

CHIKUNGUNYA FEVER: A GLOBAL BURDEN INCLUDING BANGLADESH

MEDICINE

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ABSTRACT

Chikungunya fever is an acute illness caused by chikungunya virus (CHIKV) belonging to the Alphavirus genus of the Togaviridae family. The virus is transmitted by mosquitoes, mostly *Aedes aegypti* and *Aedes albopictus*. Chikungunya fever is primarily tropical disease occurring in Africa, Asia and Indian Ocean islands. From the arrival of the Chikungunya virus (CHIKV) in the Americas in 2013 until March 2016, approximately two million cases of the disease have been reported. In Brazil, the virus was first identified in 2014 and thousands of people have been affected. It is also not uncommon in Bangladesh. In 2008, 2009, 2011, 2014, 2016 and also 2017, several sporadic cases have been reported from different parts of the country. So, burden of Chikungunya virus infection is increasing day by day. This fever is highly symptomatic; characterized by fever, petechial or maculopapular rash and severe arthralgia and arthritis. The disease is self-limiting but a part of the patients suffers from a long-lasting arthritis similar to rheumatoid arthritis. On the other side, it is difficult to distinguish chikungunya and dengue based on clinical findings alone. Both the viruses transmitted by the same mosquitoes. So, underdiagnosis or misdiagnosis of chikungunya everywhere. To prevent further outbreak, awareness by the medical personnel, minimizing the vector density and taking appropriate control measures in the hospital setting is crucial.

KEYWORDS:

Chikungunya fever, Arthropod borne, Arthralgia, Arthritis, Rash, IgM antibody, RT-PCR.

Introduction

Chikungunya fever (CF) is a viral illness which is mosquito-borne that caused by an arbovirus transmitted by the *Aedes* mosquitoes.^{1,2} The name is derived from the 'makonde' dialect which means 'that which bends up', indicating the physical appearance of a patient with severe clinical features. The fever locally also named as 'Langra Jor'.³

Causative agent

Chikungunya fever is caused by virus of same name (CHIK virus in short) which is an RNA virus that belongs to the *Alphavirus* genus of the *Togaviridae*. It is a single stranded RNA virus, heat labile and sensitive to temperatures above 58° Celsius. Three lineages with distinct genotypic and antigenic characteristics have been identified: two phylogenetic-groups from Africa and one from Asia.^{3,4}

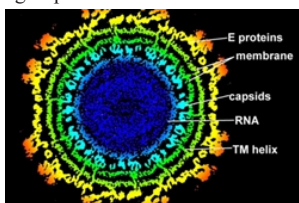


Fig-1: Chikungunya virus

Vector

Aedes aegypti is the common vector responsible for transmission in urban areas whereas *Aedes albopictus* has been implicated in rural areas.⁴ *Aedes aegypti* is the main vector of transmission of Chikungunya in Bangladesh. However, *Aedes albopictus* has also been found to be playing a part in some areas.³ The *Aedes* mosquito breeds in domestic settings such as flower vases, water-storage containers, air coolers, etc. and peri-domestic areas such as construction sites, coconut shells, discarded household junk items (tyres, plastic and metal cans) and bites during day time.⁴



Fig-2: *Aedes aegypti* & *Aedes albopictus*

Outbreak

Recently, it has also been shown that viremia are quite high and infected mosquitoes could transmit the disease to more than one person since small amounts of blood in the proboscis still carry large quantity of virus. *Aedes* mosquitoes take multiple feeds per day and it would also result in small focal outbreaks. In the initial part of outbreak, individual population is not protected which could result in larger outbreaks.³

