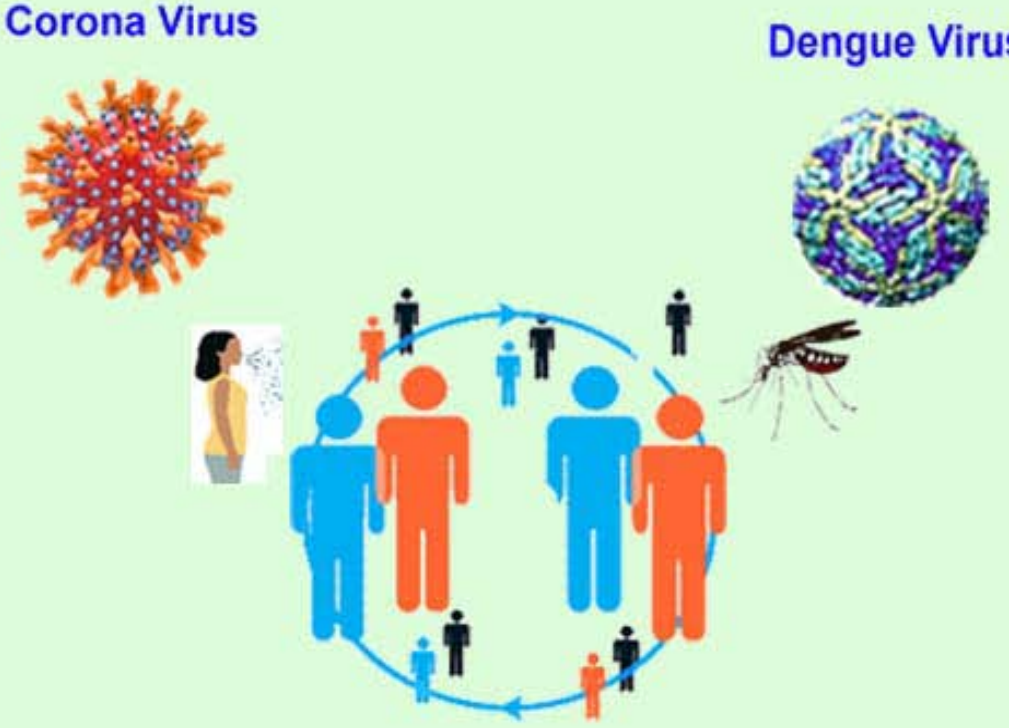
सत्यमेव जयते
Goverment Of India

National Guidelines
Dengue Case Management during Covid 19-Pandemic



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Summary

COVID-19 pandemic is soon going to complete one year of human circulation, and we are still not sure how long it is going to be there in the community. Therefore, the burden of co-infection and co-morbidities of other diseases with COVID-19 is expected to be higher in the future. The clinical management guidelines made before COVID-19 may not be applicable now for the management of patients. It is also challenging to exclude other causes of Acute Febrile Illness (AFI) such as Dengue, Chikungunya, Malaria, Scrub typhus, Leptospirosis and Typhoid, especially during the transmission season.

During COVID-19 pandemic, most of the hospitals are busy in managing COVID-19 patients. It was experienced that non-COVID patients were neglected during lockdown following the closure of OPDs and other services in health care settings. In India, the burden of vector-borne diseases is a great public health challenge, especially Dengue being an outbreak-prone disease. Dengue is endemic in all States and Union Territories in the Country except Lakshadweep and Ladakh with recurring outbreaks. The incidence of dengue has increased in the last few years. The disease has a seasonal pattern, maximum cases are reported after the monsoon during the period of July-November and it is not uniformly distributed throughout the year.

In this document, the clinical management of Dengue has been focused on the scenario of the COVID-19 pandemic. Both diseases share many similarities in signs and symptoms. Even in pathogenesis, they share many mechanisms and pathways for the progression and severity of the disease. Therefore, clinical diagnosis and management have become a challenging task. This document highlights epidemiology, pathophysiology and clinical features of both the diseases. It also defines the case classification of the co-infected cases, along with the management of Dengue cases in COVID-Dengue co-infection. Use of low molecular weight heparin and steroid in case of co-infection remains a challenging area for the clinicians; the document aims to clarify and aid the clinicians for the same.

Preventive measures such as vector control, surveillance, personal protective measures and IEC/BCC remain the pillars for Dengue control. COVID-19 pandemic presents a unique challenge in terms of limitation of movement of human resource and thus has a significant impact on integrated vector management activities as well. The guideline also highlights a roadmap that could be followed by District and State authorities, keeping in the COVID-19 situation in mind, to ensure that programmatic activities do not suffer and any impending outbreak of Dengue may be curbed at the earliest.

Chapter 1

Introduction

WHO declared COVID-19 as a global pandemic on 11th March 2020, since then the world is facing the brunt of corona pandemic and millions of people are affected across the globe. At the same time, cases of dengue fever have also been increasing in endemic countries. The monsoon season, starting from July to November, is the period of peak incidence of mosquito-borne illnesses, especially Dengue, Malaria and Chikungunya.

Dengue Fever has been in and around the South East Asia Region since the country for decades and has shown periodic upsurges. Based on epidemiological data and previous understandings, we do expect a surge in Dengue cases in India, starting from early August onwards every year. Therefore, the stage is set where both Dengue Fever and COVID-19 cases are expected to increase simultaneously. In settings like these, a Dengue Fever and COVID-19 co-infection would be difficult to manage and will put a massive burden on the already overwhelmed health care system. But the nation has shown time and again, that it excels in chaotic, gloomy conditions with the help of a clear, consolidated scientific approach and rationalizes thinking. This brings many pertinent issues such as Do Dengue, and COVID-19 have any shared linkage in pathogenesis, coinfection and comorbidities? At present, when we are struggling against COVID-19, a Dengue upsurge would add fuel to it to bring up more fiery and challenging issues to battle two viral infectious diseases as they sometimes present with overlapping signs and symptoms making them difficult to diagnose and manage. It is a well-known fact that any co-infection or co-epidemic will be a more lethal combination associated with higher mortality and morbidity. In Dengue prone zones, a person recovered from one illness will likely contract the other one or even an individual might be having these two illnesses together. They both have a large pool of asymptomatic cases with an unpredictable clinical course, and both require hospitalization and monitoring in severe cases. Fluid therapy which is the cornerstone of dengue management, might not be advisable in a co-infected patient with ARDS/Pulmonary oedema. Similarly, the approach to anticoagulation is challenging where one disease causes thrombocytopenia, and other creates a prothrombotic state. Moreover, no specific drug is available for both the disease and we are still far from successfully attaining a vaccine for both. Therefore, management depends entirely on clinical symptoms and severity. So, a clear protocol is necessary to tackle such a tricky situation and the present document sheds light on the same.

Chapter 2

Epidemiology

2.1 Epidemiology of Dengue in India

Dengue is the most rapidly spreading mosquito-borne viral disease of humankind, with a 30-fold increase in global incidence over the last five decades. Dengue is a major public health concern throughout tropical and subtropical regions of the world. Almost half the world's population lives in countries where dengue is endemic. Dengue has been identified as one of the 17 neglected tropical diseases by the World Health Organization, as mentioned in its first report on neglected tropical diseases (2010). Although the full global burden of the disease is still uncertain, the patterns are alarming for both human health and the economy. Every year, thousands of cases of Dengue Fever occur all over the country giving rise to a significant number of deaths and morbidity. Last year alone, there were 20000 deaths; 264 disability-adjusted life years (DALY) per million populations. The case-fatality rate for dengue fever varies by region and age group-wise and most fatal cases are among children and young adults.

Globally the disease is now endemic in many countries of the regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The Americas, South-East Asia and Western Pacific regions are the most seriously affected. One estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease). Another study, of the prevalence of dengue, estimates that 3.9 billion people, in 129 countries with 70% of the actual burden in Asia. Although the full global burden of the disease is uncertain, the initiation of activities to record all fever cases partly explains the sharp increase in the number of cases reported in recent years. According to WHO, a vast majority of cases are asymptomatic and hence the actual numbers of Dengue cases are underreported, many are misclassified. Dengue Fever was enlisted by the WHO as one of the ten threats to global health in 2019. The number of cases reported increased from 2.2 million in 2010 to over 4.2 million in 2019. The largest number of dengue cases ever reported globally was in 2019.

Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide lives in SEAR and WPR, which bear nearly 75% of the current global disease burden due to dengue. Out of SEAR, all 10 countries including India are endemic for dengue except the Democratic Peoples' Republic of Korea. In 2016, SEAR countries reported approximately 0.50 million cases, of which Indonesia was responsible for 40% and India 26%. The Region of the Americas reported more than 2.38 million cases in 2016, where Brazil alone contributed slightly less than 1.5 million cases, approximately 3 times higher than in 2014 (Source: WHO).

In India till date, all States/UTs, (except Ladakh) have reported dengue cases during the last two decades (even Lakshadweep has been reporting suspected dengue cases). During 1996, one of the most severe outbreaks of dengue fever occurred in Delhi, with 10252 cases and 423 deaths (country total was 16517 cases and 545 deaths). Recurring outbreaks of dengue fever have been reported from various States/UTs. The incidence of dengue is increasing in the last few years. Highest numbers of 188401 dengue cases were reported during 2017. Though in 2019

global increase in the number of Dengue Fever cases was reported, India had only reported a total of 157315 cases. During 2020, a sharp rise in Dengue was reported till March in comparison 2019, however, following the COVID-19 pandemic and subsequent lockdown reporting of cases declined. Till 18th October, only 20,202 cases and 12 deaths were reported due to dengue. The case fatality rate (CFR- deaths per 100 cases) has declined from 3.3% in 1996 to 0.3% in 2014 and sustained at 0.2% in 2015 to 2018, and 0.1% in 2019. (Source: NVBDCP)

Every year during the period of July-Nov, an upsurge in the cases of dengue has been observed. The disease has a seasonal pattern, i.e., the peak of the case after the monsoon and it is not uniformly distributed throughout the year. However, the states in southern and western parts of the country report perennial transmission.

The agent, i.e. dengue virus is categorized under the genus *Flavivirus*. The virus contains single-stranded RNA and is small in size (50nm). There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. These serotypes may be in circulation either single or more than one type can be in circulation in any area at the same time. Although all four serotypes are antigenically similar, still they are different enough to elicit cross-protection only for a few months after infection by any one of them. Infection with one serotype confers lifelong immunity to that virus serotype only.

