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REVIEW ARTICLE

Dengue and Chikungunya Infections in Children

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Abstract
Dengue and Chikungunya are two important mosquito-borne acute febrile illnesses in children. With increased urbanization and newer strains of chikungunya virus with improved transmission with *Aedes albopictus*, the at-risk population for these infections has greatly increased. Dengue fever has been classified by WHO as dengue with/ without warning signs and severe dengue. Severe dengue is associated with hemorrhagic manifestations, hypovolemia and hypotension secondary to third space loss due to capillary leak or severe end organ dysfunction. NS1 antigen detection and dengue polymerase chain reaction, [polymerase chain reaction (PCR during first 5 d)] and IgM for dengue (6th day of fever onwards) are commonly utilized diagnostic tests. Appropriate fluid therapy with timely tapering of intravenous fluid rate with hematocrit, treatment of hemorrhagic manifestations and clinical monitoring are the mainstay of dengue treatment. Chikungunya has less severe course with shorter febrile phase with prominent and persistent joint symptoms. PCR and IgM against chikungunya are appropriate investigations. Treatment is supportive for chikungunya infection with appropriate joint pain relief.

Keywords Dengue · Chikungunya · Hemorrhagic fever · Tropical infections · Aedes

Introduction

Dengue and Chikungunya are important mosquito-transmitted viral infections having significant mortality and morbidity. Both have similar transmission and some overlap of clinical features. The authors hereby describe these two conditions with aspects which are significant to practicing pediatricians.

Dengue

How Common is Dengue and What are the Temporal Trends in Epidemiology?

Estimations suggest that nearly 60 million new cases of apparent dengue infection present every year. In India, 5 lakh dengue patients are admitted in various hospitals every year. Nearly 10,000 deaths are attributed to dengue infection yearly. Secondary to rapid urbanization and overcrowding, temporal trends suggest that incidence of dengue nearly doubled in every decade since 1990 [1].

How is Dengue Fever Transmitted?

Dengue fever is caused by dengue virus (DENV) which has four serotypes, DENV 1, 2, 3 and 4. It is an arbovirus with single stranded RNA belonging to genus Flavivirus, family Flaviviridae. Recently a fifth serotype, DENV5 has been reported from Malaysia but exact characterization of the virus has not been done [2]. Mosquitoes are the primary transmitting host; *Aedes aegypti*, a day biting mosquito, is the most common vector. These mosquitoes dwell in fresh water collections in household like water tanks, coolers, pots, puddles, etc. Once the mosquito feeds on the infected human, virus replicates inside the mosquito gut and disseminates to salivary glands to be injected in new human being when the mosquito bites again. This time duration is called extrinsic incubation period and ranges from 8 to 12 d. Symptoms appear in humans after 4–10 d of mosquito bite (intrinsic incubation period) [3]. *Aedes albopictus* has also been implicated in transmission of dengue and has been increasing globally, especially in Thailand and Indian Ocean region.

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Pathogenesis: How Does Dengue Cause Severe Disease?

Once bitten by infected mosquito, virus spreads to local lymph nodes and then disseminates to reticulo-endothelial system where it proliferates and causes viremia. This viremia is associated with fever and systemic signs. After initial febrile period of usually 4–5 d, critical phase starts. Both innate and cellular immunity act against the virus, releasing abundant cytokines (interferon gamma, tumor necrosis factor, inerleukin-2 *etc*), which leads to increased permeability of capillaries without significant structural changes in endothelium [4]. Antibody enhancement during second dengue infection of different strain is due to anti pre-E and E protein antibodies which leads to enhanced internalization of viruses but does not lead to neutralization of virus; hence uncontrolled inflammatory response ensues [5]. Capillary leak is hallmark of critical phase, causing shift of intravascular fluid to extravascular spaces and hence, intravascular hypovolemia.

