglobulin M; IgG, immunoglobulin G; M, month

3.3. NCVBDC (earlier NVBDCP) Laboratory Network

National Center for Vector Borne Diseases Control (NCVBDC), Government of India (GoI) has identified a network of laboratories (Sentinel Surveillance Hospitals and Apex Referral Laboratories) for surveillance of Chikungunya fever cases across the country since 2007. Numbers are increasing yearly to augment the free diagnostic facilities in all endemic areas, which were 110 in 2007 and 783 in 2022. They are linked with 17 Apex Referral Laboratories (ARLs) with advanced diagnostic facilities for backup support. For details, please refer to the NCVBDC website (https://ncvbdc.mohfw.gov.in).

These laboratories receive the samples, diagnose and regularly send the report to districts/ municipal health authorities to implement preventive measures to interrupt the transmission. Chikungunya IgM MAC ELISA test kits (1 Kit= 96 tests) are provided to the identified laboratories through the National Institute of Virology (NIV), Pune, since 2007. NCVBDC bears the cost for all testing. Buffer stock is also maintained at NIV, Pune, to meet any emergency in case of an outbreak in newer areas and to avoid stock out.

Chapter 4

CASE DEFINITION AND DIFFERENTIAL DIAGNOSIS

4.1. Case Definition

Suspected case: A patient meeting the following clinical criteria with or without a history of travel to or having left a known endemic area 15 days prior to the onset of symptoms:
Clinical Criteria:

1) Acute febrile illness
2) Arthralgia/arthritis
3) With or without skin rash

Confirmed case: Confirmed case is defined as when one of the following tests is positive:

- **MAC ELISA-** Presence ofvirus-specific IgM antibodies in a single serum sample collected in the acute or convalescent phase. Four-fold increase in IgG values in samples collected at least three weeks apart.
- Isolation of virus
- Presence of viral RNA by RT-PCR

Merits and demerits of different tests are shown in **Table 2.**

Table 2. Comparison of various tests available for diagnosis of Chikungunya

	Technique	Merits	Demerits
1.	Serology -Anti CHIK-IgM	• Widely available • Technical expertiseisnot required	• Sensitivity 85%-90% • IgM antibody may persist for months • Not useful in first 7 days of illness
2.	Serology Anti CHIK IgG	• Useful in Post-acute and chronicarthralgia	• Not useful in first 7 days of illness
3.	Virus isolation in cell culture • *A.albopictus*C6/36 clone • Vero cell line etc	• Gold standard technique • Source of virus antigen • Genotyping study can be done	• Require facilities and skill • Require BSL-3 Lab
4.	RT-PCR	• High sensitivity and specificity	• Reagents and equipments are costly • Limited to reference centers
5	Antigen detection test	• Can potentially diagnose in 1st week of illness	• Not available commercially

4.2. Differential diagnosis

Fever with arthralgia is a common manifestation of various illnesses. Some of the diseases which can be considered as close differential diagnoses are:

- Dengue fever
- Malaria
- Leptospirosis
- Enteric fever
- Rheumatic fever
- Reactive arthritis
- Rickettsial disease
- COVID-19

(1) **Dengue fever:** It is the closest differential diagnosis of chikungunya fever. The importance of differentiating the two illnesses is that severe Dengue can be fatal in up to 10% of patients, and the mortality can be reduced to <0.1% if it is diagnosed early and treated with adequate hydration, while chikungunya fever is rarely fatal. Dengue fever commonly presents with low back pain, hypotension, and petechial/ purpuric rash. Active bleeding from body cavities is also more common in dengue fever. A comparison of Chikungunya with Dengue is shown in **Table 3.**

(2) **Malaria:** Malaria is characterized by fever, malaise, nausea, vomiting, abdominal pain, diarrhea, myalgia, and anemia. The patient can present with a high fever and may also complain of joint pains. Periodicity of fever and alteration of consciousness/seizures may also be present in severe cases. In all acute febrile illnesses, especially with multi-organ involvement in tropics/endemic regions, the differential diagnosis of malaria should be kept and ruled out by microscopic test or by malaria rapid card test, as co-infection may also occur.

(3) **Leptospirosis:** A diagnosis of leptospirosis should always be considered in patients with severe myalgia localized to calf muscles with conjunctival congestion/or subconjunctival hemorrhage with or without renal involvement or jaundice in a person with high-risk occupations (leading to skin contact with contaminated water) in appropriate epidemiological settings.

(4) **Rheumatic fever:** More common in children and presents with fleeting (migratory) polyarthritis predominantly affecting the large joints. Modified Jones criteria should be the basis for diagnosis. Raised anti-streptolysin-O (ASO) titer and a history of recent sore throat are other points to be noted for making the diagnosis.

(5) **Reactive arthritis:** In patients with inflammatory arthritis that follows after 3-4 weeks of gastrointestinal or genitourinary infection, diagnosis of reactive inflammatory arthritis should be considered. The other hallmark features are enthesitis, dactylitis, and inflammatory backache.

(6) **Rickettsial Disease (Scrub Typhus):** The scrub typhus infection can present with fever, rash, thrombocytopenia, and joint pains. The diagnosis requires a high index of

suspicion, a history of exposure to shrubs (farmer/ field worker), recent travel, and a recent outbreak in the region needs to be documented. Eschar, when present, should alert the physician for a diagnosis of scrub typhus and appropriate serology requested. As per available information, Scrub Typhus cases have been increasing in recent years from various States/UTs.

Table 3. Comparison of clinical manifestations of Chikungunya and Dengue fever

	Features	**Chikungunya**	**Dengue**
1.	Presentation	Fever with joint pains	Fever, headache, myalgias, bleeding manifestations
2.	Fever	Abrupt onset, lasting 3-5 days	Acute onset, lasting 5-7 days
3.	Rash	Appears on day 2 or 3	Appears between days 5-7
4.	Polyarthralgia/ polyarthritis	Frequent	Less common
5.	Musculoskeletal symptoms	Arthralgia predominant	Myalgia predominant
6.	Bleeding manifestations	Uncommon	Common
7.	Organ involvement	Rare	Common
8.	Hypovolemic shock	Rare	Frequent in severe form
9.	Leukopenia	Infrequent	Common
10.	Thrombocytopenia	Infrequent	Common
11.	Hematocrit	Normal	High

Chapter 5

CLINICAL MANIFESTATIONS AND PATHOGENESIS OF CHIKUNGUNYA

5.1. Incubation period:

CHIK virus causes an acute febrile illness with an incubation period of 3-7 days (range 2-12 days).Viremia persists for up to 7 days from the onset of symptoms.