History

Chikungunya virus (CHIKV) was first isolated from the blood of a febrile patient in Tanzania in 1953. Since then it has been identified repeatedly in west, central and southern Africa and many areas of Asia. Since 1960, the outbreaks of the disease in South Eastern Asia were reported from India, Sri Lanka, Myanmar, Thailand, Indonesia, Philippines and Malaysia. In the Indian sub-continent, first isolation of the virus was done in Calcutta during 1963. Subsequently, there have been several reports of Chikungunya virus infection during 60's in different parts of India viz: Kolkata, Pondicherry and Chennai in Tamil Nadu, Rajamundry, Vishakapatnam and Kakinada in Andhra Pradesh, Sagar in Madhya Pradesh and Nagpur in Maharashtra. The last outbreak of Chikungunya infection in 20th century occurred in India during 1973. Thereafter, after a quiescence of 2-3 decades during 2006 reports of large scale outbreaks of fever caused by Chikungunya in several parts of India have confirmed the re-emergence of this virus in the country with 13.9 million clinically suspected and 2001 laboratory confirmed cases.⁵ In Bangladesh, The 1st one was in Poba upozilla in Rajshahi district affecting 32 people in 2008. The 2nd outbreak was in Shathiya upazilla of Pabna in 2009.⁶ In late October 2011, a local health official from Dohar Sub-district, Dhaka District, reported an outbreak of undiagnosed fever and joint pain and that was Chikungunya.⁷ In the Americas, from 2013 to March 2016, approximately two million cases of the disease have been reported. In Brazil, the virus was identified in 2014 and thousands of people have been affected.⁸

Epidemiology

A high vector density is seen in the post monsoon season that enhances the transmission. Chikungunya fever epidemics display cyclical and seasonal trends. There is an inter-epidemic period of 4-8 years (sometimes as long as 20 years). Outbreaks are most likely to occur in post-monsoon period when the vector density is very high. During inter-epidemic periods, a number of vertebrates have been identified as reservoirs. These include monkeys, rodents, birds, and other vertebrates. There is no significant sex predilection and the virus

causes illness in almost all age groups.³

Re-emergence

The re-emergence of Chikungunya may be due to a variety of social, environmental, behavioral and biological factors. Lack of herd immunity may have probably led to its rapid outbreak across several states of India and also in Bangladesh.⁵

Transmission

The human infections are acquired by the bite of infected *Aedes aegypti*/*Aedes albopictus* mosquitoes, which are day biters and epidemics are sustained by human-mosquito-human transmission. The incubation period (time from infection to illness) can be 2-12 days, but is usually 3-7 days.³

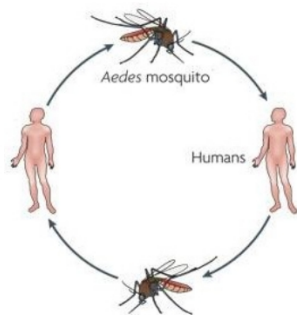


Fig-3: Transmission of Chikungunya virus

Pathogenesis

In humans, the bite of an infected mosquito leads to deposition of Chikungunya virus (CHIKV) in the subcutaneous tissue resulting in viremia (10^7 to 10^{12} RNA copies/ml).^{2,5} At the early stage of the disease, the organs targeted for chikungunya virus replication were lymphoid tissues, liver, CNS, joints, and muscle, and the persistence of chikungunya virus could be found later in the lymphoid organs, liver, joints, and muscle, macrophages being the main reservoir.² A febrile response signals viral replication with release of inflammatory cytokines. Replicating virus in the synovial fluid, endosteum and periosteum of the affected bones induce complement activated immune complex mediated arthritis. There is no synovial lymphocytosis, bone or cartilage destruction. CHIKV can also cause CNS manifestations in the form of encephalitis, encephalomyelitis and optic neuritis.⁵

Clinical presentations

CHIK virus causes an acute febrile illness with an incubation period of 3-7 days (can be 2-12 days). Fever, arthralgia with or without rash are the hallmark of Chikungunya fever.

Table I

Clinical features of Chikungunya fever^{3,4}

Common in all age group	Infrequent	Seen in children
Fever (92%)	Stomatitis (25%)	Photophobia
Arthralgia (87%)	Photosensitive	Retro-orbital pain
Backache (67%)	Hyperpigmentation (20%)	Vomiting
Headache (62%)	Oral ulcers (15%)	Diarrhea
Rash (50%)	Exfoliative dermatitis (5%)	Mental confusion
Arthritis		Signs of meningeal irritation

Fever: The fever varies from low grade to high grade, lasting usually for 24 to 48 hours. It rises abruptly in some, reaching 39-40°C, with chills and rigor, no diurnal variation, usually subsides with use of antipyretics.³