Severe dengue infection is complicated by shock, bleeding diathesis or severe end organ dysfunction. Shock is primarily due to hypovolemia secondary to severe capillary leak. Uncorrected hypovolemia leads to circulatory failure and impaired perfusion of vital organs and multiorgan dysfunction. Myocardial dysfunction is also implicated in some cases [6]. Bleeding in dengue is multifactorial and is due to thrombocytopenia, coagulopathy, endothelial dysfunction and hepatic dysfunction. Degree of thrombocytopenia does not correlate with severity of bleeding [7]. Multi-organ dysfunction is usually an outcome of prolonged poor perfusion of end organs due to inadequate fluid resuscitation. Occasionally DENV causes direct cytopathic effects.

What are Clinical Manifestations of Dengue Fever?

Typically, dengue fever is a biphasic fever with afebrile period in-between. The initial febrile phase usually lasts 3–7 d and is associated with myalgias, headache, retrosternal pain, conjunctival injection and joint pain. Pain abdomen, epigastric tenderness and vomiting are other clinical features. Severe bodyaches are common; hence it is also termed as bone break fever. In about one-fourth of patients, generalised blanchable erythema is seen on days 2–4. Mild hemorrhagic manifestations like petechiae and epistaxis may be seen towards end of this phase. Tourniquet test is done by inflating blood pressure cuff between systolic and diastolic pressure around the arm for 5 min. It is considered positive if ≥10 petechiae/square inch appear on the arm just below cubital fossa. Sensitivity and specificity of tourniquet test is poor [8].

Critical phase is associated with capillary leakage which usually begins with improvement in fever. Critical phase lasts for approximately 48 h. Severe plasma leakage leads to intravascular volume depletion and hence features of shock like cool extremities, prolonged capillary refill, tachycardia, poor pulses, narrow pulse pressure which can progress to hypotensive shock. Clinical examination should attempt to look for clinical evidence of capillary leak in form of pleural effusion and ascites. Hepatomegaly is common. Various bleeding manifestations are mild skin bleeds (petechiae and ecchymoses), epistaxis and gastrointestinal hemorrhage. Sudden occult bleed should be suspected in patients with sudden fall in hemoglobin and worsening of shock.

Recovery phase starts with absorption of leaked fluid leading to intravascular fluid overload which can manifest as bradycardia, hypertension and polyuria. If fluids are not adequately titrated, it can manifest as severe features of fluid overload in form of pulmonary edema and congestive cardiac failure. Fever may reappear during this phase. Pruritic rash is common. Rash typically has erythematous maculopapular lesion with areas of hypopigmentation, spread over trunk and extremities, giving appearance of "islands of white in sea of red".

Atypical manifestations have been described with severe end organ involvement, defined as "expanded dengue syndrome". Gastrointestinal manifestations include hepatitis, acalculous cholecystitis, parotitis *etc*. Neurological involvement manifests as encephalopathy, encephalitis, seizure, intracranial bleed *etc*. Other manifestations include myocarditis, pericarditis, renal failure, *etc* [9]. Underlying co-morbidities like hypertension and hemoglobinopathies can modify the clinical course.

Important differential diagnoses are other viral hemorrhagic fevers, severe bacterial sepsis, scrub typhus, severe malaria, *etc*.

What is the Current Case Classification Used in Dengue Fever?

World Health Organisation (WHO) updated the classification for dengue fever in 2009. The new classification diagnoses cases as dengue with or without warning signs and severe dengue [10]. Detailed classification is given in Table 1.

How Do We Investigate a Case of Suspected Dengue Fever?

Laboratory investigations can be divided into investigations aimed at confirming the diagnosis and investigations for case management and supportive evidence.