5.2. Clinical Features:

Chikungunya fever usually presents with the classic triad of abrupt onset fever, arthralgias/ arthritis, and rash. Out of these, the rash is present inconsistently in the patients. Patients with chikungunya fever are mostly symptomatic. However, asymptomatic infections are reported in 3% to 25% of cases.
Clinical presentation of Chikungunya usually follows 3 phases

a) Acute phase : Less than 3 weeks
b) Sub-acute phase: > 3 weeks to 3 months
c) Chronic phase : > 3 months

Most patients in the acute phase have significant morbidity due to arthritis. Complications in the acute phase are rare and observed only in 0.5% of cases. The elderly population, chronic alcohol abuse, and patients with prior comorbidities are vulnerable to get complications of Chikungunya fever. It must be kept in mind that systemic complications are very uncommon in the high-risk groups too, and any organ dysfunction should alert the physician for a diligent search for co-infections.

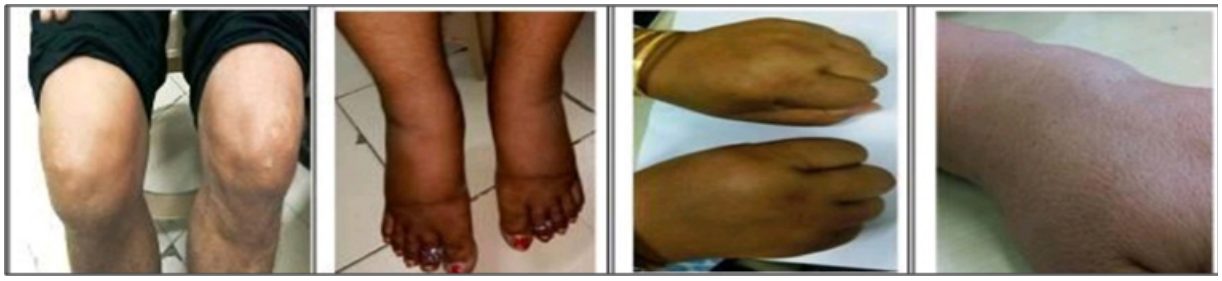
5.2.1 Acute phase

The clinical manifestations seen in the acute phase are summarized below:

- **Fever:** The fever varies from low grade to high grade, usually lasting for 3 to 5 days, but may sometimes last up to 2 weeks. It has an abrupt onset and may be biphasic. It usually responds to antipyretics. Asthenia and anorexia are expected after the regression of the acute symptoms.

- **Arthralgia/Arthritis:** Soon after the onset of fever, most patients develop severe debilitating polyarthralgia. Arthralgias are usually polyarticular, symmetrical, and involve peripheral joints, predominantly small joints. Proximal larger joints (knees, shoulders) may also get involved.

Figure 4: Joint involvement in Chikungunya infection

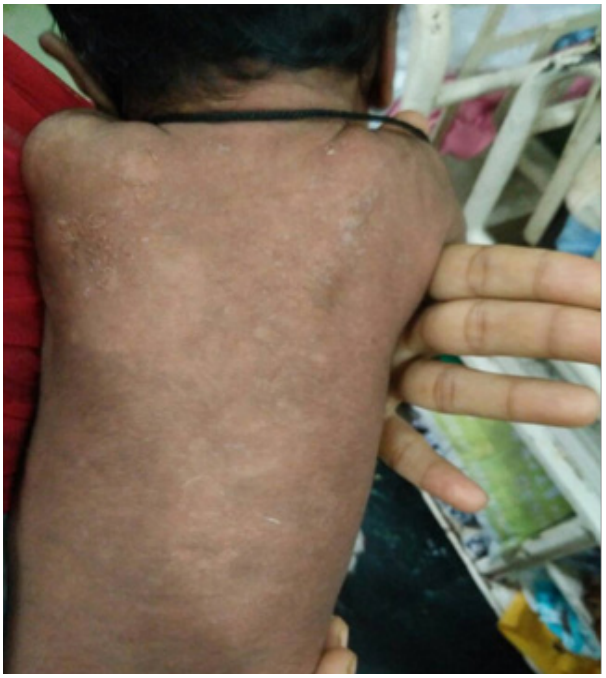


Courtesy: Dept. of Medicine, AIIMS, New Delhi

- **Rash:** The frequency of rash in patients reported is highly variable as per the literature, thus (**Fig. 4**) making it the least reliable sign in the classic triad (fever, arthralgia/ arthritis, and rash). The rash usually appears between the 2nd and 5th day of fever and may involve the face, chest, abdomen, limbs, palms, and soles. Various cutaneous manifestations, including morbilliform maculopapular rash, bullous rash, nasal blotchy erythema, exfoliative dermatitis, epidermolysis bullosa in children, intertriginous aphthous like ulcers, purpura, vasculitic lesions, facial edema, cutaneous pruritus (foot arch), localized petechiae and gingivorrhagia have been described. Most skin lesions recovered completely except in cases where the photosensitive hyperpigmentation may persist (**Fig. 5**).

- **Neurological manifestations:**
Albeit rare, various neurological complications are described in chikungunya fever. These include meningoencephalitis, myeloradiculitis, myeloneuropathy, Guillain Barre syndrome, external ophthalmoplegia, facial palsy, sensorineural deafness, acute disseminated encephalomyelitis, and optic neuritis. Out of these, encephalitis seems to be the most common manifestation. Encephalitis occurs simultaneously or within a few days of systemic symptoms and viremia onset. On the contrary, certain neurological complications like myelitis, Guillain Barre syndrome, and optic neuritis have been observed after a delay of more than two weeks

Figure 5 – Skin rash in Chikungunya fever



- **Cardiovascular manifestations:** Heart failure, arrhythmia, myocarditis, and myocardial infarction have been reported.

- **Ocular manifestations:** Anterior uveitis (granulomatous and non-granulomatous) is the commonest ocular involvement in chikungunya. Conjunctivitis, episcleritis, keratitis, bilateral neuroretinitis, multifocal choroiditis, optic neuritis, retrobulbar-neuro retinitis, exudative retinal detachment, panuveitis, and central retinal artery occlusion have been reported. The visual prognosis generally is good.

- **Renal manifestations:** Acute renal failure or exacerbation of preexisting renal dysfunction.
- **Hepatic manifestations:** Elevated SGOT and SGPT.

- **Pulmonary manifestations:** Pneumonitis

- **Metabolic manifestations:** Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

- **Hemorrhagic manifestations:** Very uncommon, but epistaxis, bleeding gums, and subconjunctival hemorrhage may occur.

Symptomatology observed in the acute phase of Chikungunya in India and other countries is given in **Table 4**.

Table 4: Symptomatology in the acute phase of Chikungunya

Symptoms	India*	Reunion outbreak, 2005-6**	Malaysian outbreak, 1998**	Maldivies outbreak 2019**
Fever	100	100	100	100
Arthralgia/Arthritis	96-100	100	78	82/58
Rash	31-94	39	50	54
Myalgia	80-99	60.6	50	80
Headache/Backache	55-97	70/NA	50/50	74/NA
Total no of cases	**1638**	**504**	**51**	**50**

5.2.2 Sub-acute phase (3 weeks - 3 months)

Chikungunya is a self-limiting disease; however, sequelae may be seen particularly in a severe form of the disease in some patients. These patients may have arthritis, synovitis with or without effusion, tenosynovitis, or bursitis. The relative frequency of post-chikungunya musculoskeletal involvement is highly variable in different observational studies. Joint involvement may be continuous or intermittent, with symptoms interspersed with asymptomatic periods. Fortunately, most of the patients will improve with time. There may often be intense asthenia in the post-acute phase and neuropsychological changes, especially when the pain is intense. The spectra of musculoskeletal involvement in the sub-acute phase have been summarized in **Table 5**.

