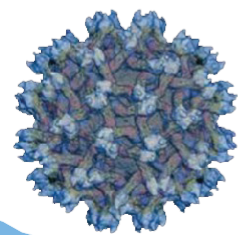
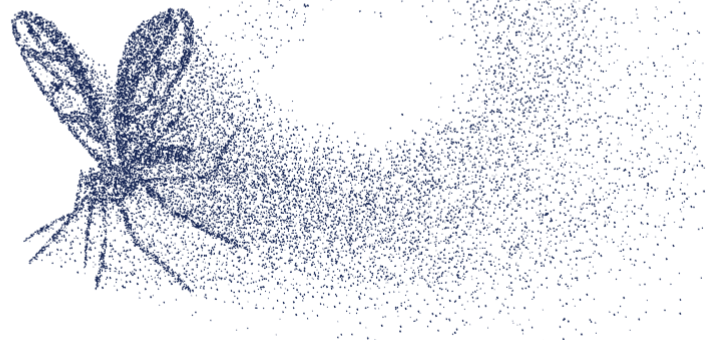




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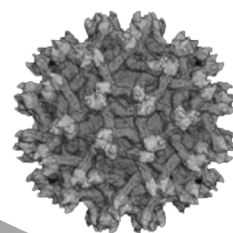
National Guidelines for Clinical Management of **Dengue Fever** 2023



National Center for Vector Borne Diseases Control
22-Shamnath Marg, New Delhi-110054
(Directorate General of Health Services)
Ministry of Health & Family Welfare
Government of India

National Guidelines
for Clinical
Management of

Dengue Fever 2023



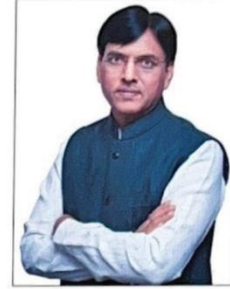


डॉ. मनसुख मांडविया
DR. MANSUKH MANDAVIYA



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अमृत महोत्सव

मंत्री
स्वास्थ्य एवं परिवार कल्याण
व रसायन एवं उर्वरक
भारत सरकार
Minister
Health & Family Welfare
and Chemicals & Fertilizers
Government of India



MESSAGE

Dengue is one of the public health concerns in India. Multiple approaches are required to minimize the risk associated with Dengue. Besides prevention part, due to non availability of specific drug for treatment and vaccine for prevention, management of cases becomes crucial to avert deaths due to Dengue. The earlier National guidelines on Clinical Management of Dengue Fever developed in 2007 and 2014 had substantially brought down the mortality associated with Dengue through better case management. These are also used by Medical Colleges as reference for teaching and management of cases.

In recent years, there were advancements in the field globally, and a need has been felt to update the existing guidelines to meet the requirement of the Clinicians. I am happy that the National Center for Vector Borne Diseases Control (NCVBDC, earlier NVBDCP) has updated the Clinical Guidelines by involving subject Experts from premier Central Government Institutions. I congratulate NCVBDC and the Experts for their efforts in timely accomplishment of the task

I believe that these Guidelines will be a useful resource for all Clinicians involved in the management of Dengue cases and also helpful in rendering guidance for referral of cases from peripheral hospitals.

(Dr. Mansukh Mandaviya)

प्रो. एस.पी. सिंह बघेल
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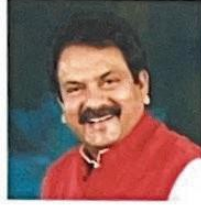
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GOVERNMENT OF INDIA



संदेश

डेंगू, एडीज मच्छरों से होने वाला एक रोग है, जो लद्दाख को छोड़कर भारत के सभी राज्यों एवं केंद्र शासित प्रदेशों में फैलता है तथा सार्वजनिक स्वास्थ्य के लिए एक चिंता का विषय है। डेंगू के विस्तार को कम करने के लिए विभिन्न क्रियाकलापों की आवश्यकता होती है। विशिष्ट दवा एवं टीके की अनुपलब्धता के कारण रोकथाम के उपायों के अतिरिक्त डेंगू से होने वाली मौतों को कम करने में रोग-प्रबंधन महत्वपूर्ण हो जाता है। डेंगू संक्रमण के हल्के या गंभीर लक्षण हो सकते हैं। वर्ष 2007 और 2014 में राष्ट्रीय वैक्टर जनित रोग नियंत्रण कार्यक्रम (वर्तमान राष्ट्रीय वैक्टर जनित रोग नियंत्रण केंद्र-एन.सी.वी.बी.डी.सी.) द्वारा विकसित राष्ट्रीय दिशा-निर्देशों ने डेंगू से जुड़ी मृत्यु-दर में कमी लाने में अहम योगदान दिया है। देश भर में इन दिशा-निर्देशों के विस्तृत प्रसार हेतु इन्हें सभी राज्यों के साथ साझा किया गया था, साथ ही, समय-समय पर चिकित्सकों के लिए राष्ट्रीय स्तर पर प्रशिक्षण-सत्र भी आयोजित किये गए। मेडिकल कॉलेजों द्वारा राष्ट्रीय दिशा-निर्देशों का उपयोग शिक्षण और प्रबंधन के लिए संदर्भ ग्रन्थ के रूप में भी किया जाता है।

हाल के वर्षों में, विश्व स्तर पर चिकित्सा के क्षेत्र में बहुत प्रगति हुई है अतः चिकित्सकों के लिए मौजूदा दिशा-निर्देशों के नवीनीकरण की आवश्यकता अनुभव की गई। मुझे खुशी है कि प्रस्तुत दिशा-निर्देश चिकित्सा क्षेत्र के राष्ट्रीय विशेषज्ञों के साथ परामर्श के बाद विकसित किए गये हैं। मैं इस कार्य को समयानुकूल पूरा करने के लिए राष्ट्रीय विशेषज्ञों और एन.सी.वी.बी.डी.सी. को उनके अथक प्रयासों के लिए बधाई देता हूँ। मेरा मानना है कि ये दिशा-निर्देश मेडिकल कॉलेजों में पढ़ाये जाने के साथ-साथ डेंगू उपचार में लिप्त सभी चिकित्सकों के लिए भी एक उपयोगी संदर्भ सामग्री सिद्ध होंगे और बेहतर नैदानिक प्रबंधन से, डेंगू पीड़ित व्यक्तियों को राहत मिलने के साथ ही डेंगू से होने वाली जनहानि में भी कमी होगी।

एस.पी. सिंह बघेल

(प्रो. एस.पी. सिंह बघेल)



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सचिव
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SECRETARY



सायमेव जयते
75
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स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Government of India
Department of Health and Family Welfare
Ministry of Health and Family Welfare



Message

Dengue has been posing a major public health problem in India since the last few decades. It contributes not only to morbidity and mortality but also imposes economic burden, loss of working days and impacts the overall quality of life. Besides prevention and control, management of cases is crucial in minimizing the risk due to Dengue. This highlights the need of updation of our knowledge to understand the newer developments in clinical management of dengue.

It gives me immense pleasure that National Center for Vector Borne Diseases Control (NCVBDC- earlier NVBDCP) has in a timely manner initiated the task of involving the subject Experts to revisit the available guidelines at Global and National level and update the existing National guidelines on Dengue.

I wish that all those who deal with Dengue patients will make the best use of these Guidelines to further reduce the complications and mortality due to Dengue.

(Rajesh Bhushan)



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सत्यमेव जयते



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MESSAGE

Dengue is a mosquito-borne infection with major public health consequences throughout tropical and subtropical regions of the world. The Indian subcontinent is endemic for Dengue with its diverse climatic conditions and landscape. During the last few decades, significant geographical spread of dengue has been observed in the country with an increase in the number and frequency of outbreaks. There are various factors responsible for increase in incidence of dengue like rapid urbanization with unplanned construction activities, increased population movement associated with travel & trade, sub-optimal solid waste management, inadequate water supply and climate change responsible for spread of Dengue.

As there is no specific treatment for Dengue, cases are managed symptomatically. The Government of India developed National Guidelines for Management of Dengue Fever in 2007 and 2014 and shared with States for wider circulation which have been proved useful in minimizing the risk of associated complications and Case Fatality Rate for Dengue significantly.

I am happy to share that the said guidelines have again been updated by National Centre for Vector Borne Disease Control (NCVBDC), MoHFW, Govt. of India involving the team of National Experts incorporating the recent developments, which will further improve the case management and minimize the suffering of Dengue infected persons and the same would avert deaths due to Dengue.


(Rajiv Manjhi)



प्रो.(डॉ.) अतुल गोयल

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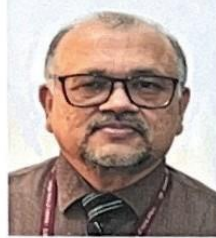
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DIRECTOR GENERAL OF HEALTH SERVICES



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स्वास्थ्य सेवा महानिदेशालय
Government of India
Ministry of Health & Family Welfare
Directorate General of Health Services



FOREWORD

Dengue, an arbo-viral disease continues to be a matter of concern in India not only from a public health point of view but also morbidity and mortality due its complex epidemiology and clinical behaviour. Tropical climate of India is conducive and suitable for *Aedes* vector proliferation. During monsoon and post-monsoon period, numbers of Dengue cases increase due to high vector density. Various ecological and man-made factors have compounded the spread of the disease across the country except Ladakh which is at a high altitude.

In absence of specific drug or vaccine, management of Dengue is largely symptomatic. For this, case management guidelines were developed by Government of India for Dengue case management between 2007 - 2014. This has resulted in a decrease in Case Fatality Rate during the last decade. In 2020, Government of India developed 'National Guidelines on Dengue Case Management during Covid-19 pandemic.

Now, in view of newer trends in the field and recent scientific literature and increasing co-morbidities of Dengue with non-communicable diseases, the guidelines for Dengue case management have been updated and revised by National Experts under umbrella of NCVBDC (Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India) to disseminate this updated information for health practitioners throughout the country.

I am sure that the States will circulate these guidelines to all its facilities. It will be helpful in capacity building of Clinicians for better management of cases based to minimize the complications and avert deaths associated with Dengue.

(Atul Goel)

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सत्यमेव जयते



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NATIONAL CENTER FOR VECTOR BORNE DISEASES CONTROL
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Ministry of Health & Family Welfare, Govt. of India



Preface

Dengue, an acute viral disease transmitted by *Aedes* mosquito has become a major burden for public health in India causing large scale outbreaks with increased risk in recent years. Every year, it is spreading to newer geographical areas. Earlier an urban disease, it is now being frequently reported from rural areas, as well. Presently, all States (except Ladakh) are reporting Dengue cases. All the four Dengue virus serotypes viz., DENV1, DENV2, DENV3 and DENV4 have been isolated from different parts of the country.