Diagnostic Tests

Diagnostic tests are aimed at detection of virus particles (viral antigens, viral RNA or viral culture) and antibodies against virus. Viremia is present in initial 4–5 d; hence

Table 1 WHO 2009 dengue case classification [10]

Dengue ± warning signs		Severe dengue
Probable Dengue	*Warning signs*	*Severe plasma leakage*
Lives in/travel to dengue endemic region Fever and 2 of following • Nausea and vomiting • Rash • Aches and pains • Tourniquet test positive • Leukopenia • Any warning sign	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargement >2 cm • Laboratory: increase in hematocrit concurrent with rapid decrease in platelet count	leading to • Shock (dengue shock syndrome) • Fluid accumulation with respiratory distress. *Severe bleeding* *Severe organ involvement* • Liver: AST or ALT ≥1000 IU/L • Neurological: Impaired consciousness • Heart and other organs
Laboratory confirmed dengue: Important when no signs of plasma leakage		

AST Aspartate aminotransferase, *ALT* Alanine aminotransferase

detection of virus particles may be done in initial 5 d. Antibodies appear by second half of first week, making it the first line investigation after 5 d.

Polymerase chain reaction (PCR) and NS1 antigen detection tests and viral culture are done in first 5 d. PCR assays are highly specific (nearly 100%) with good sensitivity (60–100%), but costly and not easily available. NS1 antigen detection test by enzyme linked immunosorbent assay (ELISA) is most commonly used test with good sensitivity (57%–98%) and specificity (100%). Point of care NS1 ELISA strips alone or as a combination strip with anti-DENV IgM/IgG has shown variable sensitivity (60%–99%) and specificity (upto 100%). These point of care tests are important adjuncts in the diagnosis within emergency room where diagnosis is in doubt [11, 12]. PCR and virus culture are not routinely used in clinical settings; they are frequently used in research. Anti-DENV IgM can be detected by capture ELISA. Sixth day onwards, sensitivity of this test ranges from 93 to 99% [13].

Other Investigations

Complete blood count serves as an important screening test. Leukopenia, thrombocytopenia, and increased hematocrit point towards dengue infection. Increased hematocrit (>20%) is marker of clinically significant capillary leak. Hematocrit is monitored frequently while titrating fluid therapy for admitted patients. It is important to send sample to blood bank for cross-match and keep blood products ready, especially in severe dengue patients. Other investigations include blood gas (acidosis, increased lactate), liver function test (hepatitis), coagulation profile, renal function test, and chest X-ray (if associated respiratory distress). In cases with atypical presentation investigations for identification of other diagnoses possibilities like peripheral smear, antigen card test for malaria and assay for malaria, blood culture for enteric fever and sepsis, IgM ELISA or Weil-Felix test for scrub typhus, IgM for chikungunya, serology for leptospira, *etc*. need to be sent.

What are the Indications for Admission and Referral?

Indications for admission are [10]:

1. Severe dengue
2. Presence of warning signs (Table 1)
3. High risk group: Infants
4. Underlying co-morbidities like hemoglobinopathies, immunocompromised patients, chronic therapy with steroids, anticoagulants or immunosuppressants, heart disease, hypertension, and diabetes

How to Manage Dengue Patients with Different Severity?

Case management is as per the WHO guidelines for dengue with focus on adequate fluid resuscitation. Patients are managed as outpatients or admitted, based on severity grading [10].

Outpatient Management

Patients with probable or laboratory confirmed dengue without warning signs or co-morbidities can be managed at home. Adequate rest and good fluid intake are necessary. Patient should pass urine at least once in 6 h. Oral rehydration salt solution (ORS) and home-based solutions with salt and sugar are preferred. Fever control with paracetamol (10-15 mg/kg/dose, 4–6 hourly) and tepid sponging is advised. Non-steroidal anti-inflammatory agents should not be given due to risk of bleeding due to platelet dysfunction, and gastritis.

Patients should be reviewed daily with clinical examination till fever subsides. Hematocrit and blood counts should be repeated only if clinically indicated. Patient and caretakers should be explained about warning signs and that they should report to the emergency if any warning signs appear.