Table 5: Clinical spectra of symptoms in thesub-acute phase of Chikungunya

Musculoskeletal involvement	Manifestation
Joint inflammatory involvement	Arthritis
Peri-articular inflammatory involvement	Tenosynovitis, enthesitis, bursitis
Others	Soft tissue edema, stiffness, worsening of other preexisting diseases

Predictors of chronic musculoskeletal involvement include age (> 45 years), female gender, previous history of the rheumatological disease, and severe initial rheumatic manifestations.

5.2.3 Chronic phase (> 3 months)

The chronic stage can last a few months to several years. The rheumatic involvement in the chronic phase of illness may be either non-inflammatory musculoskeletal disorders (MSD) or chronic inflammatory rheumatisms (CIR). The former is more common and has a better prognosis. The clinical spectra of pCHIK-MSD and pCHIK-CIR are outlined in **Table 6**.

Table 6:The clinical spectra of chronic post-Chikungunya rheumatic manifestations

Post-Chikungunya Chronic Inflammatory Rheumatism (pCHIK-CIR) • De novo pCHIK-CIR • Worsening of pre-existing CIR
Post Chikungunya Musculoskeletal Disorder (pCHIK-MSD) • **Local** – Mono or oligo articular involvement, other local complications (capsulitis, tendinopathy, bursitis, exacerbation of previously injured areas) • **Diffuse** – distal polyarthralgia with edema

A possibility of pCHIK-CIR is considered if

- Rheumatic signs are absent before the infection
- The symptoms continue (intermittently/persistently) till the diagnosis of CIR
- CHIK seropositivity is confirmed
- Other differential diagnoses are ruled out

This chronic stage may culminate in one of the following outcomes -

1. The disease progresses to resolution (spontaneously or with treatment) without sequelae.
2. There is prolonged persistence of joint and/or general symptoms.
3. There is an aggravation of symptoms because of inflammatory or degenerative processes.

5.3 High-Risk groups

Patients with the conditions shown in **Table 7** are considered high-risk. Chikungunya infection with these conditions in patients is likely to develop severe manifestation and adverse outcomes.

Table 7: High-risk population in Chikungunya infection

Hypertension Diabetes CAD/CVD Geriatric age Pregnancy COPD Hypothyroid	Dengue Malaria Tuberculosis Enteric fever HIV

Patients with ages below one year and above 65 years and pregnant females are also at greater risk for complications. The clinicians must closely monitor them.

5.3.1 Chikungunya in Children

The clinical manifestation of CHIKV fever in the pediatric population varies.The clinical presentation in various pediatric age groups population has been discussed.

Clinical profile of Chikungunya in infants
Thecommon clinical features noticed in infants with chikungunya fever are

- Fever
- Seizures
- Loose stools
- Peripheral cyanosis (without any hemodynamic alteration)
- Edema
- Dermatological manifestations (generalized erythema, maculopapular rash, vesiculobullous lesions, and skin peeling)

The seizures are often atypical febrile seizures. Diarrhea is usually found between the 3rd to the 5th day of illness, subsides by the 7th to 8th day, and is usually not associated with blood. Edema of the lower extremities may be observed by the 3rd to 4th day of illness. It usually subsides spontaneously by the seventh day of illness.

Vesiculobullous lesions typically appear on the 4th day of illness over the lower limbs and then spread to involve the perineum, abdomen, chest, and upper limb, sparing the face and scalp. This is followed by the peeling of the skin by the sixth day. There may be severe perianal involvement in the form of erythema and peeling in children with bullous lesions. The healing of skin lesions is usually accomplished by the tenth day of illness. The recovery may leave behind hyperpigmented scars or hypopigmented lesions. Histopathologically, skin lesions show lymphocytic infiltration around dermal blood vessels.

Lethargy, poor feeding, excessive crying, and irritability are other manifestations of Chikungunya in infants. Arthralgia/Arthritis, which is more common in adults and older children, is usually not observed in infants. Infrequently, bleeding manifestations (epistaxis, bleeding from gums, subconjunctival bleed, positive Hess test, petechial or purpuric rash), aphthous ulcers over the scrotum, and freckle-like hyperpigmentation over the orofacial region may be observed. Cardiovascular assessment (including echocardiography) should be considered in neonates with chikungunya fever. Preterm and full-term neonates are at increased risk of severe neurological damage due to inefficient type I interferon response.

Clinical profile of congenital chikungunya infection

The observed vertical transmission rate ranges between 27.7% and 48.29%. The clinical manifestations of congenital chikungunya infection include fever, irritability, maculopapular rash, bullous dermatitis, hyperalgesia, respiratory distress, sepsis, distal cyanosis, diffuse abdominal pain, diarrhea, necrotizing enterocolitis, adenopathies, meningoencephalitis, myocarditis, pericarditis, hemodynamic instability, and diffuse limb edema. Increased incidence of meconium-stained amniotic fluid and meconium aspiration syndrome has been reported. Echocardiography may identify pericardial effusion, myocardial hypertrophy, ventricular dysfunction, and coronary artery dilatation. Congenital malformations have not been attributed to chikungunya infection. Necrotizing enterocolitis and sepsis are associated with poor prognosis.

Usually, all infected neonates are symptomatic and present from day 3 to day 7 of illness (median: day 4). The mean interval between onset of maternal disease and onset of neonatal illness is 5 days. The mean duration of fever is 3 days. Severe complications may include meningoencephalitis, myocarditis, seizures, and acute respiratory failure. Higher rates of complications may be observed due to higher viral concentrations observed in this age group. The congenital infection may also result in significant neurological sequelae. The neurocognitive outcome of neonates infected by mother-to-child transmission was investigated in the Chimere cohort on an average of 21 months after infection. Neurocognitive delays in coordination, language, sociability, movement, and posture were documented in p-CHIKV infected children. On follow-up, neonates with severe CHIKV encephalopathy have more powerful outcomes and may develop microcephaly or cerebral palsy. MRI scans show severe restrictions of white matter areas, predominantly in the frontal lobes. A follow-up of the Chimere cohort revealed that neurocognitive dysfunction might also be found in infected neonates with prostration. This group of neonates was previously thought to have a good prognosis. Thus infected neonates should be monitored throughout childhood to pick up potential long-term morbidities such as neurocognitive sequelae, microcephaly, and cerebral palsy.

Ill-defined dark pigmentation over the centrofacial area with flagellate pigmentation on the trunk and patchy pigmentation over the extremities and knuckles may provide a clue for retrospective diagnosis of congenital Chikungunya. Such hyperpigmentation may persist for several weeks to months.