The four dengue virus types (DENV1-4) called as dengue virus serotypes form a phylogenetic group and differ in nucleotide sequence from each other. These are closely related to one another than to other flaviviruses and form an antigenic complex of their own. Within each serotype, subtypes or genotypes are detected based on their phylogenetic analysis of the genomic region in the envelope gene. The four dengue virus serotypes can cocirculate in the endemic areas because the immunity to one serotype does not protect from the infection by a heterologous serotype. Individual variation occurs in antibody responses to dengue virus. The secondary infections are associated with elevated risks of severe disease outcomes. The primary and secondary infections are distinguishable based on their antibody responses. The ability of all DENV serotypes to utilize pre-existing heterotypic *Flavivirus* antibody to enhance infection is a unique feature of dengue which distinguishes it from all other flaviviruses and is considered to be the primary basis of pathogenesis. All four serotypes are isolated from India.

Most of the time the dengue infection is asymptomatic and the exact cause of severity among some patients is not clearly understood when there is an interaction between agent and host. Infected people play a significant role in introducing dengue virus in circulation by their movement to newer areas.

Dengue viruses are transmitted from an infected person to others by the bite of female *Aedes* (*Ae.*) mosquitoes. In India, *Aedes aegypti* is the main vector in most urban areas; however, *Ae. albopictus* is also incriminated in many states. But other species like *Ae. polynesiensis* and *Ae. niveus* have also been incriminated as secondary vectors in some countries. The climatic conditions particularly temperature and rainfall play a vital role in the life cycle, breeding and longevity of vectors and thus transmission of the disease. *Aedes* is a day time feeder and can fly up to a limited distance of 400 meters. In the absence of any vaccine or specific drug for dengue, vector control is very significant in preventing disease transmission.

Ae. aegypti breeding was more common in urban areas and as such, the disease was observed to be most prevalent in urban areas. However, the trend is now changing due to socio-economic and man-made ecological changes that have resulted in the invasion of *Ae. aegypti* mosquitoes into the rural areas, which has significantly contributed to the rural invasion of the disease.

Ae. aegypti breeds almost entirely in domestic human-made water receptacles found in and around households, water storage containers, water reservoir, overhead tanks, desert coolers, unused tyres, coconut shells, disposable cups, unused grinding stone, industrial and domestic junk, construction sites, etc. *Ae. albopictus* prefers natural larval habitats which include tree holes, latex collecting cups in a rubber plantation, leaf axils, bamboo stumps, coconut shells, etc. However, *Ae. albopictus* breeding has been reported recently in domestic habitats as well.

The *Ae. aegypti* usually becomes infected with dengue virus when it takes a blood meal from a person during the acute febrile (viraemia) phase of the illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infective, and the virus is transmitted when the infected female mosquito bites and injects its saliva into the wound of the person and through this the cycle of dengue continues. Dengue begins abruptly after an intrinsic incubation period of 4 to 7 days (range 3-14 days). There is also evidence that vertical transmission of the virus from infected female mosquitoes to the next generation occurs. Though primarily transmission occurs through the bite of a vector, there are reports of dengue transmission through blood transfusion and organ transplantation. There are also reports of congenital dengue infections occurred in neonates born to mothers infected very late in pregnancy.

2.2 Epidemiology of COVID-19 in India

The coronavirus belongs to a category of pathogens, which mostly attack the respiratory system of human beings. Coronavirus outbreaks have emerged earlier also in the form of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). There are various epidemiological and operational factors which converted this disease from being an outbreak in China to a full-blown pandemic affecting the whole world. The epidemiological triangle depicts the interrelation of host (who carries the disease), agent (virus) and environment of a specific place at a given time. Since December 2019, the intensity of the spread of COVID-19 from Wuhan (China) to other parts of the world varies at different paces. India recorded its first COVID-19 case on 30th January 2020 and since then it has spread like wildfire across India.

The persons with active infection of novel coronavirus are the main pool of infection. Direct person-to-person transmission occurs through close contact, mainly through respiratory droplets that are released when the infected person coughs, sneezes, or talks. These droplets may also land on surfaces, where the virus remains viable. Infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. The median incubation period is 5.1 days (range 2–14 days). The precise interval during which an individual with COVID-19 is infectious is uncertain. As per the current evidence, the period of infectivity starts 2 days before the onset of symptoms and lasts up to 8-9 days in most of the cases.

Almost all states and union territories have reported cases and mortality varies from state to state. Till 20th October, 2020, a total 76,49,102 confirmed cases and 1,15,950 deaths were

reported due to COVID-19. The state-wise COVID-19 situation may be seen at https://www.mohfw.gov.in

2.3 Coinfections of Dengue and COVID-19

WHO in the guidance document for clinical management of COVID-19 dated 27th May 2020 suggests that in areas with other endemic infections that cause fever, such as Malaria, Dengue, tuberculosis (TB) etc., as part of the screening, febrile patients should be tested as per routine protocols, irrespective of the presence of respiratory signs and symptoms, since coinfection with COVID-19 may coexist in such a setting.

In India, as per available information, Assam, Chandigarh, Daman & Diu, Delhi, Goa, Gujarat, Karnataka, Kerala, Maharashtra, Odisha, Punjab and Uttar Pradesh have reported cases of Dengue with COVID-19 co-infection. Besides, deaths due to COVID-19 having co-infection of dengue have been reported from the States of Assam, Maharahstra, Punjab and Delhi.

2.4 Why Co-infection: A Public Health Challenge

- Difficult to distinguish symptoms and signs because of their overlapping initial clinical presentations and laboratory parameters.
- They both have an unpredictable clinical course and both generally require in-hospital monitoring for management. A high index of suspicion will be required to identify Dengue-COVID-19 co-infections.
- Most of the hospitals are busy with managing COVID-19 at present, and a very little window is open to tackling another disease outbreak.
- Most of the cases of COVID-19 and dengue are asymptomatic (about 80%). In a setting of coinfection, one might enhance the severity of the other.
- IV fluid therapy is challenging in coinfected patients due to early development of ARDS/pulmonary oedema.
- Treatment with Low molecular weight heparin for management of COVID-19 may enhance bleeding in the presence of dengue, especially with low platelet count.
- False positivity is also reported among co-infection, which may create a diagnostic challenge.
- Both viral diseases do not have any specific antivirals drugs or any vaccine.

2.5 Phylogeny of the viruses

SARS-CoV-2 is a beta coronaviridae belonging to the coronaviridae family of Nidovirale order. This family of enveloped coronaviruses characteristically infects mammals and birds causing mainly respiratory tract infection and diarrhoea in humans. They contain a positive-sense single-stranded RNA genome one of the largest among the RNA viruses and a nucleocapsid of helical symmetry under an envelope containing multiple surface proteins which gives them a crown-like

appearance. SARS-CoV-2 carrying a genetic homology of 82% with SARS-CoV-1 (2003) and 50% genetic homology with MERS-CoV is under Baltimore class IV.

Dengue is a mosquito-borne arbovirus belonging to the Flaviviridae family containing a positive single-stranded RNA genome. It is an enveloped virus having nucleocapsid with icosahedral symmetry. Like SARS-CoV-2, it is also a Baltimore Class IV virus. The ss-RNA takes the help of host cytoplasmic proteins to replicate and like SARS-CoV-2 dengue also replicates in the cytoplasm of the infected cells. There are 4 serotypes of dengue, and in hyperendemic regions, multiple serotypes are found to be cocirculating.

So, both of them are enveloped ss-RNA (non-segmented) viruses which are in the same Baltimore group IV. Other structural and pathophysiological similarities have been discussed in details in the diagnostic and pathogenesis part, respectively.

Chapter 3

Pathogenesis

3.1 Pathogenesis of Dengue

The agent, i.e. dengue virus, is categorized under the genus Flavivirus. There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. These serotypes may be in circulation either single or more than one can be in circulation in any area at the same time. Although all four serotypes are antigenically similar, still they are different enough to elicit cross-protection for a few months after infection by any one of them.

Molecular epidemiology

The four dengue virus types (DENV1-4) called as dengue virus serotypes form a phylogenetic group and differ in nucleotide sequence from each other. These are closely related to one another than to other flaviviruses and form an antigenic complex of their own. The following subtypes or genotypes are also detected within each serotype based on their phylogenetic analysis of the genomic region in the envelope gene:

Serotype : Subtype/Genotype

- DENV-1: Three
- DENV-2: Six
- DENV-3: Four
- DENV-4: Four

The dengue virus genome is composed of three structural protein genes encoding the nucleocapsid of core protein (C), a membrane-associated protein (M), an envelope protein(E) and seven nonstructural (NS) proteins - NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. The functions for all the individual NS-proteins are not well characterized. However, NS1 protein has been shown to interact with the host immune system and known to evoke T-cell responses. In dengue virus infection, patients have measurable levels of NS1 protein in the blood, which are utilized as a diagnostic marker of the infection.

3.2 Pathophysiology of Dengue Fever

The exact pathophysiology of Dengue Fever is not clearly understood but clinically the course of illness can be characterized by early infection, viral dissemination, immune response and subsequent viral clearance. Host immune response plays an important role in the pathogenesis as well. Various mechanisms are proposed to explain the signs and symptoms observed in a patient, and most have the following central themes:

i. Antibody-dependent enhancement (ADE)
ii. Cytokine Storm
iii. Vasculopathy
iv. Coagulopathy

The dengue virus is taken up initially by dendritic cells and after antigen processing is presented to the T cells. Dengue virus has three principal proteins that are targeted by the host immune response.

- E protein,
- (pre-M) precursor membrane protein,
- NS1.

E protein-specific antibodies cause neutralization of infection and block attachment to cell receptors.

NS1 is not found in the virion; NS1-specific antibodies are therefore incapable of neutralization of infection but can direct complement-mediated lysis of infected cells.

Pre-M–specific antibodies bind to partially matured virions only and show poor neutralization of infection but can mediate ADE.

As a result of infection, there are two types of antibodies being produced, neutralizing and non-neutralizing. Neutralization requires a threshold level of antibodies. The neutralizing antibodies can protect against a specific serotype of the virus. The non-neutralizing antibodies bind to but do not neutralize an infecting virus. After the formation of virus-antibody complex, viral entry is enhanced into the host cells, specifically dendritic cells and macrophages. Once inside the cell, the virus replicates and generates higher virus titres in the blood. This phenomenon is known as Antibody-Dependent Enhancement (ADE) of infection. Dengue virus-specific CD4+ and CD8+ T cells lyse dengue virus-infected cells and produce cytokines such as IFN-gamma, tumour necrosis factor (TNF)-alpha, and lymphotoxin, all of which results in a "Cytokine storm" and ultimately leads to more severe disease. IFN-gamma also enhances the expression of immunoglobulin receptors, which augments the antibody-dependent enhancement of infection.

The clinical manifestation of dengue stands upon the shoulders of two modes of pathogenesis; Vasculopathy and Coagulopathy.

