J MEDICINE 2017; 18: 92-108

Review Article

Chikungunya

MD. ROBED AMIN,[1] MD. MUJIBUR RAHMAN,[2] QUAZI TARIKUL ISLAM[3]

Introduction:

Chikungunya is a mosquito-borne illness of humans caused by the chikungunya virus (CHIKV in short) that belongs to the *Alphavirus* genus of the family *Togaviridae*.[1] The disease is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes which are the main vectors of chikungunya in Asia and the Indian ocean islands. The name 'chikungunya' derives from a root verb in the Kimakonde language, meaning "to become contorted" and describes the stooped appearance of sufferers with joint pain.[2] The disease typically consists of an acute illness with fever, skin rash, and incapacitating arthralgia. The disease may evolve into three phase. The acute phase is from day 1 to day 21. The subacute phase is from day 21 to day 90. The chronic phase starts from 3 months to onwards.[3]

The joint pain in the different phases of Chikungunya disease causes important physical incapacity that significantly impacts the quality of life of affected patients. The suffering related to the infection is not limited to pain; a significant portion of patients experience mental health and sleeping disorders and mood swings.[4,5] The chronic joint complaints in the chronic phase can assume the patterns of other chronic inflammatory diseases.

There are few studies or guidelines in the literature regarding the approach to pain treatment.

Paracetamol, non-steroidal anti-inflammatories (NSAIDs), corticosteroids, codeine, and morphine, the use of methotrexate, chloroquine, sulfasalazine and biological has also been reported in patients with chronic pain.[6,7,8,9,10,11]

Search Criteria and Methods:

An intensive search on chikungunya was done through online from 1960 onwards in English language article. The pubmed search was done through Mesh heading of chikungunya, clinical guidance, recommendation guideline. The national guidelines of different countries (e.g. Brazil French, India, and Bangladesh) were also scrutinized for making general statement and therapeutic options. The lack of quality RCT leads to search quality observation studies for making therapeutic recommendation. The level of evidence was not mentioned in this review due to lack of homogenous review criteria or lack of meta-analysis in different papers. The method used to pre-pare these recommendations was expert consensus because of the lack of literature data, or data with a low level of evidence. It had for advantage to synthesize information to define the degree of agreement within the group of selected experts. It also allowed determining the level of agreement among experts and identifying and selecting non-consensual points.

Global perspective:

The first incidence of Chikungunya virus epidemic was first came into light in 1952 with its first ravage in East Africa followed by several epidemics in Asia.[10] Including Philippines (1954, 1956 and 1968), Thailand, Cambodia, Vietnam, India, Myanmar and Srilanka. The re-emergence of CHIKV infection was also found in democratic Republic in Congo in 1999-2000, Java in 2001-2003 and in the islands of South western Indian ocean i. e Myotte, Seychilles and Mauritus.[13] Imported cases from these islands were found in Europe in the beginning of 21st century. According to Euro-surveillance, 2006; 307 cases were found in France, 197 in Italy, 17 cases in Germany, 9 in United Kingdom, 12 in Belgium and 1 in each Czech Republic and Norway.[3,12,13] CHIKV arrived in the America in 2013. From March, 2013 to March, 2016 approximately two million cases of Chikungunya virus infection have been reported in South American regions including Brazil, Columbia, Venezuela etc. In Brazil, the virus was first identified in 2014 and thousands of people became infected.

In the Indian sub-continent, first isolation of the virus was done in Kolkata in 1963 followed by several reports of CHIKV infection in different parts of India during 1960s. The first outbreak occurred in India in 1973. Then after a long inter-epidemic, period of three decade, again in 2006, a large scale outbreak of Chikungunya fever took place.[14]

1. Associate Professor of Medicine, Dhaka Medical College, Dhaka.
2. Professor of Medicine, Dhaka Medical College, Dhaka.
3. Professor of Medicine, Popular Medical College, Dhaka.

Corresponding author: Dr Md. Robed Amin, Associate Professor of Medicine, Dhaka Medical College, Room no-502, Department of Medicine, Dhaka Medical College Hospital-2, Dhaka, Bangladesh. Email-robedamin@yahoo. com. Mob: 01711725787.

The incapacitating arthralgia raised the doubt about the infection in the early period of 2006. The diagnosis was confirmed as Chikungunya virus infection with laboratory findings. During 2006, a total of 13,90. 322 clinically suspected cases of Chikungunya infection were reported from 16 states of India, which came down to an amount of 27,553 cases in 2015.[15,16] It confirmed the re-emergence of this virus in this sub-continent. It may be multifactorial, which includes social, environmental, behavioral and biological factors. In 2016, a big CHIKV epidemic affected our neighboring country India which compelled their public health system to formulate guideline to manage acute Chikungunya cases and their sequel.[14,15,16]

Fig 1: *Global distribution of Chikungunya (WHO report)*

Bangladesh Situation:

In 2006, an increase in the incidence of Chikungunya in India rationalized prompt testing of serum samples collected from febrile patients from two different surveillance projects in Dhaka, Bangladesh. However one hundred seventy-five serum samples tested were found no antibodies against Chikungunya virus[17]. In 2008, the first recognized outbreak of Chikungunya in Bangladesh was identified in Paba, Rajshahi, the northwest area of the country. Transmission appeared to be geographically limited to two villages in Paba in northwestern Bangladesh and 32 cases were identifies as having chikungunya.[18] The 2nd outbreak was in Shathiya upazilla of Pabna in 2009.[19,20]

In late October 2011, an outbreak of fever and severe joint pain was reported by a local health official in Dohar Sub-district in Dhaka District. An outbreak investigation team was deployed at the end of November where team from Institute of Epidemiology Disease Control and Research (IEDCR) and International Centre for Diarrhoeal Disease Research, (ICDDRB) of Bangladesh in Char Kushai village, Dohar, Dhaka. Data collected in all 897 households in the village in 3,840 residents with or without symptoms. Among them; 1105 (29%) of household members met the suspected case definition of chikungunya. There were no differences in attack rates by gender among children <10 years of age; however, females were more likely to report illness than males for every other age group and the differences were greatest among residents aged 31–40 years (28% of males vs 50% of females) and 41–50 years (29% vs 53%). Sixty-four percent of households had at least one suspected case, while 15% had three or more. Twenty-two percent of suspected cases (245/1105) provided blood for testing and 80% (196/245) of them had IgM antibodies against Chikungunya virus. [21] As Chikungunya infection gives life-long immunity,[22] so the consistently high attack rates by all age group in that investigation suggest that Chikungunya was new to that geographic area. A. albopictus hatched from 89% of the larvae collected in the village suggests that this vector was likely responsible for transmission during this outbreak. As A. albopictus has a tendency to breed in water compartments close to homes and to feed during the day.[23]

In 2012 an outbreak of chikungunya was reported in the village of Palpara in Tangail district, 100 km northwest of the capital, Dhaka. The IEDCR and ICDDRB teams investigated the outbreak by interviewing 1,933 individuals from 460 households. A total of 364 (18%) individuals reported having suffered from symptoms consistent with chikungunya infection. Chikungunya infection was confirmed using serology in a subset of 175 cases. The mean age of cases was 30 y (range: 0–80) and 958 (57%) of cases were female. Sixty-four percent of individuals (n = 1,238) in that study admitted to use antimosquito coils on a daily basis.[24] Detailed epidemiological data and mathematical models were used to show the transmission pattern and risk factors. It was found that viral spread was largely driven by transmissions at distances not much farther away than neighboring households. Human mobility in rural Bangladesh especially in woman is very limited with individuals spending >50% of the time in and around the home. The Aedes mosquito, responsible for chikungunya and dengue transmission, does not travel very far and often stays within the same residence for days[25] was observed by relapse recapture experiments.

Fig 2: *Bangladesh map with hot spot during outbreak 2012. (Copyright-IEDCR,BD News)*

Assuming the Metropolitan city of Dhaka as a potential area of outbreak, the Institute of Epidemiology, Disease Control and Research (IEDCR) in Dhaka has reported the presence of chikungunya in the capital city of Dhaka after 2012 outbreak in Dohar, Dhaka, advising the public to be aware of the mosquito bite. In Aug and Sep in 2012 from every 10th house, a total of 600 people, in the Sutrapur, Dhanmondhi, Motijheel and Mohakhali areas were tested for chikungunya and they had found recent infections in 33 percent people among the tested blood.[26] In addition, three percent have been found with past infections. Since December 2016 to extended ongoing 2017, this is the outstanding fourth outbreak of chikungunya in Bangladesh.

Beside these outbreaks, sporadic cases of chikungunya was observed from Bangladesh (reported and unreported). In 1999, in Chittagong Medical College Hospital, a young boy was suspected to have chikungunya (Personal communication Prof M A Faiz). A case series of 6 chikungunya was reported in 2013[27]. Another review was reported in next year with updated information.[28]

Virus:

Chikungunya virus is an *Alphavirus* with a positive sense single-stranded RNA genome of approximately 11. 6kb2 (Figure 2). [29] The "molecular signatures" of chikungunya virus, which constitute genetic fingerprints, in virus envelope protein E1 have also been found.[30] The virion is 70 nm in diameter and itis composed of repeating units of the E1 and E2 transmem-brane glycoproteins (240 heterodimers of E2/E1 arranged as trimeric spikes on its surface), the capsid (C), a host-derived lipid bilayer, and a single molecule of genome RNA. The nsPs are translated fromgenomic RNA and the structural proteins from a subgenomic RNA (Fig. 1).[31] Two precursors of non-structural proteins are translated from the viral mRNA,and cleavage of these precursors generates nsP1—nsP4.[32] These proteins assemble to form the viral replication com-plex, which synthesizes a full-length negative-strand RNAintermediate. This serves as the template for the synthe-sis of both subgenomic (26S) and genomic (49S) RNAs. The subgenomic RNA drives the expression of the C—pE2—6K—E1polyprotein precursor, which is processed by autoprotoly-sis. The capsid is released, and further processing generates the pE2 and E1 glycoproteins. PreE2 and E1 associate in the Golgi and are exported to the plasma membrane, where pE2is cleaved into E2 and E3. Binding of the viral nucleocapsid to the viral RNA and the recruitment of the membrane-associated envelope glycoproteins promote viral assembly. The assembled alphavirus particle, with an icosahedral core, buds at the cell membrane.

