National Guideline for Clinical Management of DENGUE

2022

Ministério da Saúde

World Health Organization
Timor-Leste

National Guideline for Clinical Management of Dengue 2022

Department of Communicable Diseases
Ministry of Health
Democratic Republic of Timor-Leste.

Contents

Message from the Hon'ble Minister of Health

Timor-Leste is facing a huge burden of dengue, which necessitates a paradigm shift in our approach and strategy. There is an urgent need for management and upgradation of systems for dengue control programme at all levels. Considering the gravity of the crisis, the country's health sector needs continuous commitment across the government and private sectors and the civil society.

This National Guideline for Clinical Management of Dengue will help to prioritize issues and develop programmes and policies towards managing dengue in Timor-Leste. On behalf of the Ministry of Health, I would like to acknowledge the technical assistance of WHO in developing this guideline and welcome the continuation of this partnership and collaboration in the coming years.

The increased burden of dengue calls for concentrated efforts not just in healthcare but also in terms of awareness within communities. Dengue is a vector borne disease, which can be easily prevented if each one of us adopts some simple measures like maintaining cleanliness in our homes and surroundings, clearing stagnated water that can lead to mosquito breeding, using mosquito repellents whenever possible, wearing full sleeved clothing to avoid mosquito bites among others. It is also important for each one of us to be aware about dengue symptoms and reach out to a qualified healthcare professional soon as we experience any symptoms.

Treatment of dengue is mostly symptomatic. But it is crucial that patients seek treatment in time to avoid severe complications of dengue which can be potentially fatal. Another crucial aspect for dengue treatment is that healthcare facilities and healthcare providers should be equipped to treat these cases with a well-defined protocol. The National Guideline for Clinical Management of Dengue will act as the protocol and this document with play a critical role in management of dengue and reducing deaths cause by the disease.

I encourage everyone to join in the endeavour towards a dengue-free Timor-Leste, and a healthy future for all our people.

dr. Odete Maria Freitas Belo, MPH
H.E. Minister of Health
Democratic Republic of Timor-Leste

Message from WHO Representative

The global incidence of dengue has grown dramatically, and about half of the world's population is now at risk. An estimated 100–400 million dengue infections occur each year. However, over 80% cases are generally mild and asymptomatic, and hence the actual number of dengue cases are under-reported. Many cases are also misdiagnosed as other febrile illnesses.

There has been an eight-fold rise in the number of dengue cases reported to WHO over the last two decades, from 505 430 cases in 2000 to over 2.4 million in 2010, and 5.2 million in 2019. Reported deaths between the year 2000 and 2015 increased from 960 to 4032, affecting mostly the younger age group. The total number of cases seemingly decreased during years 2020–2021, as well as for reported deaths. However, the data is not yet complete and COVID-19 pandemic might have further hampered case reporting in several countries.

The alarming increase in the number of cases is partly explained by a change in national practices to record and report dengue to the Ministries of Health, and to the WHO. However, it also represents national governments' recognition of the disease burden. At a time when the COVID-19 pandemic is placing immense pressure on health care and management systems worldwide, WHO has emphasized the importance of sustaining efforts to prevent, detect and treat vector-borne diseases such as dengue and other arboviral diseases. The combined impact of the COVID-19 and dengue epidemics could have devastating consequences on the populations at risk.

Data from Timor-Leste shows that the country has a huge burden of dengue. The emergence of all four types of dengue viruses (serotypes) represents a pandemic. Mortality from dengue can be reduced to zero by immediately implementing timely appropriate clinical management at various levels, including the primary health care. This National Guideline for Clinical Management of Dengue will strengthen the ability and preparedness to address the epidemic. I congratulate the Ministry of Health for initiating the formation of these national guidelines, as they will go a long way in managing dengue cases and reducing dengue related mortality.

I sincerely hope that the Ministry of Health will enable developing appropriate mechanisms for monitoring the risk factors and undertake evaluation of policies and programmes to control dengue. I assure continued technical support from the WHO realise these endeavours.

Dr Arvind Mathur
WHO Representative
Democratic Republic of Timor-Leste

Acknowledgements

Preface

Dengue fever is an arboviral infection spread by *Aedes* mosquitoes rapidly spreading globally and emerging as a major public health challenge in tropical and sub-tropical regions of world. It can lead to a wide spectrum of symptoms ranging from extremely mild to severe form of diseases with multi organ involvement and even mortality in some of the cases. It is estimated that approximately 70% of cases are asymptomatic, which may not be captured by the surveillance mechanism, making it tough to ascertain the exact burden of disease. It is also estimated that 390 million dengue virus infections take place every year and 96 million patients manifest clinically with varied symptoms.

South-East Asia region contributes to more than half of the global burden of dengue. In spite of the control efforts, there has been a significant increase in the number of dengue cases over the years, though improvement has been made in case management and reduction of case fatality rate below 0.5%. The factors responsible for high burden of dengue in the region are expansion and distribution of dengue mosquito vector and viruses viz. high rates of population growth, inadequate water supply and poor water storage practices, lack of civic amenities leading to poor and improper solid waste management, rise in global commerce and tourism, global warming, and the development of hyper-endemicity in urban areas, etc. Dengue is an important public health problem in Timor-Leste. Many outbreaks have been reported during past few years, and Dili, the capital of Timor-Leste, has contributed significantly to the morbidity and mortality of dengue every year.

The development of the "National Guideline for Clinical Management of Dengue" is part of the important work carried out by WHO. Developing the guidelines was a complex process involving various national and international public health experts and scholars. It is important and necessary to recognize the complex epidemiological landscape involving multiple social and environmental determinants that favours transmission dynamics and causes outbreak of dengue in the country every year, despite the various efforts and interventions deployed to prevent and control the spread of the virus. Hence, efforts were made to incorporate various references, which were consulted as scientific evidence, to formulate recommendations aimed at improving clinical management by the thematic experts.

In all, the Guideline has 14 chapters covering extensively new insights into epidemiology of dengue fever, integrated vector management, pathogenesis, clinical manifestations, case diagnosis and management, case classification and severity of coinfections, surveillance, management of dengue in adults, infants and children, the primary health care approach, role of nursing care, etc. This Guideline has been prepared to make widely available practical information on clinical management of dengue. Health professionals involved in vector control and other public health officials at various levels, including the nongovernmental organisations working on public health issues, and laboratory personnel would be able to make use of this guideline, and bring uniformity in dengue case management across the country. It is envisioned that the wealth of information presented in this Guideline will prove useful to effectively combat dengue fever; and ultimately reduce the burden and risk of the disease in Timor-Leste.

Abbreviations

AKI	acute kidney injury
aPTT	activated partial thromboplastin time
CAD	coronary artery diseases
CAP	community acquired pneumonia
CBNAAT	Cartridge-based nucleic acid amplification test
CFR	case fatality rate
CHC	community health centre
CSF	cerebrospinal fluid
DENV	dengue virus
DHF	dengue haemorrhagic fever
DIC	disseminated intravascular coagulation
DLC	differential leukocyte count
DSS	dengue shock syndrome
EIP	extrinsic incubation period
ELISA	enzyme-linked immunosorbent assay
FDP	fibrinogen degradation products
HAP	hospital acquired pneumonia
HLH	haemophagocytic lymphohistiocytosis
ICP	intracranial pressure
IHR	international health regulations
IIP	intrinsic incubation period
IPD	inpatient department
ITP	idiopathic thrombocytopenic purpura
NSAID	non-steroidal anti-inflammatory drug
OPD	outpatient department
ORS	oral rehydration solution
PCV	packed cell volume
PIP	programme implementation plan
RAT	rapid antigen test
RDT	rapid diagnostic test
RT-PCR	reverse-transcriptase polymerase chain reaction
SARS	severe acute respiratory syndrome
SSH	sentinel surveillance hospitals
TLC	total leukocyte count
VBD	vector-borne diseases

Chapter 1

Introduction

Dengue is a mosquito-borne arboviral infection rapidly spreading globally and emerging as a major public health challenge in tropical and sub-tropical regions of world. It is transmitted by *Aedes* mosquito (*Aedes aegypti* and *Aedes albopictus*), which also spreads Zika, chikungunya and yellow fever.

Dengue is caused by a virus of the *Flaviviridae* family. There are four serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV-3 and DENV-4). Infection with one serotype provides lifelong immunity against that serotype and provides partial and temporary immunity to other serotypes. Dengue can lead to a wide spectrum of symptoms ranging from extremely mild to severe form of diseases with multi organ involvement and even mortality in some of the cases.

Dengue virus (DENV) is transmitted to healthy human host through vectors. There is evidence of the possibility of vertical transmission from mother to new born baby, but its transmission rate appears low and linked to timing of the dengue infection during the pregnancy.

1.1 Global burden

It is estimated that approximately 70% of cases are asymptomatic, which may not be captured by the surveillance mechanism, making it tough to ascertain exact burden of disease. It is also estimated that 390 million dengue virus infections take place every year and 96 million patients manifest clinically with varied symptoms. The number of dengue cases reported to WHO increased over eight-fold over the last two decades---from 505 430 cases in 2000to over 2.4 million in 2010, and 5.2 million in 2019.

1.2 Dengue in South-East Asia

Despite the risk of infection existing in 129 countries, 70% of the actual burden is in Asia. As per estimates, 1.3 billion population live in dengue endemic areas of 10 countries of the South-East Asia Region. In South-East Asia region, dengue has been reported from all countries except the Democratic People's Republic of Korea. The region contributes to more than half of the global burden of dengue. Five countries (India, Indonesia, Myanmar, Sri Lanka and Thailand) are among the 30 most highly endemic countries in the world. In spite of the control efforts, there has been a significant increase in the number of dengue cases over the years, though improvement has been made in case management and reduction of case fatality rate (CFR) below 0.5%.

Burden of dengue cases has increased by 46% (from 451 442 to 658 301) from 2015 to 2019, whereas deaths have decreased by 2% (from 1584 to 1555),[1] The factors responsible for high burden of dengue in the region are expansion and distribution of dengue mosquito vector and viruses viz. high rates of population growth, inadequate water supply and poor water storage practices, lack of civic amenities leading to poor and improper solid waste management, rise in global commerce and tourism, global warming, and the development of hyper-endemicity in urban areas, etc. The current situation of the high burden of dengue cases, when there is no proper treatment, increases the need for preventive measures.

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[1] https://www.who.int/southeastasia/health-topics/dengue-and-severe-dengue

1.3 National burden in Timor-Leste

Dengue is an important public health problem in Timor-Leste, and many outbreaks have been reported during past few years. Dili, the capital of Timor-Leste, has contributed significantly to the morbidity and mortality of dengue every year. Reported during the wettest and hottest months of the year (December–February), dengue is mostly being diagnosed based on the clinical findings.

Chapter 2

Epidemiology of dengue fever

2.1 Epidemiological triad

Epidemiological triad represents a model for disease causation. The triad consists of an agent, a host and an environment. There needs to be an interaction between these three factors for disease causation. In epidemiological triad of dengue, agent is a virus (DENV), the host includes human beings of all age groups and both sex are susceptible, and the environment includes multiple factors that influence breeding sites and climatic factors. The interaction between three factors is through vector and this is a classic example of the *Aedes* mosquito causing infection. The mosquito ingests DENV from an infected host and it is harmless to the mosquito. The extrinsic incubation period (EIP) of dengue is 8–12 days and begins with a mosquito taking up an infective blood meal from a viraemic human host and becomes infectious once DENV reaches the salivary glands and has completed the EIP.

2.2 Virus

The dengue viruses belong to the genus *Flavivirus* and family *Flaviviridae*. This is small virus and contains single-strand RNA as genome. DENV is composed of three structural protein genes, i.e., core protein (C) a membrane-associated protein (M), an envelope protein (E), and seven non-structural protein (NS) genes (Fig. 1). Among non-structural proteins, glycoprotein NS1 is of diagnostic importance.

Figure 1. Structure of dengue virus
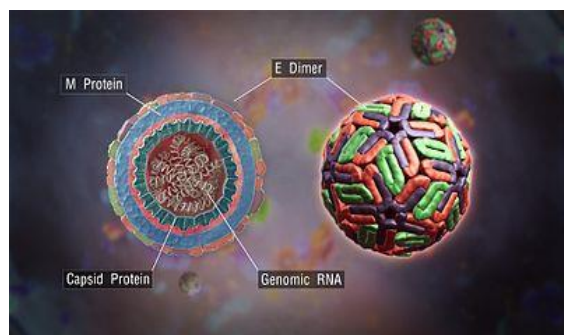
There are four serotypes of DENV, designated as DENV-1, DENV-2, DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that virus serotype. However, cross-immunity to the other serotypes after recovery is only partial, and temporary. Genetic variation also occurs within each serotype in the form of "sub-types" or "genotypes". Currently, three sub-types have been identified for DENV-1, six for DENV-2, four for DENV-3 and four for DENV-4. Any change in serotype of DENV is associated with severe form of disease and may lead to high mortality. The four serotypes of dengue can co-circulate in endemic areas. Secondary infection with another serotype leads to severe form of dengue. Primary and secondary dengue infection can be distinguished on the basis of their antibody response.

2.3 Host

Dengue viruses have adopted to humans in an evolutionary process. Any age of the population can be infected with DENV. There are no infection rate differences among gender.

The viraemia among humans builds up high titres two days before the onset of fever and lasts 5–7 days after the onset of fever. During these periods vector species gets infected and the humans become dead-ends for transmission. The susceptibility of humans depends upon their immune

status. DENV-2 is more likely to result in severe disease as compared with other serotypes. Immunity to each of the four serotypes may vary over time due to natural population growth. Past exposure to other serotypes may lead to outbreak situation, even though vector density may be low. Travel to dengue endemic areas is an important risk factor. Travel of a patient in viraemic stage to non-endemic area may introduce infection in that area.

High-risk hosts include extremes of age, pregnancy, patients prone for blood loss, e.g., peptic ulcers, anaemia, patients on steroids/NSAIDs, chronic comorbid illnesses like diabetes, hypertension, and coronary artery and kidney diseases.

2.4 Environment

Dengue is disease of tropical and sub-tropical countries. Environmental factors have been associated with resurgence of dengue infection in these regions. Initially dengue was limited to urban areas, but now peri-urban and rural settings have reported infections. Transportation and migration of human host and vector have led to spread of the disease to newer geographical locations. Manmade factors such as excessive use of non-biodegradable plastics and improper solid waste management have added to breeding habitat of vector leading to multiple breeding sites. Areas that lack 24 x 7 water supply and containers, which may not have proper lids are ideal sites for mosquito breeding. Increased urbanization with lack of civic amenities has been linked to the resurgence of dengue. Life cycle of *Aedes* is influenced by climatic factor. Ideal temperature for survival of *Aedes* is 16 °C to 30 °C and relative humidity is 60–80%.

Climate change also may affect transmission, as dengue mosquitoes reproduce more quickly and bite more frequently at higher temperature climatic conditions.

2.5 Vectors of dengue

Aedes (Stegomyia) aegypti (*Ae. aegypti*) and *Aedes (Stegomyia) albopictus* (*Ae. albopictus*) are the two important vectors of dengue. The infection is transmitted by the bite of infected female mosquito. The female lays eggs on surface above water line. Under ambient conditions, the adult emerges from egg in 7–10 days. The eggs can withstand desiccation even up to one year and larvae may emerge when eggs will come in contact with water.

a) Aedes aegypti
Aedes aegypti mosquito originates from Africa, but now got adapted to the peri-domestic environment by breeding in water-storage containers. During17th to 19th centuries it got introduced to the "New World" and South-East Asia. Increased transport, human contact, urbanization, water storage habits, etc., have helped in its extension from urban to rural areas. Vector has strong affinity for human blood, and it has developed high vectorial capacity for transmission of dengue. It is a day biter and habitat includes man-made containers/water storage sites in domestic and peri-domestic areas, i.e., water storage tanks and small containers, desert coolers, ornamental fountains, animal drinking bowls/bird water pots, potted plants/flower vases, discarded tires, bottles, pots and pans, broken appliances, solid waste collecting rain water, etc. Average survival for *Aedes aegypti* is approximately 30 days.

b) Aedes (Stegomyia) albopictus
Aedes albopictus is an Asian species indigenous to South-East Asia and islands of the Western Pacific and the Indian Ocean (Fig. 2). It can lead to serious outbreaks of arboviral diseases, as it is a

competent vector of at least 22 arboviruses, especially DENV (all four serotypes). It is primarily a forest species that has adapted to rural, suburban and urban human environments. *Aedes albopictus* oviposits and develops in tree holes, bamboo stumps and leaf axils in forest habitats, and in artificial containers in urban settings. It is an indiscriminate blood-feeder and more zoophagic than *Ae. aegypti*. Its flight range may be up to 500 metres, and has average survival of approximately 8 weeks.

2.6 Transmission cycle

The transmission cycle starts with bite of both infected female *Ae. aegypti* or *Ae. albopictus* mosquito (Fig. 3). After ingestion of the infected blood meal, the virus replicates in the epithelial cell lining of the mid gut and enters into haemocoel to infect the salivary glands. The phase of ingestion of virus by mosquito and till saliva becomes infective is call EIP that lasts from 8–12 days. Once a

Figure 2. Presence of *Aedes albopictus*

mosquito has become infective, it remains so for the rest of its life. The intrinsic incubation period (IIP) covers the period from the entry of virus in human host and onset of clinical manifestation. It may take 3–14 days and on an average IIP is 5–7 days.
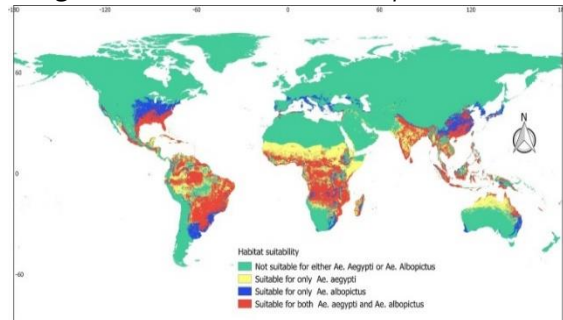
Figure 3. Transmission cycle
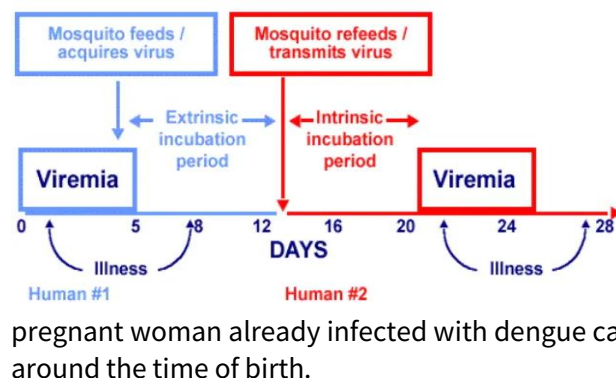
It has been reported in many countries that virus may enter the fully developed eggs at the time of oviposition. Transovarial dengue virus has been reported to occur prior to the reporting of human cases. Transovarial dengue infection in *Ae. aegypti* larvae has been reported to maintain or enhance the epidemics. Transmission has also been reported from mother to child, where pregnant woman already infected with dengue can pass the virus to her fetus during pregnancy or around the time of birth.

2.7 Seasonality and intensity of transmission

Dengue transmission usually occurs during the rainy season. This is attributed to ambient temperature and humidity. Multiple secondary breeding habitats are created due to rain water collection. Ambient climatic factors also lead to longer mosquito survival.

Areas with dry climate, water storage and other manmade containers remain the most preferred breeding sites. Ambient temperature also reduces the extrinsic incubation period of the virus as well. Tropical and sub-tropical climate influence dengue transmission by creating abundance and distribution of vectors. Precipitation is an important factor by providing water for aquatic stages of mosquito, i.e., larvae and pupa. Excessive rainfall will flush away all larvae, which may get killed. Lighter rains may replenish existing breeding sites and maintain higher levels of humidity, which assist in dispersal and survival of adult mosquitoes. There is a lag phase between rains and appearance of cases, which provides an opportunity to programme managers to carry out vector control measures along with source reduction. The temperature range for *Aedes* vector lies between 14 °C and 18 °C at the lower end and 35 °C and 40 °C at the upper end. Vector species is a domestic

breeder and remains insulated by fitting into human ecological requirements. The ideal humidity for vector growth is 60–80%.

2.8 Other arboviral infections

Arboviral infections is a term used to describe a group of viral infections transmitted to humans by a group of insects known as arthropods. There are many strains of arbovirus. Insects that can infect humans with arboviruses include fleas, ticks, gnats, and mosquitoes. There are more than 130 arbovirus that affect humans. There are three main genera of arboviruses that cause infections in humans. They are: flavivirus, togavirus and bunyavirus.

Aedes-transmitted arbovirus are presenting as major public health challenge across the globe. *Aedes*-borne arboviral diseases include dengue, chikungunya, Zika, and yellow fever. The viruses belong to different families, but these diseases share common geographic distribution as these agents are transmitted to human host through bite of infected female *Aedes* mosquito. Migration, community movements and transportation may introduce these viruses in newer geographical locations. Climate change with environmental adaptation of the mosquito vectors also pose the threat of increased risk of these infections.

Human host may not present with any clinical signs and symptoms of infections caused by arboviruses. However, symptoms may can range from a mild flu-like illness to encephalitis. Dengue patient may be asymptomatic, present with fever, headache, muscle aches, joint pain, nausea/vomiting/diarrhoea, pain in abdomen or rash or sever dengue with organs involvement. Chikungunya patient may present with fever and severe joint pain. Other symptoms include muscle pain, joint swelling, headache, nausea, fatigue and rash. It shares some clinical signs with dengue and Zika, which may lead to misdiagnosis in areas where they are common. Due to the challenges in accurate diagnosis for chikungunya, there is no real estimate of the burden of disease. There is no specific treatment/vaccination.