Vasculopathy

Clinical presentation of dengue fever varies widely. While most symptomatic patients recover after a short illness, small proportion progress to more severe disease, typically manifesting as a vasculopathy characterized by plasma leakage and a haemorrhagic diathesis. Plasma leakage may be profound, sometimes resulting in life-threatening illness. More commonly, hypotension is caused by plasma leakage, which may be mild and transient or progress to profound shock with an undetectable pulse and blood pressure. A transient disturbance in the function of the endothelial glycocalyx layer is seen during infection and leads to temporarily alteration in characteristics of fibre matrix of the endothelium. Anti-NS1 antibody acts as autoantibodies that cross-react with platelets and non-infected endothelial cells and triggers intracellular signalling leading to disturbances in capillary permeability. Plasma leakage is caused by a diffuse increase in capillary permeability and manifests as a combination of haemoconcentration, pleural, pericardial effusion or ascites and various organ involvements. The severity of organ involvement

and shock correlates with the degree of vasculopathy. It usually becomes evident on 3rd to 7th day of illness.

Coagulopathy

The causes of coagulopathy usually seen in dengue fever are multifactorial and the exact underlying mechanism remains unclear. An increase in activated Partial Thromboplastin Time (aPTT) and reduction in fibrinogen concentrations are relatively consistent findings in most cases. Thrombocytopenia associated with coagulopathy increases the severity of haemorrhage. Release of heparan sulphate or chondroitin sulphate (molecules similar in structure to heparin that can mimic its function of anticoagulation) from the glycocalyx also contributes to coagulopathy.

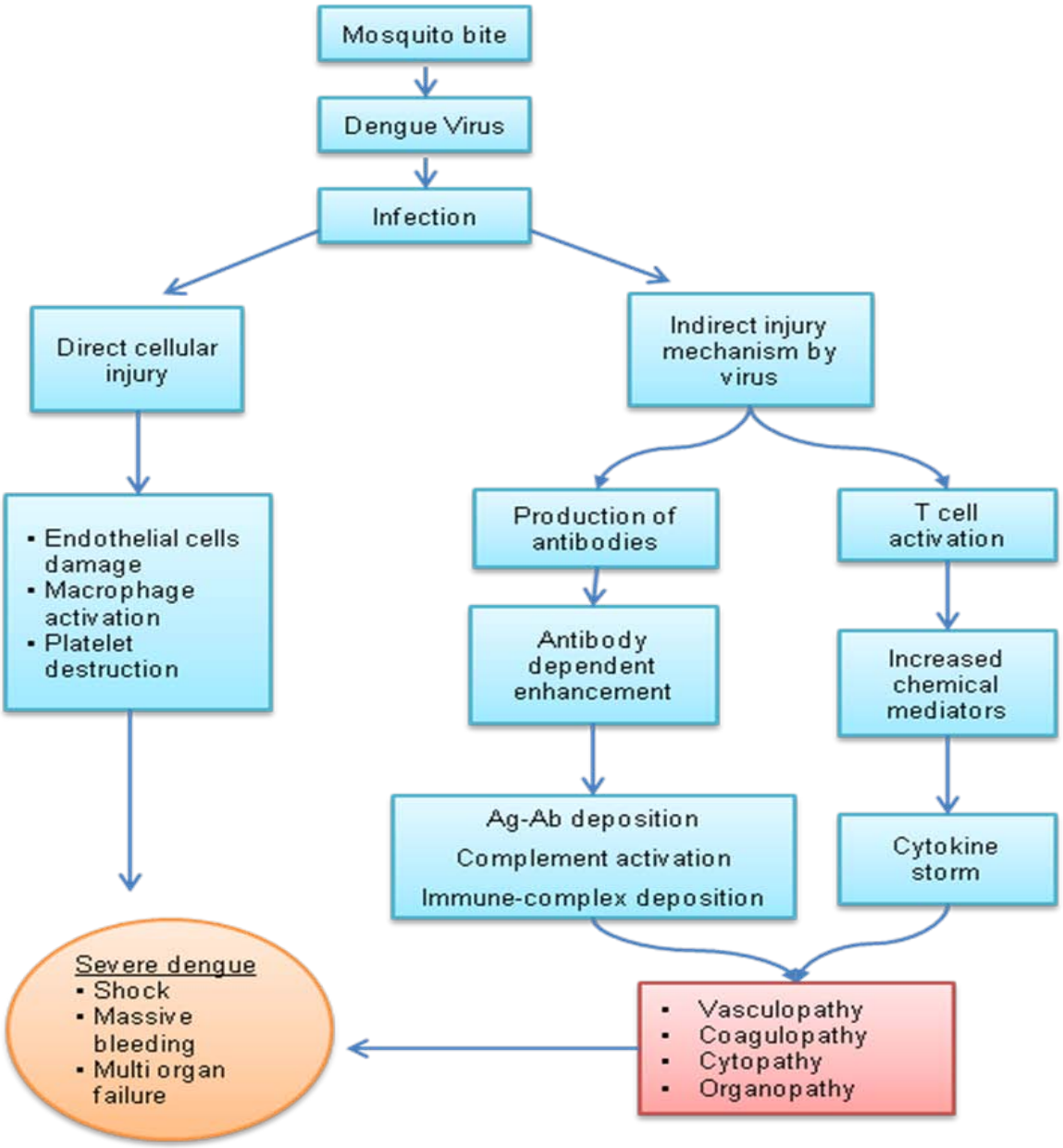


Figure- 1: Pathogenesis of Dengue Fever

3.3 Pathogenesis of COVID-19

Viral Entry:

Coronaviruses are transmitted chiefly via respiratory droplets. The first step of infection is virus binding to a host cell target receptors. SARS-CoV-2 principally binds to the airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lungs, all of which express ACE2 receptors, with the help of the spike proteins. This S protein comprises two subunits S1 and S2. S1 subunit has the receptor-binding domain, which upon binding the ACE2 receptors triggers endocytosis. S1 is cleaved by an endosomal protease, and this releases fusion peptide which enters into host membrane associated with folding of S2 component on itself to bring HR1 and HR2 together. This leads to membrane fusion and releases into the target cell. The cell wall serine protease TMPRSS2 is also required to process the SARS CoV 2 spike protein and facilitate the host cell entry.

Immune response to the Corona virus and the basis of severe disease

SARS-CoV-2 is a cytopathic virus; entry into the cells leads to proptosis and subsequent triggering of inflammatory response recruits macrophages and monocytes that release cytokines and prime adaptive T and B cell immune response. The pattern recognition receptors of alveolar macrophages detect the pathogen-associated molecular patterns (PAMP) and cell damage-associated molecular patterns (DAMP) including ATP DNA and ASC oligomers. It leads to a wave of local inflammation mediated by secretion of pro-inflammatory cytokines and chemokines IL-6. IFN y, MCP 1, IP-10. These cytokines attract blood monocytes and lymphocytes to the infected site and cause lymphopenia and increased neutrophil-lymphocyte ratio. In most of the patients, the recruited cells clear the infection in the lung the immune response recedes and the patient recovers, however, in some patients, when a dysfunctional immune response occurs, which triggers a cytokine storm that leads to widespread lung inflammation and tissue damage. Unrestrained inflammatory cell infiltration can itself mediate damage in the lung through excessive secretion of proteases and reactive oxygen species. Together they result in diffuse alveolar damage, including desquamation of alveolar cells, hyaline membrane formation and pulmonary oedema which limits the gas exchange in the lung. In addition to local damage, cytokine storm can cause septic shock and multi-organ failure. Aged people are at increased risk of such dysfunctional immune response though the exact reason is not known; one reason may be that ageing lung microenvironment causing altered dendritic cell maturation and migration to the lymphoid organs.

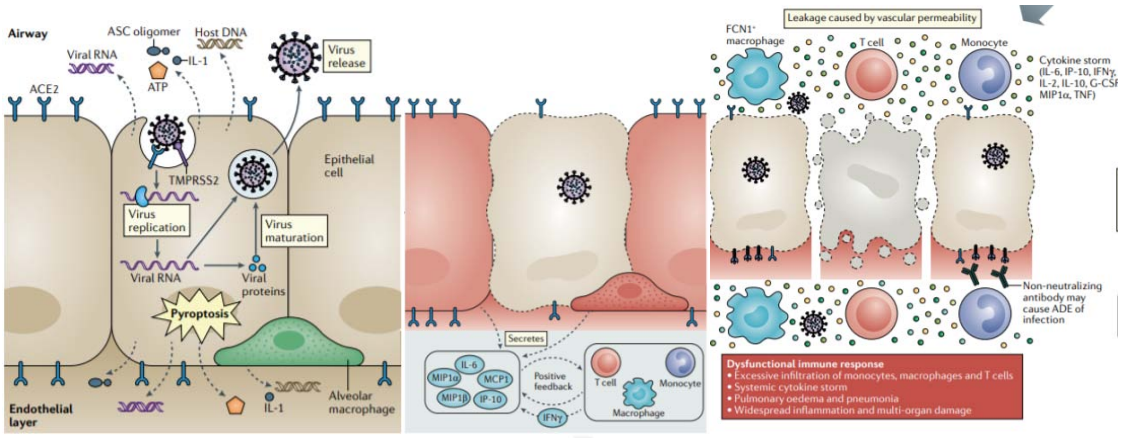


Figure- 2: Viral entry and pathogenesis

Source. *Nat Rev Immunol. 2020 06;20(6):363-74*

The evasion of the host innate immune response also plays a significant role in viral persistence. It can occur at various stages of interferon signalling pathways including PRR recognition of viral RNA, and PRR signalling through TBK1/ Inhibitor of NFkβ kinase subunit ε (IKKε), TRAF3, IRF3 by preventing the downstream interferon signalling through STAT1 and by promoting host RNA degradation and by inhibiting host protein translation. Also, nonstructural protein like nsp14 can initiate cap formation in viral RNA like the host RNA so that the cytosolic PRRs can't recognize them apart from these multiple nonstructural proteins takes part in evasion of host immunity which leads to enhanced pathogenicity of the virus.