Arthralgia & arthritis: The joint symptoms usually start with arthralgia or arthritis. Involvement is symmetric and often ankles wrists and small joints of the hand are the worst affected. Migratory polyarthritides with effusions may be seen, but resolves in the majority. Larger joints like knee and shoulder and spine were also involved. Pain tends to be worse in the morning, relieved by mild exercise and exacerbated by aggressive movements. The pain may be relieved for 2-3 days and then reappear in a saddle back pattern.³



Fig-4: Chikungunya arthritis

Backache: The classical bending phenomenon was probably due to the lower limb and back involvement which forced the patient to stoop down and bend forward.⁴

Headache: One of the prodromal symptom and could persist during the 1st week of illness.⁵

Rash: Transient maculopapular rash is seen in up to 50% patients. The maculopapular eruption persisted for more than 2 days in approximately 10% cases. Intertriginous aphthous-like ulcers and vesiculobullous eruptions were noticed in some. A few persons had angiomatous lesions and fewer had purpuras. Epidermolysis bullosa was an observation in children.⁴



Fig-5: Maculopapular rash in Chikungunya

Stomatitis & oral ulcers: Stomatitis was observed in 25% and oral ulcers in 15% of patients.⁴

Photosensitive hyperpigmentation: Nasal blotchy erythema followed by photosensitive hyperpigmentation (20%) was observed more commonly in the recent epidemic.⁴

Exfoliative dermatitis: Exfoliative dermatitis affecting limbs and face was seen in around 5% cases.⁴

Photophobia & retro-orbital pain: Though commonly seen in dengue cases it may be encountered in few cases of Chikungunya.⁵

Neurological manifestations: Neurologic manifestations such as encephalitis, meningo-encephalitis, meningeal syndrome, febrile seizures, acute encephalopathy, Guillain-Barre syndrome and myelitis were reported.^{3,4}

Ocular manifestations: Neuro-retinitis and uveitis in one or both eyes may occur. The main ocular manifestation associated with the recent epidemic outbreak of chikungunya virus infection in South India included granulomatous and nongranulomatous anterior uveitis, optic neuritis, retro-bulbar neuritis, and dendritic lesions. Majority of the patients recover with good vision.^{3,4}

Chikungunya in infants & children

Clinical manifestations in children are very variable ranging from asymptomatic to severe disease. Children can have minor haemorrhagic manifestations, lymphadenopathy swelling of eyelids, pharyngitis and watery stools. Unusual clinical features include seizures, altered sensorium, blindness due to retro-bulbar neuritis and acute flaccid paralysis. Infants can have constitutional symptoms like, lethargy, irritability and excessive crying in addition to fever. The most characteristic feature of the infection in infants was acrocyanosis and symmetrical superficial vesicobullous lesions. Erythematous asymmetrical macules and patches were observed which later progressed to morbilliform rashes. The face and oral cavity was spared in all observed patients. Viruses may be detected in cerebrospinal fluid.⁵

Chikungunya in neonate

During the outbreak in Réunion Island, 38 neonatal cases were studied retrospectively. All of them developed symptoms between Day 3 and Day 7 (mean, Day 4). Mean interval between the onset in mothers and in the babies was five days. Frequent and prominent signs in the neonates were rashes (82%), fever (79%) and peripheral edema (58%).⁹ Poor feeding, pain, seizures, meningoencephalitis, and echocardiographic abnormalities are also observed in the newborn.³ Raised serum aspartate aminotransferase level (77%), reduced platelet count (76%), diminished prothrombin value (65%), and low lymphocyte count (47%) were observed. Seizures and hemorrhagic and hemodynamic complications were noted. Positive RT-PCR in CSF and abnormalities on magnetic resonance imaging (MRI) studies of the brain were noted in high percentage of neurological cases, (22/24 and 14/25 respectively).⁹ Mothers are encouraged to breast feed their infants.³