Zika virus is a mosquito-borne flavivirus, which was first identified in monkeys in Uganda in 1947. It was later identified in humans in 1952 in Uganda and the United Republic of Tanzania. Symptoms are generally mild and may include fever, rash, conjunctivitis, muscle and joint pain, malaise or headache. They typically last for 2–7 days. Zika virus infection during pregnancy may cause microcephaly and other congenital malformations in new-born babies. An increased risk of neurologic complications is associated with Zika virus infection like Guillain-Barré syndrome (GBS). Yellow fever is a viral haemorrhagic disease transmitted by infected mosquitoes, and yellow refers to the jaundice seen in some patients. Symptoms of yellow fever include fever, headache, jaundice, muscle pain, nausea, vomiting and fatigue. The virus is endemic in tropical areas of Africa and Central and South America. Yellow fever can be prevented by an extremely effective vaccine. A single dose of yellow fever vaccine offers sustained immunity and life-long protection against the disease. Among the *Aedes*-transmitted arbovirus diseases, only yellow fever has got an effective vaccine. Yellow fever vaccine and international health regulations (IHR) have resulted in prevention of spread of yellow fever to newer geographical locations.

Since *Aedes* remain a common vector for these four arbovirus diseases, the integrated approach for vector control will help in their control.

Chapter 3

Disease surveillance

3.1 Situational analysis

Dengue has been emerging as a major public health concern in Timor-Leste. The Guidelines of the Asia-Pacific Dengue Strategic Plan 2008–2015) have been used for prevention and control of dengue in the country. Dili District, being the capital of Timor-Leste, contributes significantly to the burden of dengue and deaths due to dengue every year. Dengue is mostly being diagnosed based on the clinical findings. Dengue surveillance data are collected by the Department of Epidemiological Surveillance at the Ministry of Health. Dengue cases are reported during the wettest and hottest months (December–February)of the year. Municipality- and year-wise dengue cases and deaths as reported in Timor-Leste are given in Table 1.

Table 1. Municipality-and year-wise dengue cases and deaths

Municipality	2016		2017		2018		2019		2020		2021	
	C	D	C	D	C	D	C	D	C	D	C	D
Aileu	0	0	0	0	0	0	0	0	2	0	0	0
Ainaro	0	0	0	0	0	0	5	0	6	0	7	0
Baucau	18	0	16	0	0	0	11	0	53	1	56	0
Bobonaro	9	0	23	0	6	0	0	0	14	0	41	0
Covalima	0	0	2	1	3	1	14	1	53	1	26	2
Dili	212	2	408	1	223	1	620	4	815	7	524	4
Ermera	1	0	51	0	3	0	94	1	318	0	13	0
Lautem	0	0	42	0	3	0	20	0	32	0	7	0
Liquica	1	0	0	0	1	0	126	1	74	1	7	0
Manatuto	9	1	1	0	91	0	65	0	64	0	33	0
Manufahi	1	0	3	0	0	0	18	0	7	0	15	1
Oecusse	0	0	0	0	0	0	2	1	13	0	0	0
Viqueque	0	0	4	0	0	0	1	0	0	0	8	0
Total	**251**	**3**	**550**	**2**	**330**	**2**	**976**	**8**	**1451**	**10**	**737**	**7**

Note: C = Case, D = Death

Years 2019 and 2020 reported an outbreak in Timor-Leste, when 976 dengue cases with eight deaths and 1451 cases with 10 deaths were reported, respectively in both the years. In 2021, 737 dengue cases with seven deaths have been notified (till 13th December 2021). The CFR has been reported as 0.7 in 2020 (Fig. 4). In 2020, many countries reported less number of dengue cases due to COVID-19 restrictions, but Timor-Leste reported an outbreak. In 2021, two deaths have been reported due to dengue haemorrhagic fever (DHF) and five deaths attributed to dengue shock syndrome (DSS).

Rising number of dengue cases have been attributed to highly seasonal with inter annual variation and climate factor including mean temperature and precipitation, indoors and outdoors domestic water storage containers. Dengue is not a priority disease and hence lacks funding support for implementation of dengue prevention programmes.

Figure 4. Year-wise dengue cases and case fatality rate
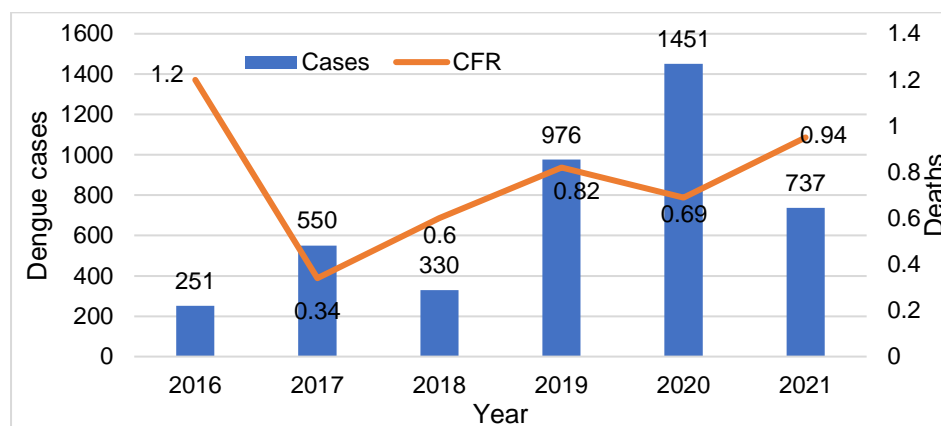
Figure 5. Age-wise distribution of percentage of dengue cases
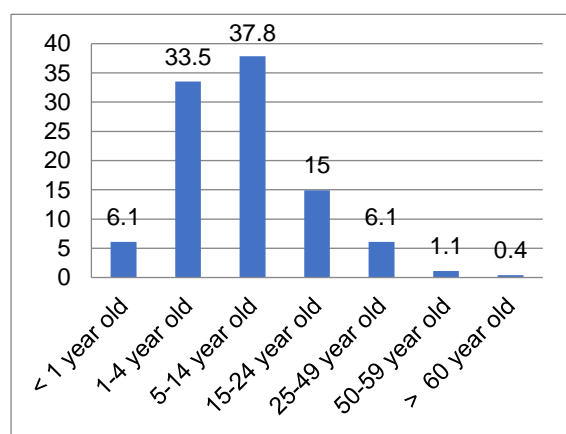
Dengue has been reported predominantly in paediatric age group in Timor-Leste (Fig. 5). In 2021, 33.5% and 37.9% cases were reported in the age group of 1–4 years and age group of 5–14 years, respectively. Dili District has reported maximum number of dengue cases over the years. Besides paediatric cases, dengue has also been reported in the age group of 15–24 years, thereby showing that it is establishing endemicity in Dili.

3.2 Notification of dengue cases

Dengue has been declared a notifiable disease. An MIS cell may be established under the District/Municipal VBD Officer with a nodal officer for monitoring and transmission of surveillance data and reports. It should be the responsibility of all health facilities and labs to report all cases of dengue to the MIS cell. They should provide name, address and contact number of positive case. In urban areas, Sub District VBD Supervisor/Inspector under District/Municipal VBD Officer should carry out epidemiological/entomological investigation and submit report within 24 h. This mandatory reporting will lead to notification of large number of cases, but will project actual burden of disease. This will transform into better and adequate resource allocation, i.e., human resource, logistics and budgetary allocation. Penalty/punishments may be made for non-reporting of notifiable disease for encouraging spread of disease and causing threat to public health at large.

3.3 Strengthening of hospitals and laboratories for case notification

At present clinical-based diagnostic criteria are being followed with support of some rapid diagnostic test (RDT) kits from WHO. Existing infrastructure needs to be strengthened and RDT kits must be made available in all 71 health facilities. All 33 private hospitals may be directed to follow the same diagnostic criteria. Dengue cases tested with RDT kits are classified as probable cases. Due to resource constraints, RDT kits with high sensitivity and specificity may be used in all health institutions and all positive cases tested with RDT kits may be notified as dengue cases for burden estimation.

Major hospitals from different districts may be equipped with facilities for MAC-ELISA test. Cases tested positive with IgM test by ELISA kit will be regarded as confirmed dengue cases. Regional hospital/medical colleges may be provided with facilities for serotyping test. These health facilities must be equipped with facility of ELISA Reader and washer with trained manpower. Prevalent serotype can be assessed for severity and action taken accordingly. Serotyping will also facilitate information to hospitals to be prepared for severe dengue cases. Capacity-building programmes for microbiologist/pathologist and lab technicians may be organised for testing and interpreting rapid and ELISA-based tests.

During COVID-19 pandemic many labs were strengthened for providing diagnostic facilities. These labs may also be coordinated for strengthening diagnostic facilities for dengue.

Private hospitals and labs must be identified and encouraged in all districts for reporting dengue cases. The clinical guidelines with diagnostic criteria based on clinical manifestations and lab diagnosis may also be provided to all hospitals and labs in the private sector. Medical associations may be involved for this purpose and linkage between government and private hospitals should be established. In case private labs do not have facilities for RDK or ELISA they may be linked with government institutions and a notification may be issued by the district concerned in this regard. Private hospitals will also maintain line listing of all cases and share with the District VBD Officer.

3.4 Sentinel surveillance for dengue

Passive surveillance is followed in most of health facilities. It may also be termed reactive surveillance. It has limitations that by the time data are analysed and transmitted, the disease has already spread in the community and does not provide any forecasting techniques. The programme must employ a proactive surveillance system that will permit prediction of dengue outbreak. Sentinel surveillance system must have facilities for serological/virological surveillance, which will further monitor the dengue virus transmission in community/geographical locations during inter-epidemic periods. This will also raise alert for programme managers for effective control measures in the areas. All major government hospitals may be designated as Sentinel Surveillance Hospitals (SSH), which should have trained manpower, i.e., microbiologist/pathologist and lab technicians and equipped with ELISA Reader and washer with uniform diagnostic kits with high sensitivity and specificity. Similarly private hospitals with these facilities may also be included in the list of SSH.

During non-transmission these hospitals will test 10%samples of fever cases visiting them every month. This will provide forecasting tool for detection of dengue during non-transmission season. These hospitals may be asked to provide training on diagnostics and case management for smaller hospitals in the districts.

3.5 Case reporting and notification

Dengue surveillance can be performed by clinical surveillance (Syndromic surveillance) by physicians/paediatricians and lab surveillance, where tests are carried out for detection of virus or antibodies.

Uniform diagnostic criteria may be adopted by all health facilities. When a case is detected in one of the health facilities (Health post, CHC or hospital) same must be communicated within 24 h to the municipal authorities for investigation and taking necessary preventive and control measures. Monitoring system must follow daily, weekly and monthly reporting. All reports must be submitted by email only. A software may also be developed, and user ID and password may be provided to all

CHCs, government hospital and major private hospitals. The access to software can be provided to all concerned officers depending on their role. This information should include contact details, age/sex of patients, residence address, work place address, and any history of travel during incubation. This investigation report must be supported by entomological surveillance.

Chapter 4
Programme planning

Malaria, dengue and filariasis are the main vector-borne diseases (VBDs) in Timor-Leste. Malaria cases have shown declining trend and it can be taken up for the elimination phase. Filariasis is also in its post-MDA surveillance and on the verge of elimination as a public health problem However, dengue is emerging as a challenge with cases taking outbreak proportions. This may lead to endemicity in Timor-Leste. Multiple agencies are involved in programme implementation, and lack of integrated programme further makes it challenging to assess the burden of disease and prepare the programme implementation plan (PIP). Multi-pronged approach is adopted for prevention and control of dengue. The objective of this plan is to decrease the incidence of dengue to a level, where it ceases to be a public health challenge and to reduce the CFR due to dengue. While planning PIP some components need to be adopted/strengthened. Some of these components have also been discussed in detail in the previous chapters, others are given below:

1. Disease surveillance
2. Diagnosis and case management
3. Vector surveillance
4. Integrated vector management
   - Vector management
   - Behaviour change communication
   - Inter-sectoral coordination
5. Capacity-building
6. Legislation and law enforcement
7. Monitoring and supervision
8. Operational research.

As part of the preventive and control measures at various levels, the following actions may be taken:

a) Household

Intensifying efforts to reduce larval habitats in and around houses by covering all water storage containers in the house to prevent egg-laying by mosquito, and emptying, drying water tanks, containers, coolers, birdbaths, pets' water bowls, plant pots and drip trays at least once every week.

- Discard all waste articles, tyres, etc. that are lying in open and may hold water during rains. Tyres should be properly disposed. If there is no proper disposal system, it may be buried under the ground, though it is not an ideal disposal system, as it may releases chemicals, pollute water and soil, thereby creating an environmental hazard
- Check for gutters and flat roofs regularly for any clogging and water stagnation
- Carry out spray with commercially available safe aerosols (Pyrethroid-based)
- Rooms including closets and kitchens should be sprayed (by removing/covering all food items properly). Room may be closed for 15–20 min for effective results and time of spray should coincide with biting time of the *Ae. aegypti* mosquito, e.g., early morning or late afternoon

- Take personal protection measures, i.e., protective clothing (full sleeved shirts and full pants during day time), and using commercially available repellents
- Use insecticide-treated mosquito nets while sleeping during day time
- Ensure doors and windows have screens/wire mesh
- Larvivorous fishes (e.g., Gambusia/Guppy) may be introduced in ornamental water tanks/garden
- Pass the message on preventive measures to different peer groups.

b) Community

Activities may be under taken by different groups, i.e., resident welfare associations (RWAs), nongovernmental organisations (NGOs), self-help groups (SHGs), and faith-based organisations (FBOs). These groups should reinforce the house-hold measures in larger aspects and launch campaigns in raising awareness. The awareness campaigns should include common signs and symptoms of *Aedes*-transmitted arboviral diseases, warning signs, home care, preventive and control measures. Some of the activities are as follows:

- Ensure all overhead water storage tanks have well-fitted lids and overflow pipe has a wire mesh to prevent the entry of mosquito
- Create awareness among local residents to observe dry day ever week and follow all measures suggested under household level
- These groups can identify construction sites and advice the builder/contractor on the need for taking antilarval measures at these sites
- The groups may volunteer and undertake special campaigns at places of historical importance or of tourist attractions
- Community groups may carry out cleaning and covering water storage containers
- Keeping the surroundings clean and organising sanitation measures
- Carry out cleaning weeds and tall grass to reduce resting places for adult mosquitoes
- Promoting use of mosquito nets to protect infants and small children from mosquito bites during day time
- Coordinating and participating with local health authorities in organising camps for insecticide treatment of community owned mosquito nets/curtains
- In case water containers cannot be emptied, coordination with the health authorities for application of temephos granules (1 ppm).
- Mobilize households to cooperate during spraying/fogging.

c) Institutions (Hospitals, schools, colleges, other institutions, offices, etc.)

- Designating a nodal officer and his/her team to check every week for *Aedes* larval habitats inside the premises, i.e., overhead tanks, ground water storage tanks, air coolers, planters, flower pots, etc.
- Ensuring source reduction by covering all water tanks with mosquito proof lids
- Emptying, drying water containers, coolers, plant pots at least once each week
- Checking for clogged gutters and flat roofs for any water accumulation
- Introducing larvivorous fishes (e.g., Gambusia/Guppy) in ornamental water tanks/garden
- Carrying out indoor space spraying with pyrethrum 2% or cyphenothrin, etc.
- Promoting personal protection measures

- Putting tight-fitting screens/wire mesh on doors/windows
- Reporting all fever cases (suspected dengue) to local health authorities.

CONSTRUCTION SITES

- Water collection can occur in all available artificial containers at construction sites
- Disease transmitting mosquitoes reproduce freely in these containers
- Construction workers and nearby communities are exposed to these mosquitoes and therefore suffer from Vector Borne Diseases
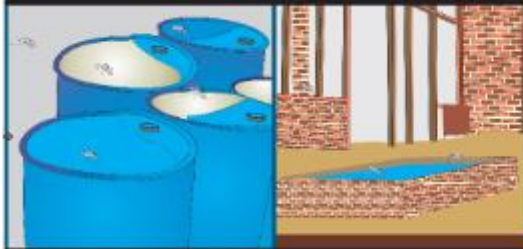
Problem: Stagnant water in equipment and machinery

Solution: Apply one of these on weekly basis
- Clear water and scrub container
- Use temephos @ 1mg/ltr, if breeding persists

Problem: Water stored in containers like curing tanks, drums, etc.

Solution: Apply one of these
- Cover all containers
- Discard, if not required
- Store under shelter
- Use temephos @ 1mg/ltr, if breeding persists
- Introduce larvivorus fishes

Problem: Water collection in lift shaft areas, pits, tarpaulin, temporary drainage etc.

Solution: Apply whichever applicable
- Place tarpulin without grooves
- Clean drainage weekly
- Use temephos @ 1mg/ltr, if breeding persists

Problem: Debris, Discarded items and Receptacles holding water

Solution:
- Discard unwanted articles or
- Put them under shelter/cove

CONTRACTOR IS PRIMARILY RESPONSIBLE TO CONTROL MOSQUITO BREEDING AT THE CONSTRUCTION SITE IN CONSULTATION WITH PUBLIC HEALTH DEPARTMENT

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DOMESTIC BREEDING SITES

- A number of potential mosquito breeding sites exists in a house
- Few of these containers hold water throughout the year and support breeding of Aedes
- These containers act as mother-fod and referred as key containers
- During transmission season, Aedes spread from key containers to seasonal containers and transmit disease(s)

Problem: Water stagnation on the roof of the house

Solution:
- Clear the water blockage in roof gutters and drainage weekly
- Don't keep any solid waste on roof tops
- Use mosquito proof covers on overhead tanks
- Avoid any designer construction which can hold water
- Use temephos @1mg/ltr, if breeding persists

Problem: Water storage in underground water storage tanks and containers

Solution:
- Use air tight lids for underground tanks
- Clean and scrub the surface of water storage containers every week
- Turn over (upside down) or cover containers weekly at all times
- Use temephos @1mg/ltr, if breeding persists

Problem: Water collection in artificial fountains, bird pots, flower pots

Solution:
- Drain out and scrub artificial containers weekly
- Use flower gel to grow lucky bamboo

Problem: Other containers

Solution:
- Clear and cover cistern properly on weekly basis
- Cover the containers properly
- Clean and scrub the tray/ cooler weekly

COMMUNITY SHOULD DEVOTE 1 HOUR IN A WEEK
TO CLEAN AND SCRUB ALL DOMESTIC BREEDING SITES

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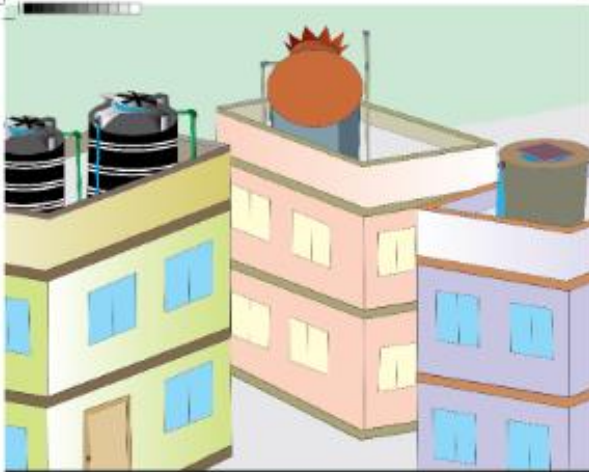
OVER HEAD WATER TANKS (OHTS)

- OHTs act as mother-foci and referred as key containers
- Overhead Water Tanks (OHTs) are potential breeding site for Anopheles (Malaria vectors), Aedes (Dengue, Chikungunya & Zika vectors) and Culex (Filariasis vectors) mosquitoes
- Eggs of Aedes mosquitoes can remain dry for months & hatch when in contact with water
- Breeding in OHTs occurs throughout the year

Problem: Lids of synthetic plastic OHTs get damaged by heat/ temperature/ wild monkeys

Problem: Concrete Cement Tanks, normally covered with improper slabs, provide enough space for mosquitoes to enter

Problem: Inaccessible tanks

Problem: Designer tanks

Solution:

- Cover the lid of OHTs properly
- Fix ladders to access OHTs for inspection, repair and maintenance.
- Set up mosquito-proof strainers and screens that have a mesh size of about 1mm on overflows, outlets, and all other entry points.
- Overflow pipe should always be directed downwards.
- Avoid designer OHTs
- Use temephos @1mg/ltr, if breeding persists

PREVENT WATER TANK FROM MOSQUITO BREEDING, IT WILL PROTECT US FROM DEADLY DISEASES

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PERI-DOMESTIC BREEDING SITES

- Various mosquito breeding sites exist around houses like artificial fountains, curing tanks, pools, discarded tyres, solid waste, plastic drums, tree holes, leaf axils, etc.
- These breeding sites get infested by holding rain water for long period
- Most of these containers are infested with Aedes vector breeding during transmission season

Problem: Water stagnation in public places like parks, schools and malls etc.

Solution:
- Use temephos @1mg/ltr, if breeding persists
- Clear the water collection and scrub the containers weekly
- For permanent water bodies, use small mosquito larva eating fishes

School

MALL
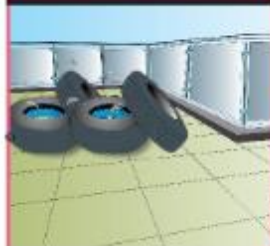
Problem: Rain Water collection in solid waste

Solution: Apply one of these
- Don't keep solid waste open
- Strengthen garbage management system by collecting them for disposal periodically

Problem: Water collection in tree holes, coconut shells and leaf axils etc.

Solution:
- Fill tree holes with soil
- Coconut shells should be buried or store in the soil
- Spray temephos @1mg/ltr, if breeding persists

WET GARBAGE

DRY GARBAGE
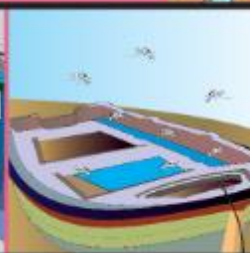
Problem: Rain water collection in miscellaneous containers

Solution:
- Clear and scrub the surface of water storage containers every week
- Use temephos @1mg/ltr, if breeding persists
- Don't keep discarded items like bin/boat/pots exposed for water collection (keep them inverted)

COMMUNITY/RWA SHOULD ADOPT NEIGHBOURHOOD PUBLIC PLACES AND DEVOTE 1 HR/WEEK TO CLEAN, SCRUB AND REMOVE BREEDING SITES AROUND THE HOUSE

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Chapter 5
Laboratory diagnosis

Early clinical suspicion and confirmatory diagnosis of dengue infection help in the early initiation of effective management to reduce morbidity and mortality. Early detection of dengue cases helps in predicting the possible outbreak in a geographical area. This parameter helps rapid response team for prevention and control of vectors and gear up the health care system for clinical management. Confirmatory diagnosis of dengue cases helps in estimating the burden of the disease. It is also important to look for coinfections, which are prevalent in the region such as enteric fever, malaria, scrub typhus, leptospirosis, and other causes of acute febrile illness, etc.