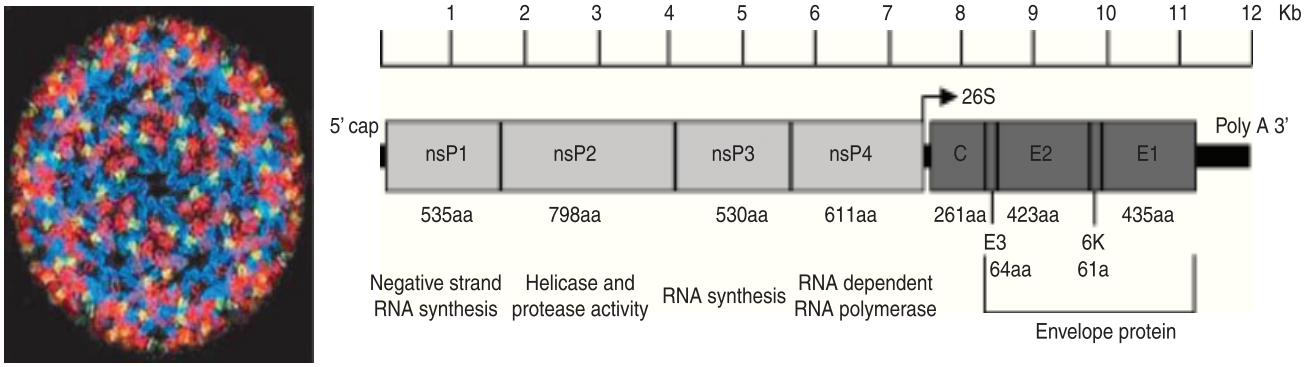

Fig 3(a,b): *Chikungunya virus and Organization of the chikungunya virus genome*

Alphaviruses enter target cells by endocytosis. A few receptors (DC-SIGN, L-SIGN, heparin sulphate, laminin and integrins) have been implicated in this process, but their precise roles have not been clearly proven.[31] Recently,prohibitin was identified as CHIKV receptor protein.[31,32] Fol-lowing endocytosis, the acidic environment of the endosome triggers conformational changes in the viral envelope that expose the E1 peptide, which mediates virus-host cell membrane fusion. This allows cytoplasmic delivery of the core and release of the viral genome.

Vectors and transmission:

Chikungunya virus is transmitted by Aedes mosquitoes *(Ae. Aegypti* & *Ae. albopictus*) which breed in clean water collections in containers, tanks, disposables, junk material in domestic and peri-domestic situations besides natural habitats like tree holes, plantations etc. Like Dengue its transmission is also related to rainfall and temperature. In recent years, it has been observed that during the period of monsoon and post-monsoon there is an upsurge in the cases because population of the vector fluctuates with rainfall and its life span is influenced by temperature and humidity. A high vector density in the post-monsoon season enhances virus transmission. The tansmission cycle are divided into enzootic and urban. In Africa, an enzootic cycle occurs in forested habitats where arboreal mosquitoes, principally *Aedes* spp, serve as vectors. Evidence points to nonhuman primates as the principal reservoir and amplification host in enzootic cycle whereas human are the host during epidemics.[33] (Fig 4) The enzootic transmission cycle can spill over to infect people who live nearby, and enzootic mosquito vectors may be involved in interhuman transmission during small outbreaks. Epidemics also occur in Africa when CHIKV is introduced into urban areas where the more anthropophilic vectors, *Aedes aegypti* and *Aedes albopictus*, can initiate human—mosquito—human transmission.[34] The endemic/epidemic cycle results in high levels of human exposure to mosquito transmission, particularly because these vectors live in close proximity to people.

Aedes aegypti is the main vector of transmission of Chikungunya in Bangladesh. However, Aedes albopictus has[35] been found to be playing a part in some areas. They are principally day biters. Eggs of these vectors have the ability to withstand desiccation for more than a year. This could result in the virus to remain in nature for long periods and cause outbreaks. Flight range of these vector mosquitoes are less making the outbreaks to occur in clusters, especially in congested localities. Recently, it has also been shown that viraemia 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.

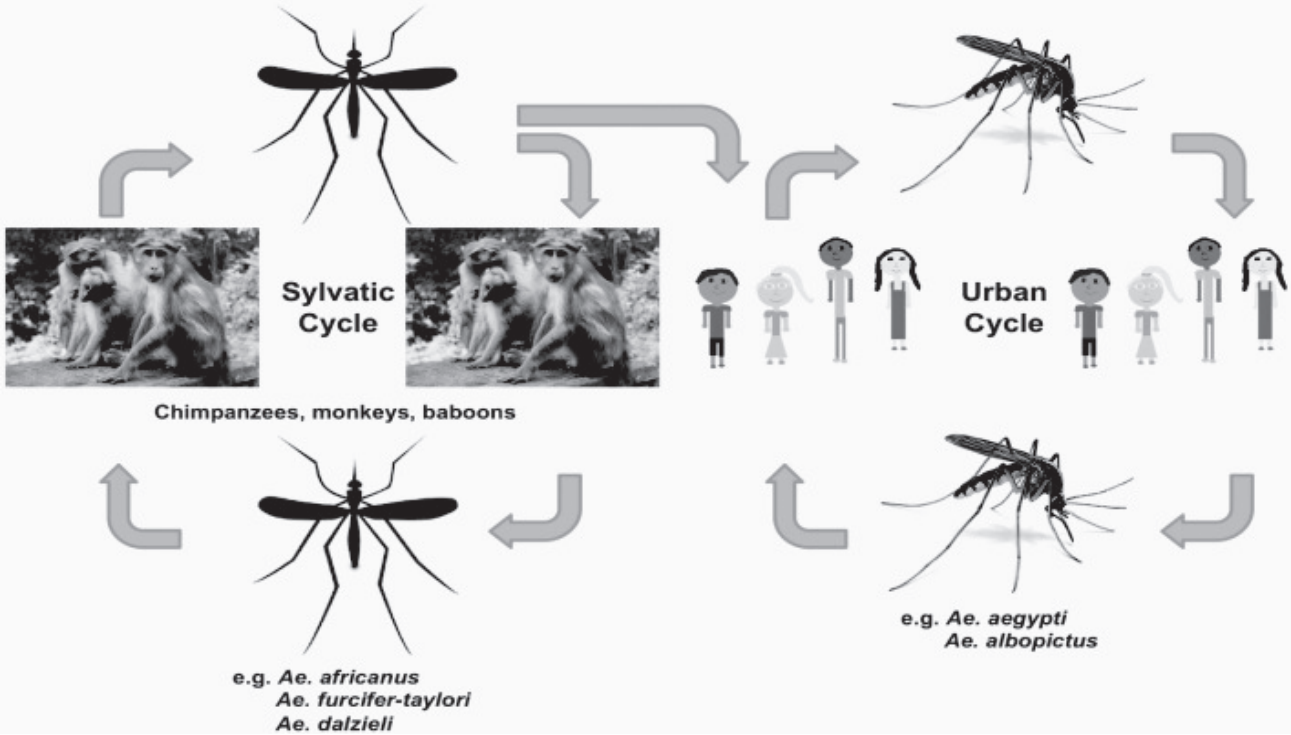

Fig 4: *The sylvatic cycle reside in primates but during outbreak the urban cycle consist of man mosquito man cycle.*

The aedes aegypti adult females prefer to feed on humans, often take several partial blood meals during a single gonotrophic cycle, ovipo sit in artificial containers as their preferred larval sites, and rest inside houses with ready access to human hosts. [35]*A. albopictus* is both zoophilic and anthropophilic, aggressive, silent, active all-day long, and has a longer lifespan than other mosquitoes (up to 8 weeks). In recent decades it has expanded to several areas previously known to be *Aedes*-free. [36,37] It seems that most new introductions of *A. albopictus* have been caused by vegetative eggs contained in timber and tires exported from Asia throughout theworld.[37] The human infections are acquired by the bite of infected Ae. aegypti /Ae. Albopictus mosquitoes, which are day biters and epidemics are sustained by human-mosquito-human transmission.