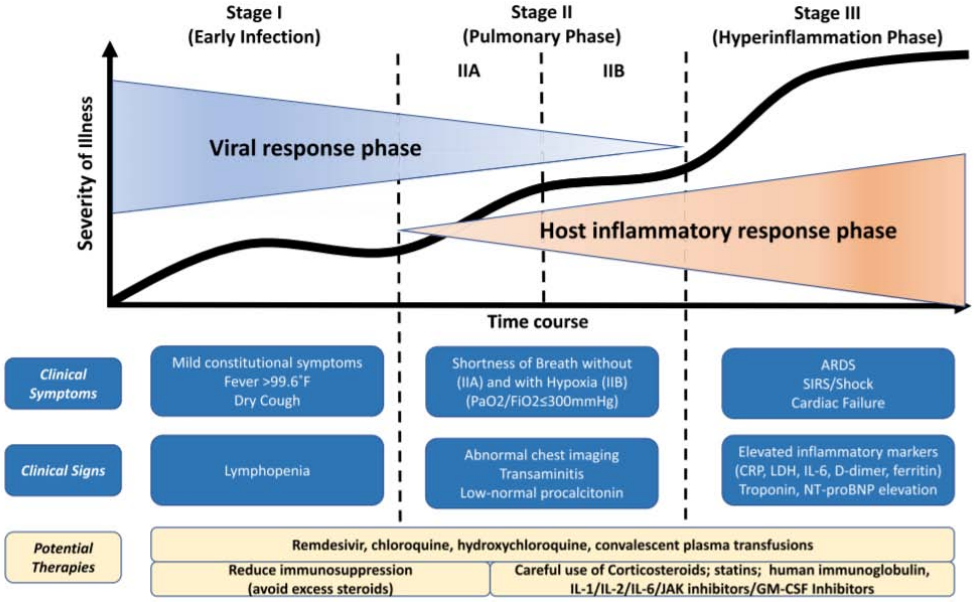


Figure- 3: Clinico pathophysiological correlation

Source. *J Heart Lung Transplant*. 2020;39(5):405-407. doi:10.1016/j.healun.2020.03.012

Stage 1

This phase occurs at the time of early inoculation of the virus and early establishment of the disease. This phase is accompanied by mild and non-specific symptoms such as fever malaise and dry cough. At this phase, the virus binds to the target cells expressing ACE2 receptors in the respiratory system.

Stage 2

A stage of established viral Pneumonia with or without the development of hypoxia. At this stage, most COVID-19 patients need to gets hospitalized and requires monitoring. Markers of systemic inflammation are increased in the blood.

Stage 3

Most severe stage of illness manifests as an extrapulmonary systemic hyper inflammation syndrome. Inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, MIP-1-α, TNF-α, CRP, Ferritin and D-dimer are significantly elevated. A form akin to develop secondary HLH may occur in this stage. At this stage, shock, respiratory failure and even cardiopulmonary collapse can happen.

3.4 Impact of Co-infection on the severity of the disease

Dengue primarily gets transmitted by mosquito bite, initially infects the LHCs in the dermis or the peripheral blood monocytes which later on carries the viral particle to draining lymph node and primes the T cell and B cell. On the other hand, the route of entry of coronaviruses is the respiratory tract. Both the viruses multiply in the host cellular cytoplasm and there is a striking similarity between host immunity evasion strategies between them. In a setting of the dysfunctional immune response, both can cause a cytokine storm that leads to both local and systemic tissue damage. Both the viruses have been implicated in causing an antibody-dependent enhancement in the setting of secondary infection. Whether cross-reactive antibodies can also give rise to ADE or not, this requires further research.

3.5 Diagnostic approach to Co-infection

When a patient comes with acute febrile illness, it should be kept in mind the endemic diseases of the region and the seasonal outbreak pattern of the infections and choose the diagnostic tests accordingly. The chief differentials of the AFI become Dengue, Malaria, Typhoid, Leptospirosis and Scrub Typhus.

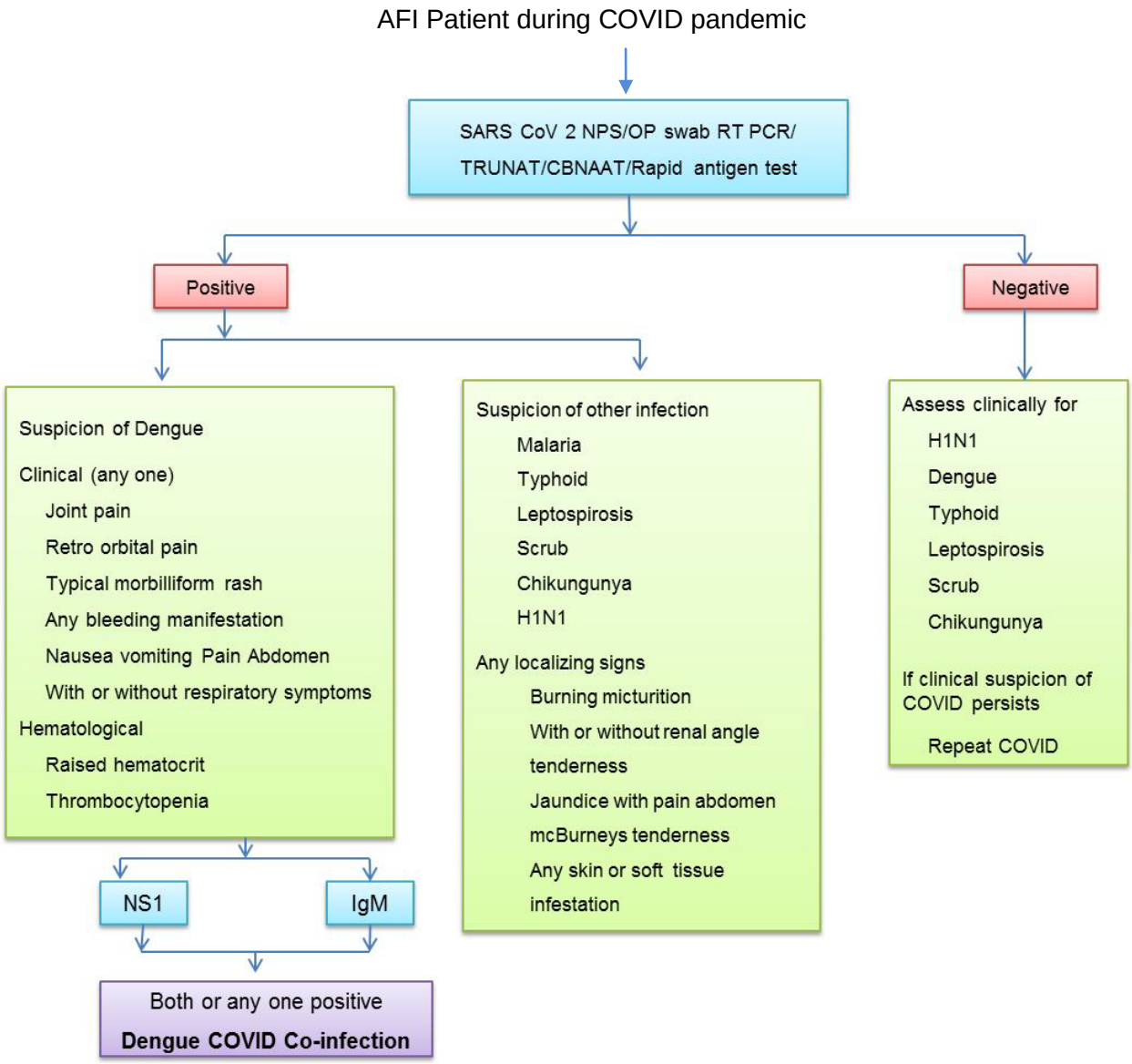


Figure-4: Diagnostic approach to Co-infection Workup of AFI patients during COVID-19 pandemic

Studies have shown there is a chance of cross-reactive antibody formation, so false positivity can't be ruled out at this moment. If a patient presents late, say after 5 days IgM for dengue should be tested and if fever less than or equal to 5 days NS1 and PCR should be tested. To term it a co-infection on 21-35 days, COVID-19 antibody titer can be measured as it will be proven that SARS-CoV-2 has primed the immune cells of the body. However, the chances of false-positive results to be always kept in mind.

Some of the logistic issues should be taken care of like the fever clinics and emergency screening areas should have round the clock provision for dengue and malaria testing. The patient is needed to be sampled for these infections based on strong clinical suspicion. Because once the patient is admitted under a COVID-19 ward, testing for microbiological evaluation becomes tougher and is often not thought about in clinical practice. Screening area physicians should be vigilant about coinfection and look for it in all AFI patients especially during post-monsoon season.

Chapter 4

Clinical Features

4.1 Clinical features of dengue

Case definition of dengue fever

Probable Dengue fever:

A case compatible with the clinical description of dengue fever during the outbreak and/or Non-ELISA based NS1/IgM positive so RDT reports are probable due to poor sensitivity and specificity

Confirmed Dengue Fever:

A case compatible with the clinical descriptions of dengue fever with at least one of the following:

- Demonstration of dengue virus antigen in a serum sample by NS1-ELISA
- Demonstration of IgM antibody titer by ELISA in the single serum sample
- IgG seroconversion in paired sera after 2 weeks with a fourfold increase of IgG titer
- Detection of viral nucleic acid by PCR
- Isolation of the virus (virus culture positive) from serum, plasma or leucocytes).

Natural Course of Dengue Infection

The clinical course of illness passes through the following three phases (Figure- 5):

- Febrile phase
- Critical phase
- Convalescent phase

Febrile phase

The onset of dengue fever is usually with a sudden rise in temperature which may be biphasic, lasting 2-7 days and commonly associated with headache, flushing, retro-orbital pain and/or rash, myalgia, maculopapular or rubelliform rash which and usually appear after 3rd or 4th day of fever and is commonly seen on the face, neck and another part of the body, it generally fades away in the latter half of febrile phase. Cases with unusual haemorrhagic manifestations or severity may be seen in persons with coinfection with other organisms or in those having co-morbid illnesses.

Critical phase (Leakage phase)

Dengue patients usually enter the critical phase after 3 to 4 days of onset of the fever. During this phase plasma leakage and haemoconcentration occurs in most cases and patients may develop hypotension. Abnormal haemostasis and plasma leakage lead to bleeding, hypotension and fluid accumulation in pleural, pericardial or abdominal cavities. High morbidity and mortality areare usually seen in cases with multiple organ involvement or severe metabolic derangements. The period of plasma leakage usually lasts for 36-48 hrs.

Convalescent phase (recovery phase)

During this phase, the extracellular fluid, which was lost due to capillary leakage, returns to the circulatory system and signs and symptoms of the patient improve. This phase usually starts after 6-7 days of fever and lasts for 2-3 days. Longer convalescence period may be expected in some patients with severe shock, multiple organ involvement and other complications requiring specific treatment. The patient may develop pulmonary oedema due to fluid overload during this phase, especially if the fluid replacement rate is not reviewed and revised periodically.