The first evidence about the occurrence of dengue fever from India was reported in 1956 from Vellore district in Tamil Nadu and the first outbreak of Dengue Hemorrhagic Fever (DHF) occurred in Calcutta (now Kolkata, West Bengal) in 1963. During 1996, country experienced its first outbreak, thereafter increased number of cases and deaths were reported in subsequent years due to various epidemiological factors like rapid urbanization, population movement, increased socio-developmental activities etc. The increasing trend may also be attributed to better reporting and surveillance through the identified network of Sentinel Surveillance Hospitals with laboratory facility. This network has been expanded every year to augment free diagnosis across the Country. Though the cases were increasing, the Case Fatality Rate due to Dengue has decreased significantly due to improved case management and early referral of patients. It is sustained at <1.0% at National level since 2008.

The National Guidelines for Management of Dengue fever were developed by National Vector Borne Disease Control Programme (now National Center for Vector Borne Diseases Control- NCVBDC), Government of India in 2007, updated in 2014 and shared with States for wider dissemination. This helped in minimizing the Case Fatality Rate for Dengue. The present guidelines have pooled the experience and knowledge of the experts and a standard protocol for management of Dengue addressing various issues including patho-physiology, clinical manifestations, case management and referral of patients from periphery has been developed.

I heartily congratulate the team of Experts and Dengue & Chikungunya Division, NCVBDC for bringing out this updated version. I hope that these guidelines will help in further reducing the complications and mortality associated with Dengue by appropriate management of cases.

(Dr. Tanu Jain)



Swachh Bharat : An opportunity for Dengue and Malaria Control.
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Website : www.nvbdc.gov.in



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Acknowledgements

Dengue is one of the major mosquito-borne viral diseases of public health significance. In India, except Ladakh, the disease is reported from all States/UTs. As the disease is spreading to newer areas and increased numbers of cases are being reported with repeated outbreaks. In absence of any specific anti-viral drug for Dengue, proper management of cases is utmost important, hence, the available National guidelines on clinical management Dengue have been revisited and updated from time to time.

National Center for Vector Borne Diseases Control (NCVBDC) is grateful to Prof. (Dr.) Ashutosh Biswas, Director, AIIMS, Bhubaneswar and former Professor of Medicine, AIIMS, New Delhi who has taken the lead in updating these guidelines. The updated version is intended to provide guidance for the clinicians for management of Dengue Fever and to reduce the mortality due to Dengue.

NCVBDC sincerely acknowledges its gratitude to Prof. (Dr.) Atul Goel, Director General of Health Services, and Govt. of India for his valuable technical suggestions and guidance.

NCVBDC gratefully acknowledges the contributions and technical inputs of all the Experts: Dr. SK Kabra, Prof. of Pediatrics, AIIMS, New Delhi; Dr. Ghanshyam Pangtey, Director Prof. of Medicine, Lady Hardinge Medical College, New Delhi; Dr. Sameer Gulati, Prof. of Medicine, Lady Hardinge Medical College, New Delhi; Dr. Mala Chhabra, Consultant, Microbiology, Dr. RML Hospital, New Delhi; Dr. Manish Soneja, Addl. Prof. of Medicine, AIIMS, New Delhi; Dr. Pankaj Jorwal, Addl. Prof. of Medicine, AIIMS, New Delhi; Dr. Arvind Kumar, Addl. Prof., Medicine, AIIMS, New Delhi; Dr. Upendra Baitha, Assoc. Prof., Medicine AIIMS, New Delhi; Dr. Amandeep Singh, Asstt. Prof., Medicine, AIIMS, New Delhi for developing these guidelines.

The technical comments and suggestions received from Experts: Dr. Bijoy Patra, Consultant & Head (Pediatric Unit and Pediatric Intensive Care), ABVIMS & Dr. RML Hospital, New Delhi; Prof. (Dr.) Bibhuti Saha, Head, Infectious Diseases and Advanced Microbiology, School of Tropical Medicine, Kolkata; Dr. Ratnakar Sahu, Dir Prof., Dept. of Medicine, ABVIMS & Dr. RML Hospital, New Delhi; Dr. Arunansu Talukdar, Prof. of Medicine, Medical College Hospital, Kolkata are acknowledged as crucial contributions towards finalization of the guidelines.

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Abbreviations

ABCS	Acidosis, Bleeding, Calcium (Na+& K+), Sugar
ADE	Antibody-dependent enhancement
Ae	Aedes
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
ATN	Acute Tubular Necrosis
BCPP	Buffy coat pooled platelet
BP	Blood Pressure
C	Core protein
CAD	Coronary artery disease
CAP	Community acquired pneumonia
CBC	Complete blood count
CF	Complement fixation
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease
CPK	Creatine Phosphokinase
CRRT	Continuous renal replacement therapy
CRT	Capillary refill time
CSF	Cerebrospinal fluid
DALY	Disability-adjusted life years
DENV	Dengue Virus
DF	Dengue Fever
DIC	Disseminated intravascular coagulation
DLC	Differential Leukocyte Count
E	Envelope Protein
FDP	Fibrinogen degradation product
FFP	Fresh Frozen Plasma
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GOI	Government of India
HAP	Hospital acquired pneumonia
Hb	Haemoglobin
HCT	Haematocrit
HI	Haemagglutination-Inhibition
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
HUS	Hemolytic uremic syndrome

Abbreviations

ICP	Intracranial pressure
IFN	Interferon
IL	Interleukin
ITP	Infection associated haemophagocytic syndrome
IV	Intravenous
KFD	Kyasanur Forest Disease
M	Membrane associated protein
MAC-ELISA	IgM-capture enzyme-linked immunosorbent assay
NASBA	Nucleic acid sequence-based amplification
NCVBDC	National Center for Vector Borne Diseases Control
NIV	National Institute of Virology
NS	Non-structural
NSAIDS	Non steroidal anti-inflammatory drugs
NT	Neutralization test
ORS	Oral rehydration solution
PCR	Polymerase Chain Reaction
PCV	Packed cell volume
PHC	Primary Health Centre
PT	Prothrombin time
RBS	Random blood sugar
RDP	Random donor platelets
RDT	Rapid Diagnostic Test
Rh	Rhesus
RL	Ringer's lactate
RT	Reverse transcription
SDP	Single donor aphaeresis
SEAR	South-East Asia Region
TB	Tuberculosis
TNF	Tumour Necrosis factor
USG	Ultrasonography
VBD	Vector Borne Disease
VPC	Ventricular premature contraction
WHO	World Health Organization
WPR	Western Pacific Region

Chapter 1

INTRODUCTION

Dengue is the most rapidly spreading mosquito borne viral disease of mankind, with a 30-fold increase in global incidence over the last five decades. It is a major public health concern throughout tropical and subtropical regions of the world. Almost half of the world's population lives in countries where dengue is endemic. Dengue has been identified as one of the 17 neglected tropical diseases by World Health Organization (WHO) as mentioned in their first report on neglected tropical diseases (2010). Although the full global burden of the disease is still uncertain, the patterns are alarming for both human health and the economy. Every year thousands of severe cases of dengue arise. It includes 20000 deaths; 264 disability-adjusted life years (DALY) per million populations per year are lost. The case-fatality rate for dengue fever varies by country and most fatal cases are among children and young adults.

1.1 Global Scenario

Before 1970, only 9 countries had experienced severe dengue epidemics. The disease is now endemic in more than 128 countries in the WHO regions of Africa, America, the Eastern Mediterranean, South-East Asia and the Western Pacific. America, South-East Asia and Western Pacific regions are the most seriously affected.

According to WHO, a vast majority of cases are asymptomatic and hence the actual numbers of dengue cases are under reported and many cases are misclassified. One estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease). Another study, of the prevalence of dengue, estimates that 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses. Although the full global burden of the disease is uncertain, the initiation of activities to record all dengue cases, partly explains the sharp increase in the number of cases reported in recent years. The number of cases reported increased from 2.4 million in 2010 to 5.2 million in 2019. The maximum number of dengue cases reported globally was in 2019. Approximately 1.8 billion (more than 70%) population who is at risk for dengue worldwide, lives in SEAR and WPR, which contributes to nearly 75% of the current global disease burden due to dengue. All Member States in the SEARO Region except the Democratic People's Republic of Korea being endemic to dengue. 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 SEAR countries, number of dengue cases increased over 3 fold over the last decade, from 0.19 million cases in 2011 to over 0.45 million cases in 2015 and 0.68 million cases in 2019. Deaths have increased from 1050 in 2011 to 1684 in 2019. In 2020, the number of dengue cases and deaths in seven

SEAR member states dropped to 0.26 million and 928, respectively (Source: WHO).

1.2 National Scenario

Dengue virus was isolated in India during 1945 for the first time. The first evidence of occurrence of dengue fever in the country was reported during 1956 from Vellore district in Tamil Nadu. The first dengue fever outbreak occurred in Calcutta (West Bengal) in 1963. In India, till date, all States/UTs, (except Ladakh) have reported dengue cases during the last two decades (even Lakshadweep has been reporting suspected dengue cases). The states that have reported dengue fever since 1991 are shown in Figure 1.

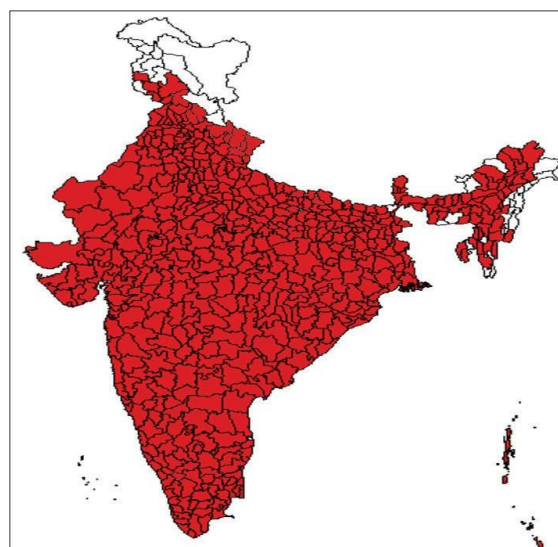


Figure 1: Areas reported Dengue cases since 1991

During 1996, one of the most severe outbreaks of dengue fever occurred in Delhi, with 10252 cases and 423 deaths being reported (country total being 16517 cases and 545 deaths).