The following laboratory tests are usually available to diagnose dengue fever:

1. Haematological test, which could help to support the diagnosis of viral haemorrhagic fever
   - Thrombocytopenia
   - Leukopenia
   - Haematocrit
   - Test for Coagulopathy (Complement C3,C4, aPTT, PT, D-Dimer and fibrinogen levels)
   - Inflammatory markers (CRP, ESR, and Ferritin)
2. Additional blood test for severity of the disease such as
   - Function test for organ involvement (liver, renal, lungs and CNS)
   - Dyselectrolytemia
   - Arterial blood gas analysis
3. Immunological ELISA-based tests: IgM and IgG antibody tests
4. Viral antigen detection: NS1Ag detection
5. Viral nucleic acid detection: PCR
6. Virus isolation for serotype and genotype
7. Haemagglutination inhibition test
8. Complement fixation test
9. Neutralization test
10. Rapid diagnostic test.

5.1 Type of dengue tests in different phases

Nucleic acid test and circulation viral antigen can be detected on the 4th to 7th day of illness. Therefore, NS1Ag is usually advised before the 5th day of illness for the diagnosis of dengue. IgM starts rising after 3–5 days of onset of illness, and hence it is usually negative before 5th day of illness. IgG antibodies start rising from the end of the first week and increases subsequently and remain for a longer period. IgG antibody is usually elevated among the people those who have past history of dengue infection. Therefore, during secondary dengue infection, IgG antibodies are detectable even in the initial phase at the end of the first week. Sometimes IgM/IgG ratio helps in differentiating primary and secondary infections. In secondary infection, the ratio is usually <1.32.

Serial paired blood samples are required sometimes to confirm or refute the diagnosis of dengue infection from other flavivirus. The optimal interval is usually 10–14 days between the paired sera, i.e., the acute phase (S1) and the convalescent phase (S2 or S3) blood specimen.

5.2 Collection of samples for CBC including haematocrit and platelet
The following are the steps for blood collection in tubes or vials:

- 2–5 mL of venous blood to be collected for testing
- Use vacuum tubes or sterile vials
- In case of delay of more than 24 h, serum may be separated and frozen
- Samples should be quickly transported to laboratory on wet ice (blood) or dry ice (serum) as soon as possible
- National/international guidelines should be followed for shipment.

5.3 ELISA-based NS1 antigen test
NS1 antigen appears as early as day 1 and detectable until 5–6 days of illness. Therefore, this test is used for the early diagnosis of dengue. NS1 antigen appears in both patients with primary and secondary dengue infection up to 6 days of the illness. The test could be performed by ELISA-based and dot blot assays at the early stages of the infection.

5.4 Serological test

a) IgM-capture enzyme-linked immunosorbent assay(MAC-ELISA)
Anti-dengue IgM antibody are developed earlier than IgG antibodies, usually detectable after the 5th day of illness. IgM may persists for more than 90 days, but in most of the patients it disappears after 60 days of illness.

MAC-ELISA positive for IgM antibody results on single serum sample are provisional and do not necessarily mean that the infection is active as the IgM antibody may persist 2–3 months after the previous infection. It is usually useful for symptomatic who are for the diagnosis of acute dengue infection.

b) IgG ELISA
Antidengue IgG antibody starts appearing little bit later than IgM antibody. IgG may be positive after the 7th day of illness. This antibody helps in differentiating primary and secondary dengue infection. IgG seroconversion in paired sera or four-fold rise of IgG titre paired sera is diagnostic for acute dengue infection.

c) IgM/IgG ratio
IgM/IgG ratio is useful to distinguish the primary and secondary infection. If the ratio is greater than 1.2, primary is suspected and if the ratio is less than 1.2, then secondary infection should be considered.

d) Haemagglutination inhibition test
It is sensitive, but less specific test. However, it is easy to perform, and requires only minimal equipment, if properly done. Nowadays this test is not performed usually for diagnosis of dengue, but may be used for sero-epidemiologic studies.

e) Complement fixation test

The test is also not commonly used for diagnosis of dengue due to its complexity and requires trained manpower. It is useful for patients with current infection, but not suitable for sero-epidemiologic studies.

f) Neutralization test

Neutralization test is the most sensitive and specific for diagnosis of dengue infection, but not routinely used in most laboratory because of expensive, complex technique and time consuming.

5.5 Isolation of dengue virus

Isolation of the dengue virus is possible if the blood sample is taken during the febrile phase (viremic phase) usually before the 5th day of illness. Specimens of those may be suitable for virus isolation collected during acute phase include serum, plasma, washed buffy coat and tissue collected from liver, spleen, lymph node and thymus. Usually it takes 7–10 days for isolation of the virus.

5.6 Rapid diagnostic test (RDTs) (NS1/IgM/IgG)

Many antidengue IgM and IgG rapid serological test kits are available commercially in the market. The advantage of the test is that the result is produced within 15 min. Due to poor sensitivity and specificity, these RDTs are not considered as confirmatory test for dengue. This test may be used as a screening test and later may be confirmed by the ELISA.

Case definition

Suspected case of dengue
Acute febrile illness with minimum two of the following: • Headache   • Retro-orbital pain   • Myalgia   • Arthralgia/bone pain   • Rash   • Haemorrhagic manifestations   • Leucopenia (wbc ≤ 5000 cells/mm^3)   • Thrombocytopenia (platelet count < 150 000 cells/mm^3)   • Rising haematocrit (5–10%)   And at least one of following: - Supportive serology on single serum sample: titre ≥1280 with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or testing positive in IgM antibody test, and   - Occurrence at the same location and time as confirmed cases of dengue fever   - RDT positive for NS1 and IgM
Confirmed case of dengue
Suspected dengue case with at least one of the following: • Isolation of dengue virus from serum, CSF or autopsy samples

• Four-fold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to dengue virus

• Detection of dengue virus or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay

• Detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction.

Figure 6. Diagnostic approach febrile illness in endemic regions of dengue, chikungunya, and malaria
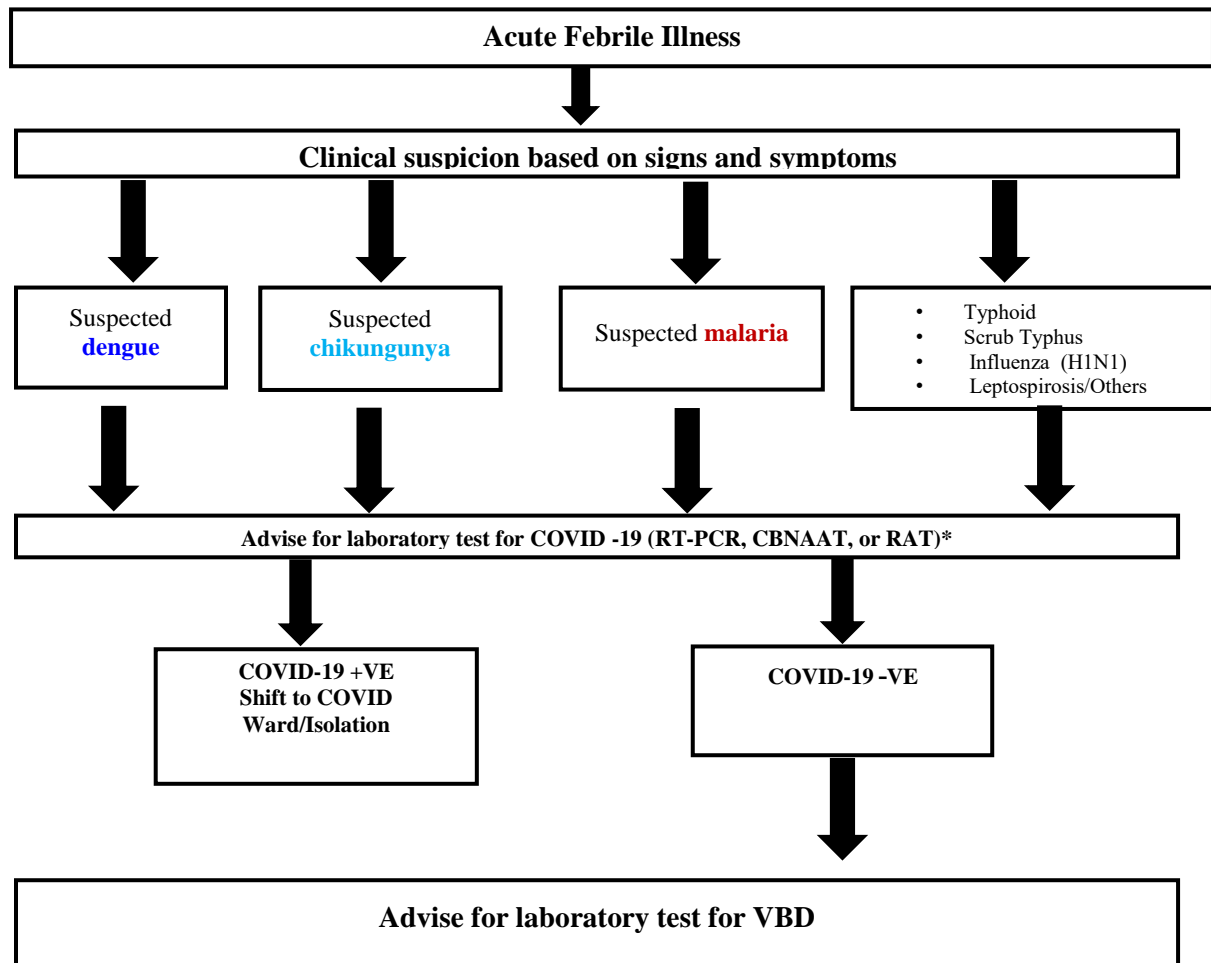
*Depending on the availability of the test

Figure 7. Diagnostic approach to suspected dengue cases

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┌─────────────────────────────────────────────────────────────────────┐
│                      ACUTE FEBRILE ILLNESS                            │
└─────────────────────────────────────────────────────────────────────┘
                                 ↓
┌─────────────────────────────────────────────────────────────────────┐
│ High-grade febrile illness (>39 °C), facial flushing, skin erythema,  │
│ retro-orbital pain, myalgia, arthralgia, nausea and vomiting, and     │
│ with or without hemorrhagic manifestations*.                          │
└─────────────────────────────────────────────────────────────────────┘
                                 ↓
┌─────────────────────────────────────────────────────────────────────┐
│            Clinical suspicion based on signs and symptoms             │
└─────────────────────────────────────────────────────────────────────┘
           ↓                                              ↓
┌─────────────────────┐              ┌──────────────────────────────────┐
│  Suspected Dengue   │              │ • Chikungunya    • Influenza (H1N1)│
└─────────────────────┘              │ • Malaria        • Leptospirosis  │
           ↓                          │ • Scrub Typhus   • Typhoid fever  │
                                      └──────────────────────────────────┘
                                                      ↓
┌─────────────────────────────────────────────────────────────────────┐
│        Laboratory test for COVID 19(RT-PCR, CBNAAT, or RAT)**         │
└─────────────────────────────────────────────────────────────────────┘
           ↓                                              ↓
┌─────────────────────┐              ┌──────────────────────────────────┐
│   COVID-19 +VE      │              │         COVID-19 –VE             │
│   Shift to COVID    │              │      Shift to IPD/OPD            │
│   Ward/Isolation    │              │         Management              │
└─────────────────────┘              └──────────────────────────────────┘
           ↓                                              ↓
┌─────────────────────────────────────────────────────────────────────┐
│                  Laboratory Confirmation for Dengue                   │
└─────────────────────────────────────────────────────────────────────┘
                                 ↓
                   ┌──────────────────────────┐
                   │    Duration of illness   │
                   └──────────────────────────┘
           ↓                                              ↓
┌─────────────────────┐                          ┌─────────────────────┐
│  Duration ≤ 5 days  │◄────────────────────────►│  Duration ≥ 5 days  │
└─────────────────────┘                          └─────────────────────┘
           ↓                                              ↓
┌─────────────────────┐                          ┌─────────────────────┐
│ • Virus isolation   │      ┌──────────┐        │ • Dengue IgM by     │
│ • Dengue RT-PCR     │─────►│ Positive │◄───────│   MAC-ELISA #       │
│ • Dengue NS1 antigen│      └──────────┘        │ • IgG seroconversion│
│   detection by ELISA│           ↑              │   in paired sera or │
│ • NS1 Antigen by RDT│           │              │   fourfold rise IgG │
└─────────────────────┘           │              │   titre             │
           ↓                      │              └─────────────────────┘
┌─────────────────────┐  ┌─────────────────────┐        ↓
│     Negative        │─►│ Repeat Dengue IgM   │─►┌─────────────────────┐
└─────────────────────┘  │     after 48 hours  │  │     Negative        │
                         └─────────────────────┘  └─────────────────────┘
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- * Haemorrhagic manifestations include petechiae, purpura, gum or nasal bleeding, gastrointestinal bleeding, haematuria, menorrhagia and positive tourniquet test.
- ** Depending on the availability of the test, RTPCR ;Real–time reverse transcriptase polymerase chain reaction; CBNAAT; Cartridge-based nucleic acid amplification test ; RAT ; Rapid antigen test)
- # IgM capture enzyme-linked immunosorbent assay (MAC-ELISA)

5.7 Dengue and COVID-19 coinfection severity

Asymptomatic dengue may be symptomatic in presence of asymptomatic COVID-19 infection. These diseases have high proportion of asymptomatic infection (over 60–70%). Symptomatic coinfection of COVID-19 and dengue may have various combinations of severity. The management of coinfection of dengue and COVID-19 depends on the predominant severity of either COVID or dengue. Among the coinfected patients, dengue may be mild, but COVID may be severe, or dengue may be severe or COVID may be mild, or both may have severe presentations as well. Therefore, it is very important to identify severity of either COVID or dengue to target the management strategy. Usually, these patients are treated in the COVID ward, which is made for the management of COVID and usually dengue management is neglected.

The case classification of severity of coinfection is given in Fig. 8. Various combinations of coinfection are possible such as D1C1, D1C2, D1C3….D3C3.

Figure 8. Case classification of severity of coinfection (Dengue and COVID-19)
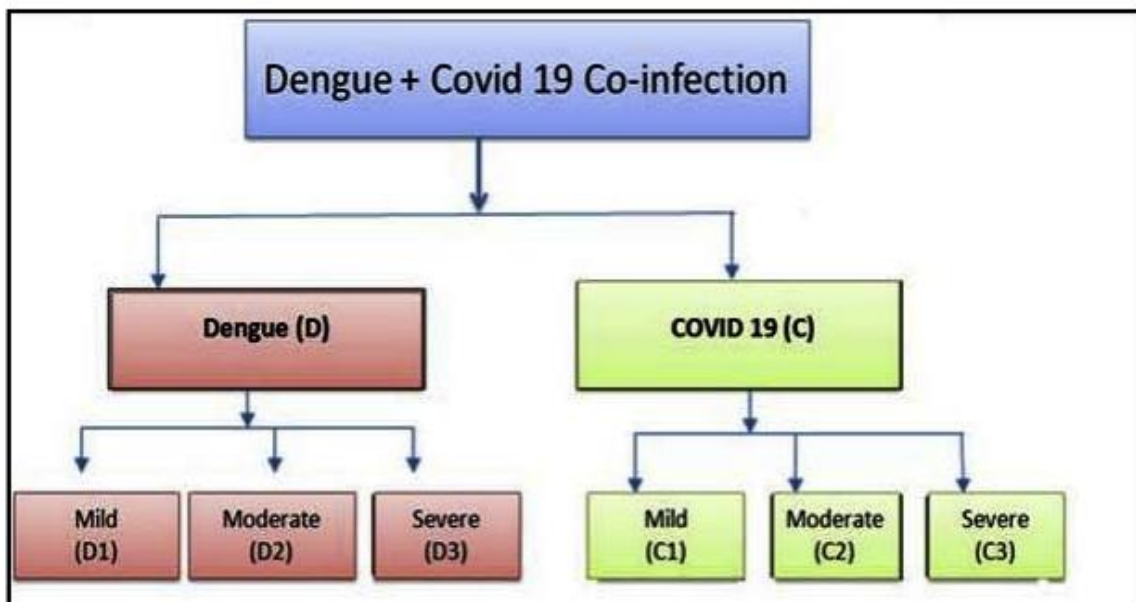
Chapter 6
Pathogenesis

The immunopathological mechanisms include a complex series of immune responses. Rapid increase in the levels of cytokines, especially tumour necrosis factor-alpha (TNF-alpha), and chemical mediators plays an important role in inducing unique clinical manifestations of severe dengue. Host immune responses play a major role in the pathogenesis of haemorrhagic dengue fever. Cross reactive antibodies that lack neutralizing activity are induced in primary infection. In secondary dengue infection, virus and non-neutralizing antibodies form virus-antibody complexes.

Antibody-dependent enhancement increases the efficiency of virus infection and may suppress type I interferon-mediated antiviral responses. Decrease in aberrant activation of T cells and overproduction of soluble factors cause an increase in vascular permeability. Decrease in DENV-induced autoantibodies against endothelial cells, platelets, and coagulatory molecules leads to their abnormal activation or dysfunction. Molecular mimicry between DENV proteins and host proteins may explain the cross-reactivity of DENV-induced autoantibodies. High level of viral load, cytokines, and chemokines are found to be associated with severity of dengue infection.

Dengue infection and immunopathogenesis:

- Immune deviation
- Cytokine overproduction
- Dengue virus-induced vasculopathy
- Dengue virus-induced coagulopathy
- Antiplatelet autoantibody
- Anti-endothelial cell autoantibody
- Molecular mimicry
- Dengue virus infects monocytes and B cells.

6.1 Cytokine storm

Various mechanisms are proposed to explain sign, symptoms and pathogenesis such as T cell-mediated antibody cross-reactivity with vascular endothelium, enhancing antibody, complement and its products and various cytokines and chemokines.

Both the innate immunity such as NK cell and complement system as well as cell-mediated immunity and adaptive immunity play important role for pathogenesis of dengue.

Immunopathogenesis of dengue:

- Macrophage – monocyte infection
- Previous infection with heterologous dengue serotype results in production of non-protective antiviral antibodies
- These Ab bind to the virion's surface Fc receptor and focus the dengue virus on to the target cells – macro/monocytes
- T cell - cytokines, interferon and TNF alpha.

The immune response is observed in primary infections; however, this is disproportionally enhanced particularly in secondary heterologous infections, where cytokine release is augmented

to initiate various pathogenetic mechanisms such as vasculopathy, coagulopathy, and organ involvement.

Various chemokines and cytokines are produced such as TNFα, IFNα, IFNγ, IL-6, IL-8, and IL-10. Some complement fragments such as C3a and C5a play a significant role in vasculopathy, coagulopathy, and bleeding.

6.2 Vasculopathy

6.2.1 Capillary leakage and shock

The vascular endothelium is involved in vasculopathy where vascular functional integrity is impaired rather than structural damage of the endothelium leading to plasma leakage during critical phase to extravascular compartment such as pleural, peritoneal and pericardial cavities. Cytokines such as TNFα, IFNα, IFNγ, IL-6, IL-8, and IL-10 break down the endothelial glycocalyx layer and lead to increased permeability of the capillaries. Complement C3a and C5a are known to enhance the vascular permeability.

Severe manifestations like haemorrhage and bleeding are usually present among patients with high viral load, cytokines, chemokines, and complements.

Table 2. Comparison between pathogenesis of dengue and COVID-19

Dengue	COVID-19
Vasculopathy > cap. leakage, shock, haemorrhagic diathesis	SARS-CoV-2 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
Coagulopathy > heparan sulphate, prolong aPTT, decrease fibrinogen > bleeding	Thrombosis URTI: Oro-pharynx and nasopharyngeal symptoms LRTI: Cough, production, pneumonia, SOB
Cytokine storm > release of different chemokines and cytokines >systemic manifestation	Cytokine storm: local inflammation by secretion of pro-inflammatory cytokines and chemokines IL-6. IFN y, MCP 1, IP-10 Systemic manifestation, shock, MODS
Organ involvement > organ dysfunction, commonly kidney, liver and CNS	Organ involvement: Lungs, liver, kidney, CNS…
Cytopathy: Thrombocytopenia, leucopenia	Cytopathy: Thrombocytopenia, leucopenia

6.3 Coagulopathy

The coagulation profile is deranged due to impairment of the following factors:

- aPTT ⇑
- Fibrinogen ⇓
- Platelets ⇓

- Disseminated intravascular coagulation (DIC)
- Procoagulants ⇑
- Anticoagulants⇓
- Enhanced fibrinolytic activity
- Release of heparan sulphate or chondroitin sulfate from the glycocalyx.

6.3.1 Causes of thrombocytopenia

- IgM type of antiplatelet antibody
- Antiplatelet antibodies + complements →lysis of platelets
- Dengue viral specific antibodies
- Bone marrow hypocellularity
- Destruction of platelet in the liver and spleen
- DIC
- Cytoadherence
- Peripheral sequestration
- Platelet dysfunction (defect in ADP release).

6.3.2 Causes of haemorrhagic in dengue

- DIC
- Thrombocytopenia
- Prolonged activated partial thromboplastin time (aPTT)
- Decreased fibrinogen level
- Increased levels of fibrinogen degradation products (FDP) and d-dimer
- Prothrombin complex deficiency (liver damage)
- Consumptive coagulopathy (mononuclear phagocytes).

Among various mechanisms those have been considered include immune complex disease, T cell-mediated, antibodies cross-reacting with vascular endothelium, enhancing antibodies, complement and its products, various soluble mediators including cytokines, selection of virulent strains and virus virulence. However, the most favoured are enhancing antibodies and memory T cells in a secondary infection resulting in cytokine tsunami. Whatever the mechanism, it ultimately targets vascular endothelium, making it a battlefield leading to severe dengue disease.

Chapter 7
Clinical manifestation

Dengue infection may present as asymptomatic or symptomatic febrile illness with a varied clinical presentation. The presentation may depend on several factors such as virus strain, previous infection, host factors like age, sex and presence of comorbidities.

7.1 Clinical features of dengue fever

After the average incubation period of 4–6 days with non-specific constitutional symptoms, the onset of fever is witnessed with a sharp rise in temperature. This may be associated with flushed face, headache, and chills. Patients also complain of retro-orbital pain, photophobia, backache, myalgia and arthralgia. Some of the atypical symptoms may include anorexia and altered taste sensation, constipation, colicky pain and abdominal tenderness. These symptoms may persist in some of the individuals for several days to few weeks as a part of postviral illness.