Chikungunya in Pregnancy

There have been cases of mother-to-fetus infection which have occurred between 3 and 4.5 months into pregnancy. Vertical transmission has been observed during near-term deliveries in the context of intrapartum viremia.⁹ Mothers afflicted with Chikungunya fever in the perinatal period (–4 days to +1 days before/after delivery) can transmit Chikungunya fever to neonates by vertical transmission. Caesarean section does not appear to prevent transmission.³ There was 19 cases of vertical transmission out of 39 women (48.7%) with intrapartum viremia were recorded. In another study, three out of nine miscarriages before 22 weeks of gestation were attributed due to Chikungunya virus infection (RT-PCR positive in amniotic fluid).⁹

Criteria for the Identification

Clinical criteria³

- Acute onset of fever >38.5°C
- Severe arthralgia/arthritis not explained by other medical conditions

Epidemiological criteria³

- Residing or having visited epidemic areas
- Having reported transmission within 15 days prior to the onset of symptoms

Laboratory Criteria³

At least one of the following tests in the acute phase:

- Virus isolation by Cell Culture
- Presence of viral RNA by Real Time PCR (RT-PCR) (Within 5 days of onset of illness)
- Presence of viral specific IgM antibody in single serum sample collected within 5 to 28 days of onset fever
- Four-fold Rise of IgG antibody in samples collected at least three weeks apart (1st sample after 7 days)

Case definitions

Chikungunya Fever should be suspected when a person develops sudden onset of fever, joint manifestations and rash (characteristic triad).^{3,4}

Possible case: A patient meeting clinical criteria^{3,4}

Probable case: A patient meeting both the clinical and epidemiological criteria^{3,4}

Confirmed case: A patient meeting the laboratory criteria, irrespective of the clinical presentation^{3,4}

High risk group

a) Co-morbid condition: Hypertension, Diabetic, CAD/CVD, Geriatric age, Pregnancy, COPD³

b) Co-infection: Dengue, Tuberculosis, Enteric fever, Pneumonia, HIV, Malaria³

Laboratory diagnosis

Routine Laboratory Investigations:³

- **CBC:** Leucopenia with lymphocyte predominance, thrombocytopenia rare.
- **ESR & CRP:** Elevated
- **SGPT:** Elevated

Specific Laboratory Investigations:³

- **Virus isolation:** By cell culture or Real Time PCR (RT-PCR) only done in IEDCR(Institute of Epidemiology, Disease Control and Research) (within 5 days of onset of illness)
- **IgM antibody (Presence):** Sample collected within 5-28 days of onset of fever
- **IgG antibody (Four-fold rise):** Sample collected at least three weeks apart (1st sample after 7 days of onset of fever)

Differential diagnosis

Chikungunya fever may not have the typical manifestations or it may co-exist with other infectious diseases like dengue fever or non-infectious diseases like rheumatoid arthritis.

I. Dengue fever: Severe back pain with purpuras or active bleeding might suggest dengue fever. Confirmatory laboratory diagnosis is possible.³

II. Reactive arthritis: In general, any arthritis that follows a febrile gastrointestinal or genitourinary infection (triggering microbes) is considered a reactive acute inflammatory arthritis if it lasts less than six months. The hallmark feature is enthesitis where collagenous structures such as tendons and ligaments insert into bone are involved. Oral mucosal ulcers are seen.³

III. Serum sickness illness: Polyarthritis may be associated with a serum sickness type reaction caused by vaccine, medication or other viral infections³

IV. Rickettsial disease: Can present with fever, rash and joint pains. Confirm by serology.³

V. Rheumatic fever: More common in the children and presents with fleeting (migratory) polyarthritis predominantly affecting the large joints. Modified Jones criteria should be the basis for diagnosis. Raised ASO titer and a history of recurrent sore throat are other points to be noted.³

VI. Malaria: Patient can present with high fevers and may also complain of joint pains. Periodicity of fever and alteration of consciousness/seizures should prompt a diagnosis for malaria.³

VII. Leptospirosis: Severe myalgia localized to calf muscles with conjunctival congestion/ or subconjunctival haemorrhage with or without oliguria or jaundice in a person with history of skin contact to contaminated water would suggest Leptospirosis.³

Chikungunya and Dengue infection: Overlap & confusion

It is difficult to distinguish chikungunya and dengue based on clinical findings alone. Both the viruses transmitted by the same mosquitoes. Chikungunya virus more likely to cause high fever, severe polyarthralgia, arthritis, rash, and lymphopenia. On the other side, Dengue virus more likely to cause neutropenia, thrombocytopenia, hemorrhage, shock, and death.³