Inpatient Management

Patient management is guided by classification of severity and hemodynamic status of the child as per the WHO guidelines 2012 [10, 14].

Dengue with Underlying Co-morbidity Patients should be encouraged to have adequate oral intake. If not adequate, intravenous (IV) maintenance fluids should be started using isotonic crystalloids such as normal saline (NS) or Ringer's lactate (RL) with or without dextrose (usually 5% dextrose normal saline solution) which are usually needed for 24–48 h. Hematocrit should be monitored every 6–12 h. Vital parameters and urine output should be monitored and danger signs should be carefully looked for. Fever control and other supportive measures should continue.

Dengue with Warning Signs Hemodynamically stable children with warning signs should be admitted and started on IV fluids (crystalloids, NS or RL) at 5–7 ml/kg/h for 2 h while obtaining sample for hematocrit. If there is no hemodynamic worsening and repeat hematocrit is decreasing, fluid rate should be gradually decreased to 3–5 ml/kg/h for 2–4 h, and then 2–3 ml/kg/h to continue. Oral fluids should be encouraged. Increasing hematocrit without hemodynamic instability should be treated with increasing the fluid rate to 5–10 ml/kg/h. Symptomatic care for vomiting and epigastric pain with antiemetics and proton pump inhibitors should be provided. Careful watching of vital parameters, urine output and bleeding should be continued. Fluids are tapered after 24–48 h.

Dengue with Compensated Shock Children presenting with shock with normal blood pressure are started on fluid resuscitation 10–20 ml/kg/h for 1 h while obtaining sample for hematocrit. If there is no response clinically or the hematocrit is increasing, another IV bolus 10–20 ml/kg (crystalloid or colloid) should be given over 1 h. Colloids are preferred if child has already received previous boluses. Options among colloids are 5% albumin, hydroxyethyl starch, gelatins *etc*. Hydroxyethyl starch is associated with coagulation dysfunction and hence should be used cautiously in bleeding patients. Gelatins can develop hypersensitivity reactions. If shock is controlled and hematocrit is stable, fluids should be tapered to IV crystalloid 7–10 ml/kg/h for 1–2 h, 5–7 ml/kg/h for 1–2 h, 3–5 ml/kg/h for 2–4 h followed by 2–3 ml/kg/h to continue. Clinical parameters and hematocrit should be frequently monitored. Any sudden fall in hematocrit along with non-improving or worsening hemodynamic status, should be treated as bleed with blood transfusion and search for site of bleeding is done.

Dengue with Hypotensive Shock Children presenting with hypotension need aggressive fluid resuscitation; immediate IV crystalloid/colloid bolus 20 ml/kg over 15–30 min should be given. Baseline hematocrit should preferably be sent. If there is no improvement in shock, check initial hematocrit and repeat it. If there is sudden fall in hematocrit, suspect bleed and transfuse whole blood or packed red blood cells. If hematocrit increases or remains same, repeat another fluid bolus (preferably colloid) 10–20 ml/kg over 30–60 min; infuse faster if hypotension is persistent. If there is still no improvement in hematocrit, give another fluid bolus (preferably colloid) 10–20 ml/kg over 30–60 min. If still child has persistent hemodynamic instability, management should be individualized with starting inotropes and actively searching for any bleeding source. If there is improvement in clinical signs, continue crystalloid/colloid 10 ml/kg/h for 1 h followed by IV crystalloid 5–7 ml/kg/h for 1–2 h; reduce to 3–5 ml/kg/h for 2–4 h; reduce to 2–3 ml/kg/h and continue. Hematocrit should be monitored every 6 hourly.

It is important to continue monitoring for hemodynamic parameters every 1–2 hourly, as hypotension and hemodynamic instability can be precipitated anytime during critical phase. Early identification and management prevents prolonged hypoperfusion of end-organs and hence limits multi-organ dysfunction.