In 2006, the country witnessed an outbreak of dengue fever with 12317 cases and 184 deaths. The incidence of dengue has been found to be increasing from past few years. During 2018, a total of 1,24,493 cases were reported; 2,05,243 in 2019; 44,585 in 2020; 1,93,752 in 2021 and 2,33,251 in 2022. The case fatality rate (CFR- deaths per 100 cases) has declined from 3.3% in 1996 to 0.3% in 2014 and sustained at 0.2% in 2015 to 2018, and 0.1% in 2019, which has been maintained at this level since then. (Source: NCVBDC)

Every year during the period of July-Nov, an upsurge in the cases of dengue has been observed. The disease has a seasonal pattern i.e., the cases peak after monsoon and it is not uniformly distributed throughout the year. However, the states in southern and western parts of the country report perennial transmission. The seasonal trends for 2018-2022 are given in Figure 2:

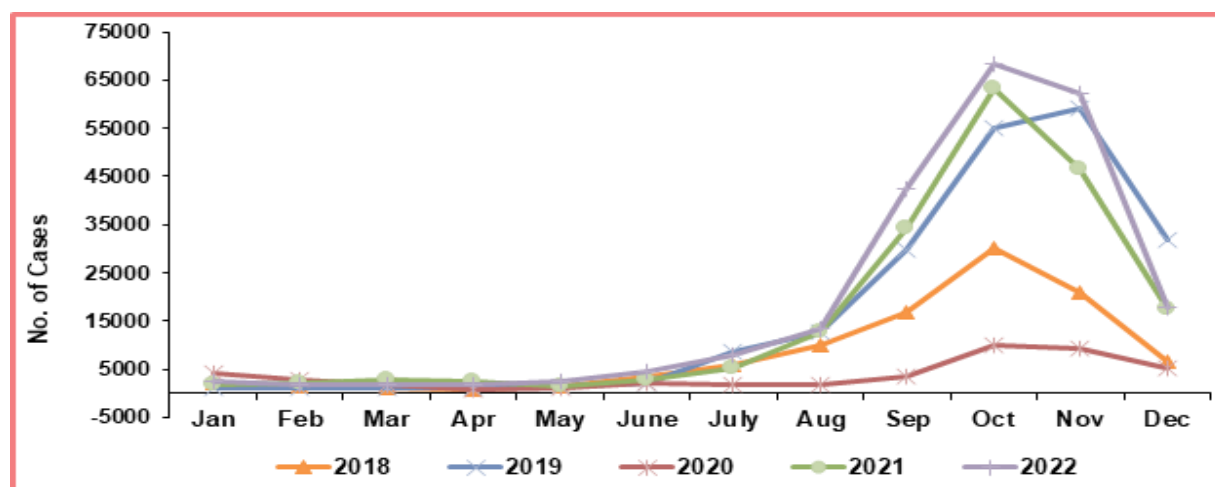


Figure 2: Seasonal trend of Dengue Cases in India 2018-2022

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

Chapter 2

EPIDEMIOLOGY

Dengue ranks as the most important, rapidly emerging mosquito-borne viral disease in recent years and is endemic in all continents. It has shown uprise due to various reasons viz., construction activities, life-style changes and deficient water management, improper water storage, stagnation of rain water in containers lying outside houses and poor water storage practices leading to proliferation of vector breeding sites in urban, peri-urban and rural areas. The Epidemiology of dengue is an intricate phenomenon which depends upon a complex relationship between epidemiological factors viz., host (man and mosquito), agent (virus) and the environment (abiotic and biotic factors). The complexity of relationship among these factors eventually determines the level of endemicity in an area. During inter-epidemic period, the transmission of Dengue remains low due to extremes of temperature with low relative humidity but during monsoon the environment becomes suitable for vectors, temperature between $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and relative humidity around 80% and innumerable small water collections result in high vector density.

2.1 Dengue virus

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

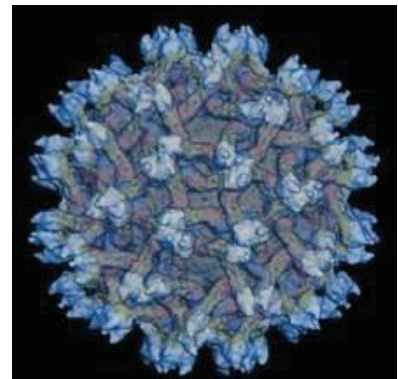


Figure 3: Dengue virus under electron microscope

2.2 Molecular epidemiology

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

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

The four dengue virus serotypes can co-circulate in the endemic areas because the immunity to one serotype does not protect from the infection by a heterotopic serotype. Individual variation occurs in antibody responses to dengue virus. The secondary infections are associated with elevated risks of severe disease outcomes. However, the primary and secondary infections are distinguishable based on their antibody responses. The ability of all DENV serotypes to utilise pre-existing heterotypic flavivirus antibody to enhance infection is a unique feature of dengue which distinguishes it from all other flavivirus and is considered to be the primary basis of pathogenesis. All four serotypes are isolated from India.

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

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

2.3 Vector

Dengue viruses are transmitted from infected person to others by the bite of female *Aedes* (*Ae*) mosquitoes. In India, *Aedes aegypti* is the main vector in most urban areas; however, *Ae. albopictus* is also incriminated in many states. But other species like *Ae. polynesiensis* and *Ae. niveus* have also been incriminated as secondary vectors in some countries.

Female *Aedes* mosquito deposits eggs singly on damp surfaces just above the water line. Under optimal conditions, the adult is emerged in seven days (after the aquatic stages in the life cycle of *Ae. aegypti*). At low temperature, it may take several weeks to emerge. However, the eggs can withstand desiccation for more than a year (can remain in viable dry condition) and emerge within 24 hours once it comes in contact with water, which is also a major hurdle in prevention and control of dengue.

The climatic conditions particularly temperature and rainfall play key role on the life cycle, breeding and longevity of vectors and thus transmission of the disease. Average survival of *Ae. aegypti* is 30 days and *Ae. albopictus* is about eight weeks. During the rainy season, when survival is longer, the risk of virus transmission is greater. *Aedes* is a day time feeder and can fly

up to a limited distance of 400 meters. In absence of any vaccine or specific drug for dengue, vector control proved to be very significant in preventing disease transmission.

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

2.4 Environmental Factors

The population of *Ae. aegypti* fluctuates with rain fall and water storage. Its life span is influenced by temperature and humidity, survives best between 16°-30°C and a relative humidity of 60-80%. *Ae. aegypti* is highly anthropophilic and rests in cool shady places. The rural spread of *Ae. aegypti* is a relatively recent occurrence associated with the societal and life style changes in rural areas coupled with developmental activities, improved transport systems etc. *Ae. albopictus*, has posed serious threats of dengue transmission in certain geographical regions endowed with sylvatic environment particularly in peninsular and North Eastern states. Climatic conditions and global warming are also influencing on the geographical spread of *Aedes* and dengue into newer areas.

2.5 Host Factor

Dengue virus infects humans and several species of lower primates. People of all ages and both genders are at risk. Secondary dengue infection is a risk factor for developing severe form of illness including passively acquired antibodies in infants. Travel to Dengue endemic area is most important risk factor. If the patient develops fever more than two weeks after travel, Dengue infection is unlikely to occur due to travel. Migration of patient during viraemia to a non-endemic area may introduce it into that area. The geographical spread of dengue has been reported to be occurring mainly by the travelling of people from endemic area to non-endemic areas.

2.6 Transmission Cycle

The *Ae. aegypti* usually becomes infected with dengue virus when it takes blood meal from a person during the acute febrile (viraemia) phase of Dengue illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infected and virus is transmitted when the infected female mosquito bites and injects its saliva into the wound of the person and in this way, the cycle of dengue continues. Dengue begins abruptly after an intrinsic incubation period of 4 to 7 days (range 3-14 days). There is also evidence that vertical transmission of Dengue virus from infected female mosquitoes to the next generation.

Though primarily transmission occurs through the bite of vector, there are reports of dengue transmission through blood transfusion and organ transplantation. There are also reports of congenital dengue infections occurred in neonates born to mothers infected very late in pregnancy.

Chapter 3

PATHOPHYSIOLOGY OF DENGUE FEVER

The exact pathophysiology of dengue virus infection leading to various disease manifestations is incompletely understood. The following stages characterize the course of illness; early infection, dissemination, immune response, and subsequent viral clearance. Host immune response plays an essential role in the pathogenesis of dengue fever. Various mechanisms are proposed to explain the signs and symptoms observed in a patient, and most have the following central themes:

- I. Antibody-dependent enhancement (ADE)
- II. Cytokine Storm
- III. Vasculopathy
- IV. Coagulopathy

3.1 Antibody-Dependent Enhancement (ADE)

The dengue virus is initially taken up by dendritic cells. After antigen processing, it is presented to the T cells. Dengue virus has three principal proteins targeted by the host immune response; envelop protein (E), precursor membrane (pre-M), and NS1. E protein-specific antibodies cause neutralization of infection and block attachment to cell receptors. Pre-M-specific antibodies bind to partially matured virions and show poor neutralization of infection but can mediate ADE. NS1 is not found in the virion; NS1-specific antibodies are therefore incapable of neutralizing the infection but can direct the complement-mediated lysis of infected cells.

As a result of infection, two types of antibodies are produced: neutralizing and non-neutralizing. Neutralization requires a threshold level of antibodies. The neutralizing antibodies can protect against a specific serotype of the virus. The non-neutralizing antibodies can bind but do not neutralize an infecting virus. After forming this virus-antibody complex, it enters the host cells, specifically dendritic cells and macrophages. Once inside the cell, the virus replicates and generates high virus titers in the blood. This phenomenon is known as Antibody-Dependent Enhancement (ADE) of infection.

3.2 Cytokine storm

CD4+ and CD8+ T cells, specific to the dengue virus, cause lysis of virus-infected cells and produce cytokines such as IFN-gamma, Tumour Necrosis Factor (TNF)-alpha, and lymphotoxin.

These cytokines result in a “**cytokine storm**” and ultimately lead to severe disease. Moreover, IFN-gamma also enhances the expression of immunoglobulin receptors, which augments the antibody-dependent enhancement of infection.

Various mechanisms are proposed to explain the clinical manifestations and pathogenesis of cytokine storm.

Mechanism of cytokine storm

- Introduction of dengue virus in Macrophage/Monocyte/dendritic cells.
- Previous infection with heterologous dengue serotype results in the production of non-protective antiviral antibodies
- These antibodies help and bind to the virion’s surface Fc gamma receptor and attach to the macrophages and monocytes.
- This lead to an amplified response of the immune system leading to excess and rapid release of cytokines (TNF alpha, Interferon-gamma, IL2, IL12, etc)
- This amplified response leads to a cytokine storm.

Therefore, this disproportionally enhanced immune response, particularly in secondary heterologous infections, is responsible for various pathogenetic mechanisms such as vasculopathy, coagulopathy, and organ involvement.

Various chemokines and cytokines are produced, such as TNF α , IFN α , IFN γ , IL6, IL8, and IL-10. Some complement fragments such as C3a and C5a also play a significant role in vasculopathy, coagulopathy, and bleeding.