A caesarian section does not appear to prevent vertical transmission of CHIKV. Close monitoring of viremic mothers should be done, and delivery should be planned in facilities with optimal maternal and neonatal care.

It should be stressed that chikungunya infection in the neonate may present as bacterial sepsis, meningoencephalitis, or metabolic encephalopathy with high fatality.

Clinical profile of Chikungunya in children

Children are placed in the high-risk group because of their propensity to severe disease manifestations. Some clinical features seen in children are distinct from those seen in adults. Some of these distinct clinical features have been enumerated as follows -

1. The rash may develop on day 1 itself at times in children. The face may also get involved even though the rash is commonly truncal in location. Enanthem is not seen.
2. Arthralgia and arthritis are uncommonly seen in children (10-15% of cases), but may be quite severe if present. Significantly, residual arthralgia is less frequent in children.
3. Febrile convulsions may occur in children with chikungunya fever. Rarely children may have focal seizures, and transient paralysis following seizures have been observed.

5.3.2 Chikungunya in Elderly

Chikungunya infection may have a complicated course in elderly people due to exacerbation of underlying medical conditions.

5.3.3 Chikungunya in Pregnancy

Infected pregnant women have similar symptoms and outcomes except for prenatal hospitalizations. There is no relation between first-trimester exposures to chikungunya fever and increased risk of abortion or congenital abnormalities. Most infections occurring during pregnancy do not appear to result in virus transmission to the fetus. However, if pregnant women have a high viral load (a day before and 5 days after the mother's first symptoms) during the early stage of labor, there is a 50% risk of transmission of infection from mother to child. When the babies are infected during birth, signs of infection appear between 3-7 days, and more than 90% of the infected newborns recover quickly without sequelae. Infected neonates have a typical clinical presentation with a characteristic triad of fever, breastfeeding difficulty, and pain. Severe manifestations can occur in 25% of cases. Immunoglobulin M generally appears between the 4th and 7th day after the onset of clinical signs but does not pass through the placental barrier. The body starts producing IgG around day 15, which passes through the placenta and confers immunity to the fetus. The infant should be tested by RT-PCR. There is no evidence to suggest that the virus is transmitted through breast milk.

5.3.4 Chikungunya in chronic diseases

Chikungunya, in patients with chronic diseases like diabetes mellitus, hypertension, cardiovascular diseases, and COPD, may lead to a complicated disease outcome. It indeed increases morbidity; thus, the treatment needs to be individualized with adequate management of the underlying disease.

5.3.5 Co-infections

Both chikungunya and dengue viruses are arboviruses and are transmitted by Aedes mosquitoes. Hence, it is not unusual to have Dengue and Chikungunya as coinfection, transmitted by the same Aedes mosquitoes. Sero-prevalence studies from India have found coinfection in 0.4 - 4.3% of patients. Concurrent infections result in illness with overlapping signs and symptoms, which makes diagnosis difficult. As discussed earlier, chikungunya patients with organ dysfunction should be diligently investigated for coinfections.

Similarly, other acute or chronic viral or bacterial infections can produce overlapping symptoms posing diagnostic challenges and increasing morbidity. Clinicians must be vigilant to the possibility of coinfections as several diseases like malaria, leptospirosis, and other viral illnesses tend to cluster during the same period

a) Chikungunya and Dengue virus co-infection: In India,theendemic area of CHIKV and DENV virus overlaps with each other and provide opportunities for mosquitoes to become infected with both viruses. Both the diseases have some common clinical manifestations, including fever with chills, polyarthralgia, nausea, headache, vomiting, and sometimes rashes. In dengue-positive cases, symptoms such as fever, rash, myalgia, and thrombocytopenia are more common compared to Chikungunya, in which arthralgia and fever are the common presenting symptoms. As fluid management is the primary mode of treatment in dengue fever,themanagement of Chikungunya during the acute phase is mainly supportive, including rest, fluids, and anti-inflammatory and analgesic agents.

b) Chikungunya and Zika virus co-infection: Zika virus infections often present with a combination of fever, joint pain, myalgia, headache, conjunctivitis, and a pruritic rash similar to Chikungunya. During outbreaks of arboviral infection, severe disease manifestations like fetal microcephaly and Guillain–Barré syndrome (GBS) are primarily seen in Zika infected patients. The number of cases of coinfection of chikungunya and zika virus is still scarce in the literature. As clinical differentiation of co-infection could not be differentiated from monoinfections, the utility of a multiplex diagnostic for these viruses is the need of today. Treatment of both the infection is supportive.

c) Chikungunya, Dengue, and Zika virus co-infection: It's a rare situation showing the combined presentation of these three infections. Clinical manifestations at presentation is almost similar in all of this arboviral monoinfection. As mentioned above, fetal microcephaly and Guillain Barre Syndrome are seen in zika virus infection, whereas encephalopathy in neonates may be seen in chikungunya fever.Plasma leakage leading to shock is the main pathogenesis of dengue fever. As fluid management is the primary treatment for Dengue,symptomatic and supportive care is the main management. Guillain Barre Syndrome due to Zika virus need to be treated with immunoglobulins or plasmapheresis.

d) Chikungunya and COVID 19 - Chikungunya presents with acute onset of moderate to high-grade continuous fever and malaise followed by a rash, myalgia, and arthralgia. Respiratory failure may ensue in the late stages. Difficulty in diagnosis has been attributed to the similar clinical presentation of both viruses. Respiratory distress is

more common in COVID 19 patients.In strong suspicion, specific diagnostic tests for both should be done to confirm the diagnosis. COVID 19 related illnesses should be managed as per the National Covid 19 management protocol.

5.4 Mortality

Chikungunya is associated with significant morbidity, but mortality is very rare. It has been documented that mortality due to Chikungunya can occur within the first few days after hospitalization. It is primarily due to neurological and respiratory complications with progression to multi-organ failure in patients with high-risk underlying conditions.

5.5 Pathogenesis

The infected mosquitoes inoculate CHIKV into the subcutaneous capillaries and the dermis. CHIKV replicates in the skin fibroblasts, dermal macrophages, dendritic cells, and possibly endothelial cells (Fig 6, 7 & 8). Thereafter, the infected cells migrate to regional lymph nodes from where CHIKV spreads to peripheral organs such as liver, spleen, muscles, and joints by the bloodstream. The neurological symptoms observed in human infection may be due to infection of the choroid plexus and meninges by the CHIKV. The pain may result due to direct infection of skeletal muscles, myotendinous insertions, and joint capsules.

The peak viral load may be as high as 10^9 to 10^{12} CHIKV RNA copies/ml blood. A high viral load is associated with an increased risk of severe disease and chronic symptoms. An innate type I interferon response leads to the production of interferons α and β, which binds to interferon α/β receptors (IFNAR). This stimulates the expression of antiviral interferon stimulating genes via the JAK/STAT signaling pathway. There is a positive correlation between interferon α and plasma viral load, and a lack of interferon response increases susceptibility to severe infection. CHIKV-specific T cells peak around the fifth day of fever. So far, there is conflicting evidence regarding the role of T cells in controlling the viral load or in pathogenesis.