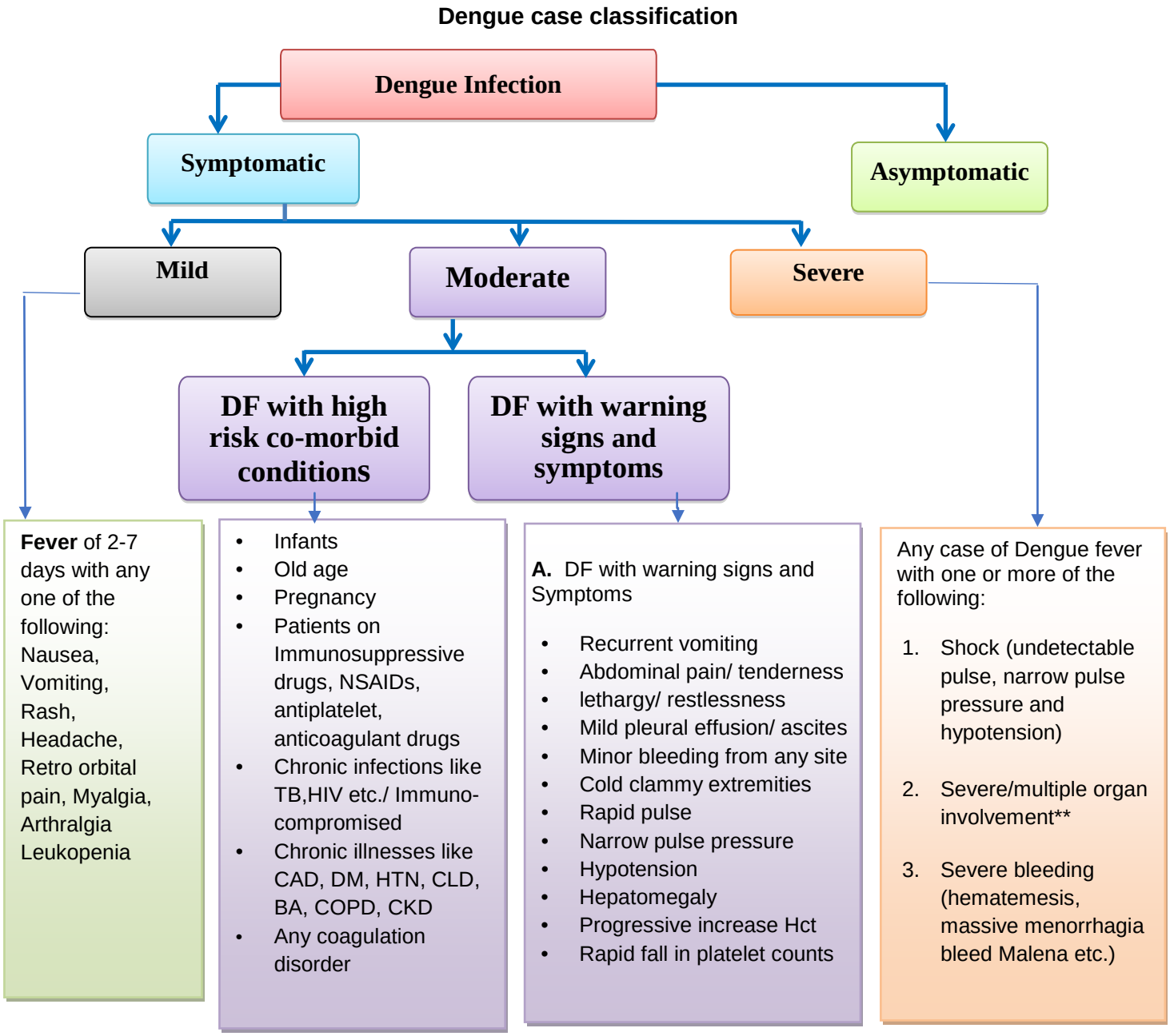


Figure-5: Dengue Fever: case classification as per the severity

4.2 Clinical features of COVID-19

COVID-19 patients reporting to various COVID-19 treatment facilities have reported the following signs and symptoms:

- Fever
- Cough
- Fatigue
- Shortness of breath
- Expectoration
- Myalgia
- Rhinorrhea, Sore throat, Diarrhoea

COVID-19 has a highly unpredictable course of illness. Based on the index presentation or in hospital presentation of shortness of breath, tachypnea and fever. The patients are generally categorized into asymptomatic, mild, moderate and severe.

Mild COVID-19

They have symptoms of uncomplicated upper respiratory tract infection such as fever cough, sore throat, malaise, and headache. They don't require any oxygen support.

Moderate COVID-19

Pneumonia with signs of severe disease

For adults and adolescents:

Fever cough shortness of breath

SpO2 < 94% (90-93%) on room air

Respiratory rate ≥ 24/min

Children: same

Infants: <2months ≥60/ min

2-11 months≥ 50/ min

1-5 years ≥ 40/ min

Severe COVID-19

Severe Pneumonia:

Clinical signs of pneumonia with

Respiratory rate ≥ 30/min

SpO2: <90% on room air

For children: Cough with dyspnea

SpO2: <90% on room air with or without central cyanosis

Not feeding well, lethargic

Fast breathing <2months: 60/min, 2-11 months: ≥ 50, 1-5 years ≥ 40

Chest indrawing

ARDS

New or worsening respiratory symptoms within one week of known clinical insult.

Chest imaging (Chest X-ray and portable bedside lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules.

Origin of Pulmonary infiltrates respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/ oedema if no risk factor present. Oxygenation impairment in adults:

Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O)

Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O)

Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O)

Sepsis

- Adults: Acute life-threatening organ dysfunction caused by a dyes-regulated host response to suspected or proven infection. Signs of organ dysfunction include altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia.
- Children: suspected or proven infection and ≥ 2 age-based Systemic Inflammatory Response Syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count.

Septic shock

- Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level > 2 mmol/L
- Children: any hypotension (SBP 2 SD below Page | 8 normal for age) or 2- 3 of the following: altered mental state; bradycardia or tachycardia (HR 160 bpm in infants and HR 150 bpm in children); prolonged capillary refill (>2 sec) or weak pulse; tachypnoea; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.
- After discussing the clinical features and spectrum of disease manifestations of two viral diseases independently, the clinical features of co-infections can be discussed.

Chapter 5

Case Classification of Co-infection (COVID-19 & Dengue)

It is observed that about 70 – 80% of COVID-19 and dengue cases are asymptomatic. So, a large portion of the co-infected population may be asymptomatic for both the diseases. However, the presence of one infection could enhance the symptoms and severity of others.

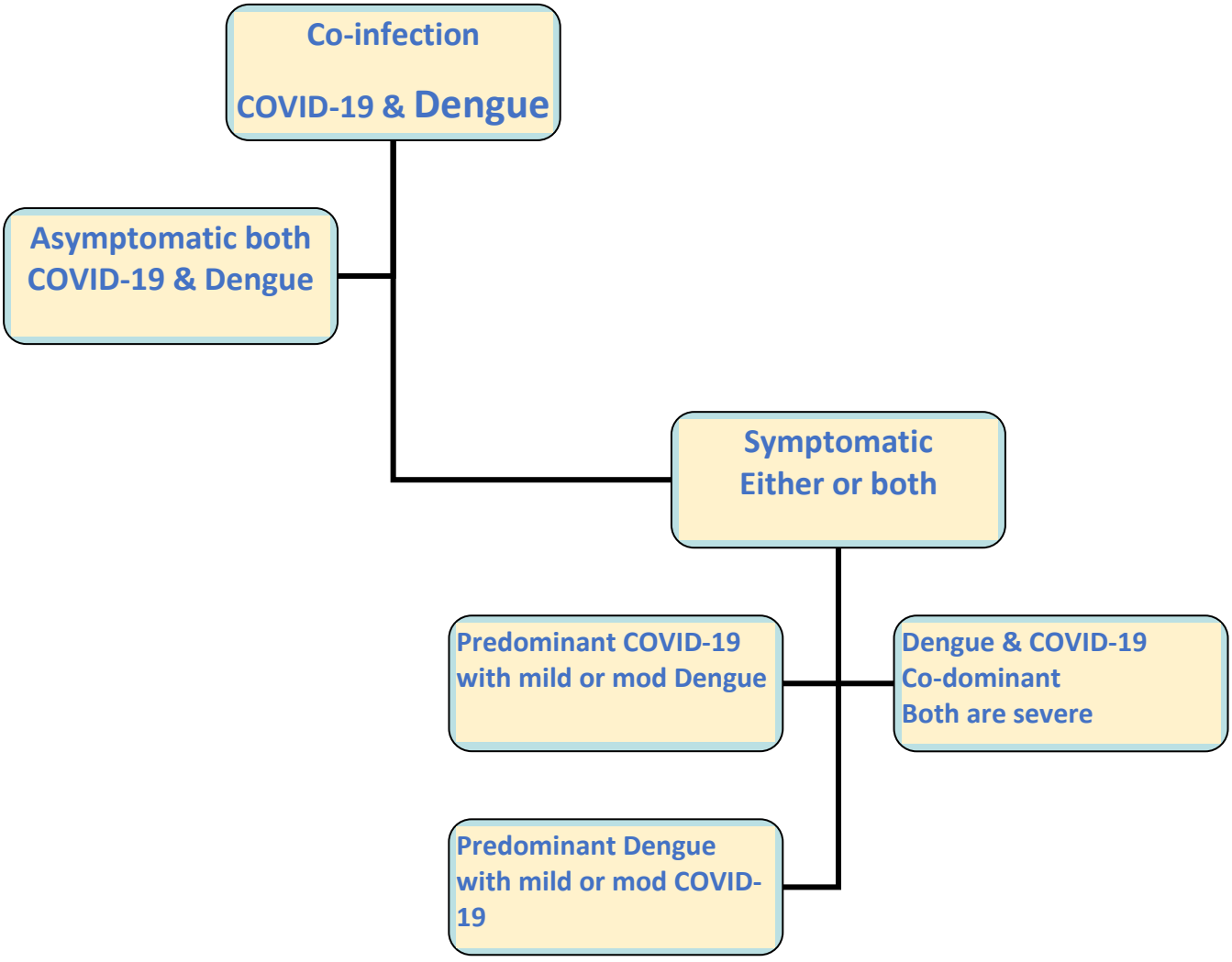


Figure-6: Case Classification of Co-infection Dengue and COVID-19

Case Classification of co-infection:

1. Asymptomatic Co-infection
2. Symptomatic co-infection
    a. Predominant Corona Viral Diseases (P-CVD)
    b. Predominant Dengue Viral Disease (P-DVD)
    c. Co-dominant co-infection (CDCI)

1. **Asymptomatic Co-infection** -As we know Dengue and COVID-19 both reported to present 70-80% cases as asymptomatic. Therefore, there might be some proportions of cases of Dengue and COVID-19 coinfections which may be either asymptomatic or mild symptomatic.

2.a COVID-19 predominant (P-CVD): a case having LRTI like features cough, fever, shortness of breath, having X-ray changes and/or CT changes suggestive of COVID-19 and has signs and symptoms of mild or moderate dengue fever.

2.b Dengue predominant (P-DVD): a case is presenting with fever, headache, retro-orbital pain later on manifesting respiratory symptoms CT and/or chest X-ray changes suggestive of mild or moderate COVID-19.