Fever

The rash in infants and young children with a nonspecific febrile illness is hard to distinguish from other viral illnesses. The body temperature is usually between 39 °C and 40 °C, lasting 4–7 days in the majority of cases, and sometimes may be biphasic. More than half of infected patients report to rash during the time of fever that initially is macular or maculopapular, and then become generalized.

Rash

The initial rash is a transient flushing erythema of face that typically occurs before or within the first 24–48 h of the onset of symptoms due to result of capillary dilatation. The second rash over face, neck, chest, and abdomen usually occurs around day 3–6 after the onset of fever and it is characterized by asymptomatic maculopapular or morbilliform eruption. In some individuals, the lesions may coalesce and are then seen as generalized confluent erythema with petechiae and rounded islands of sparing "white islands in a sea of red." At the end of febrile period or immediately after defervescence, the generalized rash may fade in some of the patients, and in others the rash may progress to generalized eruptions. The generalized rash may start on the dorsum of the hands and feet and spreads to the arms, legs, and torso and it lasts for several days and subsides without desquamation. During the convalescent phase, an additional rash a confluent, erythematous eruption with small islands of unaffected skin that is often pruritic may appear within one to two days of defervescence and may last for 1–5 days. Skin itching may be complained by few of the patients.

Haemorrhagic manifestations

Skin haemorrhagic manifestations as petechiae, purpura, or ecchymosis with positive tourniquet test are commonly seen in moderate and severe dengue cases. These manifestations usually appear after the 4th to 5th day of fever.

Other severe bleeding manifestations such as massive epistaxis, hypermenorrhoea, haematuria, intracranial bleeding, and gastrointestinal bleeding occur rarely in moderate to severe dengue and are usually associated with thrombocytopenia and coagulopathy.

Figure 9. Guidelines for diagnosis of dengue cases

Clinical approach and diagnosis of dengue

Acute febrile illness < 7 days

History
- Day of fever
- Detailed history: fever, retro orbital pain , myalgia, bleeding, poor oral intake, decrease in urine output
- Warning signs and symptoms

Clinical examination
- Pulse
- BP/postural hypotension
- Tachycardia
- Pulse pressure (narrow < 20 mmHg)
- Rash
- Mucosal bleeding
- Hepatomegaly
- Clinical evidence of pleural effusion
- Ascites

Beside tests and investigations
- Tourniquet test
- Capillary refilling time (CRT)
- Complete blood count (CBC)
- HCT
- Platelet count

Diagnosis*
1. Mild dengue (Group A)
2. Moderate dengue (Group B)
3. Severe dengue (Group C)
- With significant bleeding
- Profound shock
- Severe organ involvement
- Severe metabolic disorder
- Other severe complications

Table 3. History and physical examination in a case of dengue infection

History	Physical examination
- Date of onset of fever/illness - Quantity of oral fluid intake - Diarrhoea - Urine output (frequency, volume and time of last voiding) - Assessment of warning signs - Change in mental state/seizure/dizziness - Other important relevant history, such as family or neighbourhood dengue, travel to dengue-endemic areas, co-existing conditions (e.g., infancy, pregnancy, obesity, diabetes mellitus, hypertension), jungle trekking and swimming in waterfalls (consider leptospirosis, typhus, malaria), recent unprotected sex or drug abuse (consider acute HIV-seroconversion illness).	- Assessment of mental state - Assessment of hydration status - Assessment of hemodynamic status (Check for postural hypotension) - Fundoscopy to look for retinal bleed - Checking for quiet tachypnoea/acidotic breathing/pleural effusion - Checking for abdominal tenderness/hepatomegaly/ascites - Examination for rash and bleeding manifestations - Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

Box 1. Postural hypotension

- Let the patient lie down for 5 min, measure blood pressure and pulse rate. Thereafter let the patient stand and repeat blood pressure and pulse rate after 3 min of standing.
- A drop in systolic BP of ≥ 20 mmHg and diastolic of ≥10 mmHg indicate early shock.

Box 2. Tourniquet test

- The tourniquet test is performed by inflating a blood pressure cuff to a point mid-way between the systolic and diastolic pressures for 5 min.
- A test is considered positive when 10 or more petechiae per 2.5 cm^2 (1 inch) are observed.
- In severe dengue, the test usually gives a definite positive result (i.e., > 20 petechiae).
- The test may be negative or mildly positive during the phase of profound shock.

Warning signs

The clinicians must be aware of the warning signs in the dengue infection and one should suspect if no clinical improvement or worsening of the patient's condition just before or during the transition to afebrile phase or as the disease progresses. Warning signs are given below:

- Persistent vomiting
- Severe abdominal pain and tenderness
- Lethargy and/or restlessness, sudden behavioural changes
- Bleeding manifestations like epistaxis, melena, haematemesis, excessive menstrual, haematuria

- Syncope or giddiness
- Clinical fluid accumulation (ascites and pleural effusion)
- Lethargy and/or restlessness
- Enlarged liver (> 2 cm)
- Laboratory: Progressive increase in haematocrit with rapid decrease in platelet count.

Figure 10. Clinical features and laboratory investigations in dengue infection
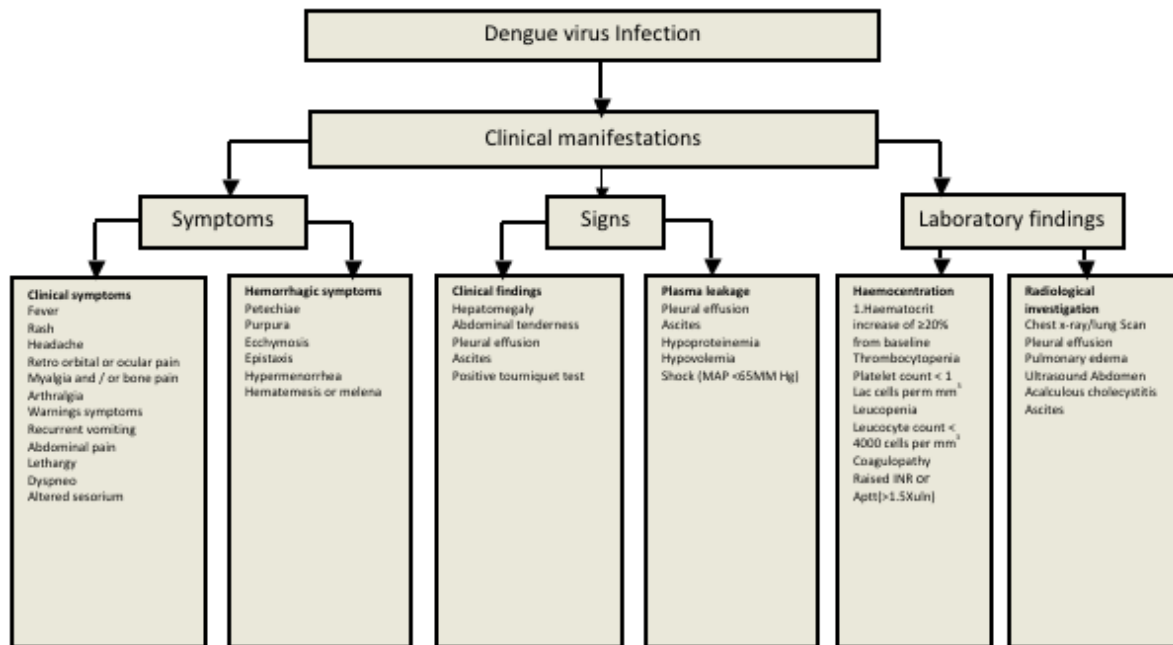
7.2 Clinical phases of dengue

Dengue fever is a dynamic illness and the average incubation period varies from 4 to 6 days (range 3–14 days). After the incubation period, fever with various non-specific constitutional symptoms such as headache, backache and malaise usually appear. Dengue infection usually evolves into three phases: the acute febrile phase observed in most of the patients and the critical and the recovery (convalescent) phases. The clinical expressions are dynamic and may change as the days go by and can also worsen unforeseen (Fig. 11).

7.2.1 Febrile phase

This phase is characterized by the sudden rise of temperature, which usually is high-grade fever (≥ 38.5 °C) and may be biphasic. This phase usually lasts for 2–7 days, and is associated with headache, flushing, vomiting, myalgia, arthralgia, and macular rash. Rash is mostly maculopapular or rubelli form, and it usually appears after the 3rd to 4th day of fever and occur over face, neck, chest, and abdomen, and it normally fades away as the fever progresses.

Haemorrhagic manifestations may be witnessed in this phase with varied severity of haemorrhagic manifestations. Most of the cases may present with skin and/or mucosal bleeding (includes gastrointestinal or vaginal) and less commonly with hematemesis, melena, heavy menstrual

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bleeding, epistaxis or haematuria. The patients with comorbidities such as peptic ulcer disease or on steroids have higher risk for haemorrhagic manifestations.

Figure. 11 Clinical phases of dengue infection
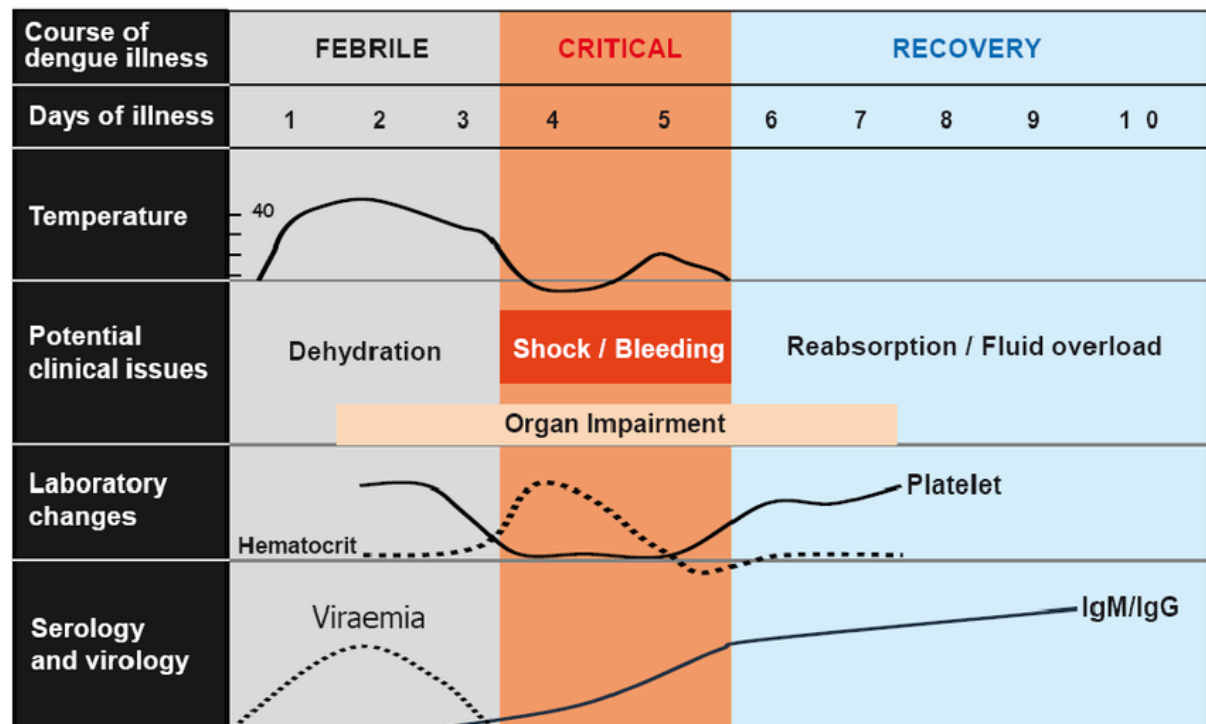
Physical examination may reveal facial puffiness, conjunctival congestion, pharyngeal erythema, lymphadenopathy, and hepatomegaly. Also, important to look for, petechiae (on the skin and/or palate), and bruising (particularly at venipuncture sites), and perform a tourniquet test.

7.2.2 Critical phase (Leakage phase)

Dengue infections that progress to a critical phase are mostly the result of secondary infections. It may occur after primary infections in individuals with comorbidities.

After the third to fourth day of fever, these patients may enter the critical phase. The phase is characterized by vasculopathy and coagulopathy leading to plasma leakage, excessive haemoconcentration and bleeding, which eventually leads to shock and organ dysfunction. The clinician needs to carefully recognize this phase by observing the warning signs as mentioned above. Haemorrhagic manifestations may be observed both in febrile phase and/or critical phase. The phase may last for about 24–48 h. The reversal of the altered vascular permeability due to endothelial dysfunction corresponds with rapid improvement in symptoms and signs.

The clinician needs to carefully recognize this phase and avoid the setting of hypotension. Radiological imaging modalities such as ultrasonography (of the chest and abdomen) and chest radiography are helpful in detection of plasma leakage.

In this phase, moderate to severe thrombocytopenia is common and the nadir of platelet counts ≤20 000 cells/mm³ may be observed, following which rapid improvement during the recovery phase.

Table 4. Parameters to determine compensated and decompensated shock

Normal circulation	Compensated shock	Decompensated/hypotensive shock
Normal sensorium	Normal sensorium with mild shock	Change of mental state – restless, combative or lethargy
Capillary refill time (< 2 sec)	Prolonged capillary refill time(> 2 sec)	Mottled skin, very prolonged capillary refill time
Extremities are warm	Cold extremities	Cold, clammy extremities
Good volume peripheral pulses	Weak and thready peripheral pulses	Feeble or absent peripheral pulses
Normal heart rate for age	Tachycardia	Tachycardia with feeble pulse
Normal blood pressure for age	Normal systolic pressure with raised diastolic pressure, postural hypotension	Profound shock/unrecordable BP
Normal pulse pressure for age	Narrowing pulse pressure	Pulse pressure (< 20 mmHg)
Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ hyperpnoea/Kussmaul breathing
Normal urine output	Reduced urine output	Oliguria or anuria

7.2.3 Convalescent phase (Recovery phase)

The extracellular fluid that was lost owing to capillary leakage returns to the circulatory system during the recovery phase, and signs and symptoms improve. This phase usually occurs after a fever has been present for 6–7 days and lasts for 2–3 days. Some patients with severe shock, organ involvement, or other issues that may require specific therapy can expect a longer recovery time. If fluid replacement is not carefully optimised, the patient may develop pulmonary oedema as a result of fluid excess. During this phase, a convalescent rash is characterized by confluent petechiae surrounding scattered pale, round areas of normal skin. A few patients may complain of skin itching.

7.3 Clinical case classification of dengue

The classification of dengue into different levels of severity has a high potential for being of practical use in the clinicians' decision as to where and how intensively the patient should be observed and treated. The model for classifying dengue was suggested by an expert group (Geneva, Switzerland, 2008) and tested in 18 countries by comparing its performance in practical settings to the existing WHO case classification. The process was finalized in 2010. For practical reasons, this guide adapted the distinction between dengue and severe dengue (Fig. 12).

Figure 12. Distinction between dengue and severe dengue

DENGUE ± WARNING SIGNS

SEVERE DENGUE

with warning signs

without

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement
- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Figure 13. Suggested new clinical case classification of dengue

Dengue

Asymptomatic

Symptomatic

A
Mild dengue
Without warning
signs (WS), +/- RF

B
Moderate dengue
With warning signs, +/- Risk
factors

C
Severe dengue

A-1
Without WS and without risk factors

A-2
Without WS and with risk factors (RF)

B-1
with WS and without RF

B-2
With warning sign and with RF

A-1:Mild fever, normal platelet count, without complications, no evidence of capillary leakage, without WS and without risk factors.
A-2 : A1 + Presence of comorbidities and other risk factors

B-1. DF with warning signs and symptoms
• Recurrent vomiting
• Abdominal pain/tenderness
• General weakness/letharginess/restlessness
• Mild pleural effusion/ascites
• Hepatomegaly
• Increased HCT >20%, with minor bleeds

B-2.
• Infants
• Old age
• Diabetes
• Hypertension
• Pregnancy
• CAD
• Haemogolobinopathies
• Immunocompromized patient (Patient on anticoagulants or immunosuppressants)
• Obesity
• CHD
• Coinfection
• Cerebral palsy and failure to thrive
• Malnutrition

C-1 Severe shock
C-2. Significant bleeding
C3- Severe organ involvement, severe metabolic disorder (Acidosis, dyseletrolytemia, other complications)

Home or OPD management/follow up/observation

Close monitoring and possibly hospitalization/observation

Hospital care management

7.3.1 Dengue without warning signs (Mild dengue -A)

The patient usually presents with fever and other symptoms like nausea, vomiting, rash, headache, pain in the muscles and joints/bones and retroorbital pain, etc. Here, the complete blood count may reveal leucopenia, but usually platelet count and haematocrit are in normal range. The other common symptoms, which are often encountered, are anorexia and altered taste sensation, constipation, colicky pain and abdominal tenderness. This class of patients usually have no complications such as evidence of capillary leakage and shock. The patients in this class can be classified 'A' and subclassified as A1 and A2. The subclass A1 involves patients with fever with other non-specific symptoms, but no warning signs and no risk factors. A2 involves patients with prior comorbidities and other high-risk factors presenting with fever and other non-specific symptoms without warning signs.

7.3.2 Dengue with warning signs and/or risk factors (Moderate dengue-B)

Here the patient present with fever with warning symptoms and signs like recurrent vomiting, abdominal tenderness, clinical or radiological evidence of pleural effusion and/or ascites. This usually occurs near the end of febrile phase and preferably at defervescence. The patients in this class can be classified 'B' and subclassified as B1 and B2. The subclass B1 involves patients with fever with other non-specific symptoms and warning signs, whereas B2 involves patients with prior comorbidities and other high-risk factors presenting with fever with warning signs.

7.3.3 Severe dengue (C)

This class of patients are those who have progressed from mild or moderate dengue to develop symptoms and signs of shock, plasma leakage, and organ dysfunction. The patients in this class can be classified 'C' and subclassified as C1, C2 and C3. The subclass C1 involves patients presenting with history of fever with severe shock, while C2 involves patients with severe bleeding, and C3 involves patients presenting with severe organ involvement, metabolic disorders (severe acidosis).

Severe dengue infection includes infection with any of the following:

- Severe plasma leakage leading to:

    - Shock
    - Fluid accumulation with respiratory distress.

- Severe bleeding (as evaluated by the treating team)
- Severe organ involvement:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1000 units/L
    - Impaired consciousness (GCS < 9)
    - Organ failure.

7.4 Clinical manifestations and complications of organ involvement

Clinical manifestation of major organ manifestations of dengue infection usually manifests in critical phase and may involve liver, central nervous system, cardiovascular system, kidney, and bacterial coinfections (Table 5).

Liver

Hepatic dysfunction is a hallmark feature seen in dengue infection due to direct viral effect. Hepatocytes and Kupffer cells have been described following resuscitation from profound shock; in many cases, it may be caused by prolonged hypoperfusion or hypoxia rather than a direct viral effect. The liver injury in dengue varies from asymptomatic hepatic transaminase elevation to fatal acute liver failure (ALF). The clinical features of hepatic involvement are abdominal pain, nausea/vomiting and anorexia. The commonest abnormality in laboratory examination is raised transaminase levels with AST levels more than ALT levels in most of the patients.

Neurologic

Neurologic manifestations include encephalopathy, intracranial bleed and seizures, and may result in devastating permanent neurologic sequelae. Clinical manifestations include fever, headache, lethargy, and some patients may have no characteristic features of infection.

Other major, but rare neurologic presentations are stroke, acute pure motor weakness, mononeuropathies, polyneuropathies, GBS, acute disseminated encephalomyelitis, and transverse myelitis. In some cases, the diagnosis can be made with help IgM antibody, or detection by polymerase chain reaction in cerebrospinal fluid.

Cardiovascular

Patients may present with severe clinical manifestations, including bleeding, organ impairment, and vasculopathy leading to increased capillary permeability causing hypovolaemic shock. The infection may lead to myocardial impairment, arrhythmias, and myocarditis. Elevated levels of troponin or B-type natriuretic peptide are found in some of the cases.

Renal

Acute kidney injury (AKI) is one of the rarer complications and the mechanisms of AKI may include shock, rhabdomyolysis, glomerulonephritis, and acute tubular necrosis.

Bacterial coinfection

Bacterial coinfection may occur following dengue infection. Although it is more observed in immunosuppressed patients, and patients with comorbidities like DM, HIV, steroid therapy, etc., with or following dengue infection. Thus, these subsets of patients should be evaluated further for bacterial infections, if persistent fever, rising white blood cell count, and signs and symptoms not fitting into dengue.

High-risk factors for severe disease:

- Infants and the children (age < 10 years) especially with malnutrition
- Elderly (age > 65 years)
- Obesity
- Pregnant women
- Female who have menstruation or abnormal vaginal bleeding
- Haemolytic diseases such as glucose-6-phosphatase dehydrogenase deficiency, thalassemia and other haemoglobinopathies
- Peptic ulcer disease
- Congenital heart disease

- Chronic diseases such as diabetes mellitus, obstructive lung diseases, cardiovascular diseases, chronic renal failure, and chronic liver disease
- Patients on long-term steroid or NSAID treatment.

Table 5. Dengue infection with organ involvement

Neurological	Febrile seizures in young children. Encephalopathy. Encephalitis/aseptic meningitis. Intracranial haemorrhages/thrombosis. Subdural effusions. Mononeuropathies/polyneuropathies/GBS. Transverse myelitis
Gastrointestinal/hepatic	Hepatitis/fulminant hepatic failure. Acalculous cholecystitis. Acute pancreatitis. Hyperplasia of Peyer's patches. Acute parotitis
Renal	Acute renal failure. Haemolytic uremic syndrome
Cardiac	Conduction abnormalities. Myocarditis. Pericarditis
Respiratory	Acute respiratory distress syndrome. Pulmonary haemorrhage
Musculoskeletal	Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis
Lymphoreticular/bone marrow	Infection associated haemophagocytic syndrome IAHS or haemophagocytic lymphohistiocytosis (HLH), idiopathic thrombocytopenic purpura (ITP) Spontaneous splenic rupture. Lymph node infarction
Eye	Macular haemorrhage. Impaired visual acuity. Optic neuritis
Others	Postinfectious fatigue syndrome, depression, hallucinations, psychosis, alopecia

7.5 Dengue fever in paediatric age group

Dengue infection occurs in all age groups of human population, and paediatric age group has been found to be mostly affected. Paediatric age group is also at high risk for morbidity and mortality. In the recent past, it has been observed that there is a paradigm shift of high incidence of dengue infection from paediatric age group to adolescent and adult.

