Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

A BRIEF REVIEW ON CHIKUNGUNYA

Megha Mahaver*, Neha Sharma, M.P. Khinchi, Mohd. Shahid Khan, Ashiya Ansari

Department of Pharmaceutical Chemistry, Kota College of Pharmacy, Kota, Rajasthan, India.

ABSTRACT-

Chikungunya is an infection caused by the Chikungunya virus. Chikungunya is an arthropod-borne virus transmitted mainly by Aedesspecies mosquitoes. Only the female are infective since they need blood meals for egg formation. Chikungunya virus (CHIKV) is an alpha virus from the Togaviridae family, which is transmitted by two types of mosquitos: Aedesalbopictus and Aedesaegypti. They mainly bite during the day, and causes epidemic tropical and subtropical countries. CHIKV is a positive-sense, single-stranded RNA virus of about 11.8 kb. There are three main genotypes, West African, Central/East African (C/EA), and Asian, the names reflecting the initial geo-graphic restriction of each type. The disease was first identified in 1952 in Tanzania. The term is from the Kimakonde language and means "to become contorted". This disease was first detected in 1952 in Makonde Plateau, which is the border area between Mozambique and Tanzania. This name of Chikungunya actually meant "that which bends up" which was derived from a Makonde word. The virus may circulate within a number of animals including birds and rodents. Chikungunya is an infection that is carried by a human which is transmitted between humans by mosquitoes. This was in reference to the stooped posture of the patient as a result of the joint pain which was a symptom of this disease. The identification of temporal windows with epidemic risk at different spatial locations is key to guiding mosquito population control campaigns

Key Words: *Chikungunya virus, Sign & Symptoms, Causes,Transmission, Mechanism, Diagnosis, Prevention, WHO Response, Treatment & Clinical management, Prognosis, Epidemiology, Conclusion*

INTRODUCTION

Chikungunya is an infection caused by the chikungunya virus (CHIKV). These typically occur two to twelve days after exposure. Other symptoms may include headache, muscle pain, joint swelling, and a rash. Most people are better within a week; however, occasionally the joint pain may last for months. The risk of death is around 1 in 1,000. The very young, old, and those with
other health problems are at risk of more severe disease. The virus is spread between people by two types of mosquitos: *Aedesalbopictus* and *Aedesaegypti*. Diagnosis is by either testing the blood for the virus's RNA or antibodies to the virus.[1]

Corresponding author
Megha Mahaver
Department of Pharmacology, Kota college of Pharmacy, Kota
Sp-1 RIICO Industrial Area, Ranpur, Kota
Mob. 7376522253

The symptoms can be mistaken for those of dengue fever and Zika fever. After a single infection it is believed most people become immune.The best means of prevention is overall mosquito control and the avoidance of bites in areas where the disease is common.This may be partly achieved by decreasing mosquitoes' access to water and with the use of insect repellent and mosquito nets.. The incubation period, defined as the time from viral exposure to symptom onset, ranges from 1 to 12 days. Acute symptoms are typically self-limiting, lasting from 3 to 10 days. Although most individuals fully recover after acute illness, some experience chronic or recurrent symptoms. Approximately 12% to 18% of affected individuals develop painful arthritis that persists for several months to years. One study reported that up to 60% of patients experienced persistent arthritis. Although

death from CHIKV infection is rare, severe manifestations, such as meningoencephalitis, myopericarditis, and bleeding disorders, may sometimes be life-threatening. Individuals at risk for more severe illness include the very young (neonates), the elderly (>65 years), and those with comorbidities (eg, cardiovascular or respiratory disease, hypertensitivity).[2]

The WHO regional office for SE Asia has developed a regional strategy consisting of six key components. The six components of the regional strategy are:

- Strengthening surveillance system for prediction, preparedness, early detection and response to chikungunya outbreaks.
- Improvement in early case detection and case management of chikungunya fever.
- Integrated vector management (IVM).
- Social mobilization and communication.
- Partnerships.
- Operational research.

This guideline for the prevention and control of chikungunya fever (CF) is intended for use by all peripheral health workers in the Region.