2.c Co-dominant Co-infection of COVID-19 and Dengue (CD-CI): Concurrent manifestation of respiratory symptoms cough, sore throat, shortness of breath and typical dengue symptoms such as headache, retro-orbital pain, joint pain associated with nausea vomiting or pain abdomen. Both infections may have severe manifestations.

Co-infected patients may have dominant dengue, dominant COVID-19 or a codominant infection. From the medical literature published so far, the relative incidence of codominant variety seems to be higher in symptomatic coinfected patients.

For all the above categories, a confirmed case will only be labelled, if microbiologically proven by RTPCR/CBNAAT/ RAT in case of COVID-19 and by NS1Antigen or IgM (ELISA based) for dengue. Among those cases where clinical presentation is suggestive but testing is negative, will come under the probable category.

Chapter 6

Treatment

Before initiation of the treatment severity of Co-infection should be assessed by signs, symptoms and investigational parameters. The treatment protocol is planned as per the dominancy and severity of infection either dengue, COVID-19 or both

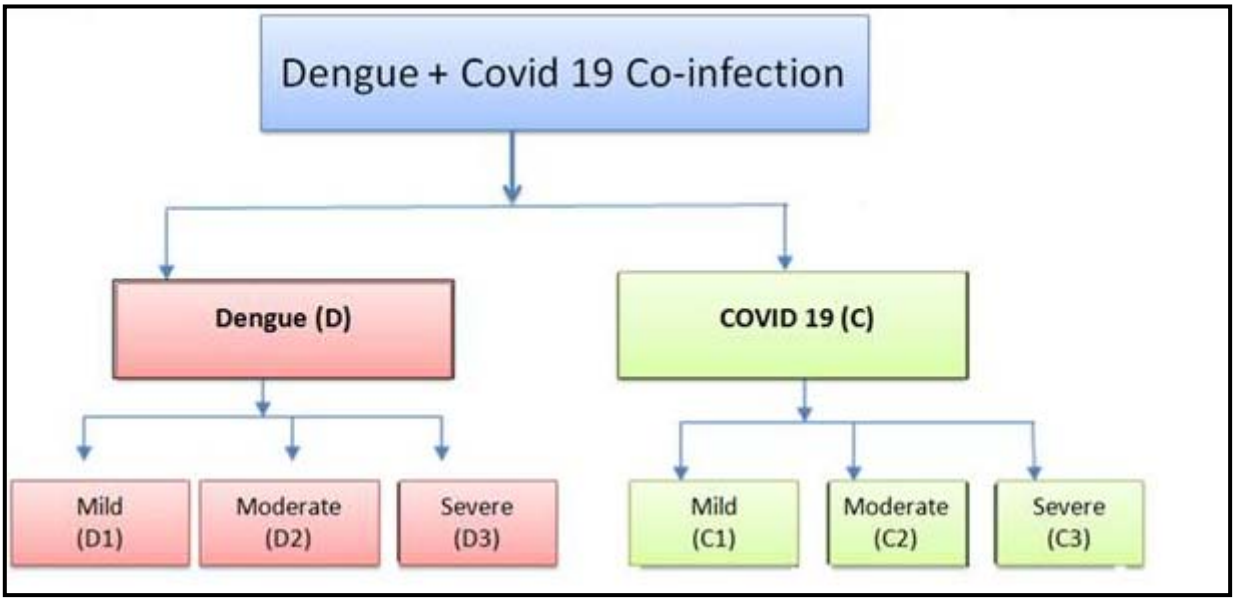


Figure-7: Case Classification of severity of Co-infection (Dengue and COVID- 19). Various combinations of coinfection are possible such as D1C1, D1C2, D1C3….D3C3

6.1 Treatment of Dengue (D)

D1 - Mild Dengue

Dengue infection without warning signs. Patients with fever, body aches, rashes or minor bleeding may be treated symptomatically. Fever and body aches are best treated with paracetamol. Salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as these may predispose to mucosal bleeds. The patient should be encouraged to drink plenty of fluids. There is no specific antiviral therapy. All patients need regular monitoring by a primary care physician for early detection of severe disease. The primary care physician/ health care worker should monitor the patient for warning signs, along with haematocrit and platelet counts. Any patient who develops warning signs as listed below should be admitted to a hospital.

D2 - Moderate Dengue

Dengue with warning signs. Patients with suspected dengue infection who have any of the following features should be admitted to the hospital:

- Abdominal pain or persistent tenderness vomiting
- Fluid accumulation in pleural cavity, abdomen or subcutaneous tissues
- Mucosal bleeds
- Lethargy, restlessness or irritability Liver enlargement >2 cm.
- Progressive increase in haematocrit with a concurrent decrease in platelet count.

These patients should be admitted in the hospital and given intravenous fluids. Crystalloids are the preferred fluids. The management of severe dengue infection demands high levels of expertise and skills for administration of fluids and electrolytes to correct hypovolemia due to leakage of serum from capillaries into the extravascular compartment. In the hospital, all children should be given Ringer's lactate or normal saline infusion at a rate of 5-10 ml/kg over one hour. After one hour, if haematocrit has decreased and vital parameters are improving; the fluid infusion rate should be decreased every hour to 3 ml/kg/hour for subsequent 24-48 hours with frequent monitoring of haematocrit and vital parameters. When the patient is stable as indicated by normal blood pressure, good oral intake and urine output, the child can be discharged.

If after one-hour haematocrit is rising and vital parameters do not show improvement, the fluid infusion rate is increased to 10 ml/kg over the next hour. In case of no further improvement, the fluid infusion rate is further increased to 15 ml/kg over the next hour (3rd hour). If no improvement is observed either in vital parameters or haematocrit at the end of 3 hours; colloids in doses of 10 ml/kg are administered. Once the haematocrit and vital parameters are stable, the infusion rate is gradually reduced and discontinued over 24-hours.