7.5.1 Vertical transmission and neonatal dengue infection

Vertical dengue infection transmission from pregnant women to their fetus has been reported in different studies and case reviews. The effect of dengue infection on pregnant women, fetus and new born should be carefully examined to access capillary leakage and bleeding tendency. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly to severe illness with pleural effusion, gastric bleeding,

circulatory failure, massive intracerebral haemorrhage. Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status or mode of delivery. However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. Passive transfer of maternal dengue antibodies to the fetus influences the occurrence of a severe development of the disease. Antibodies to the dengue in newborn infants do not appear to be associated with maternal disease severity or dengue immune status or mode of delivery. Antibodies to the dengue virus in the dengue-infected mother can cross the placenta and can cause severe dengue in newborn infants. Initial presentation may be confused with bacterial sepsis, birth trauma and other neonatal illnesses.

7.5.2 Dengue in infants

Dengue virus can cause a spectrum of outcomes in infants, ranging from asymptomatic infection to mild or clinically significant severe disease similar to older children and adults. The burden of severe dengue lies predominantly in infants of 4–9 months of age.

7.5.3 Manifestations of dengue in infants

As in older children, infants with dengue typically have high fever that usually lasts 2–7 days. Compared to older children, upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnoea), gastrointestinal symptoms (vomiting, diarrhoea), and febrile convulsions are more common in infants with dengue. It is often not possible to differentiate between dengue and other common infections in infants such as pneumonia, meningoencephalitis, measles, rotavirus infections, etc. at the febrile stage. Around the time of defervescence (which usually falls on 3–6 days of illness), an increase in capillary permeability, in parallel with increasing haematocrit levels, becomes apparent in the majority of dengue infants. The period of clinical plasma leakage lasts 24–48 h. Clinical features and laboratory findings of infant infected with dengue become more prominent during this critical phase. Skin bleeding such as petechiae, mucosal membrane bleeding (e.g., of the nose and gums), and gastrointestinal bleeding may occur. Hepatomegaly is usually noted and splenomegaly is seen in almost 10% of dengue infants. Shock occurs when a significant amount of volume of plasma is lost through leakage. The body temperature may be subnormal when shock occurs. However, a differential diagnosis of septic shock should be kept in mind in infants who have fever at the onset of shock. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. However, rise of haematocrit may not be sometimes detectable because the normal value of haematocrit in infants 2–12 months of age is relatively low and may be even lower in iron deficiency anaemia. Thrombocytopenia and leukopenia are often observed in this phase. Liver involvement is found more frequently in infants compared to children. Progression of infants with dengue is the same as that of children and adults during the recovery phase.

Chapter 8
Differential diagnosis

Every year different parts of South-East Asia witness seasonal tropical fevers in the post monsoon season. These tropical fevers include dengue, malaria, scrub typhus, zika, chikungunya, leptospirosis, enteric fever, and viral hepatitis. COVID-19 is now a new differential added in the list of acute febrile illness after the recent pandemic. Some of the cases may end up with severe complication and need of intensive care unit (ICU) care. The clinical presentation of these diseases overlaps with each other making it difficult to achieve definitive diagnosis at the time of presentation. Thus, the differential diagnosis of dengue infection is essential to be to look for other coinfection and other possible diagnosis. The differential diagnosis of dengue infection includes:

a) Other viral haemorrhagic fevers
Other viruses capable of causing haemorrhagic fever include Ebola virus, Marburg virus, Lassa virus, yellow fever virus, Crimean-Congo haemorrhagic fever, hantavirus (haemorrhagic fever with renal syndrome), and Zika. These illnesses can cause severe multiorgan system illness accompanied by haemorrhage. The diseases may be distinguished based on relevant epidemiologic exposure and polymerase chain reaction or serologic testing.

b) Chikungunya
Chikungunya virus and DENV cause similar symptoms and signs and are transmitted by the same mosquito vector. In studies comparing the two diseases, joint pain was reported somewhat more often by patients with chikungunya, whereas abdominal pain and leukopenia were more common in those with dengue. Joint swelling is highly specific for chikungunya; bleeding manifestations and thrombocytopenia are relatively specific for dengue. The diagnosis of chikungunya virus infection is established via serology or reverse-transcriptase polymerase chain reaction (RT-PCR).

c) Zika virus infection
DENV and Zika virus infections have similar clinical manifestations and are transmitted by the same mosquito vector. Unlike DENV infection, Zika is commonly associated with conjunctivitis. Coinfection with Zika, chikungunya, and DENVs has been described. The diagnosis of Zika virus infection is established via serology or RT-PCR.

d) Malaria
Malaria is characterized by fever, malaise, nausea, vomiting, abdominal pain, diarrhoea, myalgia, and anemia. The diagnosis of malaria is established by visualization of parasites on peripheral smear.

e) Typhoid fever
Clinical manifestations of typhoid fever include fever, bradycardia, abdominal pain, and rash. The diagnosis is established by stool and/or blood culture.

f) Leptospirosis
Leptospirosis is characterized by fever, rigors, myalgia, conjunctival suffusion, and headache. Less common symptoms and signs include cough, nausea, vomiting, diarrhoea, abdominal pain, and arthralgia. The diagnosis is established via serology.

g) Parvovirus B19

In children, parvovirus presents most commonly as a mild febrile illness characterized by an erythematous malar rash followed by a lacy rash over the trunk and extremities. In adults, parvovirus may present as an acute arthritis involving the small joints of the hands, wrists, knees, and feet, with or without a rash. The diagnosis may establish via serology or nucleic acid testing.

h) Acute HIV infection

A variety of symptoms and signs may occur in association with acute HIV infection; the most common findings are fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache. Other manifestations include painful mucocutaneous ulceration and aseptic meningitis. Diagnostic testing consists of an HIV immunoassay (ideally, a combination antigen/antibody immunoassay) and an HIV virologic (viral load) test.

i) Viral hepatitis

Causes of viral hepatitis include hepatitis A, B, C, D, and E. Hepatitis A and E are acute infections transmitted by the fecal-oral route, whereas hepatitis B, C, and D can present acutely or chronically and are transmitted by body fluids. They are distinguished via serology and PCR.

j) Rickettsial infection

Rickettsial infections with similar manifestations as DENV infection include African tick bite fever and relapsing fever. African tick bite fever is observed among travelers to Africa and the Caribbean and is characterized by headache, fever, myalgia, solitary or multiple eschars with regional lymphadenopathy, and generalized rash. Relapsing fever is characterized by fever, headache, neck stiffness, arthralgia, myalgia, and nausea. The diagnosis is established via serology. Diagnostic tools include direct smear and polymerase chain reaction.

k) Sepsis

Sepsis due to bacteremia may present with fever, tachycardia, and altered mental status. Diagnosis requires blood culture.

l) Influenza

Symptoms of influenza virus infection include abrupt onset of fever, headache, myalgia, and malaise, accompanied by manifestations of respiratory-tract illness, such as cough, sore throat, and rhinitis. The diagnosis is established via molecular testing of a nasopharyngeal specimen; other diagnostic tools are also available.

m) Coronavirus disease 2019 (COVID-19)

Symptoms of COVID-19 include fever, cough, and/or dyspnoea; other features, including upper respiratory tract symptoms, myalgias, diarrhoea, and loss of senses of smell or taste are also common. Laboratory manifestations may include lymphopenia and elevated liver enzymes. The diagnosis is established via molecular testing of a nasopharyngeal specimen; other diagnostic tools are also available.

Chapter 9
Clinical management

Dengue fever is most common in older children, adolescents and adults. It is generally an acute febrile illness, and sometimes biphasic fever with severe headache, myalgias, arthralgias, rashes, leukopenia and thrombocytopenia may also be observed. Although dengue fever may be benign, it could be an incapacitating disease with severe headache, muscle and joint and bone pains (break-bone fever), particularly in adults. Occasionally unusual haemorrhage such as gastrointestinal bleeding, hypermenorrhea and massive epistaxis may occur.

The spectrum of dengue infection includes asymptomatic to symptomatic infection. Symptomatic infection is characterized by plasma leakage, haemorrhagic manifestations and organ involvement. The illness starts abruptly and is followed by three phases---the febrile, critical and recovery phase.

9.1 Triage of suspected dengue patients
During dengue outbreak, hospital authorities should organize a fever clinic (AFI) to screen and triage suspected dengue patients and designate space and beds for admission.

9.1.1 Primary triage
- Usually triage should be performed by a person who is clinically trained in diagnosis and identification of warning signs in dengue
- Moderate to severe or critical cases of B and C groups should be referred directly to a trained nurse/medical assistant in emergency ward
- For the patients with mild (A) to moderate (B) group assess the following:
  - Duration of fever
  - Presence of warning signs
  - High-risk groups (comorbidities and coinfection)
  - Tourniquet test to be conducted
  - Vital signs including temperature, blood pressure, pulse rate and respiratory rate
  - Peripheral perfusion by palpation of pulse volume, and colour of extremities, and capillary refill time
- **Recommendations for CBC (including haematocrit and platelet count) and RBS**
  - All febrile patients at the first visit
  - All patients with warning signs
  - All patients with fever > 3 days
  - All patients with shock
- **Immediate medical consultation is recommended for the following:**
  - Patients with classes B and C, especially those whose illness lasts>3–4 days
  - Patients with shock
  - Patients with hypoglycaemia
  - Patients with classes B and C with leukopenia and thrombocytopenia.

9.2 Approach to clinical management

Depending on the clinical manifestations, presence of warning signs and other high-risk factors, patients may be classified as the following:

- Group A-1 and A-2: May be managed on OPD basis
- Group B-1 and B-2: Observation or admission for in-hospital management
- Group C-1, C-2 and C-3: Require emergency treatment and urgent referral.

9.2.1 Management of mild dengue cases at home and OPD

Both the patients and their family members should be instructed regarding the following at the outpatient department:

- Patient needs to take adequate bed rest
- Adequate intake of fluid such as milk, fruit juice, isotonic electrolyte solution, oral rehydration solution (ORS) and barley/rice water. Over-hydration in infants and young children should be carefully observed
- Body temperature should be kept below 39 °C. If the temperature goes beyond 39 °C, give the patient paracetamol. Paracetamol is available in tablet form or in syrup form. The recommended dose is 10 mg/kg/dose and should be administered in frequencies of not less than 6 h. The maximum dose for adults is 4 g/day. Avoid using too much paracetamol, and aspirin or NSAID.
- Tepid sponging of forehead, armpits, and extremities. A lukewarm shower or bath is recommended for adults.

Follow-up

- Patients should be followed-up frequently with CBC, which could detect several abnormalities such as thrombocytopenia, haematocrit rise, serum electrolytes and leukopenia, if patients with Group A or B and are not admitted or not kept for observation in hospital.
- Daily follow-up is recommended for all patients with mild to moderate severity except those who have resumed normal activities.

9.2.2 Management of dengue cases in hospital

The critical period of dengue fever refers to the period of plasma leakage, which starts around the time from febrile to afebrile phase. Rapid fall of thrombocyte count may indicate progression of severity of disease. A rising haematocrit of 10% above baseline is an early objective indicator of plasma leakage. Intravenous fluid therapy should be started in patients with poor oral intake or further increase in haematocrit, and those with warning signs.

The following parameters should be monitored:

- General condition, appetite, vomiting, bleeding and other signs and symptoms
- Peripheral perfusion can be performed as frequently as is indicated because it is an early indicator of shock and is easy and fast to perform

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- Vital signs such as temperature, pulse rate, respiratory rate and blood pressure should be checked at least every 2–4 h in non-shock patients and 1–2 h in shock patients
- Serial haematocrit should be performed at least every 4–6 h in stable cases and should be more frequent in unstable patients or those with suspected bleeding. It should be noted that haematocrit should be done before fluid resuscitation. If this is not possible, then it should be done after the fluid bolus, but not during the infusion of the bolus
- Urine output should be recorded at least every 8–12 h in uncomplicated cases and on an hourly basis in patients with profound/prolonged shock or those with fluid overload. During this period the amount of urine output should be about 0.5 mL/kg/h (this should be based on the ideal body weight).

9.2.3 Additional laboratory investigations

Adult patients and those with comorbidities or patients in shock and/or those with complications should undergo the following laboratory investigations:

- Random blood glucose
- Blood gas analysis including lactate
- Serum electrolytes (sodium, potassium and calcium)
- Renal function tests (urea and creatinine)
- Liver function tests (AST, ALT and bilirubin)
- Coagulation profile
- Right/left lateral decubitus chest radiograph
- Blood group
- Cardiac enzymes (Pro-BNP and troponin level) or ECG, if indicated among high-risk groups
- Serum amylase and ultrasound, if abdominal pain does not resolve with fluid therapy.

9.2.4 Management of dengue patients of Group A

These are patients who may be managed on OPD basis and who are:

- Able to tolerate adequate volumes of oral fluids
- Able to pass urine at least once every 6 h
- Not having any of the warning signs (particularly when fever subsides).

If the dengue patients of Group A do not require admission, they should be advised for home care and following instruction to followed:

a) Educate about warning signs and to report if they appear
- Severe abdominal pain and persistent vomiting
- Red spots patches on skin
- Bleeding from nose and gums
- Vomiting blood

- Black tarry stools
- Drowsiness or irritability
- Pale, cold or clammy skin
- Difficulty in breathing

b) Advice to consume adequate oral fluids (ORS/coconut juice), avoid carbonated drinks

c) Ensure adequate urine output (at least every 6 h)

d) Prescribe only paracetamol for fever; do not give **NSAIDs** as it may cause bleeding

e) Patients with ≥ 3 days of illness should be reviewed daily for disease progression (indicated by decreasing white blood cell and platelet counts and increasing haematocrit, defervescence (no fever) and warning signs) until they are out of the critical period.

9.2.5 Management of dengue patients of Group B

The dengue patients with warning signs and high-risk groups are considered to be as moderately ill and classified as Group B.

a) Clinical approach for the management of Group B dengue patients

- Includes dengue with warning signs or all special populations
- Should be admitted for hospital management
- Baseline HCT test should be performed before starting fluid therapy if the investigation results are available immediately. Hydration should not be delayed due to unavailability of HCT
- For obese and overweight patients, use ideal body weight for fluid calculations
- The specific warning signs should be identified or other causes such as persistent vomiting, acute gastroenteritis, hypoglycaemia, etc.
- The presence of thrombocytopenia with evidence of plasma leakage such as rising haematocrit and pleural effusion should be observed carefully for the management
- Blood glucose level and other laboratory tests may be indicated to find the causes
- In special populations without warning signs, encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% NS or RL
- They can be sent home within 12–24 h, if they show rapid recovery and are not in the critical period.

b) Specific management strategy for Group B dengue patients

- Baseline HCT before fluid therapy
- For obese and overweight patients, use ideal body weight for fluid calculations
- Adequate intravenous fluid volume may be required to maintain good perfusion and urine output of about 0.5 mL/kg/h
- Isotonic fluid: 0.9% NS or RL are preferred
- IV fluid therapy are usually needed for only 24–48 h

- Start fluid at 5–7 mL/kg/h for 1–2 h reducing to 3–5 mL/kg/h for 2–4 h and then reduce to 2–3 mL/kg/h or less according to the clinical response
- IV fluid therapy are usually needed for only 24–48 h
- Rapid fluid replacement in patients with warning signs is the key to prevent progression to the shock state.

c) Assessment of clinical status and repeat HCT and review fluid infusion rates accordingly

- If haematocrit remains the same or rises only minimally, continue fluid 2–3 mL/kg/h for another 2–4 h
- If the vital signs are worsening and HCT rising rapidly, increase the rate to 5–10 mL/kg/h for 1–2 h.

d) Monitoring of the patient

Temperature, pulse, respiratory rate, and BP should be monitored frequently until the patient is out of critical phase:

- Urine output 6 hourly
- HCT: before and after fluid replacement, then 8 hourly
- Blood glucose and other organ functions (renal profile, liver profile, coagulation profile, as indicated
- Maintain fluid balance sheet.

e) Fluid therapy in mild to moderate dengue (Non-shock)
In general, the fluid allowance (oral + IV) is about maintenance (for one day) + 5% deficit (oral and IV fluid together), to be administered over 48 h. For example, in a child weighing 20 kg, the deficit of 5% is 50 mL/kg x 20 = 1000 mL. The maintenance is 1500 mL for one day (M). Hence, the total of M + 5% is 2500 mL. This volume is to be administered over 48 h in non-shock patients. The rate of infusion of this 2500 mL may be as shown below:

Half the maintenance M/2	1.5	40–50
Maintenance (M)	3	80–100
M + 5% deficit	5	100–120
M + 7% deficit	7	120–150
M + 10% deficit	10	300–500

The rate of IV replacement should be adjusted according to the rate of plasma loss, guided by the clinical condition, vital signs, urine output and haematocrit levels.

Rate of infusion in non-shock cases

Normal maintenance fluid per hour can be calculated on the basis of the following formula* (equivalent to Holliday Segar formula):

- 4 mL/kg/h for first 10 kg body weight
- + 2 mL/kg/h for next 10 kg body weight
- + 1 mL/kg/h for subsequent kg body weight

*For overweight/obese patients calculate normal maintenance fluid based on ideal body weight (IBW), using the following formula:

- Female: 45.5 kg + 0.91(height−152.4) cm
- Male: 50.0 kg + 0.91(height−152.4) cm (20, 21).

Estimated ideal body weight for overweight or obese adults

Height (cm)	Estimated, IBW (kg) for adult males	Estimated IBW (kg) for adult females
150	50	45.5
160	57	52
170	66	61.5
180	75	70

Table 6. Requirement of fluid-based on body weight

Body weight (in kg)	Volume of fluid to be given in 24 h	Rate of fluid (mL/h)			
		R* 1	R* 2	R* 3	R* 4
10	1500	30	60	100	200
15	2000	45	60	150	300
20	2500	60	90	200	400
25	2800	75	120	250	500
30	3200	90	150	300	600
35	3500	105	180	350	700
40	3800	120	210	400	800

45	4000	135	240	450	900
50	4200	150	270	500	1000
55	4400	165	300	550	1100
60	4600	180	360	600	1200

Regimen 1- 3 mL/kg/h; **2** -6 mL/kg/h; **3** -10 mL/kg/h, and **4**- 20 mL/kg/h

- The fluid volumes mentioned are approximations.
- Normally changes should not be drastic. Do not jump from R-2 to R-4 since this can cause fluid overload. Similarly reduce fluid volume from R-4 to R-3, from R-3 to R-2 and from R-2 to R-1 in a stepwise manner.