Sign & Symptoms

- Chikungunya is characterized by an abrupt onset of fever frequently accompanied by joint pain muscle pain, headache, nausea, fatigue and rash.
- Occasional cases of eye, neurological and heart complications have been reported, as well as gastrointestinal complaints.
- Serious complications are not common, but in older people, the disease can contribute to the cause of death.
- Majority of infected people become symptomatic Incubation period usually 3–7 days (range 1–12 days).
- Acute onset of fever and polyarthralgia are the primary clinical findings.
- Other Symptoms, myalgia, arthritis, conjuctivities, nausea, vomiting, maculopapular rash.
- Lymphopenia, thrombocytopenia, elevated creatinine, and elevated hepatic transaminases are the most common clinical laboratory findings.
- Acute symptoms typically resolve within 7–10 days. Rare complications include uveitis, retontis, myocarditis, hepatitis, nephritis, bullous skin lesion, hemorrhage, meningoencephalitis, myelitis, Guillain-Barre syndrome and cranial nerve palsies.
- Persons at risk for severe disease include neonates exposed intrapartum, older adults (e.g., > 65 years), and persons with underlying medical conditions (e.g., hypertension, diabetes, or cardiovascular disease).
- Some patients might have relapse of rheumatologic symptoms (e.g. polyarthralgia, polyarthritis, tenosynovitis) in the months following acute illness.
- Typical disease symptoms in most patients (> 85%) include abrupt febrile illness (temperature usually > 38.9!C)and a maculopapular rash with articular pains and may be linked to direct or indirect effects of viral replication in these tissues.
- These rare cases have been associated with 50% of neonates born from mothers having detectable CHIKV peripartum viremia. Infected neonates endured encephalopathy and seizures, thrombocytopenia, hypotension, ventricular dysfunction, pericarditis, and hyperechoic coronary arteries.
- Moreover, white matter lesions, parenchymal hemorrhages, and early cytotoxic edema have been observed bymagnetic resonance imaging (MRI), and viral RNA was also detected in the spinal fluid.
- The 2005–2006 epidemic inLa Re' union was the first time that severe adult cases and deaths due to CHIKF were documented.
- These severe cases occurred inthose with underlying medical conditions (cardiovascular, neurological,and respiratory disorders).
- Most patients presented aglycemic impairment that revealed diabetes mellitus in 20% ofthe severe cases, often

associated with elevated levels of liverenzymes.

- Notably, there was a 22% increase in adult patientswith Guillain–Barre´ syndrome that required respiratory supportduring the La Reunion outbreak.
- Particularly in the elderly over 60 years of age, CHIKV hadprofound acute arthritogenic activities that could have contributedto chronic incapacitating arthritis described in otheralphaviral diseases.[3]
- .Rheumatic manifestations in up to 50% of the adult patient(6 months to several years postinfection) typically consistedof a febrile arthritis mainly affecting the extremities (ankles, wrists, phalanges).
- Moreover, patients with post-CHIKV rheumatoid arthritis(RA)-like illnesses were also reported.
- The development of progressive erosive arthritis was also reportedin some studies. However, in contrast towhat is known in canonical autoimmune RA, the levels ofrheumatoid factor (RF) and anti-cyclic citrullinatedpeptide(anti-CCP) antibodies were not elevated, thereby suggesting that post-CHIKV arthritis was achronic inflammatory erosive arthritis.
- Although most chikungunya virus infections result in fever and arthralgia, other clinical manifestations can occur.
- Atypical or severe clinical manifestations can be due to the direct effects of the virus, immunologic response to the virus, drug toxicity, or diseases unrelated to chikungunya virus infection.
- Some atypical or severe manifestations are more common in certain groups. For example, vesiculobullous lesions, febrile seizures, and meningoencephalitis have been reported in infants and young children.
- Since many atypical and severe clinical manifestations will be unrelated to chikungunya virus infection, healthcare providers should consider and evaluate for other etiologies.[4]

Causes

Chikungunya virus, also referred to as CHIKV, is a member of the alphavirus genus, and Togaviridae family. It is an RNA virus with a positive-sense single-stranded genome of about 11.6kb. It is a member of the Semliki Forest virus complex and is closely related to Ross River virus, O'nyong'nyong virus,. Because it is transmitted by arthropods, namely mosquitoes, it can also be referred to as an arbovirus (arthropod-borne virus).

Transmission

The virus is transmitted from human to human by the bites of infected female mosquitoes.Most commonly, the mosquitoes involved are *Aedesaegypti* and *Aedesalbopictus*, two species which can also transmit other mosquito-borne viruses, including dengue. These mosquitoes can be found biting throughout daylight hours, though there may be peaks of activity in the early morning and late afternoon. Both species are found biting outdoors.