Fig 5 (a,b): *Aedes aegypti* and *Aedes albopictus* are the primary vectors (above). Both are aggressive daytime biting mosquitoes (Copyright-CDC, Atlanta)

Pathogenesis

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. In humans, acute chikungunya virus infection is characterized by a very early viremia at fever onset that can increase up to 109 to 1012 RNA copies/ml and lasts up to 12 days. In vitro studies have shown that human epithelial and endothelial cells, primary fibroblasts, and monocyte-derived macrophages are susceptible to chikungunya virus infection, whereas activated B and T CD4+ lymphocytes, monocytes, and monocyte-derived dendritic cells were refractory to chikungunya virus infection.[38]

CHIKV infection elicits strong systemic innate responses, principally involving the production of antiviral IFN- as well as many pro-inflammatory cytokines, chemokines, and growth factors. 44 This is followed by the activation of the adaptive immunity through activation and proliferation of CD8+ T cells in the early stages of the disease. A classical switch from CD+ 8 cell to CD4+ T-cell response and the production of anti-inflammatory proteins IL-1RA and IL-2RA are characteristics of later stages of the acute phase.[38] In chikungunya production of IL-16, IL-17, monocyte chemoattractant protein 1 (MCP-1), IP-10, and MIP-1 was found very high while. the end of the acute phase is characterized by the production of proinflammatory MIF, MIP-1 , SDF- 1 , and IL-6 and IL-8 and CCL5 (RANTES). High plasma levels of IFN- , IL-4, IL-7, and IL- 12,p40, cytokines that promote the adaptive immunity, suggested the involvement of cellular responses.[39,40]

The Pathophysiology of the Pain of Chikungunya

Despite the improved understanding of joint damage associated with infection by alphaviruses, the cause of persistent symptoms remains unresolved. The inflammatory response of the host, the presence of viral products in macrophages and joint tissues, and auto-immune process may be involved in the pathogenesis. Different joint manifestations during different phases of Chikungunya fever have been described in the literature, including arthralgia, inflammatory arthritis, synovitis, enthesitis, tenosynovitis, and bursitis.[41] Experimental models of arthritis induced by alpha viruses suggest that the pathogenesis is the result of a combination of direct tissue and cell damage caused by viral replication and indirect immune activation responses in the target tissues[42]. Different cytokines, chemokines, and other inflammatory mediators are produced; these are related to the intensity of inflammation in the acute phase; are involved in the recruitment of macrophages, natural killer cells, and T lymphocytes to the site of viral replication; and cause dysregulation of inflammation in this stage, leading to the expression of other inflammatory proteins responsible for damaging the joint in the chronic phase.[42. 43,44] Viral persistence could also be a cause of chronic joint disease in a subgroup of patients. The presence of immunoglobulin M (IgM) antibodies detected months after the acute infection suggests persistence of the virus or its antigens; this may perpetuate the inflammatory process in the joints.[41,44] In an outbreak in Italy, Moro et al. reported that IgM was detected in 52% (131/249) of patients within 5 months of the contracting disease and in 13. 2% (30/227) with 12 months of disease evolution[42]. Other risk factors associated with progression to a chronic form include age >35 years, marked joint impairment in the acute phase, and pre-existing prior joint disease.[42,43,44] Some patients have polymorphisms of the human leukocyte antigens (HLA) that are associated with rheumatic diseases, such as HLA-27. These HLA polymorphisms may be involved in the pathogenesis of the disease.[41,42] A sub-group of patients present with neuropathic-type pain.[45] Neuropathic pain syndromes are caused by lesions in or dysfunction of the nervous system;

they do not directly depend on an inflammatory processes, but involve specific changes in central and peripheral nociceptive processes.[44] Therefore, it seems that the mechanisms are multifactorial and may different between patients. A clear understanding of the pathophysiologic mechanisms in patients with Chikungunya will have a direct bearing on the choice of ideal therapeutic agent to relieve the pain.

Clinical Features:

Chikungunya disease is characterized by acute transient febrile arthralgic illness, but can also lead to chronic incapacitating arthralgia. The mosquito picks up the virus from an infected person (viremia for 5 to 7 days after onset of clinical signs) during its blood-sucking meal. The virus replicates in the mosquito for a few days (extrinsic phase), and then the mosquito can transmit the virus to another person, with a new bite. Mother-to-child transmission is possible during childbirth, but not when nursing. The incubation period (time from infection to illness) can be 2-12 days, but is usually 3-7 days.[46] Acute Chikungunya fever typically lasts a few days to a couple of weeks, but some patients have prolonged fatigue lasting several weeks. Additionally, some patients have reported incapacitating joint pain, or arthritis which may last for weeks or months. The prolonged joint pain associated with CHIKV is not typical of dengue. Co-circulation of dengue fever in many areas may mean that Chikungunya fever cases are sometimes clinically misdiagnosed as dengue infections, therefore the incidence of Chikungunya fever could be much higher than what has been previously reported.[47] No deaths, neuro-invasive cases, or hemorrhagic cases related to CHIKV infection have been conclusively documented in the scientific literature.

CHIK virus infection is most often symptomatic (H" 80%of cases); the symptomatology may last from a few days to several years. Experts have defined 3 clinical stages: acute stage (D1 to D21), Sub-acute stage (from D21 to the end of the 3rd month), and chronic stage (after 3 months)[3]; The sub-acute stage and a subsequent chronic stage is not observed in all patients. Acquired immunity is usually permanent. The mortality rate of CHIK is comparable to that of seasonal influenza (H" 0. 01 to 0. 1%), and is mainly related to the patient's age (over 75 years of age) and/or to co morbidities or serious co infection.[3]

Acute stage (the first 3 weeks):

A suspected case of Chikungunya is defined as a fever of sudden onset, higher than 38. 5°C, and intense arthralgia or arthritis not explained by other conditions in a person resident of or having visited an endemic or epidemic area up to two weeks before the beginning of the symptoms.[47] In the common presentation, pyrexia occurs suddenly, along with inflammatory arthralgia and arthritis with sometimes severe pain, most frequently in the extremities (wrists, ankles, and phalanges); these symptoms last 2 to 3 weeks in some patients. Other symptoms may occur:myalgia, headache, back pain, macular to maculopapular rash, sometimes with cutaneous pruritus (foot arch) and edema of the face and extremities, polyadenopathies.[48,49] Benign bleeding (gingival bleeding, epistaxis) may occur in children, but is rare in adults. Asthenia, sometimes severe, and anorexia are common after regression of acute symptoms.

Fever

The fever varies from low grade to high grade, lasting usually for 24 to 48 hours. Fever rises abruptly in some, reaching 39-400C, with chills and rigor, no diurnal variation, usually subsides with use of antipyretics.[48]

Joint manifestation

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 polyarthritis 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.[49,50] The pain may be relieved for 2-3 days and then reappear in a saddle back pattern. There is a tendency for early and more significant involvement of joints with some trauma or degeneration. The classical bending phenomenon was probably due to the lower limb and back involvement which forced the patient to stoop down and bend forward.

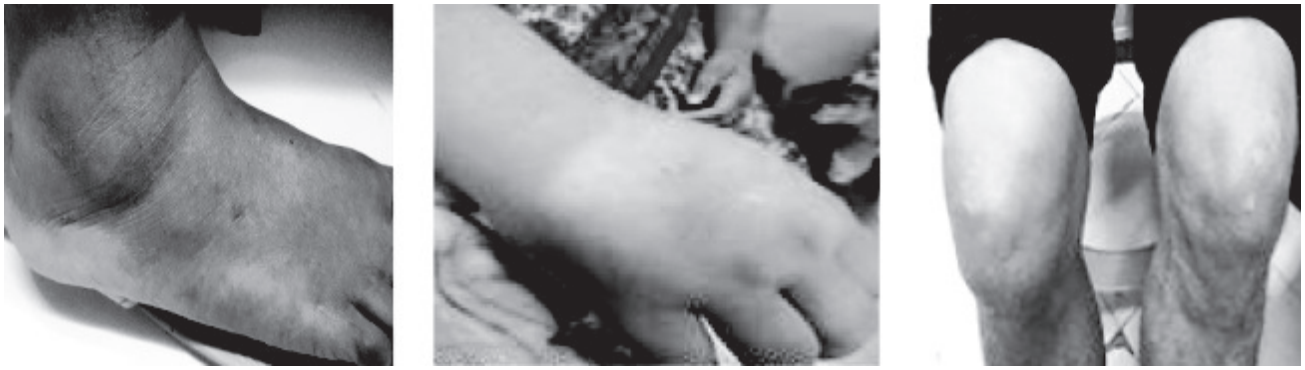

Fig 6 (a,b,c): *Arthritis of ankle, wrist and knee in acute chikungunya (copyright BSM)*

Fig 7 (a,b,c): *Rashes in hand and face (erythematous maculopapular) @ BSM, Oral Ulcer (copyright -Prof. Md. Mujibur Rahman)*

Mucocutaneous manifestation

Transient maculopapular rash is commonly seen, usually disappear within 48 hours. Other skin lesion may appear in the form of vesiculo bullous eruption, angiomatous lesions and fewer had purpuras. Epidermolysis bullosa is also seen in children. Most skin lesions recovered completely except in cases where the photosensitive hyperpigmentation persisted. Stomatitis and oral ulcers also observed.[47,49]

Neurological manifestation

Neurologic manifestations of meningo-encephalitis, encephalitis, acute encephalopathy Guillain-Barré syndrome and myelitis were reported.[49,50]

Ocular manifestation

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 non granulomatous anterior uveitis, optic neuritis, retrobulbar neuritis, and dendritic lesions. Majority of the patients recover with good vision.[51,52]

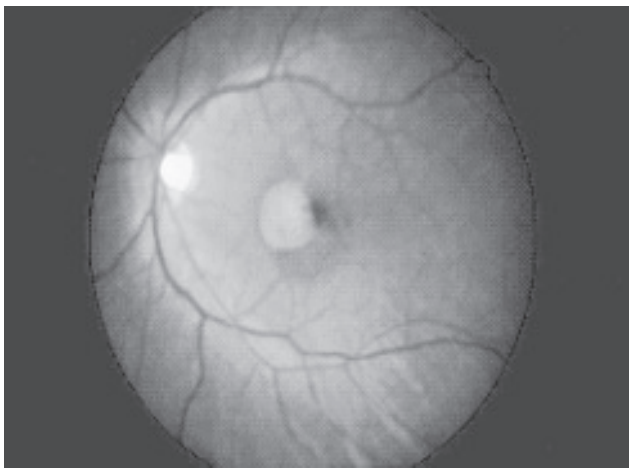

Fig 8: *Chikungunya infection with ocular manifestations: retinitis (copyright - Fazle Rabbi Chowdhury)*

Atypical presentations (not common) are observed in 0. 5%of cases, mainly in vulnerable patients (young children, elderly patients, chronic alcohol abusers, patients presenting with chronic medical conditions including systemic lupus). These are hyperalgic symptoms: gastro-intestinal symptoms (diarrhea, vomiting, abdominal pain) and neurological symptoms (confusion, optic neuritis), damage to mucous membranes (oral or genital ulceration, conjunctivitis), and malaise (hypotension and dysautonaemia). CHIK can directly induce severe atypical presentations (rhabdomyolysis, bullous dermatosis, fulminant hepatitis, meningoencephalitis or polyneuropathy, myocarditis,etc). More often, it causes decompensation of chronic cardiac, respiratory, renal, systemic (lupus), and metabolic (diabetes) diseases, or various complications (dehydration, thromboembolism, loss of autonomy).