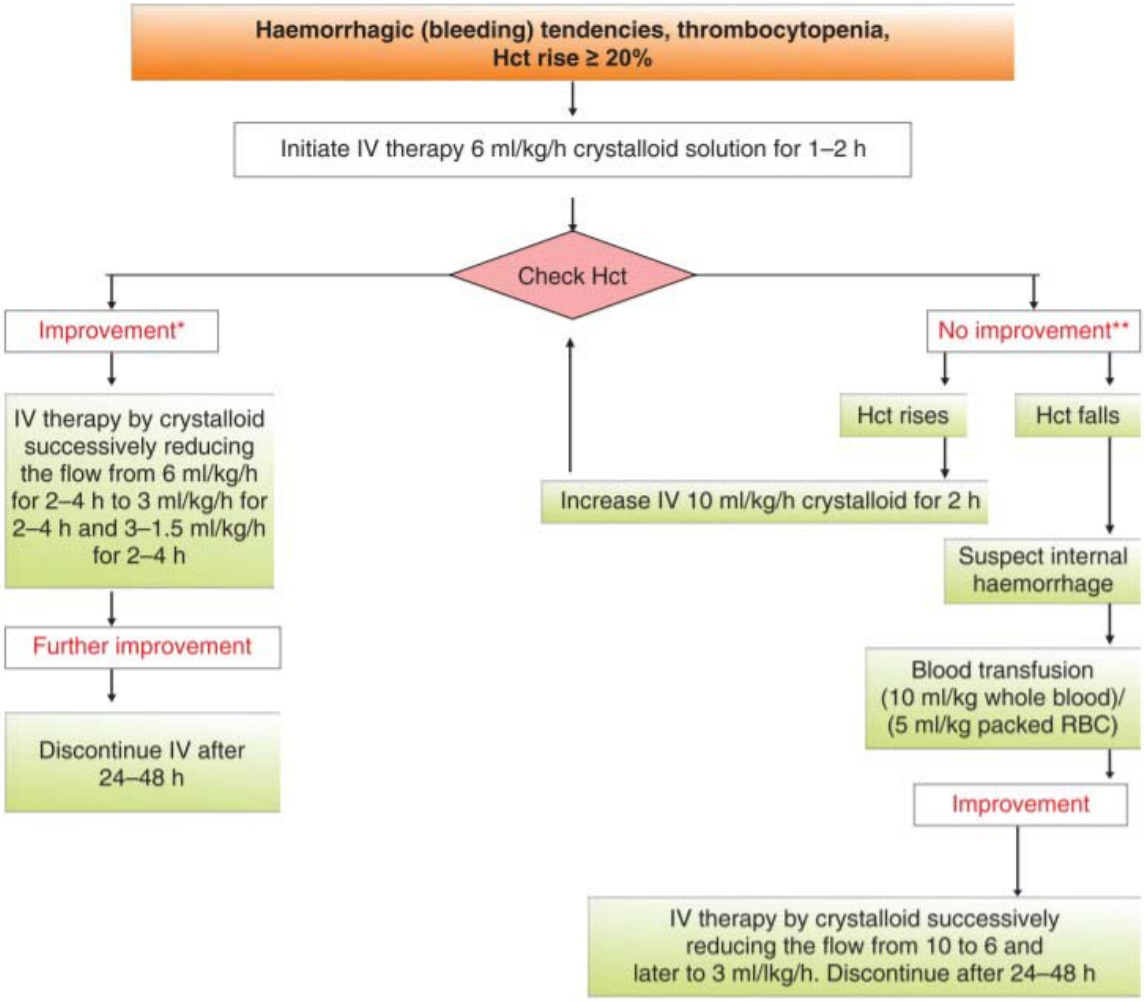


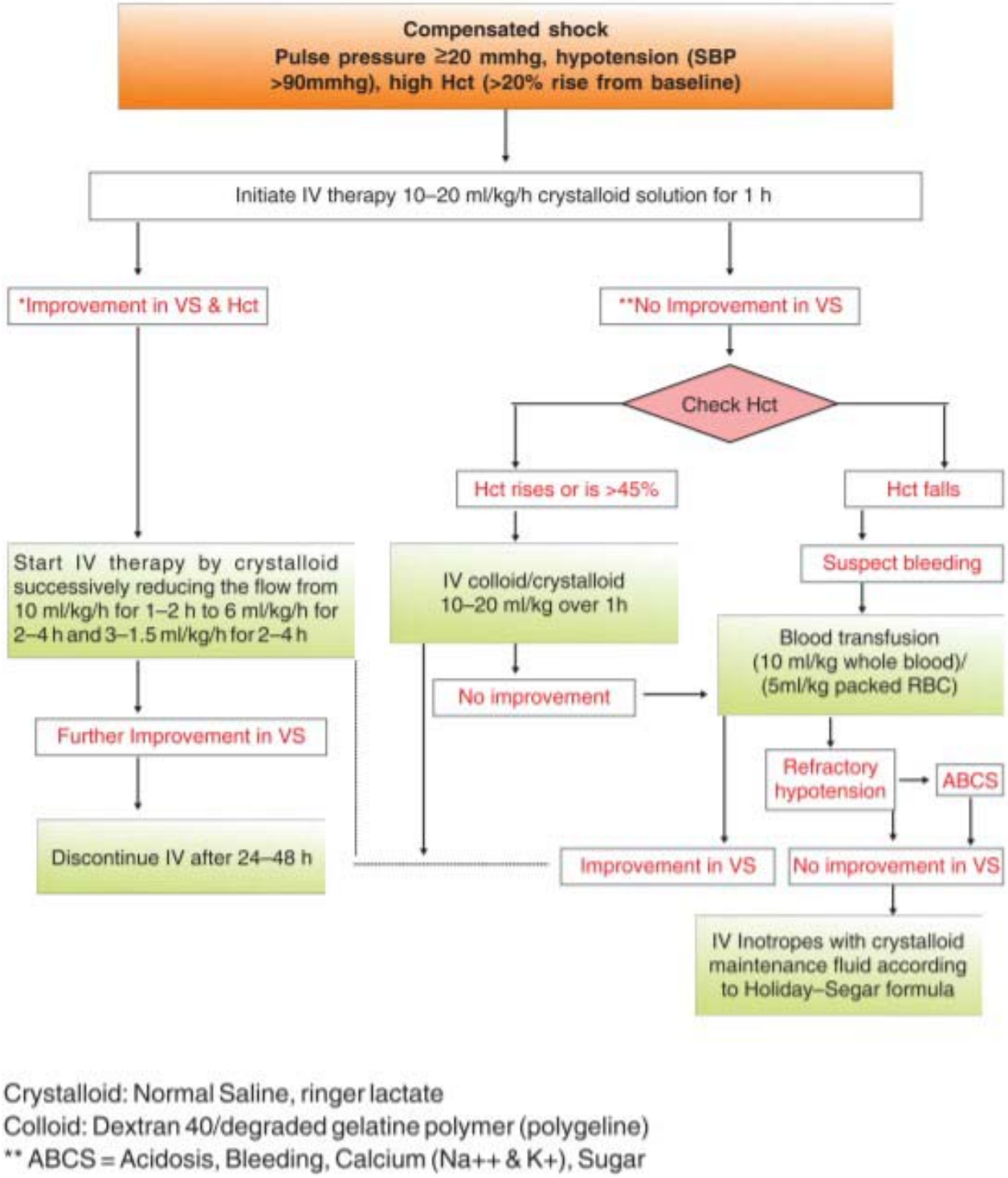
Figure-8: Fluid Management in Dengue predominant cases

D3 - Severe dengue

Patients presenting or developing any of the following complications are diagnosed to have severe dengue infection. Severe plasma leakage leading to

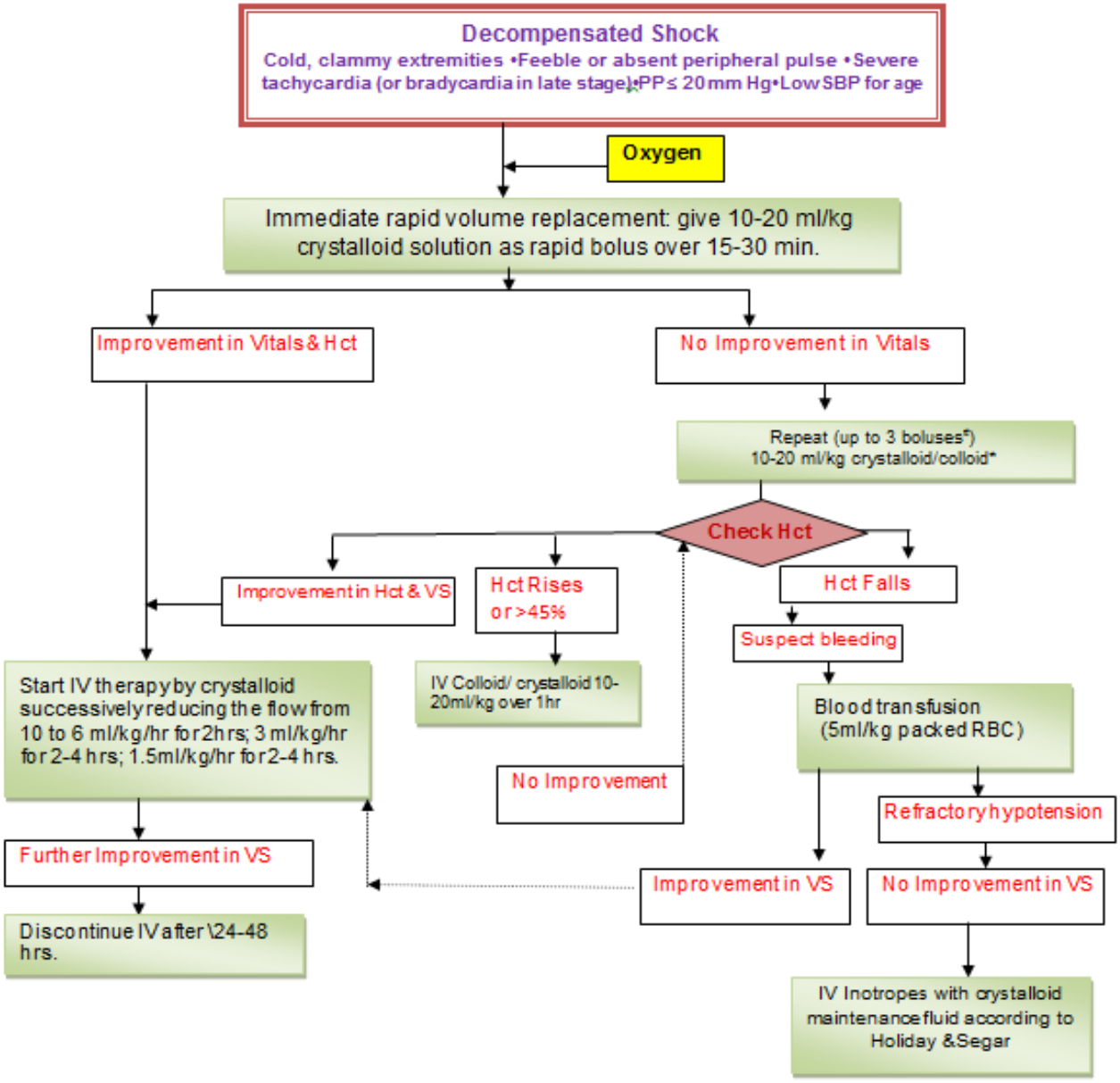
- Shock delayed capillary refill or oliguria
- Fluid accumulation in serosal cavities with respiratory distress
- Severe bleeding manifestations
- Severe organ involvement
    - Liver: Hepatomegaly, liver failure, AST or ALT $\geq$1000 units
    - CNS: Impaired consciousness
    - Heart: Myocardial dysfunction

Children classified as severe dengue should be hospitalized (preferably in PICU) and treated aggressively with supportive care. Normal saline or lactated Ringer's solution; 10-20 ml/kg is infused as a bolus. Normal saline is the better and preferred solution. In critically sick children, it is preferable to establish two peripheral IV lines. If there is no improvement in vital parameters and haematocrit is rising; colloids 10 ml/kg is infused rapidly. Alternatively, if haematocrit is falling without any improvement in vital parameters; blood transfusion should be given with the presumption that lack of improvement is due to occult blood loss. Once improvement starts, the infusion rate of fluids is gradually decreased. In addition to fluid management, oxygen should be administered to all patients with shock. The child should be closely monitored for various complications which should be identified early and managed effectively.



Crystalloid: Normal Saline, ringer lactate
Colloid: Dextran 40/degraded gelatine polymer (polygeline)
** ABCS = Acidosis, Bleeding, Calcium (Na++ & K+), Sugar

Figure-9: Management of Compensated Shock



*Colloid: Dextran 40/Degraded gelatine polymer (polygeline)

Note:

- **Improvement :** Hematocrit falls, pulse rate and blood pressure stable, urine output rises
- **No Improvement :** Hematocrit or pulse rate rises, pulse pressure below 20 mmHg, Urine output falls
- **Unstable Vital signs:** Urine output falls, signs of shock
- In cases of acidosis hyperosmolar or Ringer's lactate solution should not be used
- #A bolus is the volume administered in <30 minutes. A load is the volume administered in 30 to 60 minutes.

Figure-10: Management of Decompensated shock in dengue

6.2 Management of bleeding manifestations

Platelet counts are unreliable to predict bleeding. In a small study in which children with severe thrombocytopenia were included, platelet infusion did not alter the outcome of patients. In a recent RCT in adults with confirmed dengue infection and thrombocytopenia (≤20 000 platelets

per µL), without persistent mild bleeding or any severe bleeding, prophylactic platelet transfusion was not superior to supportive care.

- Cessation of signs of plasma leakage as suggested by stable blood pressure, pulse volume and peripheral perfusion; and decrease in haematocrit in the presence of a good pulse volume.
- Afebrile for more than 24–48 days (without the use of antipyretics).
- Resolvingbowel/abdominal symptoms.
- Improving urine output.

(i) *Fluid overload with stable hemodynamic status and the patient is out of the critical phase (more than 24-48 hours of defervescence).* In such patients, intravenous fluids should be stopped, but close monitoring continued. If necessary, oral or intravenous furosemide 0.1–0.5 mg/kg/dose once or twice daily, or a continuous infusion of furosemide 0.1 mg/kg/hour may be given. Serum potassium should be monitored and any hypokalaemia should be corrected.

(ii) *Fluid overload with stable hemodynamic status, but the patient is still in a critical phase. I*ntravenous fluids should be reduced gradually. Diuretics during the plasma leakage phase should be avoided because they may lead to intravascular volume depletion. Patients who remain in shock with low or normal haematocrit levels but show signs of fluid overload may have an occult haemorrhage. Further infusion of large volumes of intravenous fluids alone will lead to a poor outcome. Careful fresh blood transfusion should be given as soon as possible. If the patient remains in shock and the haematocrit is elevated, repeated small boluses of a colloid solution may be administered.

6.3 Management of COVID-19 (C)

Clinical Severity	**Clinical Features**	**Clinical Parameters**	**Remarks**
(C1) Mild	Patients with uncomplicated upper respiratory tract infection may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache	Without evidence of breathlessness or hypoxia (normal saturation).	i) Managed at COVID-19 Care Centre ii) Managed at home subject to fulfilment of conditions as per the guidelines
(C2) Moderate	Pneumonia with no signs of severe disease	Adolescent or adult with the presence of clinical features of dyspnea and /or hypoxia, Fever ,cough, shortness of breath SpO2 < 94% (90-93%) on room air Respiratory rate ≥ 24/min Children: same Infants: <2months ≥60/ min 2-11 months≥ 50/ min 1-5 years ≥ 40/ min	Managed in Dedicated COVID-19 Health Centre (DCHC)

C3) Severe

Severe Pneumonia

- Adolescent or adult: with clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 < 90% on room air.
- The child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO2 <90%. Severe respiratory distress (e.g. grunting, chest indrawing); signs of pneumonia with any of the following danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest in drawing, fast breathing (in breaths/min): <2 months >60: 2-11 mon >50; 1-5 years > 40. Onset: new or worsening respiratory symptoms within one week of clinical presentation.