3.3 Vasculopathy in Dengue

The clinical presentation of dengue fever varies widely. While most symptomatic patients recover after a short illness, a small proportion progresses to severe disease, manifesting as vasculopathy. It is characterized by plasma leakage and hemorrhagic diathesis. Plasma leakage may be profound and can result in life-threatening illnesses. More commonly, hypotension is caused by plasma leakage. It may be mild and transient or progress to profound shock with the absence of pulse and blood pressure. The severity of organ involvement and shock correlates with the degree of vasculopathy. It usually becomes evident on the 3rd to 7th day of illness.

Understanding the mechanism, initially, there occurs a transient disturbance in the function of the endothelial glycocalyx, which leads to a temporary alteration in the characteristics of the fiber matrix of the endothelium. Anti-NS1 antibody acts as autoantibodies and cross-react with platelets and non-infected endothelial cells, which triggers intracellular signaling and disturbances in capillary permeability. Plasma leakage occurs due to capillary permeability and manifests as a combination of haemoconcentration, pleural effusion, pericardial effusion, ascites, and multi-organ dysfunction.

3.4 Coagulopathy in Dengue

The causes of coagulopathy in dengue fever are multifactorial, and the underlying mechanism remains unclear. Primarily, relatively consistent findings are an increase in an activated Partial Thromboplastin Time (aPTT) and reduced fibrinogen concentrations. Moreover, thrombocytopenia associated with coagulopathy increases the severity of bleeding. The release of heparan sulfate or chondroitin sulfate (molecules similar in structure to heparin that can mimic its anticoagulation function) from the glycocalyx also leads to coagulopathy.

Abnormality in coagulation profile and causes of bleeding:

- APTT ↑
- Fibrinogen U
- Platelets U
- Disseminated Intravascular Coagulation (DIC)
- Enhanced fibrinolytic activity
- Release of heparan sulfate or chondroitin sulfate from the glycocalyx

3.5 Causes of thrombocytopenia

The precise mechanism of thrombocytopenia in dengue fever is not known. Multiple mechanisms contribute to low platelets in dengue fever. Although bone marrow suppression is thought to play a pivotal role, destruction of the platelets too has a significant role.

Mechanisms postulated for thrombocytopenia:

1. IgM type of anti-platelet antibody
2. Anti-platelet antibodies + complements → lysis of platelets
3. Dengue viral-specific antibodies
4. Bone marrow hypocellularity
5. Destruction of platelet in the liver and spleen (peripheral sequestration)
6. Disseminated Intravascular Coagulation (DIC)
7. Cytoadherence
8. Platelet dysfunction (defect in ADP release)

In view of COVID -19, it is important to know the difference between the pathogenesis of dengue and COVID-19. It is described and compared briefly in the table below

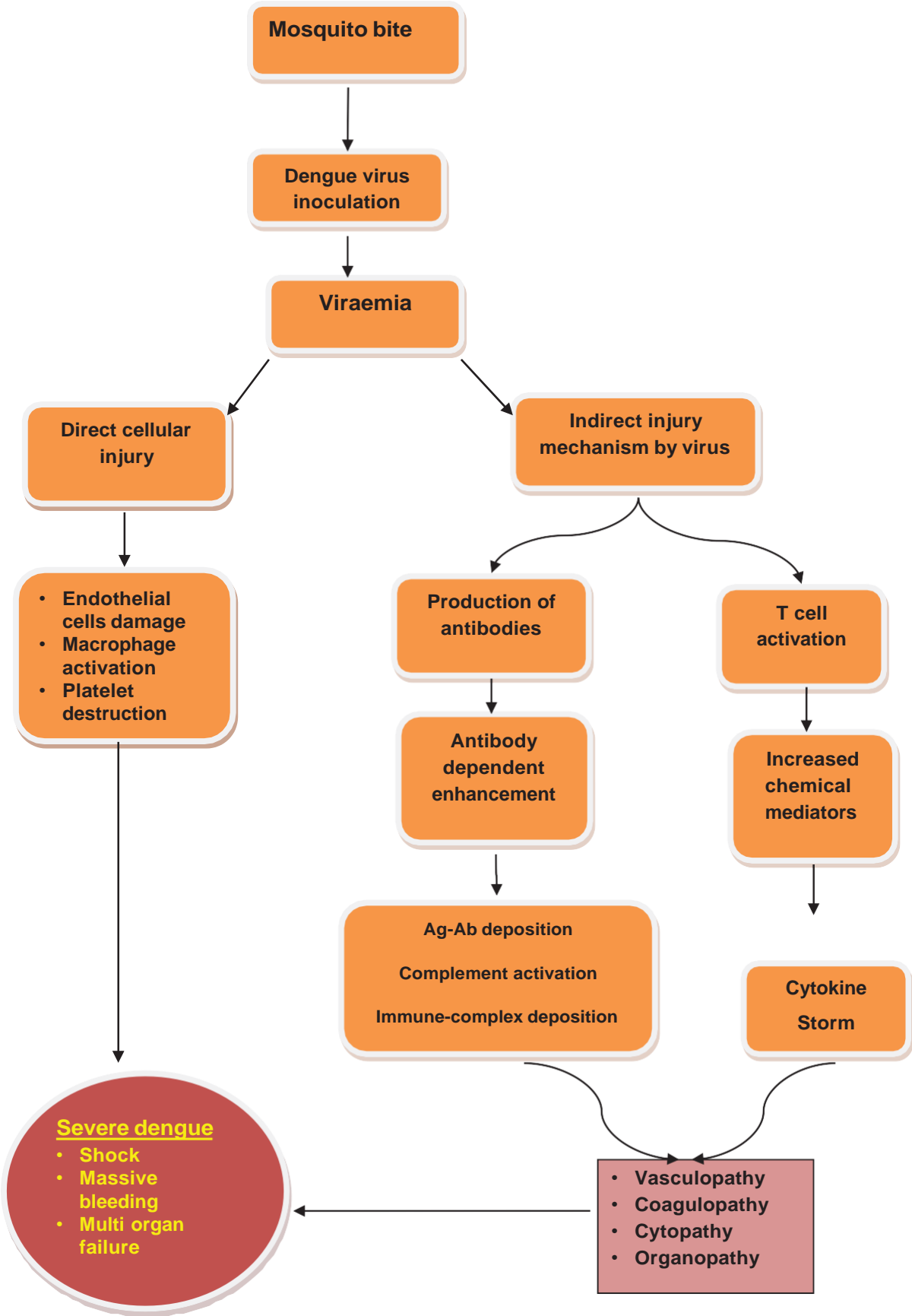
Table 1: Pathogenesis of Dengue and COVID-19

Dengue	COVID-19
Vasculopathy <ul style="list-style-type: none">• Capillary leakage• Profound Shock• Hemorrhagic 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 - (bleeding) <ul style="list-style-type: none"> • Heparan sulphate • Prolong aPTT • Decrease Fibrinogen 	Thrombosis- URTI: Oro-pharynx and Nasopharyngeal symptoms LRTI: Cough, Production, Pneumonia, dyspnoea
Cytokine storm: Release of chemokines and cytokines leading to the systemic manifestation	Cytokine Storm: Local inflammation by secretion of pro-inflammatory cytokines and chemokines IL-6, IFN γ , 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

Therefore, to summarize, infection by dengue virus causes intense immune activation. This aberrant immune activity leading to cytokine overproduction and generation of autoantibodies which act against platelets and endothelial cells. A molecular mimicry between platelets or endothelial cells with the NS-1 or pre-M protein of virus may explain the cross-reactivity of anti-NS1 or anti-preM antibody to host cells and also the subsequent attack on platelet and endothelial cells during the disease progression. Macrophage activation might be responsible for the sustained disease process with a high fatality rate. All these different mechanisms ultimately have a unifying contribution which targets vascular endothelium leading to cellular injury and contraction of endothelial cells which results in increased permeability thereby causing plasma leakage, which along with coagulopathy is responsible for the development of hemorrhage and shock.

Figure 4: Pathophysiology of Dengue



CLINICAL MANIFESTATIONS OF DENGUE FEVER

An individual infected with the dengue virus may be asymptomatic or symptomatic. The clinical manifestations range from mild fever to severe bleeding, shock, and organ dysfunction. The disease manifestation depends on factors such as age, nutrition, immune status, presence of any co-morbidities, type of strain of the dengue virus and primary or secondary dengue infection.

Dengue fever is a dynamic illness. The average incubation period varies from 4 to 6 days (ranging from 3 to 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 clinical phases such as: acute febrile phase, critical phase and recovery (convalescent) phase. The clinical presentations are dynamic and change as the disease progresses.

4.1 Clinical phases of Dengue

- **Clinical Description of Dengue:**

The clinical description of Dengue Fever includes an acute febrile illness of 2-7 days duration with two or more of the following manifestations:

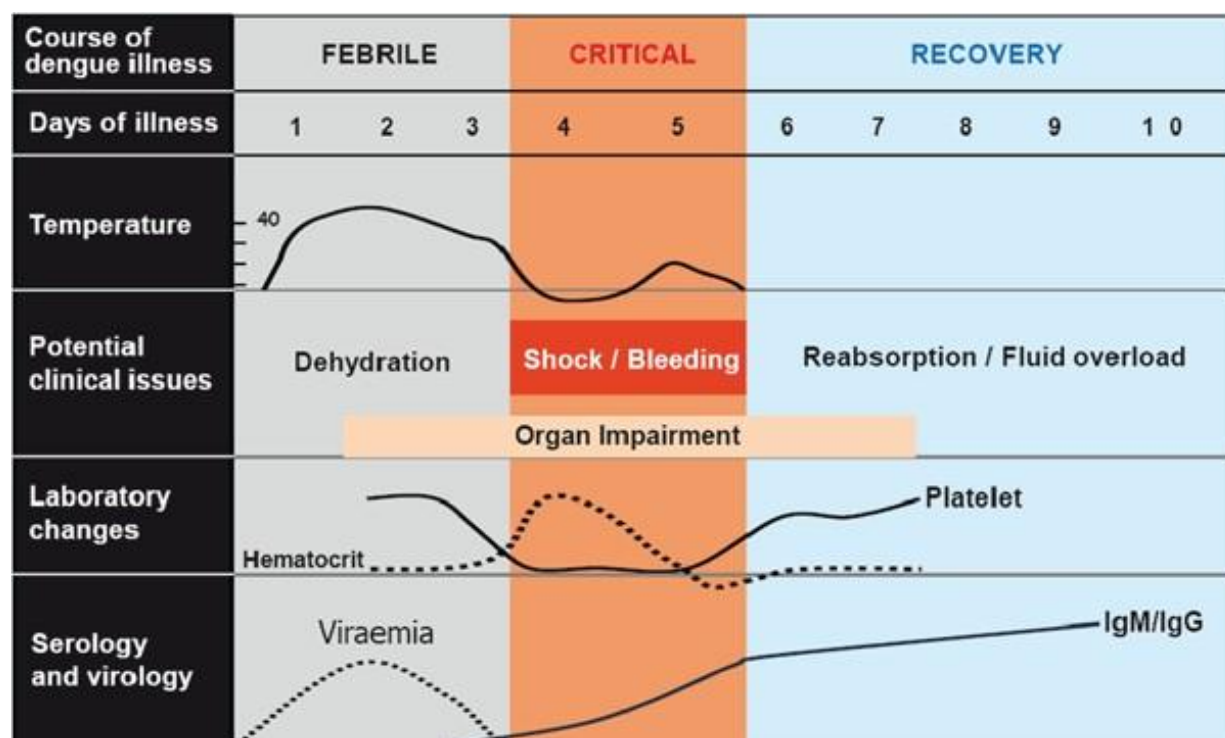
- o Headache
- o Retro-orbital pain
- o Myalgia
- o Arthralgia
- o Rash
- o Haemorrhagic Manifestations
- o Thrombocytopenia or Leucopenia
- o Warning signs and symptoms