Stimulating the innate immune system results in the production of pro-inflammatory cytokines such as IFN-γ, IL-1, IL-6, IL-8, IL-12, TNF-α, MCP-1/CCL2, MMP2, IP-10, and CXCL10, most likely from the natural killer (NK) cells and macrophages. There is a robust infiltration of target tissues with macrophages due to the chemokine MCP-1/CCL2. The occurrence of clinical symptoms has a direct correlation with viral replication and the consequent inflammatory response.

In contrast to innate immunity, adaptive immunity is elicited to protect against CHIKV reinfection. CHIKV-specific immunoglobulin M and G (IgM, IgG) are usually detected on 3-7 days and 4-10 days of fever, respectively. These antibodies have a neutralization capacity and can control virus dissemination in an individual.

Human studies and animal models have detected viral antigen and RNA from synovial tissues in the chronic phase of chikungunya infection, which may be due to active viral replication or delayed antigen clearance. It is hypothesized that the viral persistence in affected joints may explain the persistence of arthritic symptoms. The following reasons for viral persistence have been postulated:

1. CHIKV may escape detection by the immune system because of its ability to infect macrophages to form a reservoir and thereby conceal it from the immune response. It has also been postulated that CHIKV can alter the phenotype of macrophages to generate an inadequate immune response.

2. The sensitivity of CHIKV to interferon response in the initial stages of infection is lost after the replication cycle starts. Studies have indicated that the non-structural protein of CHIKV nsP1 and nsP2 interferes with interferon signaling and nsP2 inhibits the interferon response by blocking the interferon-induced JAK/STAT signaling.

3. CHIKV manages to evade killing by T-cells.

4. CHIKV can evade an antibody response by hiding in apoptotic blebs after the initiation of cell death. Phagocytosis of these apoptotic blebs allows CHIKV to infect adjacent cells and macrophages without detection by the immune system.

5. CHIKV persistence may also be explained by an inefficient immune response (immunosenescence) in the elderly.

6. Viral RNA sensing by Toll-like receptors (TLR) is an essential component of the innate immune system to recognize and restrain viral replication. TLR3 signaling is responsible for controlling CHIKV replication. Researchers have shown that impaired TLR3 signaling may lead to severe and chronic CHIKV infection. TLR3 function may get affected by genetic alterations such as single nucleotide polymorphisms (SNP). Thus, genetics may control viral persistence and the consequent severity and chronicity of the disease.

Uninterrupted replication of CHIKV in target tissues leads to apoptosis of infected cells, tissue destruction, and constant activation of the immune response. The persistent infection leads to an uninterrupted Th1 response and a blockade in shifting T cell phenotype from Th1 to Th2. An uninhibited sustained Th1 response leads to tissue injuries. The absence of a Th2 response leads to low production of Eotaxin and HGF, which further results in a failure of macrophage inhibition. Chronic infection of macrophages by CHIKV leads to prolonged production of pro-inflammatory cytokines. Over time, the fluctuation of chronic symptoms may be explained by alternating sequences of persistent viral replication and partial viral clearance.

Exploring the pathogenesis of Chikungunya in pediatric age group a new set of immune signatures in children has been observed – IL 18, IL 2Ra, IFN α 2, G CSF, and MIG. This may explain the difference in clinical manifestations in children compared to adults, particularly in the frequency of joint affliction and rheumatic sequelae.