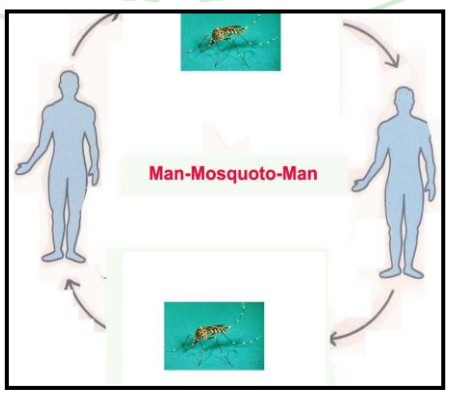

Figure.1 Transmission cycle of Chikungunya

Common modes of transmission include vertical transmission, which is transmission from mother to child during pregnancy or at birth. Transmission via infected blood products.

Other modes of transmission

- Documented rarely
  - Intrapartum from viremic mother to child
  - In utero transmission resulting in miscarriage
  - Percutaneous needle stick
  - Laboratory exposure
- Theortical concern
  - Blood transfusion
  - Organ or tissue transplantation

Mechanism

The chikungunya virus is passed to humans when a bite from an infected mosquito breaks the skin and introduces the virus into the body. The pathogenesis of chikungunya infection in humans is still poorly understood, despite recent outbreaks. It appears that *in vitro*, chikungunya virus is able to replicate in human epithelial and endothelial cells, primary fibroblasts, and monocyte-derived macrophages. Viral replication is highly cytopathic, but susceptible to type-I andII interferon. *In vivo*, in studies using living cells, chikungunya virus appears to replicate in fibroblasts, skeletal muscle progenitor cells, and myofibers.

The type-1 interferon response seems to play an important role in the host's response to chikungunya infection. Upon infection with chikungunya, the host's fibroblasts produce type-1 alpha and beta interferon (IFN-αandIFN-β). In mouse studies, deficiencies in INF-1 in mice exposed to the virus because increased morbidity and mortality. The chikungunya-specific upstream components of the type-1 interferon pathway involved in the host's response to chikungunya infection are still unknown. Nonetheless, mouse studies suggest that IPS-1 is an important factor, and that IRF3 and IRF7 are important in an age-dependent manner. Mouse studies also suggest that chikungunya evades host defenses and counters the type-I interferon response by producing NS2, a nonstructural protein that degrades RBP1 and turns off the host cell's ability to transcribe DNA. NS2 interferes with the JAK-STAT signaling pathway and prevents STAT from becoming phosphorylated.[5]

In the acute phase of chikungunya, the virus is typically present in the areas where symptoms present, specifically skeletal muscles, and joints. In the chronic phase, it is suggested that viral persistence (the inability of the body to entirely rid itself of the virus), lack of clearance of the antigen, or both, contribute to joint pain. The inflammation response during both the acute and chronic phase of the disease results in part from interactions between the virus and monocytes and macrophages. Chikungunya virus disease in humans is associated with elevated serum levels of specific cytokines and chemokines. High levels of specific cytokines have been linked to more severe acute disease: interleukin-6 (IL-6), IL-1β, RANTES, monocyte chemoattractant protein 1 (MCP-1), monokine induced by gamma interferon (MIG), and interferon gamma-induced protein 10 (IP-10). Cytokines may also contribute to chronic chikungunya virus disease, as persistent joint pain has been associated with elevated levels of IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF).[36] In those with chronic symptoms, a mild elevation of C-reactive protein (CRP) has been observed, suggesting ongoing chronic inflammation.[6] However, there is little evidence linking chronic chikungunya virus disease and the development of autoimmunity.

Diagnosis

Chikungunya is diagnosed on the basis of clinical, epidemiological, and laboratory criteria. Clinically, acute onset of high fever and severe joint pain would lead to suspicion of chikungunya.

Epidemiological criteria consist of whether the individual has traveled to or spent time in an area in which chikungunya is present

within the last twelve days (i.e. the potential incubation period). Laboratory criteria include a decreased lymphocyte count consistent with viremia. However a definitive laboratory diagnosis can be accomplished through viral isolation, RT-PCR, or serological diagnosis.[7]

Virus isolation provides the most definitive diagnosis, but takes one to two weeks for completion and must be carried out in biosafety level III laboratories. The technique involves exposing specific cell linesto samples from whole blood and identifying chikungunya virus-specific responses. RT-PCR using nested primer pairs is used to amplify several chikungunya-specific genes from whole blood, generating thousands to millions of copies of the genes in order to identify them. RT-PCR can also be used to quantify the viral load in the blood. Using RT-PCR, diagnostic results can be available in one to two days.