Case Definition: The case definition is as given below in Box 1:

Box: 1

<p>Probable Dengue Fever: A case compatible with clinical description (see above) of dengue fever during outbreak.</p> <p>OR Non-ELISA based NS 1 antigen/IgM Positive (A positive test by RDT will be considered as probable due to poor sensitivity and specificity of currently available RDTs)</p> <p>Confirmed Dengue Fever: A case compatible with the clinical description (see above) of Dengue Fever with at least one of the following</p> <ul style="list-style-type: none"> • Isolation of dengue virus (Virus culture +VE) from serum, plasma, leucocytes • Demonstration of IgM antibody titre by ELISA positive in single serum sample • Demonstration of dengue virus antigen in serum sample by NS1-ELISA • IgG seroconversion in paired sera after 2 weeks of four-fold increase of IgG titre • Detection of viral nucleic acid by polymerase chain reaction (PCR)
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Figure 5: Clinical phases of dengue infection



• **Febrile phase:**

This phase is characterized by the sudden rise of body temperature, which is usually high-grade ($\geq 38.5^{\circ}\text{C}$) and may be biphasic. This phase may last for 2-7 days and is associated with headache, flushing, vomiting, myalgia, arthralgia, and macular rash. The rash is primarily maculopapular or rubelliform. It usually appears after the 3rd to 4th day of fever and occurs over the face, neck, chest, and abdomen. It usually fades away as the fever progresses.

Bleeding manifestations may be observed in this phase, depending on the severity of the disease. Most of the cases may present with skin and mucosal bleeding (including gastrointestinal or vaginal) and less commonly with hematemesis, melena, heavy menstrual bleeding, epistaxis, or hematuria. Patients with comorbidities such as peptic ulcer disease or on steroids have a higher risk for hemorrhagic manifestations.

Physical examination may reveal facial puffiness, conjunctival congestion, pharyngeal erythema, lymphadenopathy, and hepatomegaly. It is also essential to look for petechiae (on the skin and palate) and bruising (particularly at venipuncture sites) and perform a tourniquet test.

- **Critical phase (leakage phase)**

From the febrile phase 5- 10 % of the patients may progress to the critical phase and commonly observed in patients who have a history of previous dengue infection (secondary infection). This may also occur after primary infection in patients with comorbidities and active co-infections. This phase usually begins after 3rd or 4th day of fever and may last about 24 to 48 hours. This phase is characterized by vasculopathy and coagulopathy, leading to plasma leakage, excessive haemoconcentration, bleeding, eventually leading to shock and organ dysfunction. The clinicians need to be carefully in recognizing and observing the warning signs of critical phase at the early stage mentioned in Box no 2.

Box: 2

Warning symptoms and signs

- Persistent vomiting
- Abdominal pain and tenderness
- Lethargy and/or restlessness, sudden behavioral changes
- Bleeding manifestations like epistaxis, melena, haematemesis, excessive menstrual bleeding, and haematuria
- Syncope or giddiness
- Clinical fluid accumulation (ascites and pleural effusion)
- Enlarged Liver(>2cm)
- Laboratory: Progressive increase in haematocrit with a rapid decrease in platelet count

Hemorrhagic manifestations may be sometimes observed both in the febrile and critical phases. Radiological imaging modalities such as ultrasonography (of the chest and abdomen) and chest radiographs are helpful in the detection of plasma leakage. Early detection of shock is vital for better prognosis and various parameters to determine compensated and decompensated shock are shown in the table-2.

Table 2: Various parameters to determine compensated and decompensated shock

Normal Circulation	Compensated shock	Decompensated /Hypotensive shock
Normal sensorium	Normal sensorium with shock	Change of mental state – restless, combative or lethargy
Capillary refill time (<2 sec)	Prolonged capillary refill time (>2 sec)	Mottled skin, prolonged capillary refill time
Extremities are warm	Cold extremities	Cold, clammy extremities
Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral pulses
Normal heart rate for age	Tachycardia	Tachycardia
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 (<20 mmHg)	Pulse pressure variable
Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ hyperpnoea/ Kussmaul’s breathing
Urine output -normal	Urine output -reduced	Oliguria or anuria

- **Convalescent phase (Recovery phase)**

With the timing and optimal management during critical phase patients start recovering and passes through the recovery phase. Majority of the patients from febrile phase also pass through this recovery phase for the complete cure. In this recovery phase the extracellular fluid loss owing to capillary leakage returns to the circulatory system during the recovery phase, and signs and symptoms improve. This phase occurs after the critical phase and lasts 2-3 days. The patient develops a convalescent rash characterized by confluent erythematous eruption with sparing areas of normal skin. It is often pruritic. 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 optimized, the patient may develop pulmonary edema as a result of fluid excess.

After knowing the clinical phases, it's essential to know the approach to diagnosing dengue patients. A flow diagram depicting the history, investigations, and classification of dengue cases is shown below.

Figure 6: Approach to diagnosis of dengue

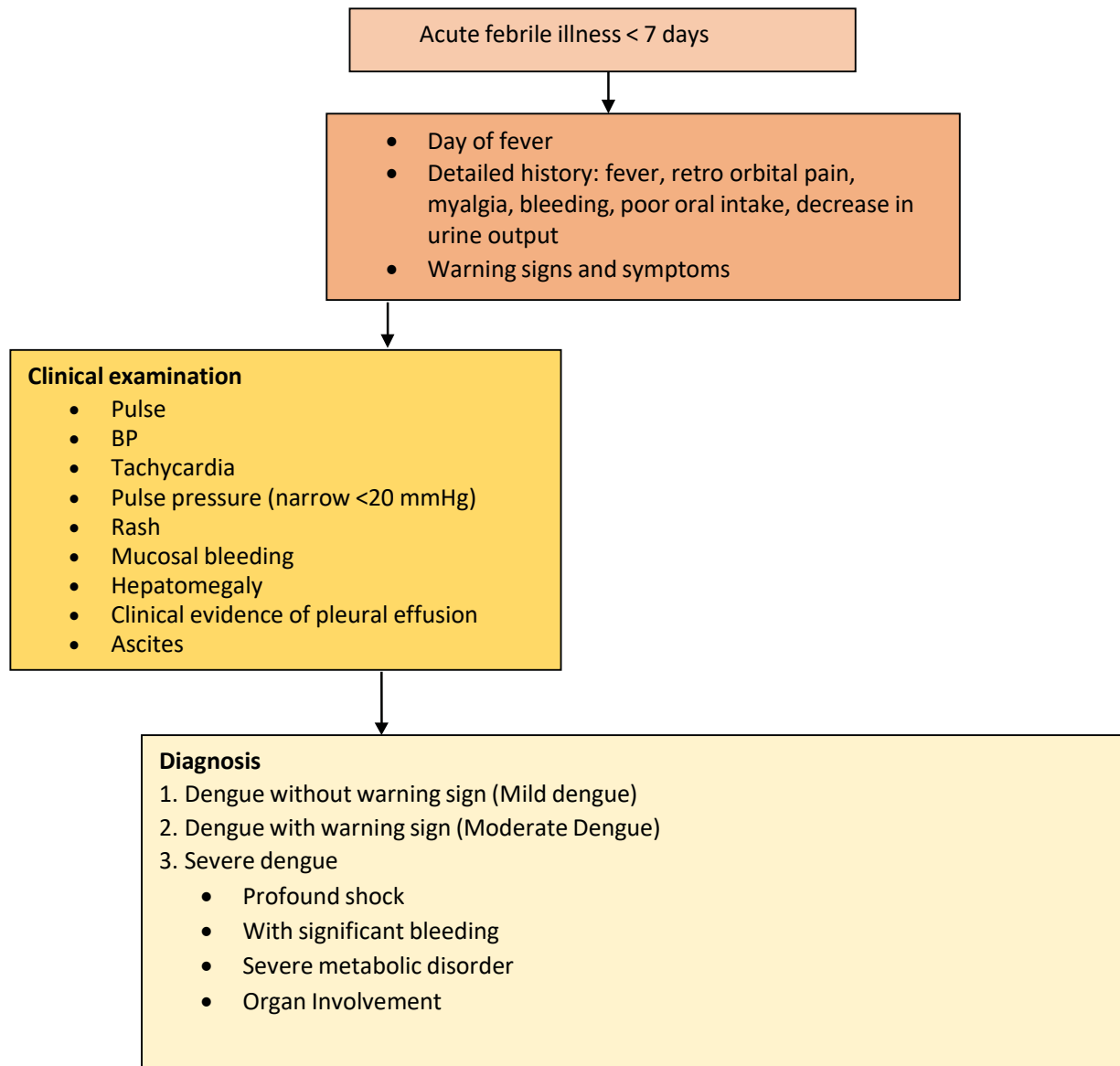
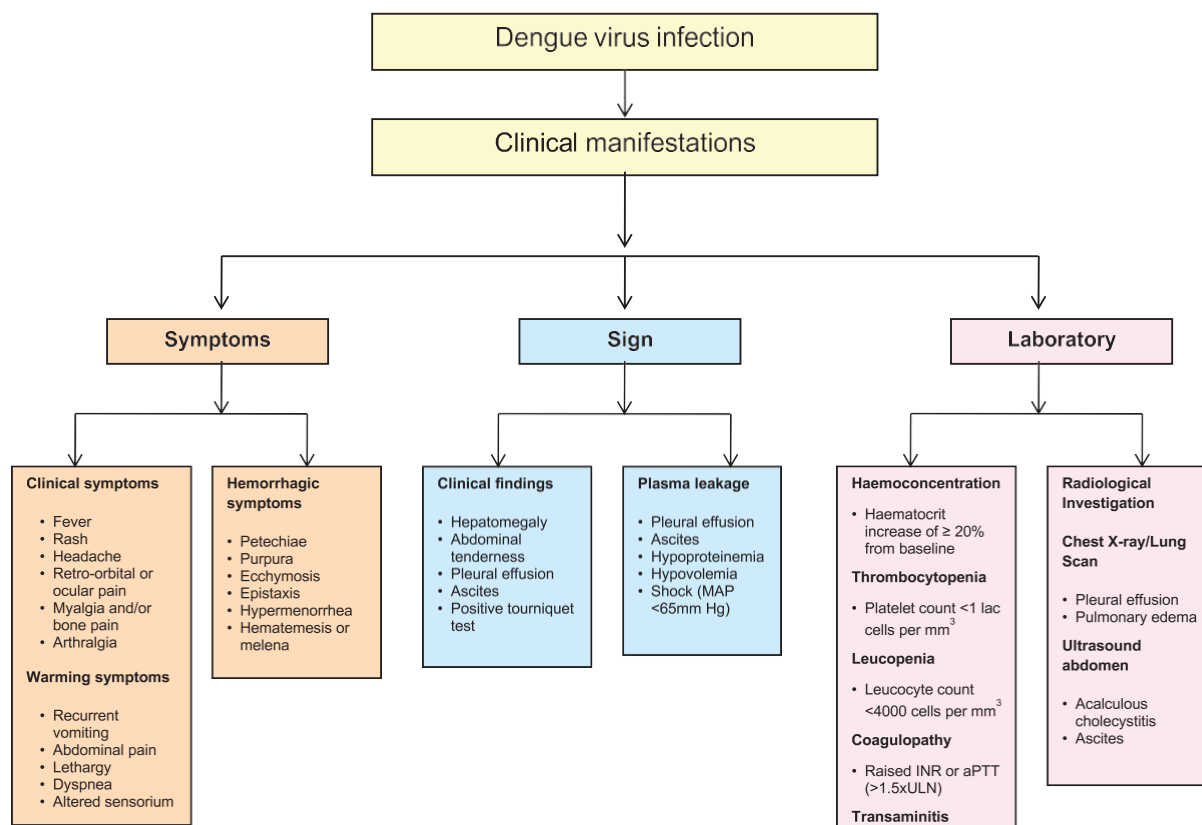