Figure 14. Hospital management for dengue patients with warning signs in adults
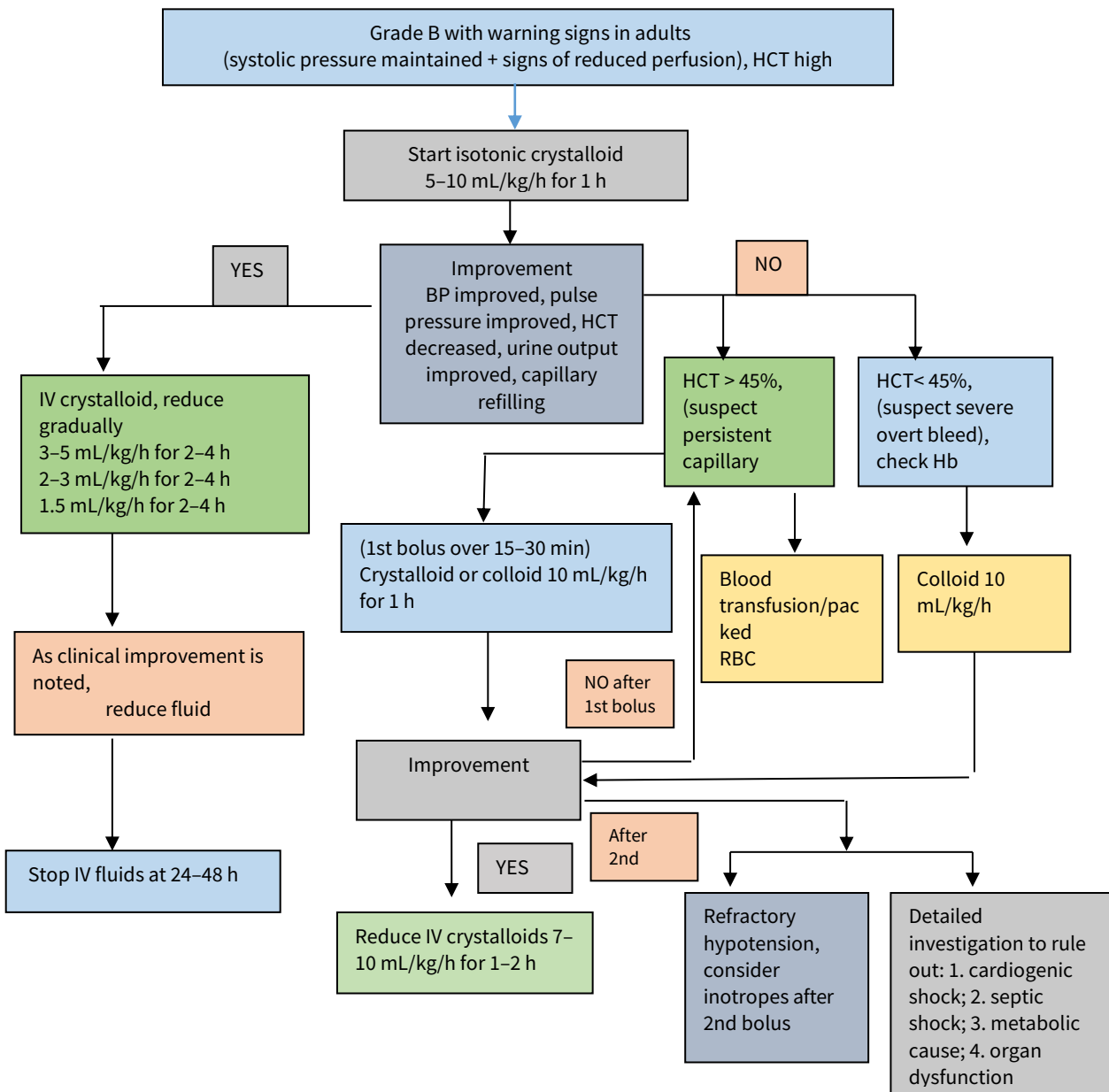
Figure 15. Group B: Hospital management for dengue patients with warning signs in children
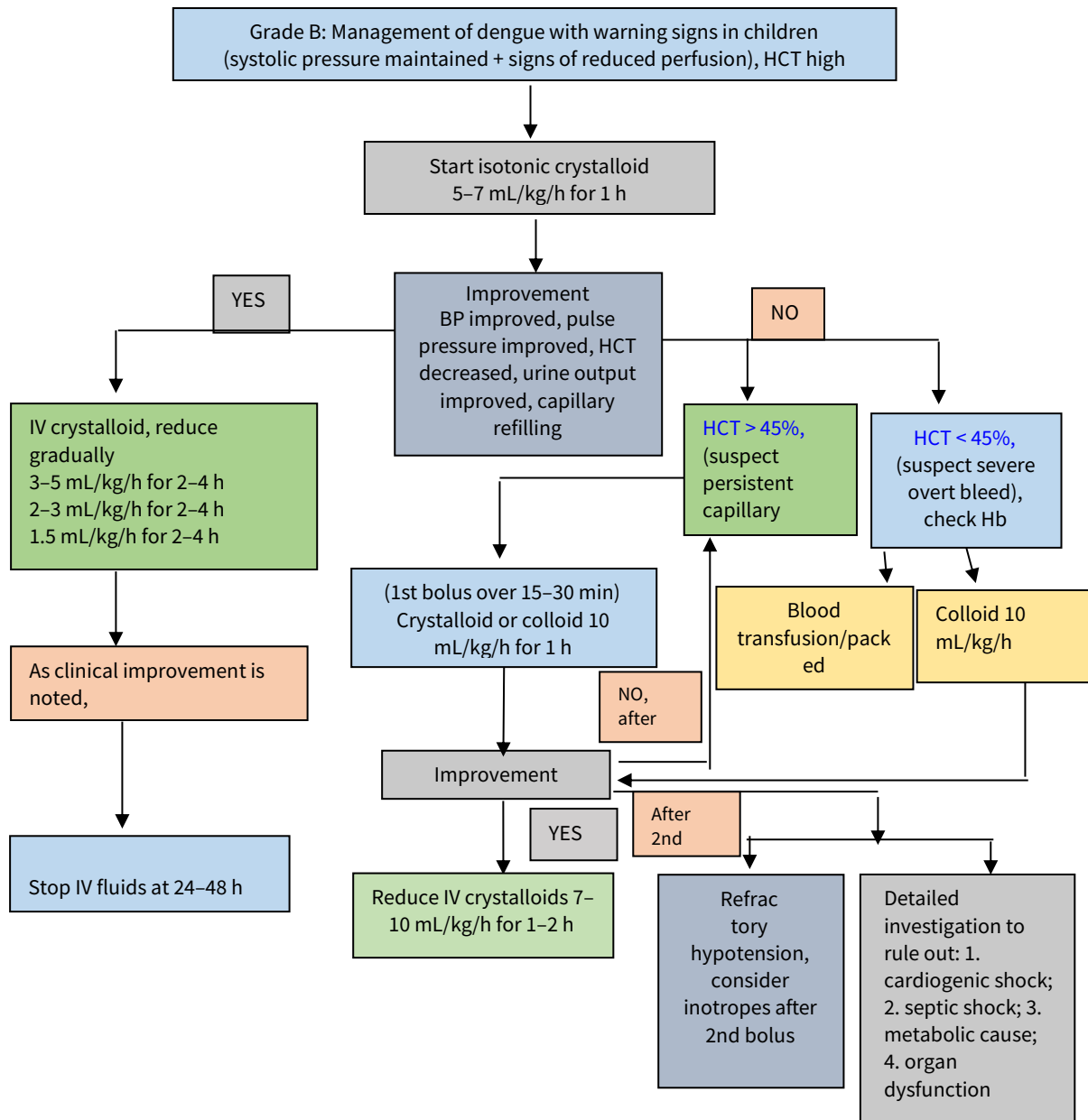
9.2.6 Management of dengue patients of Group C

These are patients with severe dengue who require emergency treatment and urgent referral because they are in the critical phase of the disease and have:

- Severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress
- Severe haemorrhage
- Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis)
- Severe metabolic abnormalities.

9.2.7 Principles of management of severe dengue (C)

- Refer all patients after stabilization for admission to a hospital with blood transfusion facilities
- Judicious IV fluid resuscitation is essential
- Prefer a crystalloid solution (NS or RL) sufficient to maintain an effective circulation during the period of plasma leakage (usually for 24–48 h) and adjust fluid accordingly
- Obtain HCT levels before hydrating patient; lack of HCT should not delay start of hydration
- Monitor ABC and vital signs every 5–30 min
- Use IBW for overweight and obese patients while calculating fluid rates
- All shock patients should have their blood group taken and a cross-match carried out
- Blood transfusion should be given only to patients with established severe bleeding, or suspected severe bleeding (fall in HCT) with unexplained hypotension.

9.2.8 Treatment of severe dengue

Severe dengue is a medical emergency. It requires immediate medical care at a clinic or hospital.

a) IV fluid therapy during the critical period

The general principles of fluid therapy in DHF include the following:

- ***Isotonic crystalloid solutions should be used throughout the critical period*** except in the very young infants < 6 months of age in whom 0.45% sodium chloride may be used
- Hyper-oncotic colloid solutions (osmolarity of > 300 mOsm/L) such as dextran 40 or starch solutions may be used in patients with massive plasma leakage, and those not responding to the minimum volume of crystalloid. Iso-oncotic colloid solutions such as plasma and haemaccel may not be as effective
- A volume of about maintenance +5% dehydration should be given to maintain a "just adequate" intravascular volume and circulation
- The duration of IV fluid therapy should not exceed 24–48 h for those with shock. However, for those patients who do not have shock, the duration of IV fluid therapy may have to be longer, but not more than 60–72 h. This is because the latter group of patients has just entered the plasma leakage period, while shock patients have experienced a longer duration of plasma leakage before IV therapy is begun
- In obese patients, the ideal body weight should be used as a guide to calculate the fluid volume.

Table 7. Guide to calculate the fluid volume

Ideal body weight (kg)	Maintenance (mL)	M+5% deficit (mL)	Ideal body weight (kg)	Maintenance (mL)	M + 5% deficit (mL)
5	500	750	35	1800	3550
10	1000	1500	40	1900	3900
15	1250	2000	45	2000	4250
20	1500	2500	50	2100	4600
25	1600	2850	55	2200	4950
30	1700	3200	60	2300	5300

b) Requirement of fluid based on ideal body weight

Platelet transfusion is not recommended for thrombocytopenia (no prophylaxis platelet transfusion). It may be considered in adults with underlying hypertension and very severe thrombocytopenia less than 10 000 cell/mm^3.

c) Management of shock

Hypovolemic shock caused by plasma leakage and characterized by increased systemic vascular resistance, manifested by narrowed pulse pressure (systolic pressure is maintained with increased diastolic pressure, e.g., 100/90 mmHg). When hypotension is present, one should suspect that severe bleeding, and often concealed gastrointestinal bleeding, may have occurred in addition to the plasma leakage.

It is essential that the rate of IV fluid be reduced as peripheral perfusion improves; but it must be continued for a minimum duration of 24 h and discontinued by 36–48 h. Excessive fluids will cause massive effusions due to the increased capillary permeability.

Table 8. Treatment of compensated shock

Group C: Dengue with compensated shock				
Measure HCT 1 then give **Ringer lactate** (1st bolus) Children: 10–20 mL/kg in 15–30 min Adults: 5–10 mL/kg in 15–30 min				
If improvement (no signs of shock present) Reduction of rate: Children: **Ringer lactate** 10 mL/kg/h for 1–2 h 7 mL/kg/h for 2 h 5 mL/kg/h for 4 h 3 mL/kg/h Adults: **Ringer lactate** 5–7 mL/kg/h for 1–2 h 3–5 mL/kg/h for 2–4 h 2–3 mL/kg/h for 2–4 h	HCT increases or stays/elevated Children: Crystalloid 10–20 mL/kg in 15–30 min (2nd bolus) 10 mL/kg in 15–30 min7 mL/kg in 15–30 min Adults: Crystalloid 10–20 mL/kg in 15–30 min (2nd bolus)	HCT 2 decreases[b] Look for severe haemorrhage		
	if improvement(no signs of shock present) Children: **Ringer lactate** according to "Reduction of rate in children" Adults: **Ringer lactate** 7–10 ml/kg/h for 1–2 h Then according to "Reduction of rate in adults"	If no improvement (signs of shock present) Measure HCT3 and proceed as above from "Measure HCT 2".	No severe haemorrhage Children and adults: Crystalloid10–20 mL/kg in 1 h Evaluate need for transfusion if no improvement.	Severe haemorrhage Transfuse Children and adults: **Fresh whole blood** 10–20 mL/kg
		Verify presence of signs of shock, of fluid overload and measure HCT, then reduce the rate as in "reduction of rate", if signs of shock are absent		
● Reduce the rate when HR and BP normalise. Always check for the signs of fluid overload ● Continue for 24–36 h (Less if PO hydration is tolerated). Supplemental boluses of crystalloids or colloids may be necessary in the next 24 h. Do not administer IV fluids for more than 48 h.				

Figure 16. Group C: Hospital management for dengue patients with compensated shock in adult patients
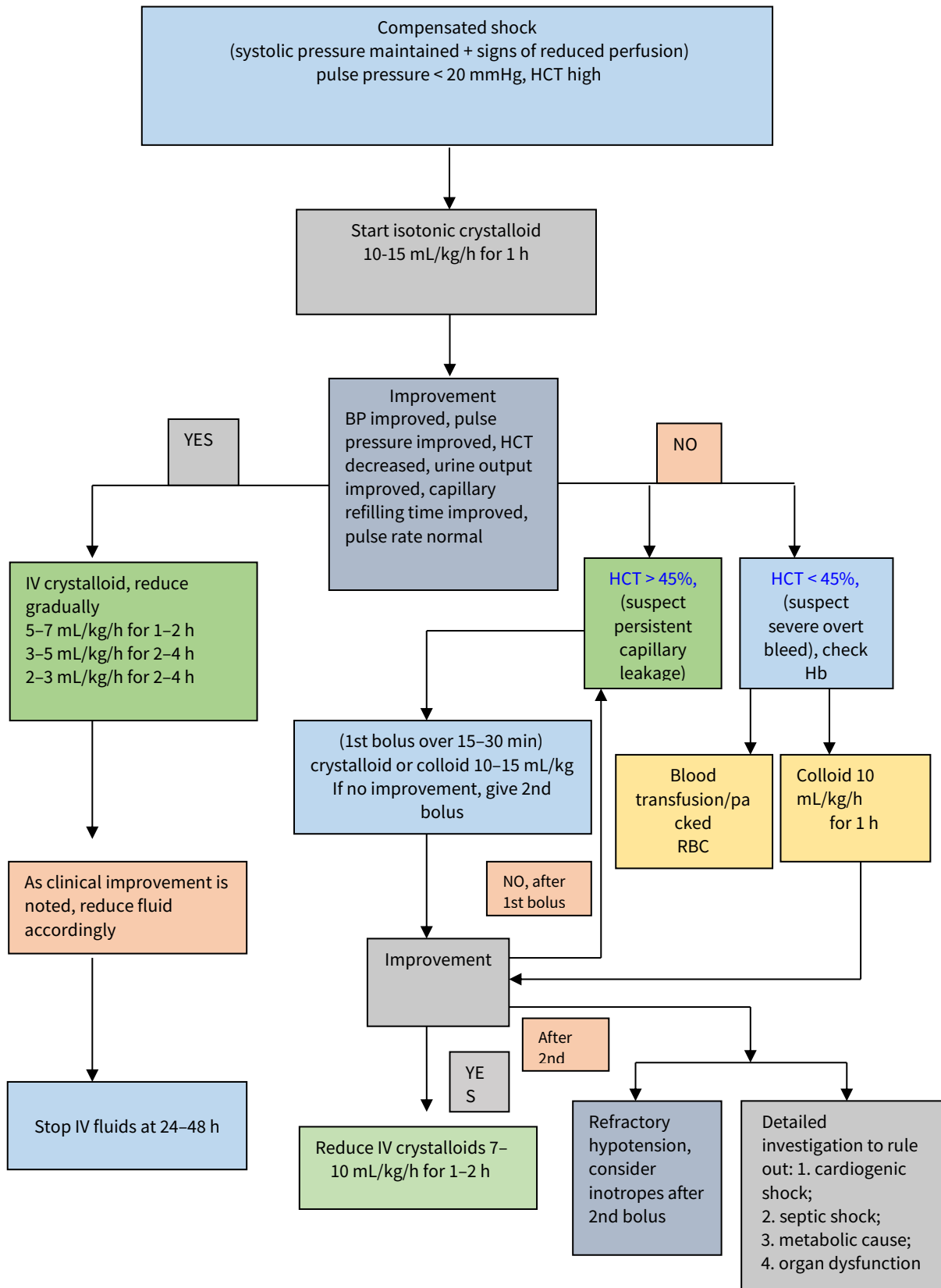
Figure 17. Group C: Hospital management for dengue patients with compensated shock in child patients

Compensated shock
(systolic pressure maintained + signs of reduced perfusion)
pulse pressure < 20 mmHg, HCT high

Start isotonic crystalloid
7–10 mL/kg/h for 1 h

Improvement
BP improved, pulse pressure improved, HCT decreased, urine output improved, capillary refilling time improved, pulse rate normal

YES

NO

IV crystalloid, reduce gradually
5–7 mL/kg/h for 1–2 h
3–5 mL/kg/h for 2–4 h
2–3 mL/kg/h for 2–4 h

HCT > 45%, (suspect persistent capillary leakage)

HCT < 45%, (suspect severe overt bleed), check Hb

(1st bolus over 15–30 min) crystalloid or colloid 7–10 mL/kg

Blood transfusion/packed RBC

Colloid 10 mL/kg/h for 1 h

As clinical improvement is noted, reduce fluid

NO, after 1st

Improvement

After 2nd

Stop IV fluids at 24–48 h

YES

Reduce IV crystalloids 7–10 mL/kg/h for 1–2 h

Refractory hypotension, consider inotropes after 2nd bolus

Detailed investigation to rule out: 1. cardiogenic shock;
2. septic shock;
3. metabolic cause;
4. organ dysfunction

9.2.9 Management of decompensated shock (prolonged/profound)

The initial fluid resuscitation in decompensated shock is more vigorous. In order to quickly restore the blood pressure, laboratory investigations should be done as soon as possible. Intravenous 10–20 mL/kg of bolus fluid should be given as fast as possible, ideally within 10–15 minutes. If shock is not reversible after the first bolus, a repeat bolus and laboratory results should be pursued and corrected as soon as possible. If there is no further improvement in blood pressure a third bolus may be initiated and urgent blood transfusion should be considered as the next step (after reviewing the pre-resuscitation HCT) and followed up by closer monitoring, e.g., continuous bladder catheterization, central venous catheterization or arterial lines.

It should be noted that restoring the blood pressure is critical for survival and if this cannot be achieved quickly, then the prognosis is extremely grave. Inotropes may be used to support the blood pressure at this stage.

Table 9. Treatment of profound shock (hypotensive; undetectable pulse and BP)

Group C: Dengue with decompensated shock				
Measure HCT 1 then **Ringer lactate** or Crystalloid(if pulse pressure < 10 mmHg or severe hypotension) IV or IO: Children and adults: 20 mL/kg in 15–30 min (1st bolus)				
If improvement (no signs of shock present) Children: Crystalloid10mL/kg in 1 h Adults: Crystalloid10 mL/kg in 1 h Reduction of rate: Children: **Ringer lactate** 10 mL/kg in 1 h 7 mL/kg/h for 2 h 5 mL/kg/h for 4 h 3 mL/kg/h Adults: 5–7 mL/kg/h for 1–2 h 3–5 mL/kg/h for 2–4 h	If no improvement (Signs of shock present) Compare HCT 1(Obtained before the 1st bolus) to HCT O[a] (Obtained during the febrile phase or before the critical phase			
	HCT 1 increases or stays elevated relative to HCT O Children and adults: Crystalloid10–20 mL/kg in 30–60 min (2nd bolus) Verify the presence of the signs of shock or of fluid overload		HCT 1 decreases[b] relative to HCT O Verify the vital signs and look for signs of severe haemorrhage	
	If improvement: Children and adults: Crystalloid7–10mL/kg/h For 1–2h Then Children and adults: **Ringer lactate** as in "reduction of rate"	If no improvement: measure HCT2	No severe haemorrhage Children and adults: Crystalloid10–20 mL/kg in 30–60 min (2nd bolus) Transfuse, if no improvement	Severe haemorrhage Transfuse Children and adults: **Fresh whole blood**10–15 mL/kg

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2–3 mL/kg/h for 2–4 h		If HCT 2<HCT1: Severe haemorrhage Transfuse Children and adults: **Fresh whole blood** 10–15 mL/kg	If HCT 2≥ HCT1: No severe haemorrhage Children & adults: Crystalloid(3rd bolus) 10–20mL/kg in 30–60 min 7–10 mL/kg/h in 1–2 h	
			If improvement Children and adults: **Ringer lactate** as in "reduction of rate". If no improvement, measure HCT 3 and proceed as above from "measure HCT 2"	Verify the signs of presence of shock or fluid overload and measure HCT
Reduce the IV fluid rate when HR and BP normalise, continue for 24–48 h (or less if PO hydration tolerated). Supplemental boluses of **crystalloids** or **colloids** may be necessary in the next 24 h. Do not administer IV fluids for more than 48 h				

Note: [a]If not available, compare to population norms of haematocrit according to age. If these are not known, use the following norm [b]women and children 1 year or older, < 35% in children less than 1 year.
[b]<40–45% in men, < 35–40% in women and in children one year and older, < 30–35% in children less than one year.

Normal maintenance fluid per hour can be calculated on the basis of the following formula* (equivalent to Holliday Segar formula):

- 4 mL/kg/h for first 10 kg body weight
- + 2 mL/kg/h for next 10 kg body weight
- + 1 mL/kg/h for subsequent kg body weight

*For overweight/obese patients, calculate normal maintenance fluid based on ideal body weight (IBW), using the following formula:

- Female: 45.5 kg + 0.91(height–152.4) cm
- Male: 50.0 kg + 0.91(height–152.4) cm (20, 21)

Table 10. Estimated ideal body weight for overweight or obese adults

Height (cm)	Estimated IBW (kg) for adult males	Estimated IBW (kg) for adult females
150	50	45.5
160	57	52
170	66	61.5
180	75	70

Table 11. Requirement of fluid based on body weight

Body weight (in kg)	Volume of fluid to be given in 24 h	Rate of fluid (mL/h)			
		R* 1	R* 2	R* 3	R* 4
10	1500	30	60	100	200
15	2000	45	60	150	300
20	2500	60	90	200	400
25	2800	75	120	250	500
30	3200	90	150	300	600
35	3500	105	180	350	700
40	3800	120	210	400	800
45	4000	135	240	450	900
50	4200	150	270	500	1000
55	4400	165	300	550	1100
60	4600	180	360	600	1200

Regimens R-1- 3 mL/kg/h; R-**2** – 6 mL/kg/h; R-3**3** -10 mL/kg/h, and **R-4**- 20 mL/kg/h

Note: The fluid volumes mentioned are approximations. Normally changes should not be drastic. Do not jump from R-2 to R-4 since this can cause fluid overload. Similarly, reduce fluid volume from R-4 to R-3, from R-3 to R-2 and from R-2 to R-1 in a stepwise manner.

When to stop IV fluid therapy

IV fluids should be reduced or discontinued when any of the following signs are present:

- Stable BP, pulse and peripheral perfusion
- Haematocrit decreases in the presence of a good pulse volume
- Apyrexia (without the use of antipyretics) for more than 24–48 h
- Resolving bowel/abdominal symptoms
- Improving urine output.

Continuing IV fluid therapy beyond 48 h of the critical phase will put the patient at risk of pulmonary oedema and other complications such as thrombophlebitis.

Platelet transfusion indication

- Transfuse platelet only if bleeding is present
- Prophylactic platelet transfusion may be considered for counts < 10 000/cumm without bleed and those who may need emergency surgery.