Sub acute stage (3 weeks to 3 months):

In the subacute stage of arthralgia, a history of having had an episode of acute fever with associated edema and joint pain during an epidemic period (clinical-epidemiologic criteria) dispenses with the need to perform serologic tests in patients that seek assistance for the treatment of pain. The post-acute stage is characterized by polymorphic and associated disorders. These are dominated by the persistence of slowly regressive inflammatory arthralgia, arthritis (synovitis with or without effusion), tenosynovitis, bursitis, capsulitis and or periosteitis. The trend is a continuous mode or inflammatory attacks frequently precipitated by cold.[3,45] It often associates with deterioration of pre-existing degenerative or traumatic or unknown arthropathy such as osteoarthritis or sometimes-calcific tendinitis, and local events such as reactionary edema, entrapment syndromes, joint stiffness, or neuropathic pain. The absence of anti-inflammatory treatment, untimely excessive physical stress, and even a complete and prolonged joint rest, can have a deleterious effect on clinical recovery. This sub-acute stage may also include severe asthenia and neuropsychiatric disorders.[3,45,46] In Chikungunya subacute stage, clinical polymorphism of persistent rheumatic or systemic manifestations are observed. Involvement of other types of locoregional involvement like mechanical arthralgia, stiffness, relapse of pain in previously injured/sick areas, soft tissues edema (extremities), tunnel syndromes, small fiber neuropathy, peripheral vascular disorders (Raynaud

syndrome) are observed in different reports. Chronic fatigue, skin dyschromia, hair loss, decompensation of metabolic or endocrine diseases, decompensation of other preexisting chronic diseases anxiety, depressive syndrome, memory problems, ideational slowdown were also observed in subacute stages.[3,48,49]

The chronic stage (after the 3rd month):

It is defined by the absence of return to the pre-existing condition more than 3 months after the onset of CHIK. The chronic phase can last a few months to several years. The disease progresses to cure without sequelae, spontaneously or after treatment, or to a prolonged persistence of joint and/or general symptoms, or to aggravation because an inflammatory or degenerative process. The clinical symptomatologies are the same as in the subacute stage. It is common to observe painful rebounds on joints too strongly used considering their post-CHIK inflammatory condition. The diagnostic approach is to individualized each patient according to the presence or absence of inflammatory symptoms (arthritis, enthesitis, tenosynovitis, inflammatory arthralgia) and the number of joints involved (polyarticular if ≥ 4 joints). The level of clinical inflammatory activity and its functional impact should also be taken into account. Chronic inflammatory rheumatisms (CIR) are different from musculoskeletal disorders (MSDs). The former have the most severe functional prognosis while the MSD are the most frequent (95%).

The chikungunya infection can unmask the underneath connective tissue disease like Rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Whether these are subset of chikungunya or not are still controversial as the natural disease process of RA and AS was observed in many of the cases including seropositivity of RA test and Anti CCP antibody while HAL B 27 was found in Post chikungunya AS cases. RA is the most common post-CHIK CIR before peripheral SA. Otherwise, a non-destructive arthritis not meeting the criteria for RA or SA is called undifferentiated polyarthritis (IP), regardless of age, and only after ruling out other causes of polyarthritis (microcrystalline, autoimmune, granulomatous secondary to chronic viral hepatitis, etc.). At the individual level, the part of CHIK in CIR depends on the absence of rheumatic signs before infection, the continuous symptoms of acute infection to CIR, the CHIK seropositivity, and ruling out of differential diagnoses.[3,46,48,49] Patients not meeting the definition of post-CHIK CIR are classified as presenting with other MSDs. A systematic study after Chikungunya infection for CIR study revealed the pattern of Rheumatism is like this:

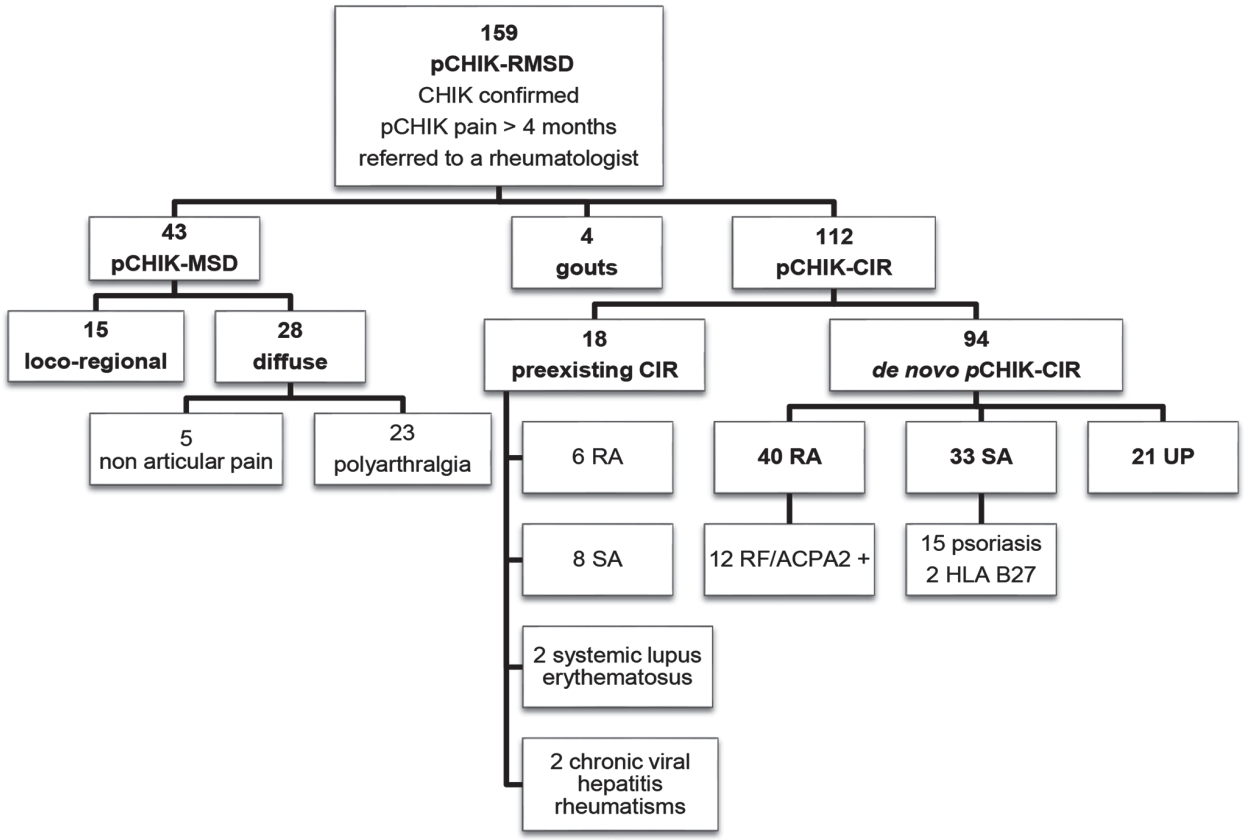

Table 1: *Nosologic flow-chart of patients referred to a rheumatologist for post-chikungunya (pCHIK) persistent rheumatic musculoskeletal pain, Saint-Denis, Reunion Island, 2006–2012.*

This observation showed that Post chikungunya induced RA and AS is even more (although they were de novo during chik infection) rather natural course of RA and AS.

There are several validated tools to use for pain; however, the VAS is one of the simplest and can be applied by any health professional. Another scale used widely in Brazil[53] is the face scale. It can be used with small children and elderly people with cognitive deficits. However, despite the simplicity of the tool, it is important to remember that pain is a subjective perception and therefore, has a relationship with social, cognitive, and psychological aspects. It is necessary that while measuring pain, the patient should be informed of the importance of being truthful, and that there is an approach for each type of pain and numbering in order to avoid methodologic failures; patients often report a very high level of pain (9-10 in VAS) in fear of not receiving analgesics if the numbers are too low. The NS 4[45,53] system was used for neuropathic pain in many outbreaks. The initial and then regular assessment of inflammatory activity(number of nighttime awakenings, morning stiffness, number of painful joints and swollen joints, CRP or ESR) and that of the functional impact (type scale RAPID3 or DAS28) guide treatment decisions.[3,53]

Chikungunya and Pregnancy:
CHIK does not increase the risk of miscarriage, fetal death in utero, and birth defects; but maternal-neonatal transmission can occur in viremic women during childbirth (caesarean section is not protective). Fifty percent of neonates are infected when they are born the day before or 5 days after the mother's first symptoms. The CHIK can be either congenital or neonatal (by mosquito bite after birth) and in both cases, infected neonates have a typical and constant clinical presentation occurring after a median incubation period of 4 days (3–7 D): characteristic triad with fever/difficulty to breast-feed/pain; thrombocytopenia; lymphopenia; and moderate hepatic cytolysis. Severe stereotypical presentations occur in 25% of cases[3,46]: encephalopathy with progressive cerebral edema and/or hemodynamic disorders inducing severe sepsis; hemorrhagic complications due to intravascular coagulation; and cardiomyopathy. The mortality rate of severe presentations is 50%, the risk of post encephalopathy psychomotor sequelae is important. The disease presentation in infants (> 28 days and < 2 years of age) and children is often similar to that of adults. Nevertheless, some atypical or complicated presentations have been reported: hyperalgesia resistant to analgesic treatment, extensive bullous rash, hemodynamic disorders, dehydration, food intolerance, seizures, and meningeal syndrome.[3,46,53]

Lab Diagnosis:
Diagnosis of Chikungunya fever is typically clinical in endemic areas and where epidemic has occurred. But it has a number of differentials and laboratory diagnosis is often critical to establish the diagnosis.[54]

So, specific virologic/serologic investigations are mostly reserved for patients with alarm signs, severe cases, atypical manifestations, or in cases of difficult differential diagnosis.