Table 3: Clinical assessment of dengue patient

History	Physical examination
<ul style="list-style-type: none"> • Date of onset of fever/illness • Quantity of oral fluid intake • Diarrhoea • Urine output (frequency, volume and time of last voiding) • Assessment of warning symptoms/ 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). 	<ul style="list-style-type: none"> • Assessment of mental state • Assessment of hydration status • Assessment of hemodynamic status (Check for postural hypotension) • Fundus examination for retinal bleed • Look for tachypnoea/acidotic breathing/pleural effusion • Look for Abdominal tenderness/ hepatomegaly/ ascites • Look for rash and bleeding manifestations • Tourniquet test

Figure 7: Clinical features and lab parameters of Dengue fever



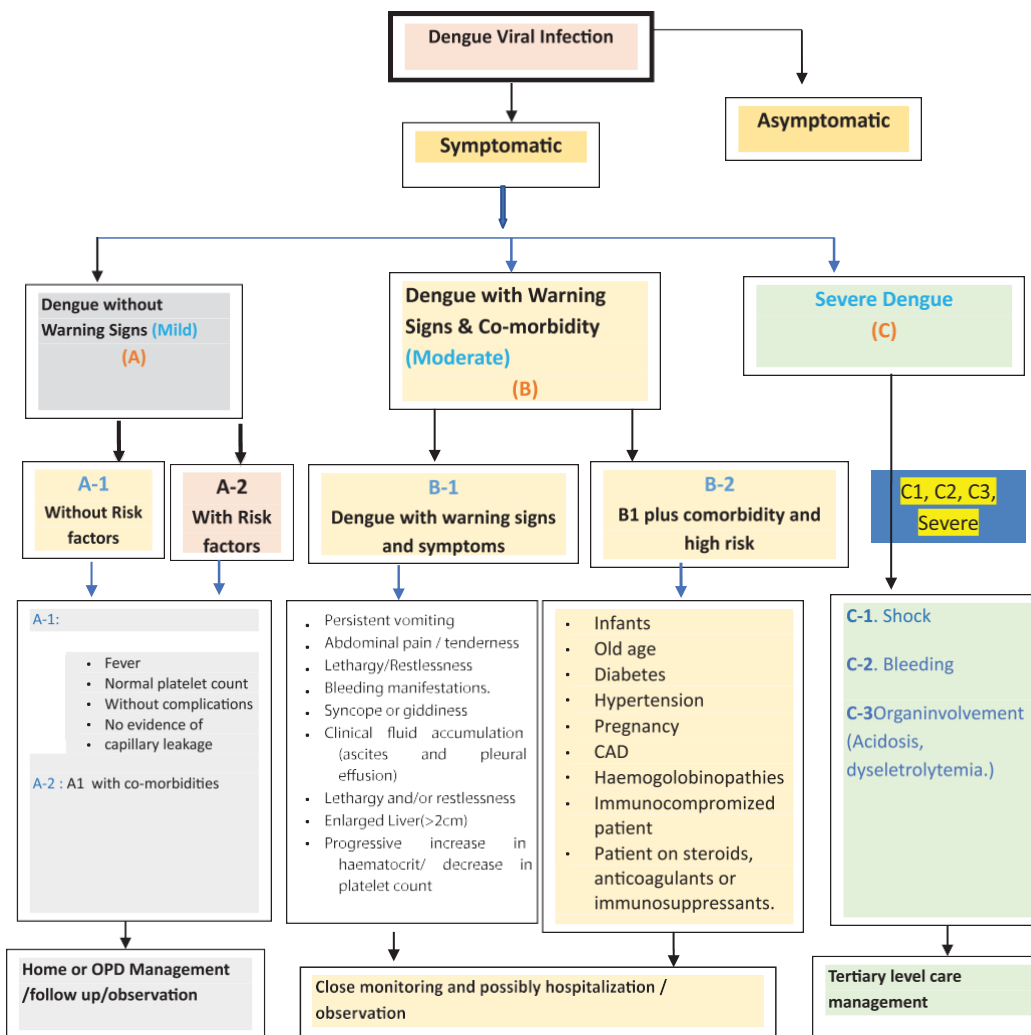
Box 3: Postural hypotension

- Ask the patient to lie down for 5 mins, measure blood pressure and pulse rate. Thereafter ask the patient to stand and repeat blood pressure and pulse rate after 3 mins of standing.
- A drop in Systolic BP of ≥ 20 mmHg and diastolic of ≥ 10 mmHg indicates postural hypotension

Box 4: 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 five minutes.
- A test is considered positive when 10 or more petechiae per 2.5sq.cm area (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.

Figure 8: Clinical case classification of dengue:



4.2 Dengue without warning signs (Mild dengue/Group A)

Mild dengue patient usually presents with fever and other symptoms like nausea, vomiting, rash, headache, myalgia, arthralgia and retroorbital pain, etc. Here, the complete blood count may reveal leucopenia but usually platelet count and hematocrit are in normal range. The other common symptoms which are often encountered are anorexia, altered taste sensation, constipation, colicky pain and abdominal tenderness. Mild dengue is subdivided as A1 and A2. The A1 involves patients with fever with other non-specific symptoms but no warning signs and A2 involves patients with prior comorbidities and other high-risk factors presenting with fever and other non-specific symptoms without warning signs.

4.3 Dengue with warning signs and/or Risk factors (Moderate dengue/Group B)

Here the patient present with fever with warning symptoms and signs (Refer Box 2). This usually occurs near the end of febrile phase and preferably at defervescence. Moderate dengue is further subdivided as B1 and B2. The 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.

4.4 Severe dengue (Group C)

These patients are those who have progressed from mild or moderate dengue to develop symptoms and signs of shock, plasma leakage, and organ dysfunction. Severe dengue involves patients presenting with history of fever with shock, patients with severe bleeding, patients presenting with severe organ involvement, and metabolic disorders (severe acidosis).

Manifestations of severe dengue

1. Severe plasma leakage leading to:
 - Shock
 - Fluid accumulation with respiratory distress
2. Severe bleeding (as evaluated by the treating team)
3. Severe organ dysfunction
4. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1000 units/L
5. Impaired consciousness (GCS < 9)

Severe dengue may lead to various organ dysfunctions which are described in the table below.

Table 5: Organ dysfunction in severe dengue

Nervous System	<ul style="list-style-type: none"> • Febrile seizures in young children • Encephalopathy • Encephalitis/aseptic meningitis • Intracranial haemorrhages/thrombosis • Subdural effusions • Mononeuropathies/polyneuropathies/Guillane-Barre Syndrome • Transverse myelitis
Gastrointestinal system	<ul style="list-style-type: none"> • Hepatitis/fulminant hepatic failure • Acalculous cholecystitis • Acute pancreatitis • Hyperplasia of Peyer's patches • Acute parotitis
Kidney	<ul style="list-style-type: none"> • Acute renal failure • Hemolytic uremic syndrome(HUS)
Heart	<ul style="list-style-type: none"> • Conduction abnormalities • Myocarditis • Pericarditis
Lungs	<ul style="list-style-type: none"> • Acute respiratory distress syndrome • Pulmonary haemorrhage
Musculoskeletal system	<ul style="list-style-type: none"> • Myositis with raised creatine phosphokinase (CPK) • Rhabdomyolysis
Lymphoreticular system	<ul style="list-style-type: none"> • Infection associated haemophagocytic syndrome • IAHS or Haemophagocytic lymphohistiocytosis (HLH) • Idiopathic thrombocytopenic purura (ITP) • Spontaneous splenic rupture • Lymph node infarction
Eye	<ul style="list-style-type: none"> • Macular haemorrhage • Impaired visual acuity • Optic neuritis
Others	<ul style="list-style-type: none"> • Post-infectious fatigue syndrome • Depression • Hallucinations • Psychosis • Alopecia

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,
- Hemolytic diseases such as glucose-6-phosphatase dehydrogenase deficiency, thalassemia and other haemoglobinopathies
- Peptic ulcer disease
- Congenital heart disease
- Chronic diseases such as diabetes mellitus, hypertension, obstructive lung diseases, cardiovascular diseases, chronic renal failure, and chronic liver disease
- Patients on long term steroid or NSAID treatment

Box 5: Risk factors for severe disease



Figure 9: Dengue patient with maculopapular rash



Figure 10: Impression mark on skin of a Dengue patient

4.5 Differential Diagnosis

- COVID-19
- Chikungunya
- Malaria
- Scrub typhus
- Enteric fever
- Pharyngitis
- Influenza
- Leptospirosis
- Meningococcal infection
- Crimean-Congo hemorrhagic fever etc.