Choice of Fluid Isotonic fluids should be used for resuscitation of dengue patients. Either crystalloids or colloids can be used. Colloids are retained in the intravascular space and hence maintain intravascular volume for longer time and facilitate resorption of fluid from interstitial space by osmotic action. Colloids are specifically preferred when child does not respond even with first bolus or there is severe respiratory distress due to third spacing. In three randomized trials in children, colloids were associated with decreased requirement of total fluid, faster recovery of hematocrit and faster correction of hemodynamic status, but no benefit in mortality [15–17]. There are concerns of bleeding diathesis with dextran colloids.

What are Indications of Blood Product Transfusion?

Whole Blood/ Packed Red Blood Cells

Patients with hemodynamic instability with bleeding, either overt or occult, detected by sudden drop in hematocrit or low/normal hematocrit with shock should be urgently transfused with fresh whole blood or packed red blood cells if whole blood is not available. Fresh whole blood transfused

should be 10–20 ml/kg or packed red blood cells should be 5–10 ml/kg.

Platelets

Thrombocytopenia is commonly associated with dengue fever but severity of thrombocytopenia is not associated with incidence of significant bleed. In a recent trial in adults, prophylactic platelet transfusion below platelet count of 20,000 per cu mm *vs*. supportive care was not associated with decrease in incidence of bleeding (21% *vs*. 26%. $p = 0.16$) while there were more adverse events in transfusion group [18]. Similar findings are observed in pediatric studies [19]. Hence, platelets should be transfused when there is clinically significant bleeding. Usual dose is 10 ml/kg of random/single donor platelet. There is no cut-off for prophylactic platelet transfusion. Bleeding is multifactorial in dengue and other contributing factors include disseminated intravascular coagulation, liver dysfunction and endothelial dysfunction; these need to be evaluated in a bleeding child with dengue fever.

Plasma

Fresh frozen plasma (FFP) is indicated when there is bleeding with coagulopathy or there is a need for massive blood transfusion. FFP dose is 10 ml/kg over 1 h. FFP should not be used as a resuscitation fluid as it is hyperosmolal, hyperglycemic, has lower albumin content and is associated with significant transfusion related side-effects [20].

What are Atypical Manifestations of Dengue Fever?

Atypical manifestations due to severe end organ dysfunction have been classified as "expanded dengue syndrome". Prolonged hypoperfusion is the most important cause for end organ dysfunction while direct cytopathic effects of DENV have also been implicated. In a study of 254 children admitted with dengue, 41% had atypical manifestation; most common being lymphadenopathy [9]. Seizure (6.7%), encephalopathy (2.7%) and intracranial bleed were most common manifestations. Hepatitis was present in 11.4%, with fulminant hepatic failure in 0.8%. Other gastrointestinal manifestations were acalculous cholecystitis, acute pancreatitis, and acute parotitis. Cardiac involvement in the form of myocarditis, pericardial effusion and cardiac arrhythmias have been described. Acute kidney injury is also seen [9]. Neurological manifestations without significant other system involvement, have been documented in some cases of DENV in cerebrospinal fluid PCR [21]. Treatment is supportive care only.

Ascites due to capillary leak can lead to intra-abdominal hypertension (intra-abdominal pressure more than 10 mmHg in children). When associated with new onset end organ dysfunction, it is classified as abdominal compartment syndrome. Abdominal compartment syndrome has been described in severe dengue in case reports [22]. Management includes cautious titration of fluids to avoid fluid overload, adequate analgesia and sedation, gastric and rectal decompression and maintenance of adequate perfusion pressure (mean arterial pressure – abdominal pressure). Peritoneal dialysis catheter can be used for the drainage to decompress the abdominal cavity, if above measures fail.

Hemophagocytic lymphohistiocytosis (HLH) has been described in dengue patients due to uncontrolled activation of T cells and macrophages leading to cytokine storm. Prolonged fever beyond 7 d and progressive persistent cytopenia should raise the suspicion. Diagnosis is based on HLH 2004 criteria [23]. Few case series have described HLH in dengue and treatment with steroid pulse therapy and IV immunoglobulin therapy shows good response [24].