Specific Investigations:
The confirmation of Chikungunya fever is through any one of the following: Isolation of virus, PCR, detection of IgM antibody and demonstration of rising titre of IgG antibody.[54,55,56,57]

Specimen:
Usually blood or serum; CSF can be sent for cases with meningo-encephalitic feature, for virus isolation and PCR:heparinized whole blood, Serum obtained from 10-15 ml of whole blood is required for serologic tests. The blood specimen is transported at 4°C. Only if the testing cannot be done immediately, the serum specimen should be separated and then stored and shipped frozen.

Virus isolation
Specific cell lines are exposed to samples from whole blood and identifying chikungunya virus- Specific responses. During acute phase (d" 6 days) virus isolation provides the most definitive diagnosis. The test is Time consuming (1-2 weeks) and the degree of success is dependent on a number of complicating factors, for example, time of collection, transportation, maintenance of cold chain, storage and processing of samples. (must be carried out in bio safety level III lab)

RT-PCR
The technique is used for diagnosing CHIK virus using nested primer pairs amplifying specific components of three structural gene regions, Capsid (C), Envelope E-2 and part of Envelope E1. Appropriate in the acute phase, since CHIKV RNA can be detected during d"8 days after symptom onset. Results can be available in 1-2 days. In special situation, RT-PCR can be designed in a multiplex format to simultaneously detect several other arboviruses, such as dengue virus [58]. RT-PCR can also be used to quantify the viral load in complicated patients. The test is costly an less available but it is the investigation of choice in acute phase, if viral confirmation warranted

Detection of Ig M antibody:
Immunoglobulin M Antibody (IgM) capture enzyme-linked immunosorbent assay (MAC-ELISA) is commonly used. Commercial ICTs available in some private laboratories ofmajor cities are specific but very low in sensitivity. The test is appropriate from 7days after symptom onset. Results are available on the same day. ELISA test is quite specific with very little cross reactivity with related alpha viruses. This is the investigation of choice in 2nd week of illness, if viral confirmation warranted

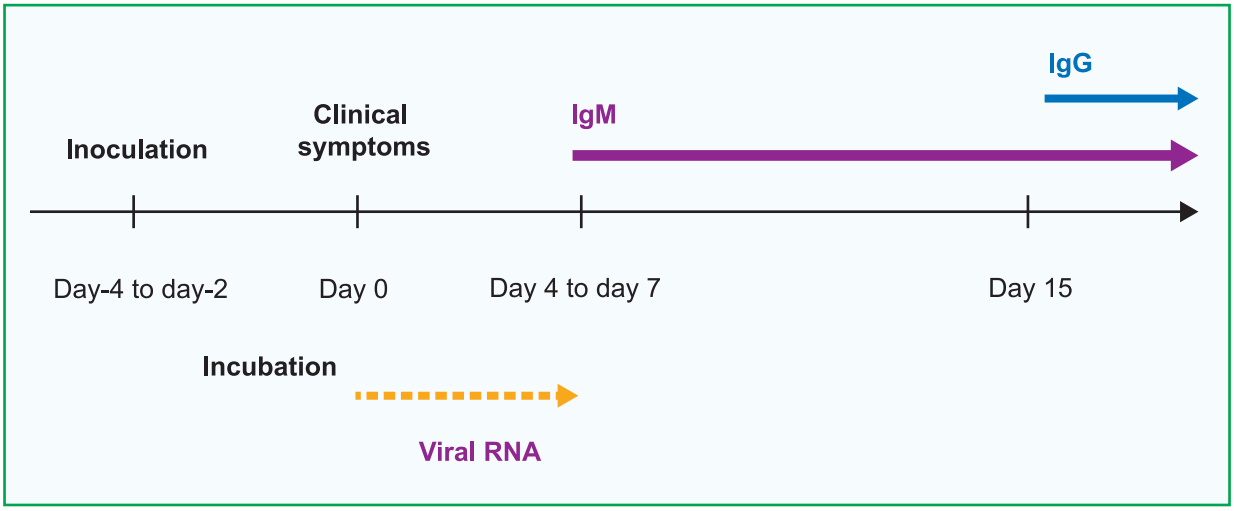

Fig 8: *Time frame for various laboratory diagnosis of Chikungunya*

Demonstration of rising titre of anti Ig G antibody:
An acute phase serum must be collected immediately after the onset of illness. Four-fold increase in IgG values in samples collected two to four weeks apart is diagnostic. This is useful in chronic phase. Results are available on the same day. Initial sample should be collected during acute phase preferably after7days[55,56,57]

Recommended general investigations in different clinical settings:
In acute phase Complete blood count: The total leucocyte count is usually on the lower side (below 5000 cells / cu. mm). Lymphopenia is common. When the lymphocyte count is less than 1000 per cubic millimeter, it is closely associated with viremia. A low platelet count (below 50 000 per cu. mm) should alert the possibility of dengue fever. The peripheral smear has to be examined for malarial parasite as well. Erythrocyte sedimentation rate is usually elevated. C - reactive protein: increased during the acute phase and may remain elevated for few weeks[19,20]. Transaminases, creatinine and electrolytes may be necessary in at-risk patients or those who are severely ill. ALT/AST are raised in acute phase. CSF study should be done if features of encephalopathy and/or meningitis are present.

Chronic phase: Along with the above, the followings should be considered in patients refractory to treatment or with persisting pain, autoantibodies like Rheumatoid factor; Anti-citrullinated protein antibody; and Anti-nuclear antibodies should be done as well as molecular markers like HLA-B27

In **complicated case** Serum creatinine, eGFR, Serum Electrolytes,, Serum aminotransferases, alkaline phosphatase, bilirubin, prothrombin time, serum ammonia, ECG, Chest X-ray, CSF study, MRI of brain can be done accordingly[20]

Assay Sensibility (%) Specificity (%) PPV (%) NPV (%)RT-PCR 88. 5 100 100 97. 5Standard Diagnostics Chikungunya IgM ELISA 3. 9 92. 5 10 81. 6Novatech Chikungunya IgM Capture ELISA 76. 9 91. 9 100 97. 5Novatech Chikungunya IgG Capture ELISA 80 100 100 95. 6*Source*: Modified and adapted from Blacksell. 71,89—91PPV, positive predictive value; NPV, negative predictive value; RT-PCR, reverse transcriptase-polymerase reaction; IgM, immunoglobulinM; IgG, Immunoglobulin G; ELISA, enzyme-linked immunosorbent assay.

Table-II
Accuracies and sensitivities of different chikungunya fever diagnostic assays.[59]

Assay	Sensitivity(%)	Specificity (%)	PPV (%)	NPV(%)
RT-PCR	88. 5	100	100	97. 5
Standard Diagnostics Chikungunya IgM ELISA	3. 9	92. 5	10	81. 6
Novatech Chikungunya IgM Capture ELISA	76. 9	91. 9	100	97. 5
Novatech Chikungunya IgG Capture ELISA	80	100	100	95. 6

Treatment:

Guiding principles of clinical management

There is no specific antiviral drug against CHIK virus**.** There is no specific vaccine against CHIK virus**.** Treatment is entirely symptomatic Paracetamol is the drug of choice with use of other analgesics if paracetamol does not provide relief**.** During the acute stage of the disease, steroids are not usually indicated because of the adverse effects. Aspirin is preferably avoided for fear of gastrointestinal and other side effects like Reye's syndrome. Mild forms of exercise and physiotherapy are recommended in recovering persons. Treatment should be instituted in all suspect cases without waiting for serological or viral confirmation. It is recommended to prevent dehydration in every case (oral or parenteral fluid intake, stopping diuretics, etc.

Acute phase:

Acetaminophen and Other analgesic: The analgesic treatment is based on acetaminophen (stage 1)in first intention. Paracetamol can be prescribed at 500-750mg, 6 hourly, but the total daily dose should not exceed at 4g because of possible hepatotoxicity.[3. 19,20,53,56,] Using NSAIDs and salicylates is not recommended in the 14 days after onset of the disease because of the risk of bleeding complications related to dengue fever unless this diagnosis is ruled out, and Reye's syndrome induced by aspirin. Using stage 2 analgesics (weak opioids) is required if acetaminophen is not effective: Tramadol is a good choice when suspicious of a neuropathic component of intense pain as, besides its action on opioid receptors, it acts as an antagonist of NMDA (*N*-methyl-D-aspartate) receptor that are involved in chronic pain.[3,53] Tramadol should be used in a dose of 50-100mg, 6 hourly. Codeine is an opioid that should be prescribed in a dose of 30mg every 6 hours and can be used with other analgesics. Tramadol alone or in combination with acetaminophen (adult formulation, pediatric formulation after 3 years of age); codeine combined to acetaminophen (adult fixed-dose combination (excluding breastfeeding), adding codeine to acetaminophen for children only after 12 years of age (at the lowest dose and for the shortest duration); clinical safety should be monitored.