Figure 18. Group C: Hospital management for dengue patients with decompensated shock in adult patients
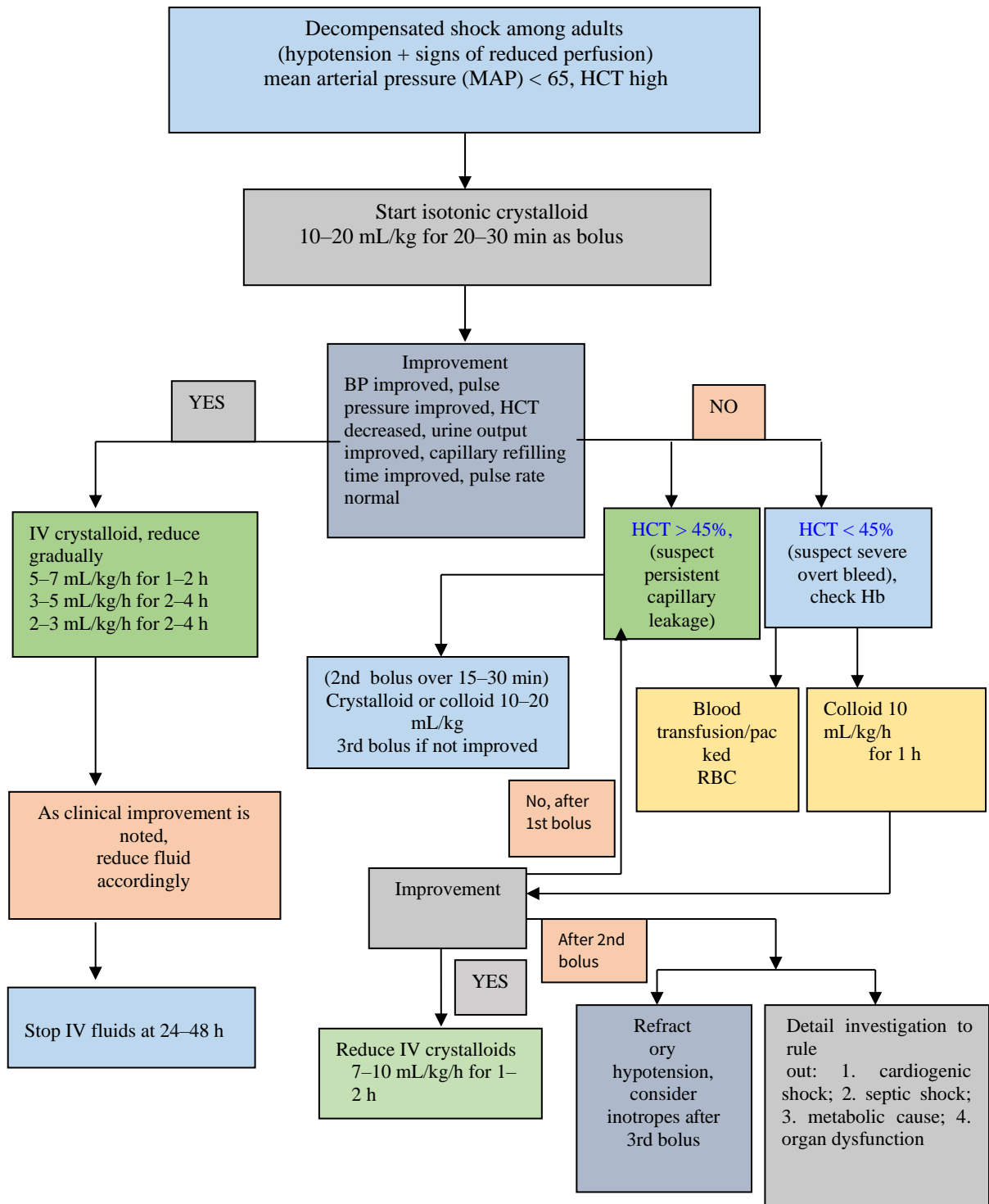
Figure 19. Group C: Hospital management for dengue patients with decompensated shock in child patient

Decompensated shock among children
(hypotension + signs of reduced perfusion)
MAP <65, HCT high

Start isotonic crystalloid
10–15 mL/kg for 20–30 min as bolus

Improvement
BP improved, pulse pressure improved, HCT decreased, urine output improved, capillary refilling time improved, pulse rate normal

YES

NO

IV crystalloid, reduce gradually
5–7 mL/kg/h for 1–2 h
3–5 mL/kg/h for 2–4 h
2–3 mL/kg/h for 2–4 h

HCT > 45%
(suspect persistent capillary leakage)

HCT < 45%
(suspect severe overt bleed), check Hb

(2nd bolus over 15–30 min) crystalloid or colloid 10–20 or 10–15 mL/kg
3rd bolus if not improved

Blood transfusion/packed RBC

Colloid 10 mL/kg/h for 1 h

As clinical improvement is noted,
reduce fluid accordingly

NO, after 1st bolus

Improvement

Stop IV fluids at 24–48 h

YES

After 2nd

Refractory hypotension, consider inotropes after 3rd bolus

Detailed investigation to rule out: 1. cardiogenic shock; 2. septic shock; 3. metabolic cause; 4. organ

Reduce IV crystalloids 7–10 mL/kg/h for 1–2 h

9.2.10 Management of severe haemorrhage

If the source of bleeding is identified, attempts should be made to stop the bleeding. Severe epistaxis, for example, may be controlled by nasal packing. Endoscopy may be required to identify internal gastrointestinal bleeding. If blood loss can be quantified, this should be replaced. However, if this cannot be quantified, aliquots of 10 mL/kg of fresh whole blood or 5 mL/kg of freshly packed red cells should be transfused. If there is no improvement, then the patient may be required one or more aliquots.

- In gastrointestinal bleeding, H-2 antagonists and proton pump inhibitors have been used, but there has been no proper study to show its efficacy
- Recombinant Factor 7 might be helpful in some patients without organ failure, but it is very expensive and generally not available.

9.2.11 Management of convalescence phase

- Convalescence can be recognized by the improvement in clinical parameters, appetite, and general well-being
- Haemodynamic state such as good peripheral perfusion and stable vital signs should be observed
- Decrease of HCT to baseline or below and dieresis are usually observed
- **Intravenous fluid should be discontinued.**

  - In those patients with massive effusion and ascites, hypervolemia may occur and diuretic therapy may be necessary to prevent pulmonary oedema
  - Hypokalaemia may be present due to stress and diuresis and should be corrected with potassium-rich fruits or supplements
  - Bradycardia is commonly found and requires intense monitoring for possible rare complications such as heart block or ventricular premature contraction (VPC)
  - Convalescence rash is found in 20–30% of patients.

- **Signs of recovery**

  - Stable pulse, blood pressure and breathing rate
  - Normal temperature
  - No evidence of external or internal bleeding
  - Return of appetite
  - No vomiting, no abdominal pain
  - Good urinary output
  - Stable haematocrit at baseline level
  - Convalescent confluent petechiae rash or itching, especially on the extremities.

9.3 Management of complications

9.3.1 Management of fluid overload

- The most common complication is fluid overload
- Review the total IV fluid therapy and clinical course, and check and correct for ABCS. All hypotonic solutions should be stopped
- In the early stage of fluid overload, switch from crystalloid to colloid solutions as bolus fluids. Dextran 40 is effective as 10 mL/kg bolus infusions, but the dose is restricted to 30 mL/kg/day because of its renal effects. Dextran 40 is excreted in the urine and will affect urine osmolarity. Patients may experience "sticky" urine because of the hyperoncotic nature of dextran 40 molecules (osmolarity about twice that of plasma). Voluven may be effective (osmolarity = 308 moSmol) and the upper limit is 50 mL/kg/day. However, no studies have been done to prove its effectiveness in cases of profound shock.
- In the late stage of fluid overload or those with frank pulmonary oedema, furosemide may be administered if the patient has stable vital signs. If they are in shock, together with fluid overload 10 mL/kg/h of colloid (dextran) should be given. When the blood pressure is stable, usually within 10–30 min of infusion, administer IV 1 mg/kg/dose of furosemide and continue with dextran infusion until completion. IV fluid should be reduced to as low as 1 mL/kg/h until discontinuation when haematocrit decreases to baseline or below (with clinical improvement).

The following points should be noted:

- These patients should have a urinary bladder catheter to monitor hourly urine output
- Furosemide should be administered during dextran infusion because the hyperoncotic nature of dextran will maintain the intravascular volume while furosemide depletes in the intravascular compartment
- After administration of furosemide, the vital signs should be monitored every 15 min for one hour to note its effects
- If there is no urine output in response to furosemide, check the intravascular volume status (CVP or lactate).

a) Detection of fluid overload in patients

- Early signs and symptoms include puffy eyelids, distended abdomen (ascites), tachypnoea, and mild dyspnoea
- Late signs and symptoms include all of the above, along with moderate to severe respiratory distress, shortness of breath and wheezing (not due to asthma), which are also an early sign of interstitial pulmonary oedema and crepitations. Restlessness/agitation and confusion are also seen among these patients

- Renal failure is excluded, implying that the patient is in an acute renal failure state. These patients may require ventilatory support soon. If the intravascular volume is inadequate or the blood pressure is unstable, check the ABCS and other electrolyte imbalances
- In cases with no response to furosemide (no urine obtained), repeated doses of furosemide and doubling of the dose are recommended. If oliguric renal failure is established, renal replacement therapy is to be done as soon as possible. These cases have poor prognosis
- Pleural and/or abdominal tapping may be indicated and can be life-saving in cases with severe respiratory distress and failure of the above management. This has to be done with extreme caution because traumatic bleeding is the most serious complication and leads to death. Discussions and explanations about the complications and the prognosis with families are mandatory before performing this procedure.

9.3.2 Management of encephalopathy

Some severe dengue patients present unusual manifestations with signs and symptoms of central nervous system (CNS) involvement, such as convulsion and/or coma. This has generally been shown to be encephalopathy, not encephalitis, which may be a result of intracranial haemorrhage or occlusion associated with DIC or hyponatremia. In recent years, there has been an increasing number of reported cases with CNS infections documented by virus isolations from the cerebrospinal fluid (CSF) or brain.

Most of the patients with encephalopathy report hepatic encephalopathy. The principal treatment of hepatic encephalopathy is to prevent the increase of intracranial pressure (ICP). Radiological imaging of the brain (CT scan or MRI) is recommended, if available, to rule out intracranial haemorrhage. The following are recommendations for supportive therapy for this condition:

- Maintain adequate airway oxygenation with oxygen therapy. Prevent/reduce ICP by the following measures:

  - Give minimal IV fluid to maintain adequate intravascular volume; ideally the total IV fluid should not be > 80% fluid maintenance
  - Switch to colloidal solution earlier if haematocrit continues to rise and a large volume of IV is needed in cases with severe plasma leakage
  - Administer a diuretic if indicated in cases with signs and symptoms of fluid overload
  - Positioning of the patient must be with the head up by 30 degrees
  - Early intubation to avoid hypercarbia and to protect the airway
  - May consider steroid to reduce ICP and dexamethasone 0.15 mg/kg/dose IV to be administered every 6–8 h.

- Decrease ammonia production by the following measures:

  - Give lactulose 5–10 mL every 6 h for induction of osmotic diarrhoea

- - Local antibiotic gets rid of bowel flora; it is not necessary if systemic antibiotics are given.

- Maintain blood sugar level at 80–100 mg/dL%. Recommend glucose infusion rate is anywhere between 4–6 mg/kg/h
- Correct acid-base and electrolyte imbalance, e.g., correct hypo/hypernatremia, hypo/hyperkalaemia, hypocalcaemia and acidosis
- Vitamin K1 IV administration; 3 mg for < 1-year-old, 5 mg for < 5-year-old and 10 mg for > 5-year-old and adult patients
- Anticonvulsants should be given for control of seizures: phenobarbital, dilantin and diazepam IV as indicated
- Transfuse blood, preferably freshly packed red cells, as indicated. Other blood components such as platelets and fresh frozen plasma may not be given because the fluid overload may cause increased ICP
- Empiric antibiotic therapy may be indicated if there are suspected superimposed bacterial infections
- H2-blockers or proton pump inhibitor may be given to alleviate gastrointestinal bleeding
- Avoid unnecessary drugs because most drugs have to be metabolized by the liver
- Consider plasmapheresis or haemodialysis or renal replacement therapy in cases with clinical deterioration.

9.4 Management of dengue in high-risk groups (Comorbidities and Coinfections)

Different comorbid illness like pregnancy, paediatric age group, hypertension, diabetes, thyroid diseases, hepatitis, heart diseases and renal diseases may contribute in the development of severe manifestations in dengue.

9.4.1 Management of dengue in pregnancy

Dengue infection in pregnancy carries the risk of more bleeding, fetal complications, low birth weight and premature birth. Risk of vertical transmission also increases during pregnancy. Pleural effusion, ascites and hypotension are commonly associated with dengue in pregnancy. Involvement of lungs and liver is also common in pregnancy. Patients may have respiratory symptom due to massive pleural effusion and high SGOT/SGPT due to liver involvement. Complications of dengue depend on the different stages of pregnancy like early, late, perk partum and postpartum period.

Pregnancy is a state of hyper dynamic circulation, and fluid replacement should be carefully done to prevent pulmonary oedema. Frequent platelet count and coagulation profile testing should be performed during dengue in pregnancy. Regular BP monitoring should also be performed. Fulminant hepatic failure, ARDS and acute renal failure in pregnancy may be associated with dengue infection.

Management of dengue infection in pregnancy should be taken seriously to reduce morbidity and mortality in mother as well as fetus.

9.4.2 Management of dengue in children

a) Management of neonatal dengue

After delivery, the newborn may go into shock, which may be confused with septic shock or birth trauma. In this case, history of febrile illness during pregnancy is important, which may help to diagnose dengue shock syndrome among neonates and infants. Close observation, symptomatic and supportive treatment are the mainstay of management.

b) Management of dengue in infants

Management of dengue among infants without warning signs: Oral rehydration should be encouraged with ORS, fruit juice and other fluids containing electrolytes and sugar, together with breastfeeding or formula feeding. Parents or caregivers should be instructed about fever control with antipyretics and tepid sponging. They should be advised to bring the infant back to the nearest hospital immediately, if the infant has any of the warning signs.

Management of dengue among infants with warning signs: When the infant has dengue with warning signs intravenous fluid therapy is indicated. In the early stage, judicious volume replacement by intravenous fluid therapy may modify the course and severity of the illness. Initially isotonic crystalloid solutions such as Ringer's lactate (RL), Ringer's acetate (RA), or 0.9% saline solution should be used. The capillary leak resolves spontaneously after 24–48 h in most of the patients.

Management of infants with severe dengue: Volume replacement in infants with dengue shock is very challenging and it should be done promptly during the period of defervescence. Each and every case should be critically analysed separately.

9.4.3 Management of dengue in comorbidities
a) Dengue viral hepatitis

Some patients may have impairment of liver function test due to dengue viral infection. In some dengue patients the AST/ALT level may be very high and PT may be prolonged. Hepatic involvement is commonly associated with pre-existing conditions like chronic viral hepatitis, liver cirrhosis and hepatomegaly due to some other cause. Patient may also develop hepatic encephalopathy due to acute liver failure. Liver involvement is also sometimes associated with dengue in pregnancy. Low albumin due to chronic liver disease may be associated with severe dengue. Gastrointestinal (GI) bleeding is common in this condition and patient may go to severe shock. These patients should be managed carefully with hepatic failure regimen with appropriate fluid and blood transfusion. If PT is prolonged intravenous vitamin K1 may be initiated in such conditions.

b) Cardiovascular involvement

Dengue associated myocarditis: Dengue infection may rarely cause acute myocarditis, which also may contribute for the development of shock. Cardiac complications may be seen in presence of coronary artery diseases(CAD), hypertension, diabetic and valvular heart disease. Management of shock with IV fluid in such case is sometimes difficult due to myocardial dysfunction. Patient may develop pulmonary oedema due to improper fluid management.

c) Dengue in CAD and heart failure

Some CAD patients, who are already taking aspirin and other antiplatelet agent, face severe bleeding during dengue infection unless these are stopped. Cardiac ischemia or electrolyte disturbances should be frequently reassessed. Patient may develop congestive or biventricular failure, and therefore should be

treated properly for better morbidity and mortality outcome. Thus, patients who are on antiplatelets or anticoagulants for various cardiovascular diseases should be carefully monitored. The antiplatelets such as aspirin and other antiplatelet drugs may be discontinued at initial stage when the patient is having platelet count less than one lakh or having minor or major bleeding manifestation with evidence of capillary leakage.

Chronic heart failure was also linked to a higher risk of fluid overload due to plasma leakage in dengue fever. Hence, it is critical to recognise early indicators of fluid overload to avoid further deterioration of the patient's state. Clinical characteristics such as periorbital oedema, respiratory discomfort, lung crepitation, symptoms of pleural effusion or ascites, and elevated jugular venous pressure should be recognized. The treatment options such as loop diuretics should be considered in patients with clinical signs of fluid overload, if the patient in hemodynamically stable.

d) Diabetes

Sometimes diabetic patients may present with severe complication in dengue when target organs are involved like diabetic retinopathy, neuropathy, nephropathy, vasculopathy, cardiomyopathy and hypertension. Due to dengue infection in diabetes the blood sugar may become uncontrollable, which may require sometimes insulin therapy for better management. Before starting treatment, a reference haematocrit level must be determined and fluid replacement should be done with caution and under the supervision of a doctor in a hospital.

e) Renal involvement

Dengue associated renal disease: Acute tubular necrosis (ATN) may develop during severe dengue as a result of shock and may complicate to AKI, if fluid therapy is not initiated in time. Renal function may be reversible, if shock is corrected within a short span of time. If the shock persists for long time patient may develop renal complications. Urine output monitoring in dengue infection is very important to assess renal involvement. Microscopic–macroscopic haematuria should be examined in all severe dengue patients. Other investigations like blood urea, creatinine, electrolytes, eGFR, bicarbonate levels also should be performed. Fluid intake should be closely monitored in case of AKI to avoid fluid overload and pulmonary oedema. There is currently a scarcity of data on the recovery of kidney functions in dengue patients who have survived a brief episode of AKI. In a recent study, it has been found that there is a high prevalence of dengue-induced AKI and its link to a subsequent risk of renal impairment. The level of renal recovery varies depending on the criteria utilised, with the majority of AKI survivors attaining less than 25% of their baseline serum creatinine.

f) Dengue in CKD

Data suggest that dengue patients with AKI deserve a careful and long-term medical follow-up, especially under nephrology care. Dengue patients may develop severe dengue in presence of diabetic nephropathy, hypertensive nephropathy, connective tissue disorders (SLE) and other pre-existing chronic diseases. A multidisciplinary approach with collaboration between physician and nephrologist is needed to decide for fluid therapy, renal replacement therapy and medications.

g) CNS involvement

Altered sensorium may develop in dengue patients due to various conditions like shock, electrolyte imbalance (due to persistent vomiting), fluid overload (dilutional hyponatremia or other electrolyte imbalance), hypoglycaemia, hepatic encephalopathy and also due to involvement of CNS by dengue virus. Acute encephalopathy or encephalitis may be seen in some patients with severe dengue. Sometimes it may be difficult to clinically exclude cerebral malaria and enteric encephalopathy, which may also appear during

same period (epidemic). Dengue serology (IgM) in CSF may help to confirm dengue encephalopathy or encephalitis.

9.4.4 Management of dengue with coinfections

In countries with dengue as an endemic disease, health care providers not only often face challenges to distinguish infections like HIV, TB, malaria, chikungunya, enteric fever and leptospira from dengue at the time of initial presentation, but also the existence of these infections in dengue cases. This is because both the illnesses exhibit nonspecific presentations, including fever, headache, abdominal pain, malaise, and nausea. They also share common laboratory findings such as leukopenia and thrombocytopenia, which creates a management dilemma for health care workers. The management of dengue is more challenging and difficult with coinfections like HIV, TB, malaria, chikungunya, enteric fever and leptospira as mostly clinical presentations are severe in presence of these coinfections. Thus, a high index of suspicion will be required to identify dengue coinfections.

a) TB

Patients may develop breathlessness and massive haemoptysis in pulmonary tuberculosis. They may also develop moderate to massive pleural effusion and ARDS. If patient has dengue in presence of TB and is on ATT, then should be closely monitored for further development of respiratory/pulmonary complications to prevent morbidity and mortality.

b) HIV

Dengue patients may have severe complications like shock, haemorrhage, significant bleeding and organ involvement among HIV and AIDS patients. Outcome of dengue infection is poor among severely immune-compromised patients, who have opportunistic infection and very low CD4 count. Multiorgan involvement may be common in dengue infection and responsible for high mortality. Management of dengue infection with HIV and AIDS should be undertaken with HIV specialist consultation.

c) Malaria

Malaria is also a common coinfection in dengue and its transmission also coincides during the same period/season. It should be excluded in the beginning without loss of much time, as it has its specific management. Antimalarial treatment should be started as soon as possible to prevent complication and better outcome during coinfection.

d) Chikungunya

It is also reported that in some geographical areas both the infections are prevalent at the same time. Acute complications are sometimes severe in dengue infection in presence of chikungunya. In case of predominant joint involvement in a dengue infection patient, chikungunya should be investigated and there is no specific antiviral therapy for treatment of chikungunya. The management during the acute phase is mainly supportive, including rest, fluids, and anti-inflammatory and analgesic agents.

e) Enteric fever

Waterborne diseases like typhoid fever and gastroenteritis are also common during monsoon season when dengue infection is also reported in large number. In the initial phase, dengue-infected patient may be more complicated with typhoid, if antibiotic treatment is started late. In high suspected cases blood culture for typhoid fever should be sent to confirm the diagnosis as Widal test may not be positive before the second week of fever. Most *Salmonella* Typhi and *Salmonella* Paratyphi isolates remain susceptible to azithromycin and third-generation cephalosporins.

f) Bacterial infections

Few patients with dengue cases experience a secondary bacterial infection usually community acquired pneumonia (CAP). In such cases, empiric antibiotic therapy as per local antibiogram needs to be considered. In admitted patients, if the respiratory symptoms and fever persists for longer duration hospital acquired pneumonia (HAP) should be suspected and should be treated accordingly with the culture and sensitivity.

g) Scrub typhus

Scrub typhus and dengue are two major causes of acute febrile illness and may co-exist together. It usually presents with sudden high-grade fever, severe headache, apathy, myalgia and generalized lymphadenopathy. A maculopapular rash may appear first on the trunk and then on the extremities and blenches within a few days. The patients may develop complications that include interstitial pneumonia (30 to 65% of cases), meningoencephalitis and myocarditis. The recommended treatment of choice for scrub typhus is doxycycline.

h) Leptospirosis

Leptospirosis apart from it presenting as febrile illness, has also the tendency to manifest as acute respiratory illness, leading to respiratory distress and shock. In areas where leptospirosis is known to cause outbreaks during monsoon/postmonsoon, the possibility of coinfection should be considered. The recommended treatment of choice for rickettsia disease are doxycycline and azithromycin.

i) Management of dengue and COVID-19 coinfection

Many of the viral infections like COVID-19, dengue, seasonal influenza, 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 countries with dengue as an endemic disease, now health care providers often face challenges to distinguish COVID-19 from dengue at the time of initial presentation. They also share common laboratory findings such as leukopenia and thrombocytopenia, which creates a management dilemma for health care workers. Thus, a high index of suspicion will be required to identify dengue and COVID-19 coinfections.

j) Case classification of coinfection (COVID-19 and dengue)

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

9.5 Case classification of coinfection

a) Asymptomatic coinfection

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.

b) Symptomatic coinfection

- Predominant corona viral disease (P-CVD)
- Predominant dengue viral disease (P-DVD)
- Codominant coinfection (CDCI).