Once critical phase is over, leaked fluid re-enters the intravascular space. This may cause features of fluid overload and in extreme cases, can lead to pulmonary edema. Such patients should be managed with fluid restriction and diuretics.

When to Plan Discharge?

As per the WHO 2012 handbook, all of the following criteria must be present at the time of discharge.

- No fever for 48 h
- Symptoms improved
- Increasing trend of platelet count
- No respiratory distress
- Stable hematocrit without intravenous fluids

Patient should be orally accepting appropriate amount of diet and liquids. Danger signs should be appropriately explained and follow-up is ensured.

How to Prevent Dengue and What is the Status of Dengue Vaccines?

Mosquito control is the core component of dengue preventive strategies. This includes environmental control with application of pesticides and preventing water collection in or around the house. Personal protection mosquito repellent creams and mosquito nets are advised.

Dengue vaccine development is an active area of research. The only WHO approved vaccine CYD-TDV (Dengvaxia) is a live attenuated quadrivalent vaccine. Efficacy of the vaccine against virologically confirmed dengue in seropositive participants ≥9 y of age is 76% but it is much lower in seronegative patients *i.e.*, 38.8%. However, efficacy against DENV 2 is poor which is implicated in severe dengue infection. There is an increased risk of hospitalization and severe dengue in seronegative patients. Hence, recent WHO position paper

recommends pre-vaccination screening with a high sensitive IgG assay against DENV for all subjects before CYD-TDV and vaccination should be restricted to population in age range of 9–45 y [25]. Usual schedule is 3 doses at 0, 6 and 12 mo. Vaccine is currently not endorsed in India. Multiple new recombinant vaccines are under development which includes DENVax, TetraVax-DV and V180 [26].

Chikungunya

How Common is Chikungunya and What are the Temporal Epidemiological Trends?

Chikungunya is a major emerging arboviral illness all over the world. Though endemic in Africa and south east Asia, chikungunya cases have been isolated from nearly half of the world. Western countries and European countries have demonstrated isolated cases and small outbreaks due to transmission of infection with travellers from endemic areas. After initial epidemics in 1950s to 1970s, there were not major outbreaks till the current epidemic ongoing since 2004 [27, 28]. India had major epidemic in 2006 affecting nearly 1.4 million people. In 2016 and 2017, the number of affected patients in India was estimated at 64057 and 62,268 respectively, compared to 2014 and 2015 when these numbers were 16,049 and 27,553 respectively [29].

How is Chikungunya Transmitted?

Chikungunya virus (CHIKV) is a single stranded RNA virus belonging to *Alphavirus* genus and Togaviridae family. It has three genotypes; West African genotype, East Central South African (ECSA) genotype and Asian genotype. Before 2006 epidemic, Asian genotype was predominant genotype in India but since 2006, major outbreaks have been described with ECSA genotype [27].

Mosquitoes (*Aedes* species) are the most important vectors for CHIKV. Transmission is horizontal while few studies also suggested trans-ovarial transmission. *Aedes aegypti* is the major vector, seen usually in urban populations. *Aedes albopictus* has been implicated in rural transmission of CHIKV, though not equally efficient. Since Indian Ocean chikungunya epidemic, the new E1 alanine to valine 226 mutant CHIKV strain has been found to have improved transmission by *Aedes albopictus*. This has increased the risk of chikungunya in the large rural and suburban populations. Extrinsic and intrinsic incubation period for chikungunya is 7–15 d and 2–4 d, respectively but new E1 A226V CHIKV strain has shorter extrinsic incubation period of only 2–4 d [30]. Mother-to-child transmission and transmission *via* blood products has been described.