Serological diagnosis requires a larger amount of blood than the other methods, and uses an ELISA assay to measure chikungunya-specific IgM levels in the blood serum. One advantage offered by serological diagnosis is that serum Ig-M is detectable from 5 days to months after the onset of symptoms, but drawbacks are that results may require two to three days, and false positives can occur with infection due to other related viruses, such as o'nyong'nyong virus and Semliki Forest virus.

Presently, there is no specific way to test for chronic signs and symptoms associated with Chikungunya fever although nonspecific laboratory findings such as C reactive protein andelevated cytokines can correlate with disease activity.[8]

Prevention

- No vaccine or medication is available to prevent chikungunya virus infection ordisease.
- Reduce mosquito exposure.
- Use air conditioning or window/door screens.
- Use mosquito repellents on exposed skin.
- Wear long-sleeved shirts and long pants.
- Wear permethrin-treated clothing.
- Empty standing water from outdoor containers.
- Support local vector control programs.
- People suspected to have chikungunya or dengue should be protected from further mosquito exposure during the first week of illness to reduce the risk of further transmission.
- People at increased risk for severe disease should consider not traveling to areas with ongoingchikungunya outbreaks.[9]

WHO Response:-

WHO responds to chikungunya by :

- Formulating evidence-based outbreak management plans;
- Providing technical support and guidance to countries for the effective management of cases and outbreaks;
- Supporting countries to improve their reporting systems;
- Providing training on clinical management, diagnosis and vector control at the regional level with some of its collaborating centres; and
- Publishing guidelines and handbooks on case management and vector control for Member States.
- WHO encourages countries to develop and maintain the capacity to detect and confirm cases, manage patients and implement social communication strategies to reduce the presence of the mosquito vectors.

TREATMENT & CLINICAL MANAGMENT

- No specific antiviral therapy; treatment is symptomatic.
- Assess hydration and hemodynamic status and provide supportive care as needed
- Evaluate for other serious conditions (e.g., dengue, malaria, and bacterial infections) and treat or manage appropriately.
- Collect specimens for diagnostic testing.
- Use acetaminophen or paracetamol for initial fever and pain control.
- If inadequate, consider using narcotics or NSAIDs.
- If the patient may have dengue, do not use aspirin or other NSAIDs (e.g., ibuprofen,

naproxen, toradol) until they have been afebrile ≥48 hours and have no warning signs for severe dengue.
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy.
- Since no specific antiviral therapy is available, treatment is symptomatic.
- Assess hydration and hemodynamic status.
- Provide supportive care as needed and manage complications.
- Evaluate for other serious conditions (e.g., dengue, malaria, bacterial infection) and treat or manage appropriately.
- Use acetaminophen or paracetamol for fever and pain control.
- If inadequate, consider using narcotics or NSAIDs.

Prognosis

The mortality rate of chikungunya is slightly less than 1 in 1000.Those over the age of 65, neonates, and those with underlying chronic medical problems are most likely to have severe complications. Neonates are vulnerable as it is possible to vertically transmit chikungunya from mother to infant during delivery, which results in high rates of morbidity, as infants lack fully developed immune systems. The likelihood of prolonged symptoms or chronic joint pain is increased with increased age and prior rheumatological disease.[10]

Epidemiology

Historically, chikungunya has been present mostly in the developing world. The disease causes an estimated 3 million infections each year. Epidemics in the Indian Ocean, Pacific Islands, and in the Americas, continue to change the distribution of the disease. In Africa, chikungunya is spread by a sylvatic cycle in which the virus largely cycles between other non-human primates, small mammals, and mosquitos between human outbreaks. During outbreaks, due to the high concentration of virus in the blood of those in the acute phase of infection, the virus can circulate from humans to mosquitoes and back to humans. The transmission of the pathogen between humans and mosquitoes that exist in urban environments was established on multiple occasions from strains occurring on the eastern half of Africa in non-human primate hosts. This emergence and spread beyond Africa may have started as early as the 18th century. Currently, available data does not indicate whether the introduction of chikungunya into Asia occurred in the 19th century or more recently, but this epidemic Asian strain causes outbreaks in India and continues to circulate in Southeast Asia. In Africa, outbreaks were typically tied to heavy rainfall causing increased mosquito population. In recent outbreaks in urban centers, the virus has spread by circulating between humans and mosquitoes.[11]