Figure 6: Pathogenesis of Chikungunya

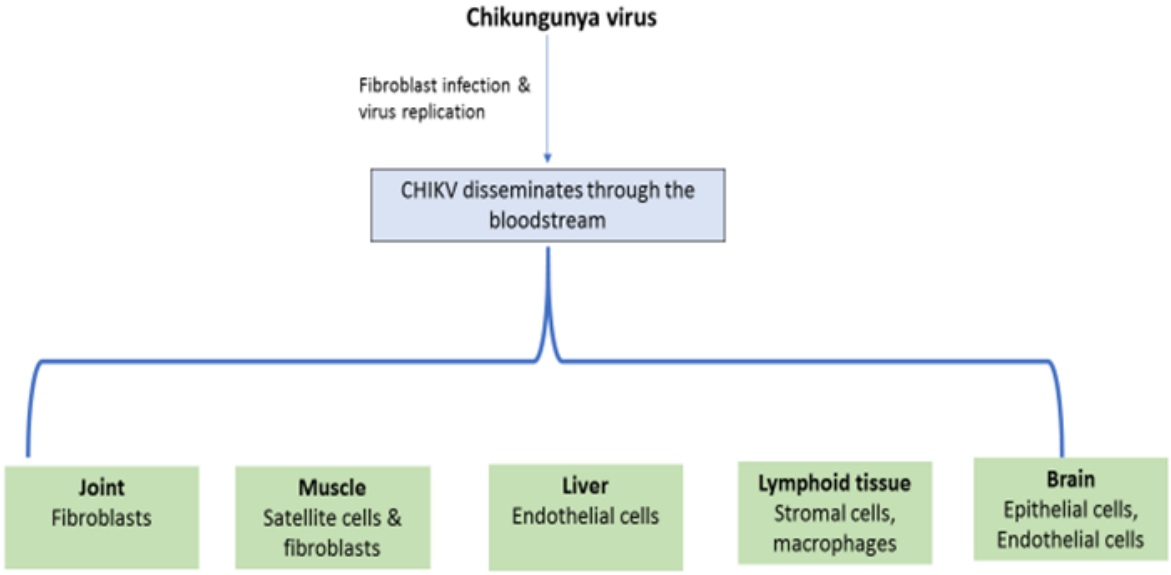


Figure 7: Chikungunya at Molecular level

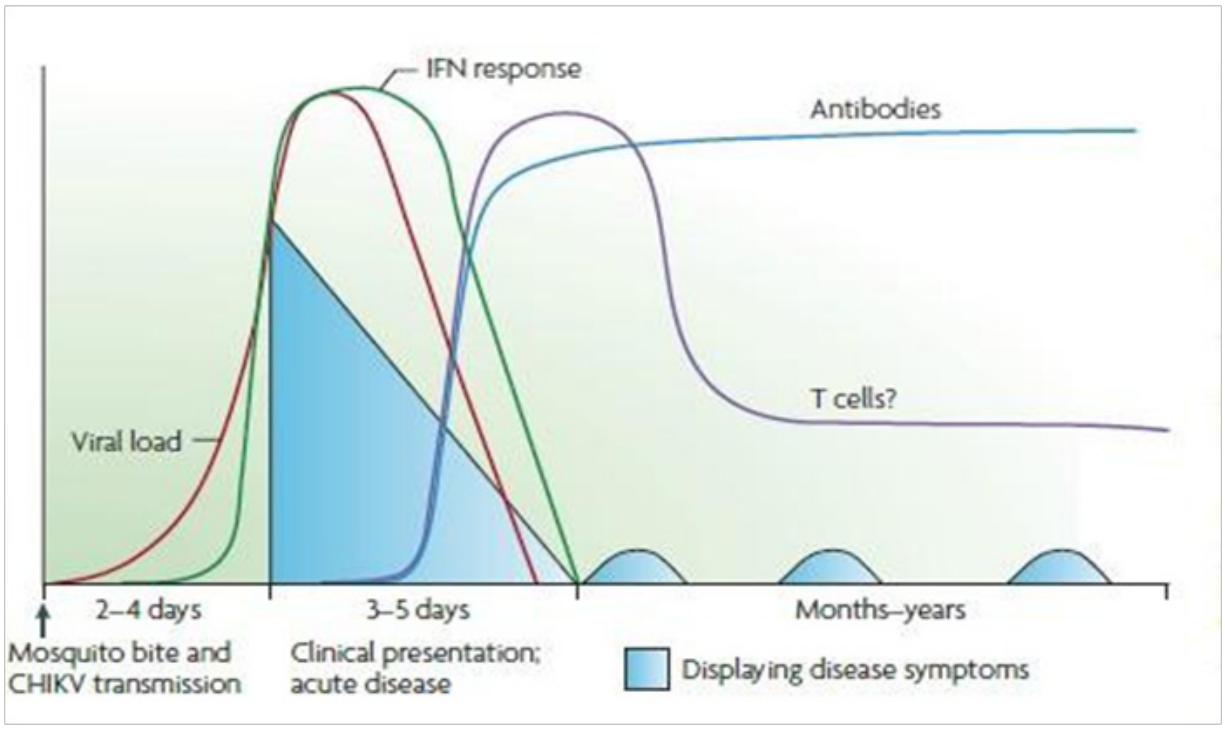
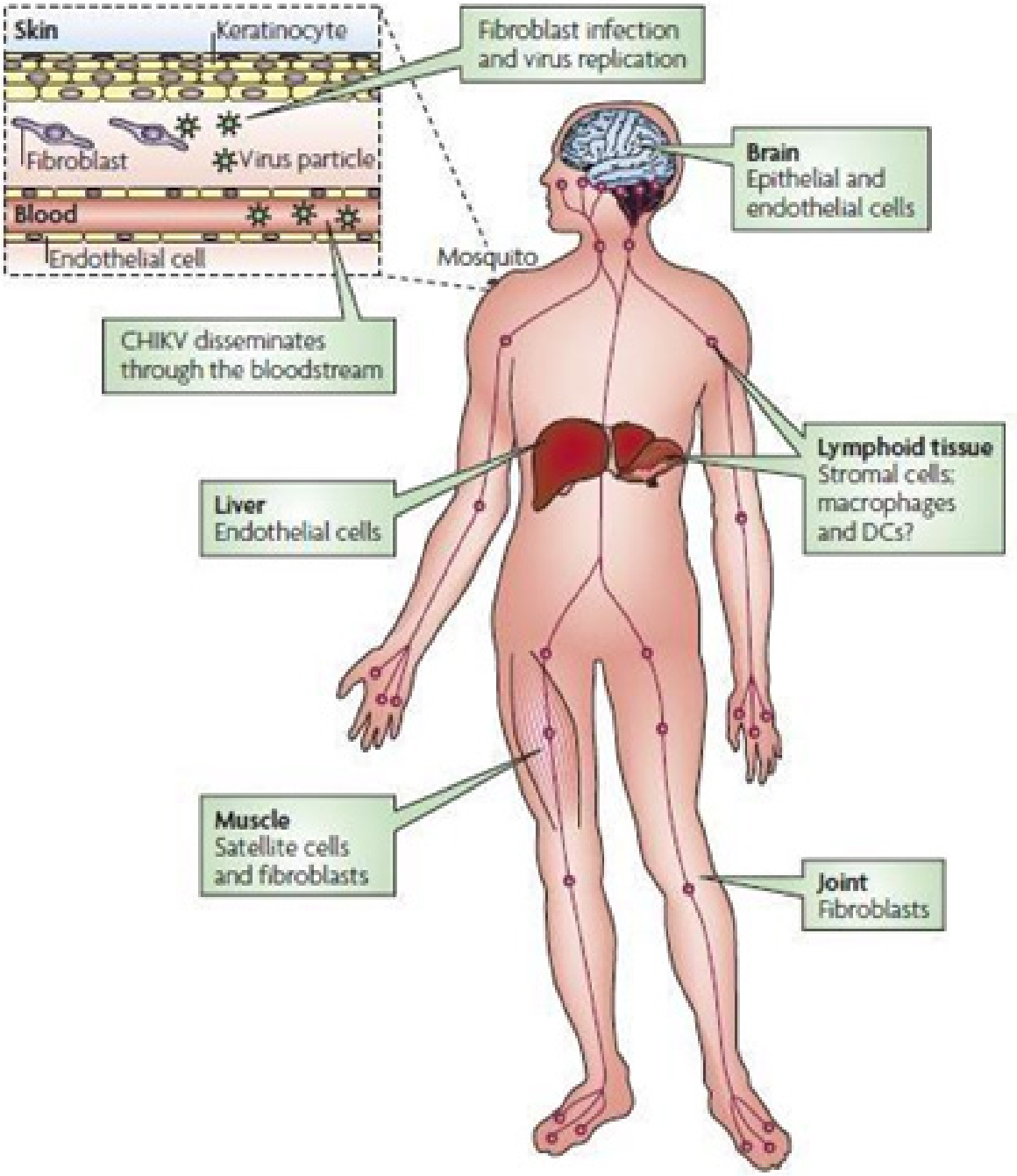


Figure 8: Pathogenesis of Chikungunya, Major human cells where chikungunya viruses exert cellular tropism



Chapter 6

CLINICAL MANAGEMENT OF CHIKUNGUNYA

Guiding principles of clinical management

The clinical management of Chikungunya is based on the phase of the disease:

1. Acute phase
2. Sub-acute phase
3. Chronic phase

6.1 Management of acute phase

Principles of management during the acute phase

- There are no antiviral drugs against chikungunya
- Treatment for chikungunya is symptomatic
- Supportive care includes analgesics, antipyretics, and fluid supplementation
- Analgesics to be given in a step-wise fashion (given below)
- Corticosteroids are not to be used in the acute phase
- Adequate rest is necessary

Clinical management during the acute stage is usually in ambulatory settings. Hospitalization is rarely indicated.