Table II

Clinical & Laboratory features of Chikungunya virus infection compared with Dengue virus infection^{5,9}

Features	Chikungunya	Dengue
Clinical signs & symptoms		
Fever Onset Duration	Acute 2-4 days	Gradual 5-7 days
Rash	Maculopapular	Maculopapular Petechial
Arthralgia Frequency Duration	Frequent May last more than a month	Less common Short duration
Hypovolemic shock	Rare	Common
Laboratory parameters		
Leukopenia	Common	Infrequent
Thrombocytopenia	Infrequent	Common
Hematocrit	Normal	High

During the outbreak from 2006-2009, there are reports of co-infection of Dengue and Chikungunya received from various States. This is not very unusual as both Dengue and Chikungunya are arbovirus diseases,

transmitted by the same *Aedes* mosquitoes. Available literature also confirm co-infection of Dengue and Chikungunya virus.⁵

Sequela

Chikungunya is a self limiting disease however in severe form of the disease sequelae can be seen. It has been observed that 90% joint symptoms resolve completely. However, some have either episodic stiffness and pain, persistent stiffness without pain or persistent painful restriction of joint movements.³ where a retrospective study has shown complete resolution in 87.9 %, 3.7 % had episodic stiffness and pain , 2.8% had persistent stiffness without pain and 5.6% had persistent painful restriction of joint movements. Enthesopathy and tendinitis of tendoachilles was observed in up to 53% of those who had musculoskeletal involvement. Neurological, emotional and dermatologic sequelae are also described.⁴

Prognosis & Outcome

Acute symptoms typically resolve within 7–10 days. Some patients might have relapse of rheumatologic symptoms (e.g., polyarthralgia, polyarthritis and tenosynovitis) in months following acute illness. In variable proportions of patients, joint pain may persist for months to years. Rare complications include uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barre syndrome, and cranial nerve palsies may develop.³

Management

Patients with suspected Chikungunya should be managed as dengue until dengue has been ruled out. For adequate management plan, chikungunya fever is classified into 3 categories based on severity of clinical presentation:³

Table III
Classify Chikungunya fever based on clinical presentation³

Mild case (Home based)	Moderate case (Home based)	Severe case (Hospital based)
- Low grade fever - Mild arthralgia - Mild focal myalgia - General weakness - Skin rash/itching	- Low to high grade persistent fever - Moderate arthralgia/arthritis - Generalized myalgia³ - Hypotension - Mild bleeding - Retro-orbital pain - Oliguria	- Persistent high grade fever - Severe arthralgia/ arthritis even after 3 days of symptomatic treatment - Persistent vomiting/diarrhea - Oliguria (<500 ml within 24 hours) - Altered sensorium - Bleeding (GI bleeding due to use of drugs e.g. analgesics) - Shock due to persistent vomiting and diarrhea - Infants/>60 years of age - Pregnancy/High risk gr.

Table IV
Home & Hospital management of Chikungunya Fever³

Home Management	Hospital Management
A. Non-Pharmacological - Consume plenty of water with - Electrolytes (approx. 2 liters with salt) - Adequate rest in a warm environment - Cold compresses may help in reducing joint damage (avoid heat) - Mild forms of exercise and physiotherapy are recommended in recovering persons B. Pharmacological - Take paracetamol tablets during periods of fever (up to 1000 mg tablets four times daily) Children may be given 50-60 mg per kg body weight per	A. Non-Pharmacological - Cold compresses may help in reducing joint damage (avoid heat) - Mild forms of exercise and physiotherapy are recommended in recovering persons B. Pharmacological - Assess for dehydration and institute proper rehydration therapy (5% DNS, normal Saline, & baby saline for pediatric cases) - Take paracetamol tablets during periods of fever (up to 1000 mg tablets four times daily) Children may be given 50-60 mg per kg body weight per day in divided doses. - Aspirin or NSAIDs should be avoided during first 10 days.