Chest imaging (Chest X-ray and portable bedside lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Origin of Pulmonary infiltrates respiratory failure not fully explained by cardiac failure or fluid overload.

- **Oxygenation impairment in adults**:

Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O)
Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O)
Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O)
When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non- ventilated patients)

- **Oxygenation impairment in Children**

Note Oxygenation Index (OI) and OSI (Oxygen Saturation Index) Use OI when available. If PaO2 not available, wean FiO2 to maintain SpO2 <97% to calculate OSI or SpO2/FiO2 ratio: using SpO2)
Bi-level (NIV or CPAP) ≥5 cm H2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤264 Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.

To be managed in Dedicated COVID-19 Health Centre (DCHC)

6.4 Management of Dengue and COVID-19 Co-infection

Many of the viral infections like COVID-19, Dengue, H1N1, and Chikungunya might present with almost similar symptomatology of fever, myalgia, running nose, malaise, etc. at least in the initial period of infection, thus making the clinical diagnosis difficult. In the eventuality of a patient being simultaneously infected with more than one virus (co-infection), the diagnostic challenge is further compounded. The following typical and specific clinical features might help in the categorical clinical diagnosis of a case. The treatment is mainly dependent on the severity or predominant infection either dengue or COVID-19 (D1-3 + C1-3).

Following are some general measures to be followed in case of Dengue and COVID-19 co-infection:

➢ Strengthening at the primary health care level is the key to manage dengue through early

clinical diagnosis and recognition of warning signs for the severity of dengue such as abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement >2 cm, and increase in haematocrit. These measures will help to prevent the progression of illness to severe dengue and deaths, which in turn will also help to reduce the number of patients that need to be referred to hospitals, thus avoiding saturation of these facilities as well as the intensive care units. Mild to moderate Dengue and COVID-19 co-infected patient should be monitored closely preferably at the hospital, as they may rapidly progress to the severe stage. Therefore, they should be referred to the higher centre at the early stage by recognizing warning signs.

➢ At the same time, all secondary and tertiary level hospitals should be prepared to manage severe dengue and COVID-19 cases.

➢ Consider development and implementation of protocols for clinical management of acute febrile illness, based on a scenario of co-circulation of arboviral diseases, COVID-19 and other respiratory viruses (e.g., influenza).

Points related to specific therapeutic options and their use in cases with co-infection:

- Fluid Therapy – Fluid therapy to be given in co-infection cases depends on the hemodynamic status of patient and degree of severity. One may follow the fluid chart given above for clinical management of dengue fever for most co-infection cases. It is only in the presence of SARI with COVID-19 that we need to be careful with aggressive fluid administration as it may lead to worsening of oxygenation and in such a scenario IVC guided fluids should be administered (where the point of care facility is available) with continuous monitoring for worsening oxygenation. Aggressive fluid resuscitation is recommended for COVID-19 patients in shock for initial resuscitation.

- LMWH – LMWH is being used and has been included in the guidelines for the management of moderate to severe COVID-19 cases as it is associated with increased thrombosis. LMWH is indicated in moderate to severe category; however, careful monitoring is required by D-dimer estimation and when the platelet count falls below 1,00,000/mm^3, it may be withheld based on the clinical condition. In any case of coinfection with active bleeding, LMWH needs to be discontinued immediately.

- Use of Corticosteroids –Dexamethasone has recently been shown to be effective in severe COVID-19 and has been recommended for the same. Usually the course of illness among coinfected patients may not be affected much, if Dexamethasone is given after dengue viremic stage i.e.,5/6 days of dengue illness. Hence, the use of steroids can be continued as per COVID-19 management guidelines.

- Tocilizumab, Antivirals and other supportive management to be continued as per the current COVID-19 guidelines.

Chapter 7

Preventive measures

Outbreaks of arboviruses transmitted by *Aedes* mosquitoes such as Dengue, Chikungunya and Zika overload health systems and also put the community at risk globally. Dengue epidemics tend to have seasonal patterns, with transmission often at peak during monsoon and post-monsoon period every year. Early detection and prompt medical attention to patients with severe dengue have helped to dramatically reduce the case fatality rate. In 2020, with a complex epidemiological scenario of simultaneous Dengue transmission with COVID-19, the situation has become more serious and placed immense pressure on health care and management systems in India like other several countries. The reality of the possible co-circulation of Dengue (DENV) and COVID-19 imposes new challenges for the management of cases that require immediate attention. Since the beginning of COVID-19 pandemic, Government of India (GoI) emphasized the crucial need to sustain efforts for prevention and control of dengue, including diagnosis and case management which is of utmost priority. The combined impact of both COVID-19 and dengue epidemics could have potentially devastating consequences in the population at risk.

Surveillance: There is a need to specifically mention in reports about the co-infection of Dengue and COVID-19 if any. Any case with a coinfection of Dengue and COVID-19 may be brought to the notice of the clinicians immediately. To monitor the situation, intensification of surveillance activities (both epidemiological and entomological) is needed at every level. As mortality is associated with both the diseases, timely preventive actions are needed to avoid further spread of transmission.

- Efforts need to be made to strengthen surveillance and differential diagnosis during laboratory confirmation in each affected locality/area.
- Expansion of criteria for the diagnosis of dengue to incorporate COVID-19 symptoms to maximize the use of available resources.
- Ensure availability of diagnostics (both NS1 and IgM) to avoid any stock out to ensure continuous surveillance at all identified health facilities.
- The line-list of suspected and confirmed cases should be shared immediately to carry out preventive measures in the affected area to contain the disease transmission.
- Ensure deputation of sufficient manpower for uninterrupted diagnostic facilities and public health measures. For this, staff engaged in COVID-19 may also be coordinated to carry out the activities which are possible with COVID-19 measures.
- Timely analysis of entomological reports to figure out hotspots of dengue and intensification of vector control measures. Entomological surveillance will help to assess the changes in trend and the impact of vector control measures.
- The larval density of the *Aedes* vector to be monitored following the safety guidelines for COVID-19. The positive containers should be treated with Temephos or eliminate the source of breeding immediately.

Vector control: Source reduction of mosquito breeding sites and adult control measures should be implemented in areas affected by or at risk of dengue following COVID-19 precautions as per guidelines.

- There is an urgent need to carry out control actions based on the stratification of areas given the potential risk of transmission of dengue in order to minimize the displacement of the health staff.

- Information from the available entomological surveys should be used to identify the key breeding sites for *Aedes*. Key containers should be monitored (and eliminated whenever possible) by the community. There is an important opportunity to convey clear messages to the community to control all their breeding sites during this time of social distancing.

- It is necessary to offer the population simple and effective options for the safe use of water storage containers. While carrying out the source reduction activities, the following measures should be followed:

    - Vector control Teams to be formed and deputed in priority areas
    - Teams need to be well sensitized for precautions before visiting the field with Personal Protection Measures for COVID-19 and must take into account additional precautions before entering the home, such as handwashing, respiratory hygiene recommendations of sneeze and cough etiquette, avoiding close/frequent contact with people with symptoms, and following distancing recommendations
    - In homes with confirmed cases of COVID-19, at the time of the visit, vector prevention and control guidelines should be provided by the health teams
    - The outdoor containers filled with water need to be thoroughly checked for *Aedes* breeding and apply anti-larval insecticides wherever needed
    - While visiting any locality, the team need to sensitize the household for preventing mosquitogenic conditions and carry out source reduction activities

- Anti-adult measures for *Aedes* mosquito: To achieve a reduction in the *Aedes* mosquito population, adult mosquito control activities with insecticides must be carried out. Anti-adult measures like Indoor Space Spray and Fogging are not carried out in routine. These need to be carried out selectively in areas wherever needed. Areas and households reporting COVID-19 cases should be avoided for these measures as the insecticide used for fogging may induce uneasiness for the breathing of the patients.

Personal Protection Measures: Community needs to be sensitized on personal protection measures for Dengue and Chikungunya while carrying out similar activities for COVID-19. Use of repellents beds nets while sleeping during daytime need to be emphasized with special focus to COVID-19 patients.

Measures required at Health facilities: Based on epidemiology, the risk of transmission of Dengue and COVID-19 need to be minimized at premises of Health facilities by taking appropriate measures for personal protection, sanitization and vector management.

IEC/BCC activities for Community involvement: All possible efforts should be made to get the community's involvement in the prevention of dengue during COVID-19.

- IEC messages can be disseminated through different media (print media needs to be avoided) for both diseases where possible. States to explore and focus on other modes of communication for IEC/BCC, e.g. social media, radio, television, posters, miking etc.
- Households should be encouraged to eliminate mosquito breeding sources, both domiciliary and peri-domiciliary.
- Avoid Inter Personnel Communication and group discussion for community mobilization during COVID-19.

Locality specific activities for Dengue amidst COVID-19: The temporal coincidence implies the two outbreaks may happen during the same period with possible co-infections with both viruses leading to the overlap of symptoms, misdiagnosis and case management. Efforts must be made to lower the population of vector mosquitoes and this should result in lowering the risk of dengue. As areas/localities are categorized in different zones (Containment zone, Buffer Zone and outside Buffer Zone), the suggestive activities for prevention and control of dengue are summarized in the table below:

Programmatic activities		Containment Zone	Buffer Zone	Outside Buffer Zone
Surveillance	Sentinel Site/Health facility surveillance	To be continued as a routine		
	Vector Surveillance	To be combined with COVID-19 activities		As routine
Diagnosis & Case Management		To be continued as a routine		
IVM	Larval Source Reduction	After assessing COVID-19 situation & disease endemicity		As routine
	Fogging & Indoor Space Spray	Only if COVID-19 situation permits		As routine
Epidemic Preparedness and Outbreak Management		To be continued as a routine		
Supply Chain Management (Drugs & Diagnostics)		To be continued as a routine		
IEC/BCC		Continued wherever possible, may be combined with COVID-19 activities		

Conclusion: There is a strong likelihood of a temporal co-occurrence of two or more infections together in a given region. This may cause co-infections with two viruses/parasite in the same individual, leading to an overlap of symptoms, thus making diagnosis and case management difficult. Alert vigil, a high index of suspicion and constant awareness of the possibility of co-infections can help physicians avert the adverse outcome of cases. Efforts must also be made to minimize the vector population before the onset of rains, thus resulting in lowering the number of Dengue, Malaria and Chikungunya cases.

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