Opioids: the opioid drugs are potent and safe analgesics, especially in cases of acute pain. Adverse effect monitoring is required, and the patient should be warned about adverse Effects.[3,53] In the doses usually prescribed by non-specialists in pain management, the risk of respiratory depression is very low; drowsiness and lethargy are the preceding warning signs.

Corticosteroids: in the acute phase of viremia, corticosteroids can be associated with increased risks and complications. It brings no beneût in the medium to long term, and because it promotes a severe rebound of arthritis and tenosynovitis.[3,53] This treatment should be discussed by specialists in case of encephalopathy, uveitis, optic neuritis, acute demyelinating encephalomyelitis, or neuropathy.[3,20,53,56]

Pregnant patients:

The recommended symptomatic treatment is acetaminophen, with a maximum dose of1 g × 4/day. All NSAIDs (including aspirin and topical presentations) are contra-indicated after 24 weeks of amenorrhea (risk of fetal renal failure and closure of the ductus arteriosus, eventually leading to fetal death in utero.[3,20,53] Cesarean section has no proved protective against the CHIK transmission to the child; cesarean section isindicated in case of FHRP alteration, as with any threatening fetal distress. Effective tocolysis can delay delivery beyond the viremic phase, and decrease the risk of neonatal transmission. ClinicalTrial. gov NCT02230163 has been shown not be effective of IVIG to prevent neonatal infection in lst trimester.

Paediatrics:

The typical pediatric presentations are treated symptomatically as for adults, without using any NSAID in infants < 3 months of age, or before 10 days; a reminder: codeine is not recommended before 12 years of age, and reserved for acetaminophen resistant cases after 12 years of age.[3,53]

Subacute Stage:

NSAID: NSAID is the treatment of first intention. NSAIDs: only to be used after the acute phase (>10-14 days). Be attentive to side effects. Renal function must be assessed in elderly people and in those with co morbidities, prior to starting treatment. Be alert for the higher risk for chronic degenerative diseases in patients such as the elderly, those with diabetes, peptic ulcer disease, nephropathy, liver disease, and cardiomyopathy, among others. Ibuprofen or naproxen should be tried early before deciding to put higher NSAID like Diclofenac or Indomethacin.[3,53]

The role of corticosteroids:

The use of corticosteroids is indicated for the disease in its sub-acute phase in patients with moderate to severe pain. The standard medication for oral use is prednisone, that has anti-infl amatory effects when taken in low doses; its anti-inflammatory effects predominate at a dose d"0.5 mg/kg per day. Given at intermediate doses (>0. 5 to <1mg/kg per day),

its effect lies between anti-inflammatory and immuno-suppressive actions, whereas in higher doses (e"1mg/kg per day) its immunosuppressive action predominates, independent of its anti-inflammatory action. For the treatment of pain, the dose is 0.5 mg/kg per day as a single dose taken in the morning.[3,20,53] If the treatment response is adequate, continue at the recommended dose until the full resolution of the joint pain. In the event of complete remission of pain, continue taking the recommended dose for 3-5 more days. If there is no relapse, start weaning by decreasing the dose by 5mg/day every 7 days. The initial dose may be maintained for up to 21 days, the average time during which there is usually no risk of inducing adrenal insufficiency. During the weaning phase, if pain recurs, return to the previous dose and try to repeat weaning only five days after symptom resolution. The weaning must be slower, with a decrease of 2. 5mg/day every seven days. In all cases, the total duration of corticosteroid treatment must be < 4 weeks; switching to an NSAID after corticosteroid therapy is recommended to avoid clinical rebound.

Chronic phase:

There are varieties of arthritis that are observed in Post chikungunya chronic phases. The outbreaks in Europe, South America and India showed there are differences in natural history and destructive arthritis in these varieties of arthritis. The pChik arthritis can be de novo Rheumatoid arthritis (pChic RA) rather natural course Rheumatoid arthritis which can also be flared during the Chik infection. There may also be de novo pChik SA which is also different from that of Natural history of Spondyloarthritis (SA). The RA component are serologically positive of Rheumatoid Arthritis (RA) test or positive AntiCCP antibody. The pChik SA is also seen to be positive of molecular marker of HLA B27. Beside these varieties, there are diffuse joint involvement (Diffuse variety) and also locoregional involvement (Locoregional variety). The undifferentiated variety is also described in these literatures which are not seropositive or molecular test positive and cannot put into any diagnostic criteria of ARA (American Rheumatology Association) or EULAR (European league for Rheumatological diseases) classification[3]. At the individuallevel, the part of CHIK in CIR depends on the absence of rheumatic signs before infection, the continuous symptoms of acute infection to CIR, the CHIK seropositivity, and ruling out of differential diagnoses. Patients not meeting the definition of post-CHIK CIR are classified as presenting with other Musculoskeletal disorder (MSD).

Table-III

Nosological classification of chronic post-chikungunya rheumatic manifestations.[3]

Chronic inflammatory rheumatisms	Other musculoskeletal disorders
Rheumatoid arthritis Spondyloarthritis t mainly peripheral, psoriatic)	*Local* Mono- or oligo-articular involvement Other local complications
Undifferentiated polyarthritis (diagnosis of exclusion)	*Diffuse* Distal polyarthralgia with edema (the lack of synovitis permits the distinction from the RS3PE) Polyalgia and effort fatigue on exertion

RS3PE: remitting symmetrical seronegative synovitis with pilling edema.

Therapeutic Management:

The management of post-CHIK CIR, with or without joint destruction, systematically requires the advice of a multidisciplinary team service including rheumatologist. The treatment goals are to limit the potentially destructive out-come, to decrease the functional and psychosocial impact, and to improve the quality of life. CHIK induced CIR can be defined to have shorter duration treatment regime rather long duration management. The medications used in this phase of treatment– hydroxychloroquine, sulphasalazine, and methotrexate – have adverse effects related to their therapeutic classes and require clinical and laboratory monitoring before and during use. They must be prescribed by qualifi ed professionals. Most studies involved a small number of patients, and different methodologies were used; thus, it is currently impossible to draw conclusions regarding the efficacy of these drugs, or to assess the superiority of different therapies in patients with chronic Chikungunya.[60,61,62,63] The use of these drugs is based on extrapolation from their use in the treatment of chronic rheumatic diseases.[3,53,60,61,62] For CHIK CIR the DMARD modality should be come at first as the destruction can be prevented early. For RA and SA, The treatment modalities are well defined for both diseases, methotrexate has a special position. The DMARD may be assessed and stopped for patients in remission after a complete response sustained for several months. Due to lack of quality scientific data, there are different expertise opinions on DMARDs. In south american guideline from Brazil, have chosen to recommend hydroxychloroquine as the treatment of first choice in the chronic phase. This recommendation is based on hydroxychloroquine's anti-inflammatory effects in the