* Depending on local epidemiology one may add additional causes like Zika Viral Disease, Kyasanur Forest Disease (KFD) etc.

DENGUE FEVER IN CHILDREN

Dengue infection in children is slightly different from older age group. Infants and children below 10 years with malnutrition are high risk group for severe dengue disease and the course can be unpredictable. Some salient features of dengue in children are discussed in this chapter

5.1 Clinical Manifestations

Dengue fever displays a broad range of clinical manifestations often with unpredictable clinical evolution and outcome. Most infections are subclinical. Infants and young children may present with an undifferentiated febrile illness. The classic presentation of dengue fever is usually seen in older children, adolescents and adults and can be described under three phases; febrile, critical and recovery phases.

1. Febrile phase: It is characterized by sudden onset of high-grade fever that may last for 2– 7 days. There may be facial flushing, skin erythema (scarlatiniform or maculopapular skin rash), generalized body aches, myalgias, arthralgias, headache, pain in eyes, back ache, anorexia, nausea and vomiting. Occasionally the patient may have a sore throat, congested pharynx and conjunctival congestion. Relative bradycardia and electrocardiographic changes may be seen in older children. A positive tourniquet test and minor hemorrhagic manifestations; petechiae and mucosal bleeding (e.g. nose and gums) may be seen in some patients. Liver may be enlarged and tender after 2-5 days and indicate an increased risk for development of severe illness. There is progressive decrease in total white cell count and platelet count

2. Critical phase: This phase is seen in some patients, between 3-7 days of onset of fever when defervescence sets in. The child may develop bleeding manifestations and shock with fall in platelet count and increase in packed cell volume (PCV). Bleeding manifestations include mucosal bleed like hematemesis, melena, bleeding per vaginum in adolescent girls and occasionally muscle hematoma. During defervescence, the patient develops features of capillary leakage in the form of puffiness, edema, ascites and pleural effusion especially on the right side. The profound leakage of plasma from capillaries may lead to hypovolemia resulting in shock-related symptoms in the form of restlessness, cold and clammy extremities, rapid thready pulse, low blood pressure with narrow pulse pressure (< 20 mm Hg), poor tissue perfusion (delayed capillary refill time) and oliguria. Some children may develop organ dysfunction such as acute kidney injury,

severe hepatitis, encephalitis or myocarditis and/or severe bleeding without any obvious plasma leakage or shock. Immunocompromised hosts may have more liver dysfunction, delayed recovery of platelets and possibly more plasma leak requiring higher fluid.

3. Recovery phase: After 24-48 hours of the critical phase, a gradual reabsorption of extravagated fluid takes place over 48-72 hours. General well-being improves, appetite returns, gastro-intestinal symptoms resolve. The hemodynamic status stabilizes and diuresis ensues. During recovery, patients may demonstrate marked erythema with extreme itching of the extremities, palms and soles. Some patients may have a skin rash suggestive of "*isles of white in a sea of red*". Due to reabsorption of extravagated plasma back into the vascular compartment, some children may develop respiratory distress due to pulmonary edema. The hematocrit stabilizes or may become lower due to the dilution. The total leukocyte count rises initially in few days followed by a gradual rise in platelet count.

5.2 Differential diagnosis

Various infections commonly seen in children in different age groups may mimic dengue. Therefore differential diagnosis for dengue infection includes influenza, malaria, enteric fever, leptospirosis, viral hepatitis, COVID 19 and less commonly meningococemia and rickettsial infections. Common infections like malaria, leptospirosis, flu and enteric fever may also occur with dengue. Several other viruses known to cause severe hemorrhagic fever like Ebola viruses and Marburg viruses have not been reported from India as yet. Two other hemorrhagic fever viruses Hanta virus and Crimean Congo hemorrhagic virus have been reported recently in India which mimic severe dengue. Wide spread chikungunya virus infections have occurred in various parts of India and South-East Asia. Its clinical manifestations are similar to dengue. However, fever is of shorter duration, thrombocytopenia and bleeding manifestations are less common. Other clinical features that are more common in chikungunya include skin eruptions, mucosal lesions, polyarthralgia and encephalopathy. Since dengue as well as chikungunya infections are endemic in most part of India, both infections may occur together. Zika, 'the emerging' flavivirus infection closely resembles dengue. Differentiating features between dengue and zika include shorter duration of fever, pronounced conjunctivitis/cervical adenopathy and lesser thrombocytopenia; bleeding manifestations and shock almost never occur. There is cross reactivity between the IgM ELISA antibodies of both dengue and Zika and hence PCR/ other specific antibody techniques are required for differentiation between the two infections.

5.3 Laboratory investigations

It is similar to that in older age group (Refer to chapter on diagnosis).

5.4 Management

5.4.1 Mild Dengue

Dengue fever without warning signs. Children with fever, bodyache, rashes or minor bleeding may be treated symptomatically. Fever and body ache are best treated with paracetamol (10-15 mg/kg/dose 4-6 times per day). Salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as these may predispose the child to develop mucosal bleeds. Child should be encouraged to drink plenty of fluids. There is no specific antiviral therapy. All patients need regular monitoring by a primary care physician for early detection of severe disease. The primary care physician/ health care worker should monitor the patient for warning signs along with hematocrit and platelet counts. Any patient who develops warning signs as mentioned in Box 2 should be admitted to a hospital.

5.4.2 Moderate Dengue

Dengue with warning signs. Children with suspected dengue infection who has any of the following features should be admitted to the hospital.

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

These patients should be admitted in the hospital and should be evaluated for oral intake, dehydration. If oral intake is poor and child is dehydrated, intravenous fluids should be given at a rate of 5-10 ml/kg over one hour. Crystalloids (Normal saline) are the preferred fluids. Vital signs and hematocrit are to be reassessed. After one hour, if hematocrit has decreased and vital parameters are improving, fluid infusion rate should be reduced to 3-5 ml/kg/hour for subsequent 24-48 hours with frequent monitoring of hematocrit and vital parameters. When the patient is stable as indicated by normal blood pressure, good oral intake and urine output with stable hematocrit, the child can be discharged.

If after one hour, hematocrit is rising and vital parameters do not show improvement, fluid infusion rate may be continued at 7- 10 ml/kg over next 1-2 hour. In case of no further improvement, severe dengue disease needs strong consideration and managed accordingly.

5.4.3 Severe dengue

The management of severe dengue infection demands high levels of expertise and skills for administration of fluids and electrolytes to correct hypovolemia due to leakage of serum from capillaries into the extravascular compartment.

Children presenting or developing any of the following complications are diagnosed to have severe dengue infection.

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

Children classified as severe dengue should be hospitalized (preferably in PICU) and treated with judicious IV fluid administration under Central venous pressure monitoring (central line or IVC compressibility by USG), Cardiac contractility (Echocardiography) ,and arterial blood pressure monitoring (non invasive, and or invasive: arterial line). In case of refractory shock with severe plasma leakage, colloid infusion may be given after 2-3 bolus of normal saline (15-20 ml each). For cardiogenic or septic shock, Vassopressor (Noradrenaline and adrenaline infusion may be started). Blood transfusion should be considered in the presence of occult or overt blood loss. In addition to fluid management, these sick children may need oxygen and ventilatory support. These children need close monitoring for various complications which should be identified early and managed effectively.

5.5 Bleeding manifestations

Platelet counts are unreliable to predict bleeding. In a small study in which children with severe thrombocytopenia were included, platelet infusion did not alter the outcome of patients. In a recent RCT in adults with confirmed dengue infection and thrombocytopenia ($\leq 20\,000$ platelets per μL), without persistent mild bleeding or any severe bleeding, prophylactic platelet transfusion was not superior to supportive care in preventing bleeding; on the other hand, administration of platelets was however associated with adverse events some of which were serious adverse events.

- (a) *Petechial spots or mild mucosal bleed but hemodynamically stable.* These patients need supportive care including bed rest, maintenance of hydration and monitoring. IM injections should be avoided. Procedures predisposing to mucosal trauma should be avoided. If indicated NG tube should be inserted with great care.

- (b) *Severe bleeding, hemodynamic instability and excessive mucosal bleeds.* These patients should be treated with blood transfusion and periodic monitoring. When massive bleeding cannot be managed with fresh blood/fresh-packed cells FFP and PRP may be considered. Platelet transfusion and FFP transfusion may be given when platelet count is low (below 50 000/cumm) with deranged PT, APTT, hypofibrinogenemia and increased D- dimer or FDP .

5.6 Fluid overload

The causes of fluid overload in dengue infection include excessive and/or too rapid infusion of intravenous fluids; incorrect use of hypotonic rather than isotonic crystalloid solutions; inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding; inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates; continuation of intravenous fluids after plasma leakage has resolved (24-48 hours after defervescence) and co-morbid conditions such as congenital heart disease, chronic lung and renal disease. Fluid overload may also occur in patients with significant fluid leak. During recovery the leaked out fluid will return back to the vascular compartment and may cause volume overload.

Fluid overload can be prevented by discontinuing IV fluids in following situations.

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

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

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

5.7 Other supportive measures

Renal replacement therapy: Renal failure is best managed with veno-venous hemodialysis. Children with shock, needing multiple vasoactive drugs, with acute kidney injury may need continuous renal replacement therapy (CRRT).

Vasopressor and inotropic therapies: These are indicated if there is no improvement in blood pressure with adequate fluid replacement despite normal or raised CVP. Commonly used drugs include dopamine, epinephrine, and dobutamine. These drugs should be administered using a central line and the child should be managed preferably in an ICU.

Standard treatment guidelines should be followed for the management of severe hepatic involvement, encephalopathy or encephalitis, cardiac conduction abnormalities and fluid and electrolyte abnormalities.

There is no therapeutic utility of corticosteroids. Blood transfusion (20 ml/kg) is indicated when shock persists despite declining hematocrit values (which are indicative of adequate fluid replacement) due to overt or internal hemorrhage.

Children with pleural effusion/ ascites should not routinely undergo fluid tapping as this may lead to deterioration in child's condition and there is risk of bleeding due to the procedure.

Failure of a patient with dengue to improve within the usual time period should prompt evaluation for complications such as superadded infection or hemophagocytic syndrome.