day in divided doses.	NSAIDs can be used in Chikungunya only when Dengue fever is adequately excluded
- Avoid self-medication with aspirin or NSAIDs. - Antihistamines can be used for itching.	- Antibiotics can be used to treat secondary bacterial infection - Antihistamines can be used for itching - Steroid has no role in acute stage - Consult with ophthalmologist or dermatologist if needed

Prevention & Control

Patient when infected can spread the infection through mosquito bite to another person. It is important to break this transmission by minimizing the vector density by community participation and taking appropriate control measures in the hospital setting by following measures:⁴

Minimizing vector population	Minimizing vector-patient contact
- Reduce larval habitats in and around the houses - Remove stagnant water from all junk items lying around in the household - Stagnating water in flower pots or similar containers should be changed daily or at least twice weekly - Drain all water stagnating after rains - Fogging and street sanitation with proper waste management - Insecticide sprays may use in vector areas around the house	- No need to isolate the patient - Have the patient rest under bed-nets, preferably permethrin impregnated nets - Have other members in the house sleep under similar bed nets - Have the patient as well as other members of the household wear full sleeves to cover extremities, preferably bright colored clothes - Wire-mesh/nets on doors and windows - Insecticide sprays/coils/mats/vaporizers may use in bed rooms, bathrooms, kitchens, nooks and corners.

Vaccine against Chikungunya

Currently there are no vaccines available in the market for preventing Chikungunya disease. However scientists have developed a working vaccine for Chikungunya. The vaccine looks like Chikungunya virus to the immune system which in turn produces antibodies against it. From the experiments on monkeys it was found that these antibodies can prevent Chikungunya infection. Monkeys were injected with the vaccine and then after 15 weeks they were injected with Chikungunya virus. It was found that the vaccine offered 100% protection from the disease. The next step for this vaccine is human testing.⁶

Present Situation in Bangladesh

In 2016, from August-September, blood was collected from every 10th house of Sutrapur, Dhanmondi, Motijheel and Mohakhali areas. More than 600 samples were collected from people between 15-60 years of age. The report stated that, 33% people were infected with chikungunya virus.¹⁰ In 2017, from February-April, Chikungunya fever was increased in Dhaka city.¹¹ In the same year, from April-May, 196 cases of chikungunya has so far been confirmed (IEDCR statement).¹²

Recent steps by WHO and Government of Bangladesh

WHO recently (28th February, 2017) provided support to the Ministry of Health to strengthen the capacity of doctors and nurses on the clinical management and prevention of Dengue, Dengue Hemorrhagic Fever and Chikungunya. A total of eight training sessions were held; seven at the divisional level and one at the Dhaka Medical College Hospital. The divisional level trainings had 32 participants (16 doctors and 16 nurses) who discussed the epidemiology, clinical manifestation, pathogenesis, diagnosis, investigation, clinical management and prevention of Dengue, Zika & Chikungunya viruses. At Dhaka Medical College Hospital, a training of trainers was held for 14 doctors and 14 nurses from 7 divisions who later carried out cascade trainings in their own divisions for 112 doctors & 112 nurses at district & upazilla-level hospitals. Trainees are now equipped to treat and manage Dengue & Dengue Hemorrhagic Fever cases.¹³

Conclusions

In recent years there have been explosive outbreaks of chikungunya fever in several parts of the South East Area (SEA) Region including Bangladesh. Within less than a decade, Chikungunya virus has become a new giant among arboviral diseases, next to dengue fever. This emergence is mostly the result of increasing urbanization & lack of

hygiene conditions that facilitating breeding of the mosquito vectors and a variety of social, environmental, behavioral and biological factors. Although the disease is self-limiting, morbidity can be very high in major outbreaks. Most of the cases remain undiagnosed or misdiagnosed due to lack of awareness and diagnostic facilities. At the same time, specific treatment is not available and there is no vaccine for the prevention of Chikungunya fever. So, 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.

Future Challenges

Despite remarkable & impressive progress in understanding of Chikungunya virus infection with lots of research & training, further study should be continued regarding:

- Identify neonates who born from chikungunya viremic mothers and reduce morbidity & mortality of them.
- Evaluate any medicine which eliminate the virus or protect body from bad effect of virus.
- Discover vaccine for prevention of responsible virus.

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