6.1.1 Domiciliary (Home Based)

- Adequate rest or activity as tolerated.
- Tab paracetamol 500 mg TDS/QID (dose not to exceed 3Gm/24 hours).
- Antacids like PPI/H2 blocker to counter gastritis.
- Tepid water sponging for high fever.
- Maintain adequate liquid intake
- Cold compression with ice packs is effective for joint pains.
- Light exercises during recovery from illness
- Avoid self-medication, particularly antibiotics, steroids, and other analgesics

Box Analgesia ladder for the acute phase of Chikungunya

Step 1: Paracetamol; adults, 3 gm/day; children, 10mg/ kg every 6 hours.
Step 2: Weak opiates when acetaminophen is ineffective. Tramadol alone or in combination with acetaminophen: • Children 3 to 12 years of age: 1-2 mg/kg every 4 or 6 hours. • Adults: 50-100 mg every 4 or 6 hours; maximum dose 400 mg/d; adults over 75, maximum dose 300 mg/d

In most ofthe patients, the disease is self-limiting. Patients with atypical manifestations and high-risk categories may need a referral to a higher center.

6.1.2 In-Hospital management

- At the primary level or point of first contact (PHC/CHC level).
- At the secondary level (District Hospital).
- At the tertiary level (Teaching hospital situations / infectious diseases specialists/ advanced care centers)

6.1.2.1 At the point of first contact (PHC/CHC level)

The medical officer must attend to all patients with febrile illness. Dengue, malaria, and other arboviral diseases and tropical illness must be excluded by history, clinical examination, and basic laboratory investigations. If the diagnosis of chikungunya fever is made, the patient should be treated symptomatically and pain management as per the analgesia ladder mentioned in the box above. Screening for atypical manifestations and organ dysfunctions should be done at the time of contact. High-risk category patients should be monitored closely. In pregnant females, antenatal care is to be given with close watch on uterine contractions and fetal heart rate. Pregnant patients should be referred to a higher center immediately if any abnormality is observed. All patients with worsening symptoms and vital signs and those with worsening neurological and respiratory manifestations should be referred to a higher center.

6.1.2.2 At the secondary level (district hospital)

The physician must evaluate all cases, and relevant investigations guided by the clinical examination should be done to establish the diagnosis and rule out other infections or co-infections. Patients in high-risk groups should be evaluated for hypotension and organ dysfunction as they may need close monitoring and hospitalization. Treat symptomatically (paracetamol, antiemetics, and intravenous fluids as required), specific management for co-infections/ co morbidities and organ dysfunction as per available facilities. Patients with severe symptoms, moderate-severe organ dysfunction, and pregnant patients with onset of uterine contractions/labor or with abnormalities of fetal heart rate monitoring should be referred to tertiary level of care.

6.1.2.3 At the tertiary care level

All patients referred to a tertiary care center should be admitted. The severity of the disease and the risk category of the patient should be assessed, and an appropriate triage should be planned accordingly. Care must be individualized, depending upon the complications and clinical condition of the patient.

6.1.3 Special population group

6.1.3.1 Pregnancy

The advice of an Obstetrician-Gynecologist should always be taken, especially when the pregnant patient is infected at full term. For those in full-term or labor, an obstetric strategy needs to be devised by the specialist to minimize the risk of mother-to-child transmission. Between one day before and five days after the fever, there is a maximum risk of mother-to-child transmission as this period coincides with maximum viremia in the mother. The caesarian section has no proven protection against chikungunya transmission to the child.

Thus few essential points to remember:

- Paracetamol is recommended for the symptomatic patient
- NSAIDs are to be avoided
- If a near term, consult an obstetrician

6.1.3.2 Newborns and children

- No NSAIDs in the first 14 days of illness. Fortunately, arthralgia in children is mild, short-lived, and responsive to paracetamol.
- Opioids should not be prescribed to children.
- Dosage of NSAIDs - Ibuprofen - 30 mg/kg/day in 3 divided doses. Naproxen - 10-15 mg/kg/day in 2 divided doses.
- Ranitidine (5-10 mg/kg/day divided 12 hrly) may be given in children. Lansoprazole < 30 kg 15 mg od; > 30 kg 30 mg od.
- Pediatric dose of PCM - 10-15 mg/kg per dose 6 hrly not to exceed 3gm/24 hrs

6.1.3.3 Co-morbid conditions

Chikungunya, in the presence of co-morbid diseases like diabetes mellitus, hypertension, cardiovascular diseases, and COPD, can lead to worsening of the underlying illness. The management needs to be individualized, considering the various combinations of underlying conditions.

Chikungunya infection may have a significant negative impact on glycaemic control in diabetes patients. A close clinical and glycaemic observation is recommended in diabetic patients, and early consideration of insulin therapy is the preferred option.

Patients with hypertension should be considered hypotensive when the mean arterial pressure (MAP) declines by 40 mmHg from the baseline. Enthusiastic blood pressure control should be discouraged as raised BP could be just an indicator of sympathetic over-activity. Beta-blockers may block the tachycardia effect of fever. In patients with heart failure, fever may cause tachycardia and increased metabolic demands leading to decompensation of cardiac functions. Such patients have limited ability to compensate for hypovolemia or hypervolemia. Non-invasive positive pressure ventilation should be considered in decompensated heart failure.

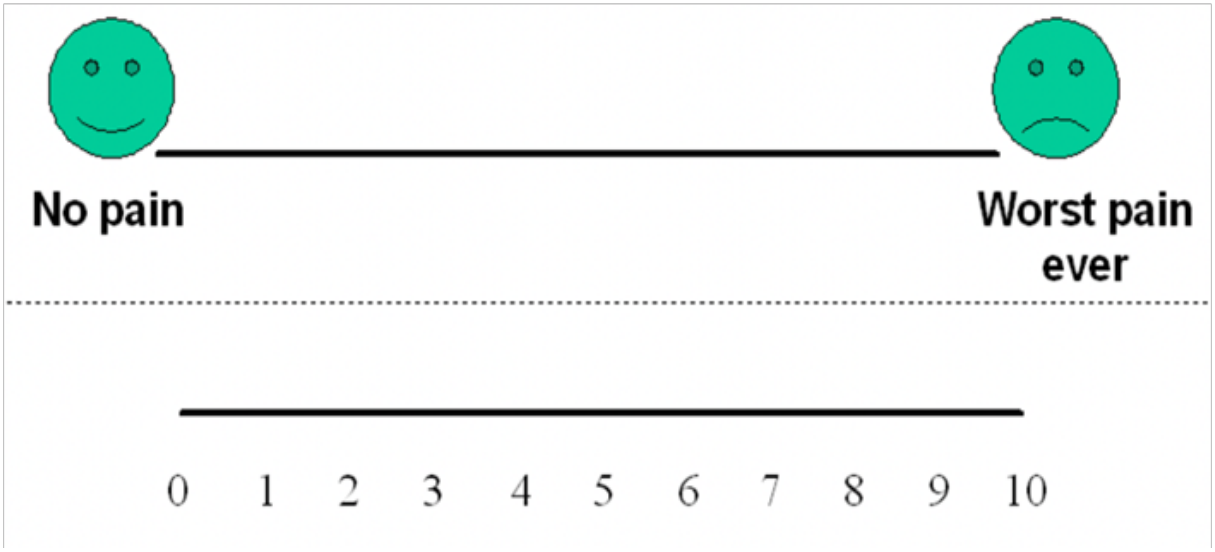
6.2 Management of sub-acute phase

Principles of management during the sub-acute phase

- Analgesics: begin with optimizing step 1/2 of the analgesic ladder along with an antineuropathic agent
- NSAIDs are indicated for persistent symptoms
- Corticosteroids are reserved for highly inflammatory polyarticular forms of illness resistant to NSAIDs or cases in which they are contraindicated
- Refer patients with severe diseases to a higher center.