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

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

Figure 20. Case classification of coinfection: Dengue and COVID-19
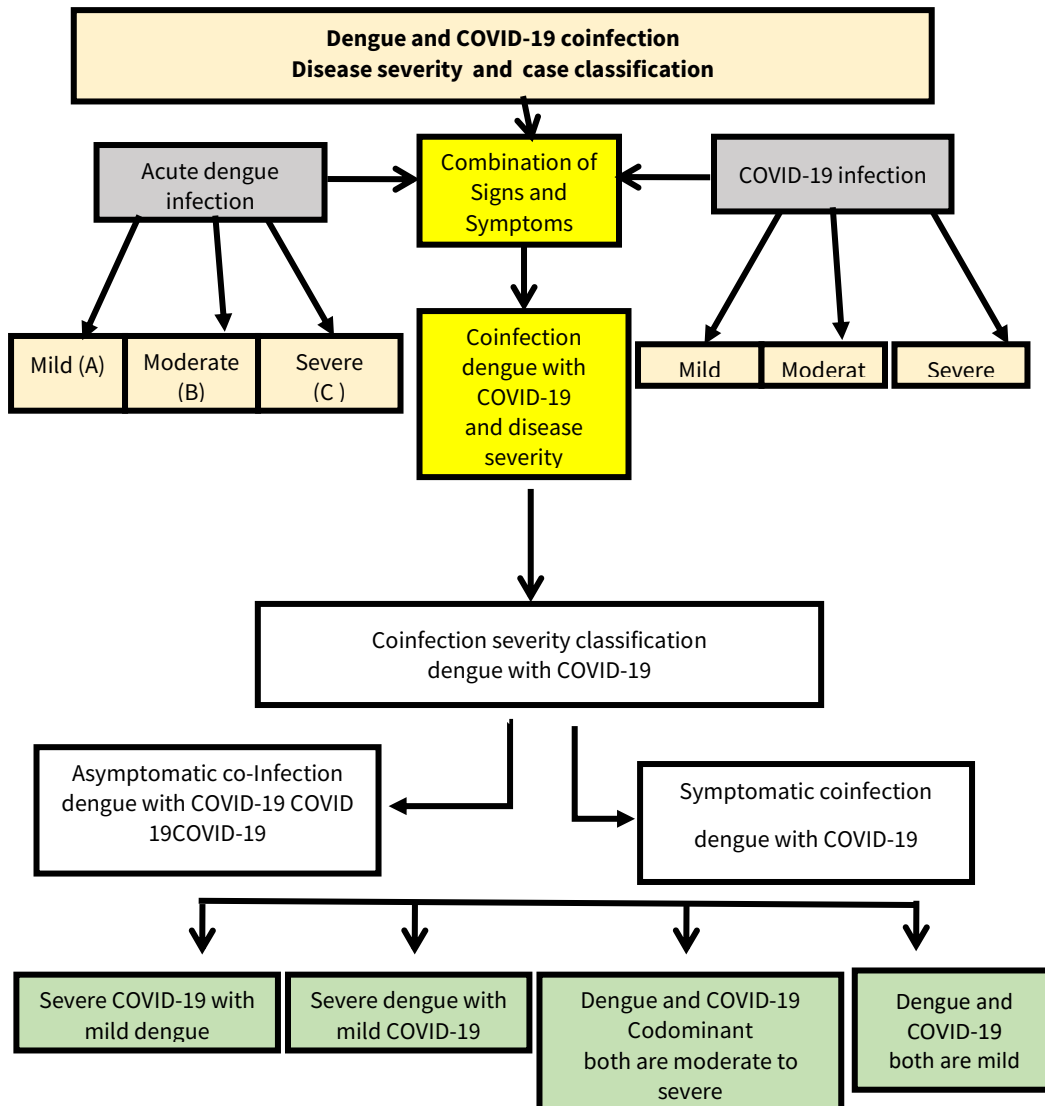
Codominant coinfection of COVID-19 and dengue (CD-CI): Concurrent manifestation of respiratory symptoms cough, sore throat, shortness of breath and typical dengue symptoms such as headache, retro-orbital pain, joint pain associated with nausea vomiting or pain abdomen. Both infections may have severe manifestations.

Coinfected 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. Cases where clinical presentation is suggestive but testing is negative, they will come under the probable category.

Treatment

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

In the eventuality of a patient being simultaneously infected with more than one virus (coinfection), the diagnostic challenge is further compounded.

The following are some general measures to be followed in case of dengue and COVID-19 coinfection:

- Strengthening 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 coinfected patient should be monitored closely, preferably at the hospital, as they may rapidly progress to 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 cocirculation of arboviral diseases, COVID-19 and other respiratory viruses (e.g., influenza).

Points related to specific therapeutic options and their use in cases with coinfection:

- Fluid therapy to be given in coinfection cases depends on the hemodynamic status of patient and degree of severity. One may follow the fluid chart given in Table 6 for clinical management of dengue fever for most coinfection 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. 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 only recommended for COVID-19 patients in shock for initial resuscitation.

- Low molecular wight heparin (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 100 000/mm^3, it may be withheld based on the clinical condition. In any case of coinfection with active bleeding, LMWH needs to be stopped immediately.

- Use of corticosteroids: Dexamethasone has recently been shown to be effective in severe COVID-19 and has been recommended for the same. Its course won't be affected much if Dexamethasone is given after five days of dengue illness. Hence, the use of steroids can be continued as per COVID-19 management guidelines.

- Tocilizumab to be used as per national management guidelines for COVID-19 management.

- Antivirals to be used as per COVID-19 management protocol.

- Other supportive management to be continued as per the current guidelines.

Chapter 10

Role of nursing care in management of dengue patients

Nursing care plays and important role for management of dengue cases. Dengue patients who are hospitalized require intensive monitoring of vital parameter, improvement and deterioration during fluid management. An extensive nursing monitoring can save lives of many patients.

a) Basic management of dengue patients in hospitals

- Close observation and intensive monitoring of vitals including sensorium, and maintenance of input-output chart
- Encourage patients for oral intake of fluids in case there is no vomiting, and patient is tolerating oral fluids well
- In case of high fever, administer paracetamol tablet/syrup or as advised by treating doctor
- Use of tourniquet test to detect petechial haemorrhage and other bleeding manifestations and immediate referral.

b) Watch for warning signs and symptoms

Presence of the following signs and symptoms require close monitoring and management:

- Respiratory distress
- Oxygen desaturation
- Severe abdominal pain
- Excessive vomiting
- Altered sensorium
- Confusion convulsions rapid
- Thready pulse
- Narrowing of pulse pressure less than 20 mmHg
- Urine output less than 0.5 mL/kg/h laboratory
- Evidence of thrombocytopenia/coagulopathy
- Rising HCT
- Metabolic acidosis
- Derangement of liver/kidney function tests.

c) Managing common problems in dengue patients

- High-grade fever: Provide tepid sponging, paracetamol tablet, and encourage intake of plenty of oral
- Abdominal pain: Severe abdominal pain may be a sign of severe complication; so remain vigilant and inform the treating doctor, estimate and record the amount of blood loss, monitor vitals and inform the doctor
- Plasma leakage: Monitor vitals, haematocrit and input/output, encourage oral intake, if possible, and start IV fluid as per instructions
- Shock or impending shock: Monitor vitals, haematocrit, sensorium and input/output, start IV fluid/inotropes as per instructions

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- Decreased urine output: First rule out catheter blockage by palpating the bladder. Flush the catheter, if blocked. Continue monitoring vitals, input/output and inform the doctor
- Respiratory distress: Check oxygen saturation and administer oxygen via facemask or nasal catheter if Sp02 < 90%, Look for pleural effusion, cardiac involvement and inform the doctor
- Convulsions/encephalopathy: Pay attention to maintenance of airway, breathing and circulation (ABC). Be ready with resuscitation set for emergency intubation and mechanical ventilation
- Fluid overload can develop during recovery phase of the illness due to fluid shifts. Closely observe for pedal oedema, neck vein engorgement and respiratory distress. Continue strict input/output monitoring during the recovery phase.

d) Providing health education and motivation

- Motivational behaviour change talks must be given to attendants of patients and patients if they are fully conscious
- Find out the common breeding sites of *Aedes* mosquitoes and adopt strategy of search and destroy the breeding sites
- Use of personal protection measures against mosquito bite
- Recognition of dangerous signs and early health-seeking behaviour
- Say NO to indiscriminate fogging as it may lead to respiratory complications in adults and drug resistance in the adult vector.

Chapter 11

Criteria for admission of patient in hospital

1. Presence of warning signs and symptoms:
   - Persistent vomiting
   - Abdominal pain and tenderness
   - Clinical fluid accumulation (ascites and pleural effusion)
   - Lethargy and/or restlessness
   - Mucosal bleed (epistaxis, melena, haematemesis, menorrhagia, haematuria
   - Enlarged liver (> 2 cm)
   - Laboratory: Progressive increase in haematocrit with rapid decrease in platelet count

2. Severe dengue
3. Intolerance to oral administration of fluids
4. Dyspnoea
5. Hypotension and narrow pulse pressure
6. Acute renal failure
7. Pregnancy
8. Coagulopathy
9. Patient living alone or far from a health facility and without any reliable means of transport.

Chapter 12

Discharge of dengue patient from hospital

Signs of recovery of patient

- Stable pulse, blood pressure and respiratory rate
- Normal temperature
- No evidence of external or internal bleeding
- Return of appetite
- No vomiting, no abdominal pain
- Good urinary output
- Stable haematocrit at baseline level
- Convalescent confluent petechiae rash or itching, especially on the extremities.

Criteria for discharging patients

- Absence of fever for at least 24 h without the use of antifever therapy
- Signs of recovery
- A minimum of 2–3 days have elapsed after recovery from shock
- No respiratory distress from pleural effusion and no ascites
- Platelet count of more than 50 000/mm^3. If not, patients can be recommended to avoid traumatic activities for at least 1–2 weeks for platelet count to become normal. In most uncomplicated cases, platelet rises to normal within 3–5 days.

Chapter 13

Management and referral of dengue cases at primary health care level

Dengue was earlier known as un urban disease. However, due to humanmade, environmental and societal changes and improper water storage practices, the vector *Ae. aegypti* has invaded rural areas. Frequent movement of the population has also helped in introduction of the virus in rural areas, leading to rural spread of the disease.

13.1 Management and referral of dengue cases at PHC level

The guidelines to be followed in the primary health centre (PHC) for the management of dengue cases and for referral of severe/complicated cases to the higher centre are given in Fig. 21.

Figure 21. Guidelines to be followed in the PHC for management of dengue
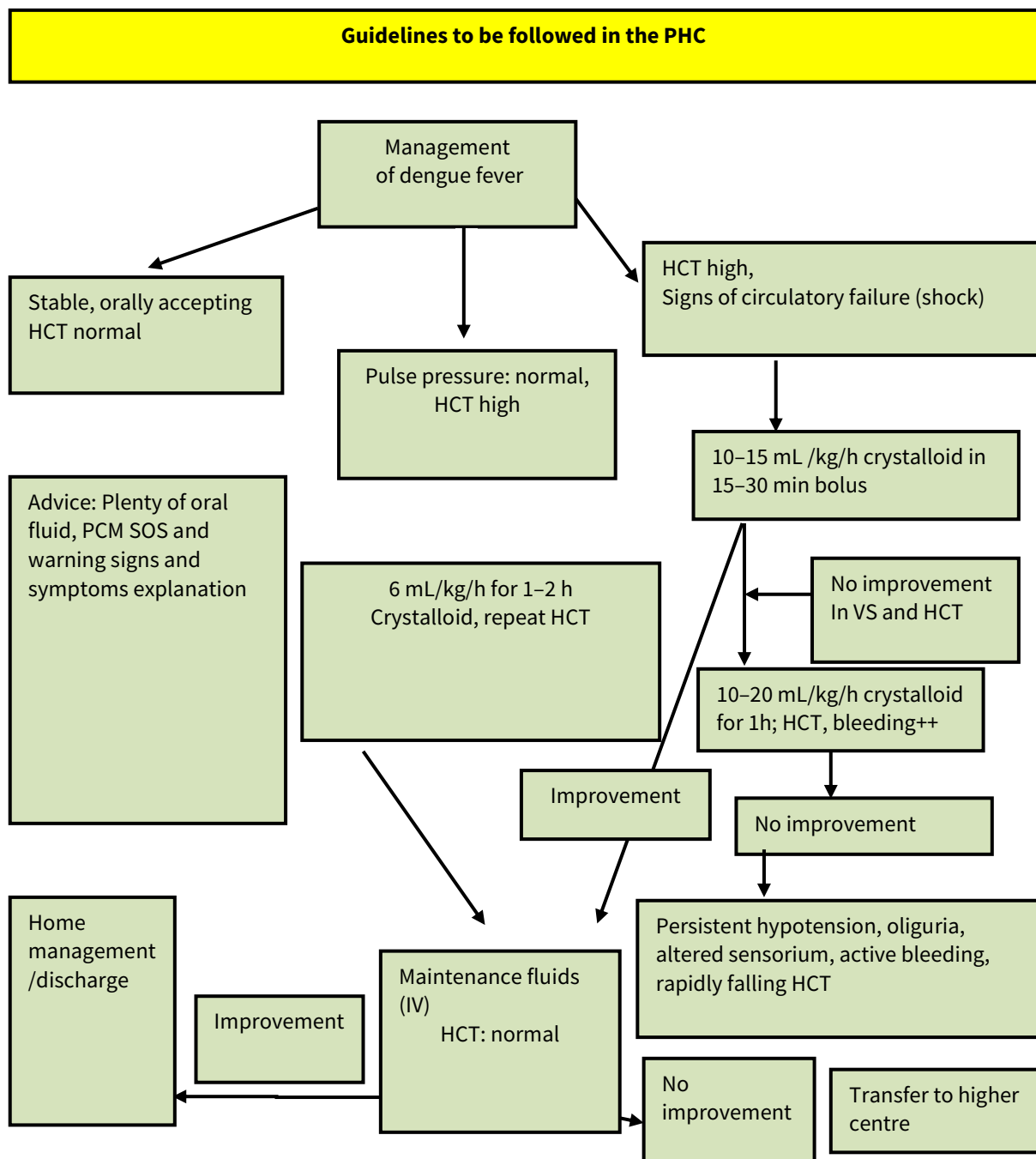
Look for comorbid illness and coinfections. **Patient should be advised to come for follow-up after 24 h for evaluation. S/he should report to the nearest hospital immediately in case of the following complaints:

- Bleeding from any site (fresh red spots on skin, black stools, red urine, nose bleed, menorrhagia)
- Severe abdominal pain, refusal to take orally/poor intake and persistent vomiting
- Not passing urine for 12 h/decreased urine output
- Restlessness, seizures, excessive crying (young infants), altered sensorium and behavioural changes and severe persistent headache
- Cold clammy skin
- Sudden drop in temperature.

Notes:

- In a medical care set-up where blood transfusion facility is not available to manage thrombocytopenia, platelets can be obtained from a nearby licensed blood bank
- Whole blood preserved at 4 °C does not have much role in correcting thrombocytopenia as platelets are preserved at 22 °C
- Follow chart for volume replacement algorithm.

Chapter 14

Ready reckoner

In an outbreak situation where it is not possible to admit every patient, it is important to prioritize to decide who needs in-hospital care the most. The following points are important to distinguish between those patients who need hospitalization and those who can be clinically managed at home.

a) Dengue corner
Consider having a dengue corner in the hospital during the transmission season, which is functional round the clock with adequate trained manpower and facilities for:

- Tourniquet test
- BP cuff of all sizes
- Lab investigations at least for CBC: Hb, HCT, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, and peripheral blood smear.

b) Lab investigations for diagnosis and confirmation

- NS 1 ELISA test to be done on patients reporting during the first 5days of fever
- Serology to be done on or after day 5 by MAC-ELISA. In an outbreak, all suspected patients of dengue need not undergo serology for purpose of clinical management.

c) Indications for domiciliary management
Patients with mild dengue fever (Class A) can be managed through home-based care. However, patients with following signs and symptoms should report immediately to nearby hospital:

- Severe abdominal pain and persistent vomiting

- Red spots or patches on skin

- Bleeding from nose and gums

- Vomiting blood

- Black tarry stools

- Drowsiness or irritability

- Pale, cold or clammy skin

- Difficulty in breathing.

d) Conditions for admission
A patient showing the following symptoms and signs should be considered for admission in hospital:

- Significant bleeding from any site
- Any warning signs and symptoms
- Persistent high-grade fever (38.5 ºC and above)

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- Impending circulatory failure – tachycardia, postural hypotension, narrow pulse pressure (< 20 mmHg, with rising diastolic pressure, e.g., 100/90 mmHg), increased capillary refilling time >2 sec
- Neurological abnormalities – restlessness, seizures, excessive crying (young infant), altered sensorium and behavioural changes, severe and persistent headache
- Drop in temperature and/or rapid deterioration in general condition
- Shock- cold clammy skin, hypotension/narrow pulse pressure, and tachypnoea.

It should be noted that a patient may remain fully conscious until a late stage.

e) Investigation for indoor patients

- Chest X-ray: PA view and lateral decubitus, one day after temperature drops
- USG abdomen and chest
- Blood biochemistry: serum electrolytes, kidney function test and liver function test, if required.

f) Indoor management of patients

i) Indications for blood transfusion (packed red blood cells [PRBC])

- Loss of blood (overt blood) -10% or more of total blood volume
- Refractory shock despite adequate fluid administration, and declining HCT
- Replacement volume should be 10 mL/kg body weight at a time and coagulogram should be done
- If fluid overload is present, packed cell volume (PCV) is to be given.

ii) Indications for platelet transfusion

- Platelet transfusion is not the mainstay of treatment in patients with DF. In general, there is no need to give prophylactic platelet, even if at platelet count >10 000/mm^3
- Prophylactic platelet transfusion may be given at levels of   <10 000/mm^3 in the absence

 of bleeding manifestations
- Prolonged shock with coagulopathy and abnormal coagulogram
- In case of systemic bleeding, platelet transfusion may be needed in addition to red cell transfusion.

g) Criteria for discharge of patients
- Absence of fever for at least 24 h without the use of antifever therapy
- No respiratory distress from pleural effusion or ascites
- Platelet count > 50 000/mm^3
- Return of appetite
- Good urine output
- Minimum of 2–3 days after recovery from shock
- Visible clinical improvement.

h) Use of whole blood/fresh frozen plasma/cryoprecipitate in coagulopathy

Use of whole blood/fresh frozen plasma/cryoprecipitate in coagulopathy is to be done in coagulopathy with bleeding as per advice of the treating physician and the patient's condition.

Note: These are only broad guidelines to assist physicians in managing patients. Decisions should be taken as per the severity of individual cases.

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Annex 1. Request form for laboratory test for the diagnosis of dengue

Request Form for Laboratory Test for the Diagnosis of Dengue

- Date of Reporting from the Laboratory:
- Health Facility:
- IPD/OPD:
- Municipality:
- Medical Doctor:
- Signature of Medical Officer:

INDIVIDUAL DATA			
Date of Consultation			
Complete Name of the Patient			
Registration No./ID No. of Patient			
Sex	F/M		
Age			
Present residential address			
Permanent address			
Village			
Suco			
Administrative Post			
Contact No.			
History of recent travel			
History of previous dengue infection	Yes/No		
Duration of illness			
HOSPITAL RECORD			
Under treatment as IPD, from date			
Under treatment as OPD, from date			
Department			
Ward			
Bed No.			
Time and data of sample collection by RDT			
Time and data of sample collection by ELISA			
INVESTIGATION			
A. Clinical Manifestation and any Related Health Issue			
Warning signs*	Present/Absent		
Any risk factors/comorbidity**			
Any other complications***			
B. Laboratory			
Test performed by ELISA	Yes/Not		
Test performed by RDT	**NS1**	**IGM**	**IGG**
FBC (full blood count)	Yes/Not		
DENGUE CLASSIFICATION BY SEVERITY			
A/Mild/without warning signs	A1/ A2		
B/Moderate/with warning signs	B1/B2		
C/Severe/Shock/Bleeding/ & Organ involvement	C1/C2/C3		

*** Warning Signs: Present/Absent**: Recurrent vomiting, abdominal pain/tenderness, general weakness/lethargies/restless, mild pleural effusion/ascites, hepatomegaly, increased HCT >20%, with minor bleeds. **** Any Risk Factors/Health Related Issues**: Infants, old age, diabetes, hypertension, pregnancy, CAD, haemoglobinopathies, immunocompromised patient (patient on anticoagulants or immunosuppressants), obesity, CHD, coinfection, cerebral palsy, and failure to thrive, malnutrition. *****Any other complications**: Please refer to the National Guidelines on Clinical Management of Dengue, 2022.

Annex 2. Reporting format for dengue

Ministério da Saúde | Reporting Format For Dengue | World Health Organization Timor-Leste

Date of Reporting to Surveillance Dept.:
Health Facility:
IPD/OPD:
Municipality:
Medical Officer:
Signature Of Medical Officer:

No.	Name and Designation of the Reporting Person	Individual Data				Sex		Age	Present Residential Address	Permanent Address	Village	Suco	Administrative Post	Contact Number	History of Recent Travel	History of Previous Dengue Infection (Yes/No)	Duration Of Illness	If IPD: Date Of Admission	If IPD:Date Of Discharge	If IPD: Date of Death	Duration Of Hospital Stay/Admission	If OPD: Duration Of OPD Followup	Department	Ward & Bed Number	Probable/Positive Dengue Case																	Dengue Classification			Observation/Comments		Week	Referral after initial clinical management
		Date of Consultation	Complete Name Of The Patient	Registration No./ID No. Of Patient		F	M																		Clinical Manifestation & Any Related Health Issue					TT		Laboratory			RDT			Severity							
																									Fever, Headache, Nausea, Myalgia, etc	Hemorrhage (Yes/No)	Warning signs: Present/Absent*	Any Risk Factors/ Co-Morbidities**	Any Other Complications***	+Ve	-Ve	Leucopenia	Trombocitopenia	Test Performed/ Not Performed (Yes/No)	Test Performed By ELISA/RDT	NS1 (+/-)	IGM (+/-)	IGG (+/-)	MILD (A1-A2)	MODERATE (B1-B2)	SEVERE (C1-C2-C3)	Discharged: Any Morbidity or Any Complications	Cause of Death		
1																																											
2																																											
3																																											
4																																											
5																																											
6																																											
7																																											
8																																											
9																																											
10																																											

* Warning Signs: Present/Absent: Recurrent vomiting, Abdominal pain/tenderness, General weakness/letharginess/restless, Mild pleural effusion/ascites, Hepatomegaly, Increased Hct >20%, With minor bleeds.