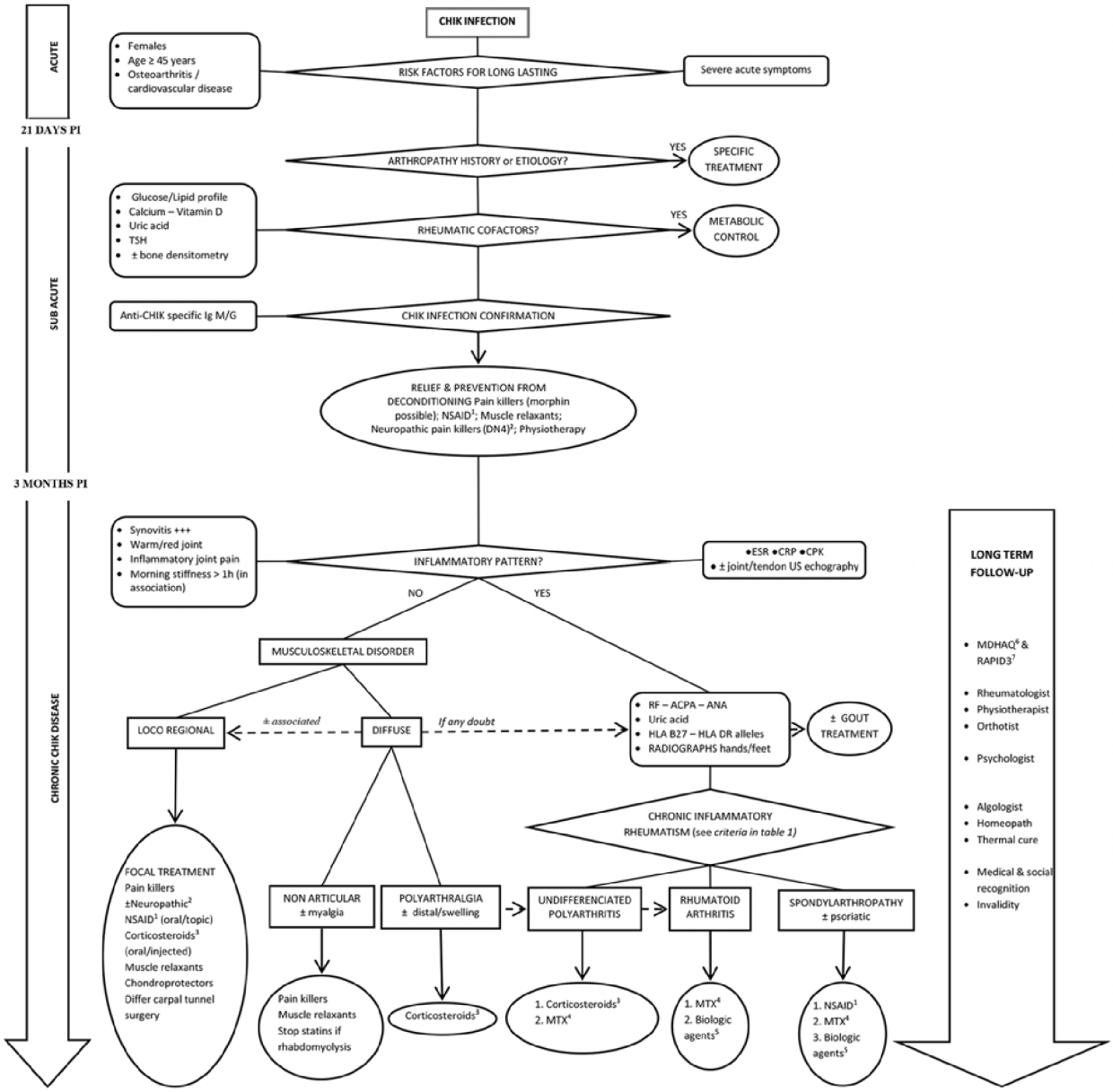

Table 4: Diagnostic and therapeutic algorithm to manage rheumatic and musculoskeletal disorders persisting after acute chikungunya (CHIK) infection, with the following abbreviations: ACPA = anti-citrullinated protein antibody; CHIK = chikungunya; CIR = chronic inflammatory rheumatisms; CPK = creatine phosphokinase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate;Ig = immunoglobulin; Pi = post-infection; MSD = musculoskeletal disorders; RF = rheumatoid factors; RMSD = rheumatic musculoskeletal disorders; TSH = Thyroid Stimulating Hormone; 1NSAID = non-steroidal anti-inflammatory drugs; 2DN4 = "Douleur Neuropathique 4"questionnaire. Neuropathic pain if _4/10 (sensitivity = 83% and specificity = 90%): use of tricyclic antidepressants, anti-epileptic drugs. 3Corticosteroids =[5–40] mg/day, short course (decrease and withdrawal within 6 months), associated with calcium and vitamin supplementation. 4MTX = methotrexate [7. 5–25] mg/week orally or injected (notably if > 15mg/week); in the absence of contraindication (hepatic, pulmonary); in association with vitamin B9 (folate as folic acid or folinic acid) 5 to 10 mg/week 48 hours after MTX is taken, Immune-modulating biologic agents = rheumatologist prescription among anti-TNF (etanercept 25mg twice a week, infliximab 3–5 mg/kg/ 6–8 weeks, adalimumab 40 mg/ 2 weeks, golimumab 50mg/month), abatacept (inhibition of T-lymphocyte activation, 500–1000 mg/ 4 weeks), rituximab (depletion of B-lymphocytes, 1000 mg repeated at 2 weeks) and tocilizumab (inhibition of interleukin-6 receptor, 8 mg/ kg/ 2 weeks). 6MDHAQ = Multi- Dimensional Health Assessment Questionnaire. 7RAPID 3 is significantly correlated with disease activity score (such as DAS28)[3]

control of arthritis and musculoskeletal pain [53,62] and its potential antiviral action, but most of all, it is a safer drug than methotrexate in the context of being prescribed by non-specialists.

The European outbreak leads to intensive good observation and French guideline developed DMARDs on the basis of variety of post CHIK arthritis. For Post CHIk RA, Methotrexate is choosen as early in first-line with alternative with other DMARDs (leflunomide, sulfasalazine) Biological agents if poor response to first line agents and unfavorable prognosis. Follow-up with DAS 28 score. For Post CHIk Spondyloarthritis, NSAIDs in first line; Methotrexate or sulfasalazine in 2nd line if peripheral synovitis; biological agents if poor response or adverse effects to NSAIDs or DMARDs. For post CHIK undifferentiated arthritis, NSAIDs in first line; corticosteroid therapy in 2nd line. Methotrexate in 3rd line or to spare corticosteroids; alternative to methotrexate is hydroxychloroquine (not validated). When MTX is contraindicated or ineffective,immune-modulating biologic agents as etanercept, rituximab, or tocilizumab can be used[64,65]. "Targeting T cells is emerging as a promising strategy for the treatment of chikungunya arthritis. Two independent experimental studies demonstrated the efficacy of abatacept and fingolimod in amelioration of disease when targeting pathogenic CD4+ T. [66,67]

Therapeutic management of other musculoskeletal disorders (non CIR):

Treatment should always be optimized by combining an analgesic, a NSAID, a local anti-inflammatory therapy in resistant sites (including joint or peritendinous infiltration), and physical therapy. The therapeutic effectiveness can be assessed in the medium term, for several weeks.

A short corticosteroid therapy must be sparingly used for multiple TMS not controlled by the first line of treatment. A switch with NSAIDs is recommended to limit the clinical rebound after weaning of the corticosteroid therapy. For resistant cases and for dependent on steroids patients a rheumatologist consultation may be needed for redesigning the diagnosis and therapeutic strategy. For sparing the steroids, technique of infiltration and other physical analgesic therapy should be sought.

Analgesic physiotherapy: Thermotherapy (mud and/or paraffin wax), of diathermy (infrared radiation, electromagnetic waves, laser, ultrasounds) Cryotherapy: ice, sprays coolers, cold packs Electrotherapy with unidirectional direct current (ionization); alternating current, transcutaneous electrical nerve stimulation (TENS)[3] or analgesic morphine drugs Spa therapy in water at 34–36 æ%C Scottish baths by alternating cold (10–15 æ%C and warm (35. 5–45 æ%C) water; begin and finish with cold water, total duration of immersion: 6–24 min, duration of cold water bath: 1 min / warm water bath: 1–3 min, number of sessions: 1–4 (with 24 hours of interval) are few modalities of analgesic physiotherapy which are recommended in every stage of chikungunya specially in chronic stage.[3]

Conclusion:

Chikungunya epidemics, with the high attack rate of CHIKV, affect a large number of people in a short period of time associated with early rain fall (early monsoon) and this is also consistently seen in Bangladesh outbreak 2017. Pain, the most frequent clinical manifestation of Chikungunya, is difficult to control, compromising the quality of life, intense psychosocial and economic repercussions, causing a serious public health problem that requires a targeted approach. A regional guideline is needed to make the targeted approach. The Bangladesh 2017 outbreak leads to development of a quick national guideline but an intensive observation will make the subsequent guideline more evidence based. It is important to emphasize that in addition to medical treatment, the approach to the management of patients with Chikungunya requires the involvement of multidisciplinary teams. General physicians, Infectious disease specialists, Rheumatologist and other specialist, nurses, pain specialists, physiotherapists, social workers, and healthcare managers are required to institute these guidelines.

References:

1. Griffin D. Alphaviruses. In: Knipe D, Howley P, editors. Field'svirology. Philadelphia: Lippincott Williams & Wilkins; 2013:651-86.
2. Enserink M. Infectious diseases. Massive outbreak draws fresh attention to little-known virus. Science. 2006;311:1085.
3. Simon F, Javelle E, Cabie A, Bouquillard E, Troisgros O, Gentile G, et al. French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. Med Mal Infect 2015;45:243-263.
4. Schilte C, Staikovsky F, Couderc T, Madec Y, Carpentier F, Kassab S, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. Plos Negleted Trop Dis 2013; 7 e2137. doi: 10. 1371/journal. pntd. 0002137.
5. Ramachadran V, Kaur P, Kanagasabai S, Vadivoo S, Murhekar M. Persistent arthralgia among Chikungunya patients and associated risk factors in Chennai, South India. J Postgrad Med 2014;60:3-6.
6. Ministério da Saúde. Secretaria de Vigilância em Saúde. Febre de Chikungunya manejo clínico. Brasília: Ministério da Saúde; 2015:1-28.

7. Caglioti C, Lalle E, Castilletti C, Carletti F, Capobianchi MR, Bordi L. Chikungunya virus infection: an overview. New Microbiol 2013;36:211-227.

8. Ali Ou Alla S, Combe B. Arthritis after infection with Chikungunya virus. Best Pract Res Clin Rheumatol 2011;25:337-346.

9. Borgherini G, Poubeau P, Jossaume A, Gouix A, Cotte L, Michault A, et al. Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on reunion island. Clin Infect Dis 2008;47:469-475.

10. World Helth Organization. (WHO). Guidelines for prevention and control of Chikungunya fever. South-East Asia: WHO; 2009:1-43.

11. Staikowsky F, Le Roux K, Schuffenecker I, Laurente P, Grivard P, Develay A, et al. Retrospective survey of Chikungunya disease in Réunion Island hospital staff. Epidemiol Infect 2008;136:196-206.

12. World Helth Organization. (WHO Outbreak and spread of chikungunya. *Weekly Epidemiological Record*. 2007 Nov 23;82(47):409-415.

13. Pialoux G, Gauzere BA, Jaureguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. *Lancet Infectious Diseases*. 2007 May;7(5): 319-27.

14. Yergolkar PN, Tandale BV, Arankalle VA, Sathe PS, Sudeep AB, Gandhe SS, Gokhle MD, Jacob GP, Hundekar SL, Mishra AC. Chikungunya outbreaks caused by African genotype, India. Emerging Infectious Diseases. 2006 Oct;12(10):1580-3.

15. Mohan A. Chikungunya fever: clinical manifestations & management. Indian Journal of Medical Research. 2006 Nov;124(5):471-4.

16. Swaroop A, Jain A, Kumhar M, Parihar N, Jain S. Chikungunya Fever. Journal, Indian Academy of Clinical Medicine. 2007;8(2):164-68.

17. icddr b, No evidence of chikungunya virus in Dhaka, Bangladesh. 2007, International Centre for Diarrhoeal Disease Research, Bangladesh. p. 1–4.

18. icddr b, First identified outbreak of Chikungunya in Bangladesh, 2008. 2009, International Centre for Diarrhoeal Disease Research, Bangladesh. p. 1-6

19. National Guideline On Clinical Management Of Chikungunya Fever; DGHS. Ministry of Health & Family Welfare, Bangladesh,May 2017.