The main objective of management during this phase is to alleviate pain and stop the progression of inflammation. The patient should be assessed clinically, including physical examination, inflammatory activity (number of nighttime awakenings, duration of early morning stiffness, number of painful joints, number of swollen joints, and CRP/ESR), and visual analog scale (VAS) for pain as shown in **Fig. 9:**

Figure 9: Visual analog scale



(http://img.medscape.com/article/742/580/VAS.pdf)

Pain management should begin at step 1 or 2 of the analgesic ladder. Paracetamol ±, opioids, ± anti-neuropathic agents should be prescribed based on the symptoms.

- **NSAIDs** may be considered for the management of pain in patients with mild VAS (score 1-3) for pain. No superiority of effectiveness on post-CHIK symptoms has been demonstrated amongst different NSAID classes. The NSAIDs are prescribed in full dose unless contraindicated. An evening dose or extended-release formulation can take care of night symptoms. The effectiveness of NSAIDs should be reassessed during the first week, and the class of NSAIDs should be changed in case of inadequate response by the 10th day. NSAID treatment may be required for several weeks depending upon the tolerance of patients. They are weaned gradually before stopping the treatment (intake every other day for at least 1 –2 weeks).

  Oral corticosteroids should be only used for the following conditions:

  1. Severe inflammatory polyarticular involvement associated with tenosynovitis or active synovitis.
  2. Patients with moderate (score 4-6) to intense (score 7-10) VAS score for pain.
  3. Resistance or contraindication to NSAIDs. A patient is considered resistant to a class of NSAIDs if the pain is not relieved in 7-10 days of use of NSAIDs at optimal dosages.

Few important points for the use of steroids:

- Prednisone is given at a dose of 10 mg/d for 5 days with a progressive reduction over 10 days.
- In severe presentations, prednisone is given in a dose of 0.5 mg/kg/day until an adequate response (adequate response is defined as the ability to walk without assistance and satisfactory pain control). Thereafter, the dose should continue till the full resolution of joint pain. After the complete resolution, the dose is continued for another 3-5 days, followed by gradual weaning by decreasing the dose by 5mg/day every seven days.
- Use of Corticosteroids should not be continued for more than 4 weeks.

  Corticosteroid infiltration may be helpful in cases of tenosynovitis, bursitis, and synovitis inadequately treated by oral therapy.

- **Disease-modifying antirheumatic drugs (DMARDs)** are not indicated before 8 weeks in the sub-acute stage of the illness. Expert consultation should be taken for patients with inadequate response to corticosteroids or those with difficult weaning.

6.3 Management of chronic phase

The treatment objectives in this phase of illness are to limit the potential joint damage, decrease the functional and psychological impact and improve the quality of life.

The following possibilities should be evaluated, and the treatment strategy should be devised in consultation with an experienced physician:

- Development of de novo pCHIK- CIR
- Worsening of previous degenerative/inflammatory conditions after Chikungunya fever.
- Development of pCHIK-MSD (loco-regional and diffuse

Principles of management during the chronic phase

NSAIDs: Some patients may be diagnosed in the chronic phase of illness. For them, these classes of drugs are utilized according to the protocol suggested in the sub-acute phase of illness.
A short course of **corticosteroids** may be used in this phase if not used previously. The dose, duration, and weaning algorithm may be the same as suggested previously in the sub-acute phase.

DMARDs: The evidence regarding using various DMARDs (methotrexate, hydroxychloroquine, sulfasalazine) in the chronic phase of Chikungunya is not very robust. Only a limited number of studies have investigated their use in this indication, and most involve a small number of patients with different methodologies. This limited evidence is insufficient to conclude the superiority of different DMARD-based therapies. Currently, the use of DMARDs is based on extrapolation from their use in the treatment of chronic rheumatic diseases.

Hydroxychloroquine should be used in optimum doses (up to 6.5 mg/kg/day, usually 400 mg/day) for 8-12 weeks, along with NSAIDs. If the response is inadequate after 8-12 weeks, other DMARDs should be considered, including methotrexate, sulfasalazine, and leflunomide. Since these medicines (DMARDs)may have more side effects and frequent laboratory monitoring is required, such patients should be managed by physicians experienced in the use of these medications.

Patients with clinical manifestations (particularly suspected inflammatory arthritis) that persist at least three months after the onset of infection should preferably be referred to a rheumatologist for further assistance in management.

- Paracetamol followed by NSAIDs according to the analgesic ladder is used for mild symptoms (Visual Analog Scale score 1-3)
- Short course of corticosteroids may be given if not used previously in the sub-acute phase for moderate (VAS score 4-6) to severe symptoms (VAS score 7-10)
- DMARDs are the mainstay of therapy for moderate to severe symptoms
- Hydroxychloroquine should be used in optimum doses (up to 6.5 mg/kg/day, usually 400 mg/day) for 8-12 weeks, along with NSAIDs
- Other DMARDs to be considered if the response to hydroxychloroquine is inadequate after 8-12 weeks
- Physical therapy and other rehabilitation techniques may be used.

Annexure 1

Countries from where Chikungunya cases have been reported

Continent/ Region	Countries from where Chikungunya cases have been reported
AFRICA	Benin, Burundi, Cameroon, Central African Republic, Comoros, Dem. Republic of the Congo, Equatorial Guinea, Gabon, Guinea, Kenya, Madagascar, Malawi, Mauritius, Mayotte, Nigeria, Republic of Congo, Reunion, Senegal, Seychelles, Sierra Leone, South Africa, Sudan, Tanzania, Uganda and Zimbabwe
ASIA	Bangladesh, Bhutan, Cambodia, China, India, Indonesia, Laos, Malaysia, Maldives, Myanmar (Burma), Pakistan, Philippines, Saudi Arabia, Singapore, Sri Lanka, Taiwan, Thailand, Timor, Vietnam and Yemen
EUROPE	France and Italy- mostly in travelers returning from endemic areas
AMERICAS	Anguilla, Antigua and Barbuda, Argentina, Aruba, Bahamas, Barbados, Belize, Bolivia, Brazil, British Virgin Islands, Cayman Islands, Colombia, Costa Rica, Curacao, Dominica, Dominican Republic, Ecuador, El Salvador, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Saint Barthelemy, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Vincent & the Grenadines, Sint Maarten, Suriname, Trinidad and Tobago, Turks and Caicos Islands, United States, US Virgin Islands and Venezuela
OCEANIA/PACIFIC ISLANDS	American Samoa, Cook Islands, Federal States of Micronesia, French Polynesia, Kiribati, New Caledonia, Papua New Guinea, Samoa, Tokelau and Tonga

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