Pathogenesis of Chikungunya Infection

After bite of chikungunya infected mosquito, clinical symptoms appear in 2–4 d. Virus grows in reticuloendothelial and myeloid tissue. Fever onset correlates with peak of viremia and most of the clinical features subside within 1 wk by clearance of virus due to adaptive immune system. Type 1 interferons are elevated during the symptomatic phase. Joints involved in chikungunya have been shown to have vascular proliferation, perivascular macrophages and synovial hyperplasia. Synovitis, enthesopathies and periosteal reaction are also common. Exact cause for arthritis is not known. Postulated mechanisms include persistence of viral particles and unmasking of autoimmune condition or pre-existing joint disease. Viral particles have been isolated from synovial macrophages for upto 18 mo after infection [31]. CHIKV is also known to infect stromal cells and choroid plexus cells of nervous system.

What are the Clinical Features of Chikungunya Infection?

Chikungunya presents as an abrupt onset acute febrile illness with high grade continuous fever which lasts for 3–5 d. Fever may have a saddle back pattern. Other common manifestations are arthralgia, bodyaches and headache. Arthralgia/ arthritis usually appear by day 2–3 of illness and involve small joint of hands and lower limb joints. Bodyaches and joint pains are severe and disabling, leading to severe restriction of activity and bending forward while standing. Nearly 50% patients develop skin manifestations, usually maculopapular rash which is generalised and is usually associated with pruritis. Some patients may develop photosensitive hyperpigmentation, stomatitis and exfoliative dermatitis. Lymphadenopathy may be seen. Most of features subside by 3 wk of illness but joint symptoms may follow a chronic persistent or relapsing course [32].

Clinical manifestations can be divided as acute (up to 3 wk), post-acute (beyond 3 wk up to 3 mo) and chronic (beyond 3 mo). Post-acute and chronic manifestations include joint and periarticular inflammatory involvement (arthritis, arthralgia, tenosynovitis, enthesitis, periostitis, *etc*.), locoregional involvement (stiffness, tunnel syndromes, Raynaud syndrome, *etc*.) and systemic manifestations (chronic fatigue, skin dyschromia, anxiety, depression, memory problems, *etc*.) [33]. Frequency of persistent joint symptoms have been described variably from 2 to 80% in different studies [34].

In neonatal age group, perinatally acquired congenital chikungunya usually presents by day 3–7 of life with typical manifestation of fever, rash and peripheral edema. Mother has acute chikungunya during delivery or can be incubating chikungunya infection at the time of delivery. Rash is usually

maculopapular which develops scarring. Hyperpigmentation is also described with congenital chikungunya. Severe manifestations like shock, myocarditis, encephalitis and respiratory failure are also common [35].

What are the Manifestations of Severe Chikungunya Infection?

Severe life-threatening manifestations in chikungunya are rare but have been described in case series. CHIKV is known to show neurotropism. Various neurological manifestations described for chikungunya infection include encephalopathy, encephalitis, Guillain-Barré syndrome, seizures, and neuropsychiatric manifestations [36]. Cerebrospinal fluid (CSF) analysis shows viral encephalitis pattern in some children. CHIKV has been isolated from CSF of encephalitis patients [37, 38].

Other severe manifestations described are hemorrhagic manifestations, multi-organ dysfunction and dengue – like shock syndrome. Comorbidities are associated with atypical manifestations of dengue infection, more commonly seen in adults [39]. Congenital infection and infection in infantile period also have complex course.

Common differential diagnoses include other tropical infections like dengue and rickettsial illness (scrub typhus), serum sickness, acute rheumatic fever *etc*. Dengue also presents with acute febrile illness with bodyaches and rash but few clinical differences exist. Joint symptoms are usually more frequent and prolonged in chikungunya while bleeding diathesis and shock are more commonly seen in dengue fever [29].

How to Diagnose Chikungunya?