20. Management of Chikungunya –a guideline, Bangladesh Society of Mediicne, May, 2017 (1st edition) P1-3

21. Khatun S, Chakraborty A, Rahman M, Banu NN, Rahman MM, Hasan SMM. An Outbreak of Chikungunya in Rural Bangladesh, 2011. PLoS Negl Trop Dis 9(7): e0003907. doi:10. 1371/journal. pntd. 0003907

22. WHO. Chikungunya. 2013; Available from: http:// www. who. int/denguecontrol/ arboviral/other_arboviral_ chikungunya/en/.

23. Schoof H. F. Mating, resting habits and dispersal of Aedes aegypti. Bull World Health Organ, 1967;36(4):600–1. PMID: 5299459

24. Salje H, Lesslera J, Paul KK, Azman AS, Rahman MW, Rahman M et al. How social structures, space, and behaviors shape the spread of infectious diseases using chikungunya as a case study. PNAS , November 22, 2016;113(47):13420–13425.

25. Harrington LC, et al. (2005) Dispersal of the dengue vector Aedes aegypti within and between rural communities. Am J Trop Med Hyg 72(2):209–220.

26. Herriman R. Bangladesh health officials report chikungunya in Dhaka, April 30, 2014. IEDCR, BDNews24 report.

27. Hassan R, Rahman M M , Moniruzzaman M, Rahim A, Barua S, Biswas R, et al. Chikungunya – an emerging infection in Bangladesh: a case series. Journal of Medical Case Reports 2014, 8:67.

28. Hoque MS, Ahmed ASMNU. Chikungunya fever and Bangladesh: Review and updates. DS (Child) H J 2012;28(2):115-122.

29. Tang J, Jose J, Chipman P, et al. Molecular links between the E2envelope glycoprotein and nucleocapsid core in Sindbis virus. JMol Biol. 2011;414:442-59

30. Kuhn R. Togaviridae. In: Knipe D, Howley P, editors. Field's virol-ogy. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2013:629-50.

31. Wintachai P, Wikan N, Kuadkitkan A, et al. Identification of pro-hibitin as a chikungunya virus receptor protein. J Med Virol. 2012;84:1757-70.

32. Schwartz O, Albert ML. Biology and pathogenesis of chikungunyavirus. Nat Rev Microbiol. 2010:491-500.

33. Diallo M, Thonnon J, Traore Lamizana M, Fontenille D. Vectors of Chikungunya virus in Senegal: current data and transmission cycles. Am J Trop Med Hyg 1999; 60: 281-286.

34. Higgs S, Vanlandingham D. Chikungunya virus and its mosquito vectors. Vector Borne Zoonotic Dis 2015; 15:231–40.

35. Rezza G, Nicoletti L, Angelini R, et al. Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 2007;370:1840–6.

36. Tsetsarkin KA, Vanlandingham DL, McGee CE, et al. A singlemutation in chikungunya virus affects vector specificity andepidemic potential. PLoS Pathog. 2007;3:e201. 17.

37. Wolfe ND, Kilbourn AM, Karesh WB, et al. Sylvatic transmissionof arboviruses among *Bornean orangutans*. Am J Trop Med Hyg. 2001;64:310-6. 18.

38. Wauquier N, Becquart P, Nkoghe D, et al. The acute phaseof Chikungunya virus infection in humans is associated with strong innate immunity and T CD8 cell activation. J Infect Dis. 2011;204:115-23.

39. Ng LF, Chow A, Sun YJ, et al. IL-1beta, IL-6, and RANTES asbiomarkers of Chikungunya severity. PLoS ONE. 2009;4:e4261. 46.

40. Kam YW, Lum FM, Teo TH, et al. Early neutralizing IgG responseto Chikungunya virus in infected patients targets a domi-nant linear epitope on the E2 glycoprotein. EMBO Mol Med. 2012;4:330-43.

41. Assunção-Miranda I, Cruz-Oliveira C, Da Poian AT. Molecular mechanisms involved in the pathogenesis of alphavirus-induced arthritis. BioMed Res Int 2013; 2013:1-11. ID 973516.

42. Hoarau JJ, Jaffar Bandjee MC, Krejbich Trotot P, Das T, Li-Pat-Yuen G, Dassa B, et al. Persistent chronic infl ammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 2010; 184:5914-5927.

43. Malvy D, Ezzedine K, Mamani-Matsuda M, Autran B, Tolou H, Receveur MC, et al. Destructive arthritis in a patient with Chikungunya virus infection with persistent specifi c IgM antibodies. BMC Infect Dis 2009; 9:200. doi: 10. 1186/1471-2334-9-200.

44. Yaseen HM, Simon F, Deparis X, Marimoutou C. Identifi cation of initial severity determinants to predict arthritis after chikungunya infection in a cohort of French gendarmes. BMC MusculoskeletDisord 2014; 15:249. doi: 10. 1186/1471-2474-15-249

45. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005; 114:29-36.

46. Guidelines on Clinical Management of Chikungunya Fever, 2016. DGHS, Ministry of Health, India

47. Brito C et al - Pharmacologic management of pain in Chikungunya. Rev Soc Bras Med Trop 49(6):668-679, November-December, 201

48. Schilte C, Staikovsky F, Couderc T, Madec Y, Carpentier F, Kassab S, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. Plos Negleted Trop Dis 2013; 7 e2137. doi: 10. 1371/journal. pntd. 0002137.

49. Ramachadran V, Kaur P, Kanagasabai S, Vadivoo S, Murhekar M. Persistent arthralgia among Chikungunya patients and associated risk factors in Chennai, South India. J Postgrad Med 2014; 60:3-6.

50. de Andrade DC, Jean S, Clavelou P, Dallel R, Bouhassira D. Chronic pain associated with the Chikungunya fever: long lasting burden of an acute illness. BMC Infect Dis 2010; 10:31.

51. Dayron F. Mart1´nez-Pulgar1´n , Fazle Rabbi Chowdhury , Wilmer E. Villamil-Gomez, Alfonso J. Rodriguez-Morales , Gabriela M. Blohm et al. Ophthalmologic aspects of chikungunya infection. http://dx. doi. org/10. 1016/j. tmaid. 2016. 05. 008

52. Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM, Babu RB, et al. Ocular manifestations associated with chikungunya. Ophthalmology 2008;115:287e91.

53. Carlos Alexandre Antunes de Brito, Ana Karla Arraes von Sohsten, Clezio Cordeiro de Sá Leitão, Rita de Cássia Coelho Moraes de Brito,Lilian David De Azevedo Valadares, Caroline Araújo Magnata da Fonte. Pharmacologic management of pain in patients with Chikungunya: a guideline. Rev Soc Bras Med Trop,Nov-Dec 2016 49(6):668-679

54. Pan American Health Organization. CHIKV surveillance in theAmericas: detection and laboratory diagnosis. Washington, DC:Pan American Health Organization; 2014.

55. Lanciotti RS, Kosoy OL, Laven JJ, et al. Chikungunya virusin US travelers returning from India, 2006. Emerg Infect Dis. 2007;13:764-7. 71.

56. NovaTec. ELISA for CHKV antigen-specific IgM; 2015. http://www. novatec-id. com/ products /infectious-diseases-new/virology-new/chikungunya-new/

57. Subhash C. Arya and NirmalaAgarwal. Commercial Antibody-Based Tests for Diagnosis of Acute Chikungunya Infection. Clin Vaccine Immunol. 2012 Mar; 19(3): 457

58. Hyde JL, Chen R, Trobaugh DW, et al. The 5_and 3_ends ofalphavirus RNAs - non-coding is not non-functional. Virus Res. 2015;206:99-107.

59. K. A. Galán-Huerta, A. M. Rivas-Estilla , I. Fernández-Salas, J. A. Farfan-Ale, J. Ramos-Jiménez. Chikungunya virus: A general overview. http://dx. doi. org/10. 1016/j. rmu. 2015. 06. 001

60. Chopra A, Saluja M, Venugopalan A. effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal pain and arthritis following chikungunya virusinfection. Arthritis Rheumatol 2014; 66:319-326

61. Javelle E, Ribera A, Degasne I, Gaüzère BA, Marimoutou C, Simon F. Specifi c management of post-chikungunya

rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006-2012. Plos Negleted Trop Dis 2015; 9:e0003603. doi: 10. 1371/journal. pntd. 0003603.

62. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allerg Immunol 2012; 42:145-153.

63. Thiberville SD, Moyen N, Dupuis-Maguiraga L, Nougairede A, Gould EA, Roques P, et al. Chikungunya fever: epidemiology,clinical syndrome, pathogenesis and therapy. Antiviral Res 2013;99:345-370.

64. Ganu MA, Ganu AS. Post-chikungunya chronic arthritis – our experience with DMARDs over two year follow up. J Assoc Physicians India 2011; 59:83-86.

65. Rosario V, Munoz-Louis R, Valdez T, Adames S, Medrano J, Paulino I, et al. Chikungunya infection in the general population and in patients with rheumatoid arthritis on biological therapy. Clin Rheumatol 2015; 34:1285-1287.

66. Teo, T H, Chan Yi-H, Lee W W L, Lum F-M, Amrun S N, Her Z, et al. Fingolimod treatment abrogates chikungunya virus-induced arthralgia. Sci. Transl. Med. http://dx. doi. org/ 10. 1126/scitranslmed. aal1333 (2017)

67. Miner, J J, Cook L E , Hong J P, Smith A M, Richner J M, Shimak R M, Young A R, et al. Therapy with CTLA4-Ig and an antiviral monoclonal antibody controls chikungunya virus arthritis. Sci. Transl. Med. http:// dx. doi. org/10. 1126/scitranslmed. aah3438 (2017).