CONCLUSION

CHIKV has reemerged as a major threat to global public health. The extent to which CHIKV becomes established in new regions remains to be seen; nevertheless, it seems likely that the current epidemic will continue to spread throughout much of the Americas. Unfortunately, specific treatments or vaccines against CHIKV infection are not yet available. A variety of CHIKV vaccine candidates are in development, including live-attenuated, inactivated, virus-like particles, subunit, DNA, and measles virus- and poxvirus-based vaccines. Many of these vaccine candidates have shown promising results in animal models and in phase I clinical trials in humans. Numerous antiviral compounds, monoclonal antibodies, and immunomodulatory drugs that could be used to prevent or treat CHIKV infection are also in the early stages of investigation. Thus, the reemergence of CHIKV and the enormous scale of the CHIKV-associated outbreaks have highlighted many critical research needs. These include increased surveillance for CHIKV infection or antibodies in humans and animals, increased mosquito control programs, implementation of protocols for detecting CHIKV in donated blood, organs, and tissues for transplantation, and increased basic and translational research to enhance our knowledge of CHIKV biology, pathogenesis, treatment, and prevention. In recent years there have been explosive

outbreaks of chikungunya fever in several parts of the SEA Region and elsewhere. Although the disease is self-limiting, morbidity can be very high in major outbreaks resulting in a heavy social and economic toll. The disease should be preventable and it would require a planned approach, besides knowledge and awareness of early warning signs, for prevention. Integrated vector management through the elimination of breeding sites, use of anti-adult and anti-larval measures and personal protection will contribute to preventing an outbreak. Community empowerment and mobilization is crucial for prevention and control of chikungunya. Adult mosquito control measures such as fogging often applied by the civic authorities as a single tool may not by itself contribute to the effective containment of an outbreak.

REFERENCE.

1. *"Chikungunya Fact sheet". WHO. April 2016. Retrieved 26 September 2016.*
2. *Chikungunya Virus Symptoms, Diagnosis, & Treatment". CDC. 6 April 2016. Retrieved 26 September 2016.*
3. *Thiberville, Simon-Djamel; Moyen, Nanikaly; Dupuis-Maguiraga, Laurence; Nougairede, Antoine; Gould, Ernest A.; Roques, Pierre; de Lamballerie, Xavier (2013). "Chikungunya fever: Epidemiology, clinical syndrome, pathogenesis and therapy". Antiviral Research. 99 (3): 345–370. doi:10.1016/j.antiviral.2013.06.009. ISSN 0166-3542*
4. *Powers AM, Logue CH (September 2007). "Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus". J. Gen. Virol. 88 (Pt 9): 2363–77. doi:10.1099/vir.0.82858-0. PMID 17698645.*
5. *Strauss and Strauss, 1994; Leunget al., 2011; Rashad et al., 2014.*
6. *Schwartz and Albert, 2010; Leung et al., 2011; Rashadet et al., 2014.*
7. *Chikungunya Virus Infections". New England Journal of Medicine. 373: 93–95. doi:10.1056/NEJMc1505501.*
8. *Santosh SR, Dash PK, Parida MM, Tiwari M and Lakshmana Rao PV. Comparative full genome analysis revealed E1: A226V shift in 2007 Indian Chikungunya virus isolates. Virus Research. 2008 Jul; 135(1): 36-41.*
9. *Caglioti, C; Lalle, E; Castilletti, C; Carletti, F; Capobianchi, MR; Bordi, L (July 2013). "Chikungunya virus infection: an overview.". The new microbiologica. 36 (3): 211–27. PMID 23912863.*
10. *Mavalankar D, Shastri P, Bandyopadhyay T, Parmar J, Ramani KV (2008). "Increased Mortality Rate Associated with Chikungunya Epidemic, Ahmedabad, India". Emerging Infectious Diseases. 14 (3): 412–5. doi:10.3201/eid1403.070720. PMC 2570824Freely accessible. PMID 18325255.*
11. *Seppa, Nathan (2 Jun 2015). "Chikungunya is on the move". Science News. Retrieved 13 June 2015.*