Chikungunya is suspected in any child with fever, joint pain with or without rash in endemic region or those who have visited endemic region within last 2 wk. Laboratory confirmation is done by viral isolation, viral RNA detection or serology.

Viral serology is commonly available and is the utilized test. IgM against CHIKV appears between 2 and 7 d of fever onset and is usually detectable after 5 d. Hence, IgM CHIKV detection is first line investigation after 5 d of illness. IgM antibody capture (MAC) ELISA and immunofluorescence are the primary methods and results are available within hours. Point of care ELISA kits are commercially available but accuracy is not well validated. IgG against CHIKV indicate past infection but paired serum can be utilized in acute infection [40].

RT-PCR is used to detect viral RNA during acute viremia phase (first 5 d of illness). Sensitivity and specificity of RT-PCR is high. Recently a rapid detection kit was tested for CHIKV with 100% sensitivity and specificity [41]. But these tests require specialized laboratories and are not widely available. Viral culture is done for research purposes only.

Apart from these, other supportive investigations include hemogram which usually demonstrates leukopenia with mild thrombocytopenia. Investigations aimed at common differential diagnosis such as dengue, scrub typhus *etc*. may be needed.

How to Treat Chikungunya Fever?

There is no specific anti-viral therapy for chikungunya fever. Treatment includes supportive care with rest, antipyretics, analgesia and adequate hydration. During acute phase, joint pain should be managed with paracetamol and NSAIDs should be avoided due to risk of bleeding due to platelet dysfunction. Severe cases with shock, bleeding *etc*. should be managed with fluids and blood component therapy like children with severe dengue with careful monitoring. Co-infections with dengue or bacteremia, should be actively searched for in cases of severe manifestations [29, 32, 33].

Post-acute joint symptoms are treated with NSAIDS. If symptoms are persistent, other options include medications for neuropathic pain (gabapentin and pregabalin). In refractory patients with severe symptoms, short course of low-dose steroids is recommended [42].

How to Manage Chronic Joint and Musculoskeletal Symptoms?

Chronic symptoms mimic inflammatory arthritis. Child should be evaluated for underlying autoimmune arthritis (Anti-nuclear antibodies and rheumatoid factor). Disease modifying anti-rheumatic drugs are used, mostly methotrexate. Other drugs include sulfasalazine, and tumor necrosis factor inhibitors. NSAIDS for pain removal and physiotherapy aimed at prevention of deformity formation and early mobilization are administered [42].

How to Prevent Chikungunya?

As of now, there is no vaccine available against CHIKV. Two vaccines, MV-CHIKV (recombinant measles virus with CHIKV surface proteins) and VRC-CHKVLP059–00-VP (virus like particles), are undergoing phase II trials [43]. Mosquito control is the sole prevention mode currently available with measures as for dengue prevention.

What is DENV-CHIKV Co-infection?

DENV and CHIKV are both transmitted by Aedes mosquitoes. Geographical areas and seasons for both the infections are similar. In high endemicity region, dual infections with DENV and CHIKV have been described. Clinical presentation

of DENV-CHIKV co-infections have course similar to either infections. Sequential infections with DENV and CHIKV infected mosquitoes or infection with dual infected mosquitoes are described mechanisms. Whether co-infections cause more severe or less severe illness is not clear [44]. Diagnosis is confirmed by detecting both viruses by RT-PCR. Specific IgM against both viruses can also be tested but this will not differentiate recent past infection from co-infections as IgM has been demonstrated to last from weeks to months [45]. Treatment is mainly supportive due to lack of specific antiviral agents for either virus. Patients with clinical feature of shock should be managed as dengue shock syndrome with appropriate fluid therapy. Larger studies aiming at routine testing of DENV and CHIKV PCR and describing clinical manifestations of co-infections compared to individual infections are needed.

Contributions ND contributed in formulating and writing the manuscript. SKK and RL contributed by formulating the plan, supervising and modifying the manuscript. RL will act as guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

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