5.8 Monitoring

In view of the dramatic course of severe dengue, monitoring of the patient is crucial in the first few hours of illness. Heart rate, respiratory rate, blood pressure and pulse pressure should be monitored every 30 minutes till the patient is stable, thereafter monitoring should be continued every 2-4 hours as long as the child is in the hospital. In critically ill children, central venous pressure and accurate urine output with an indwelling urinary catheter should be monitored. However, difficulties encountered in monitoring CVP in critically sick children are a limiting factor for its routine use. The laboratory monitoring includes serial hematocrit measurement. In monitoring hematocrit, one should bear in mind the possible effect of pre-existing anemia, severe hemorrhage and early volume replacement therapy. Presence of pleural effusion on chest X-ray or ultrasound examination or hypoalbuminemia can provide supportive evidences of plasma leakage, the distinguishing feature of severe dengue.

Platelet counts and DIC studies should be monitored closely if there is uncontrolled bleeding. If there is a declining trend during critical phase platelet count may be repeated 6 to 8 hourly. While deciding about the fluid infusion rate on the basis of hematocrit and clinical monitoring, it must be kept in mind that infusion rates decrease rapidly after the first 6 hours of intervention in most uncomplicated cases. Excessive unmonitored administration of fluids may lead to fluid overload, congestive heart failure or ARDS.

5.9 Prognosis

Dengue fever is mostly a self-limiting disease but the mortality may increase in severe dengue cases. Early recognition of shock is of paramount importance as the outcome of the patient depends on it. If shock is identified when pulse pressure starts getting narrow and intravenous fluids are administered at this stage, the outcome is excellent. Recovery is fast and majority of patients recover completely in 24-48 hours without any residual sequelae. The prognosis is grave in patients with prolonged shock and when blood pressure is not recordable. Other adverse correlates of outcome which can occur without prolonged shock include encephalitis, DIC, myocarditis, fulminant hepatitis and ARDS and may not be modifiable by early administration.

Chapter 6

LABORATORY DIAGNOSIS

In endemic areas, early symptoms of dengue fever mimic many other prevalent diseases such as Chikungunya fever, Zika virus disease, malaria, viral infections, urinary tract infection, typhoid, leptospirosis etc. Hence, for proper management exclusion of these conditions is very crucial.

6.1 Laboratory diagnosis tests:

6.1.1 ELISA based NS1 antigen tests

Dengue NS1 antigen, a highly conserved glycoprotein, produced in both membrane-associated and secretory forms, is abundant in the serum of patients during the early stages of dengue infection and has been found to be useful as a tool for the diagnosis of acute dengue infections. It is a simple test that is highly specific and shows high sensitivity.

NS1 antigen enables early detection of cases i.e., in the viremic stage, which has epidemiological significance for containing the transmission. The dengue virus NS1 ELISA antigen assay is commercially available. This assay has been evaluated for sensitivity and specificity. The NS1 assay may also be useful for differential diagnosis between flaviviruses because of the specificity of the assay.

6.1.2 IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA)

MAC-ELISA has been widely used in the past few years. It is a simple test which does not require any sophisticated equipment. It is based on detecting the dengue-specific IgM antibodies in the test serum by capturing them using anti-human IgM that was previously bound to the solid phase. This is followed by addition of dengue antigen, if the IgM antibody from the patient's serum is anti-Dengue, it will bind to the Dengue antigen. An enzyme-substrate is added to give a color reaction for easy detection.

The anti-dengue IgM antibody develop faster than IgG and is usually detectable by day 5 of the illness. However, the rapidity with which IgM develops varies considerably among patients. Some patients have detectable IgM on day's two to four after the onset of illness, while others may not develop IgM for seven to eight days after the onset. In some primary infections, detectable IgM may persist for more than 90 days, but in most patients, it wanes off to undetectable levels by 60 days. It is reasonably certain, however that the person had a

dengue infection sometime in the previous two to three months. MAC-ELISA has become an invaluable tool for surveillance of dengue fever. In areas where dengue is not endemic, it can be used in clinical surveillance for viral illness or for random, population-based sero-surveys, with the certainty that any positives detected are recent infections. It is especially useful for hospitalized patients, who are generally admitted late in the illness after detectable IgM is already present in the blood.

6.1.3 Isolation of Dengue Virus

Isolation of most strains of dengue virus from clinical specimens can be accomplished in majority of cases provided the sample is taken in the first five days of illness and processed without delay. Specimens that may be suitable for virus isolation include acute phase serum, plasma or washed buffy coat from the patient, autopsy tissues from fatal cases, especially liver, spleen, lymph nodes and thymus and mosquitoes collected in nature. Isolation of virus takes 7-10 days, hence may not be very useful for starting the management of patient with dengue fever.

6.1.4 PCR (Polymerase Chain Reaction)

Molecular diagnosis based on reverse transcription (RT-PCR), such as one-step or nested RT-PCR, nucleic acid sequence-based amplification (NASBA), or real-time RT-PCR, has gradually replaced the virus isolation method as the new standard for the detection of dengue virus in acute-phase serum samples.

6.1.5 IgG-ELISA

An IgG-ELISA has been developed that compares well to the Hemagglutination-Inhibition (HI) test. This test can also be used to differentiate primary and secondary dengue infections. The test is simple and easy to perform but not considered as a diagnostic test as it indicates past infections only.

6.1.6 Serological Tests

Besides, MAC ELISA and IgG-ELISA, there are few serological tests available for the diagnosis of dengue infection like hemagglutination-Inhibition (HI), complement fixation (CF) and neutralization test (NT) which are not commonly used due to various technical problems.

6.1.7 Rapid Diagnostic tests

A number of commercial Rapid Diagnostic Test (RDT) kits for anti-dengue IgM/IgG antibodies and NS1 antigen are commercially available at present which give the results within 15 to 25

minutes. However, the accuracy of most of these tests is not known since they have not yet been properly validated. Some of the RDTs have been independently evaluated. The results showed a high rate of false positive compared to standard tests, while others have agreed closely with standard tests. The sensitivity and specificity of some RDTs were also found to vary from batch to batch. Hence, currently, the programme does not recommend the use of RDTs for diagnosis and guiding the management of Dengue fever cases.

6.2 Collection of Samples

Laboratory diagnosis of Dengue depends on proper collection, processing, storage and shipment of the specimens. While collecting blood for serological studies from suspected cases all universal precautions should be taken.

While sending the samples for lab confirmation the day of onset of fever and day of sample collection should be mentioned to guide the laboratory for the type of test to be performed (NS1 for samples collected from day 1 to 5 and IgM after 5 days).

6.3 NCVBDC (earlier NVBDCP) Laboratory Network

National Center for Vector Borne Diseases Control (NCVBDC), Government of India (GoI) has identified a network of laboratories (Sentinel Surveillance Hospitals and Apex Referral Laboratories) for surveillance of Dengue fever cases across the country since 2007. Numbers are increasing yearly to augment the free diagnostic facilities in all endemic areas, which were 110 in 2007 and 783 in 2022. They are linked with 17 Apex Referral Laboratories (ARLs) with advanced diagnostic facilities for backup support. For details, please refer to the NCVBDC website www.ncvbdc.mohfw.gov.in.

These laboratories receive the samples, diagnose and regularly send the report to districts/ municipal health authorities to implement preventive measures to interrupt the transmission. Dengue IgM MAC ELISA test kits (1 Kit= 96 tests) are provided to the identified laboratories through the National Institute of Virology (NIV), Pune, since 2007. NCVBDC bears the cost for all testing. Buffer stock is also maintained at NIV, Pune, to meet any emergency in case of an outbreak in newer areas and to avoid stock out.

MANAGEMENT OF DENGUE FEVER

Dengue fever (DF) is common in older children, adolescents, and adults. It is generally an acute febrile illness, and the patient presents with biphasic fever with severe headache, myalgias, arthralgias, rashes, leukopenia, and thrombocytopenia. Although DF may be benign, it could be an incapacitating disease with severe headache, myalgia and polyarthralgia (break-bone fever), particularly in adults. Occasionally haemorrhages such as gastrointestinal bleeding, hypermenorrhoea and massive epistaxis may occur.

7.1 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.

- **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 dengue patients should be referred directly to a trained nurse/medical assistant in emergency ward.
- Following parameters should be assessed :
 - Duration of fever
 - Presence of warning signs
 - High-risk groups (co-morbidities and co-infection)
 - Tourniquet test
 - Vital signs including temperature, blood pressure, pulse rate, 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 random blood sugar (RBS)**
 - All patients with warning signs
 - All patients with fever >3 days

7.2 Approach to clinical management

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

- Mild dengue (A): May be managed on OPD basis
- Moderate dengue (B): Observation or admission for in-hospital management
- Severe dengue (C): Require emergency treatment and urgent referral

Management of Mild dengue patient (Group A)

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

1. 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
2. Advice to consume adequate oral fluids (ORS/Coconut juice), avoid carbonated drinks
3. Patient need to take adequate bed rest.
4. Over-hydration in infants and young children should be carefully observed.
5. Body temperature should be kept below 100°F. If the temperature goes beyond 100°F, give 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 six hours. The maximum dose for adults is 4 gm/day. Avoid using aspirin or NSAIDs.
6. Tepid sponging of forehead, armpits, and extremities. A lukewarm shower or bath is recommended for adults in case of high grade fever not responding to paracetamol.

Follow-up

- Patients should be followed-up for close monitoring of progression of the disease from mild to moderate or severe.
- During this time, clinical examination along with CBC and hematocrit should be advised according to the patient condition.

7.3 Management of moderate and severe dengue

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 warning signs and symptoms.
- Peripheral perfusion assessment should be done as frequently as indicated because it is an early indicator of shock and is easy and fast to perform.
- Vital signs such as temperature, pulse rate, respiratory rate and blood pressure should be checked at least every 2–4 hours in non-shock patients and every 1-2 hourly in patients with shock.
- Serial haematocrit should be performed at least every four to six hours 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 checked after the fluid bolus, but not during the infusion of the bolus.
- Urine output should be recorded at least every 8 to 12 hours 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).

Additional laboratory investigations:

Adult patients and those with co-morbidities 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
- Chest radiograph
- Blood Group
- Cardiac enzymes (Pro-BNP and Troponin level) or ECG if indicated among high risk groups
- Serum amylase and ultrasound abdomen.

7.3.1 Management of Moderate Dengue patients (Group B)

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

Clinical approach for the management of moderate dengue patients

- Should be admitted for in-hospital management.
- Baseline haematocrit (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.
- All warning symptoms and signs should be carefully observed.
- Blood glucose level and other laboratory tests should be done.
- Encourage oral fluids. If not tolerated, start intravenous fluid therapy of 0.9% NS or RL.
- They can be sent home within 12 to 24 hours if they show rapid recovery and are not in the critical period.

- 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/hour.
- Isotonic crystalloid fluid: 0.9% NS or RL are preferred
- Give 7-10ml / kg crystalloid solution (Hartmann's or 0.9% NSS) in 1 h.
- Evaluation of clinical improvement should be done every hourly
- If patient conditions improves (BP improved, pulse pressure improved, Hct decreased, urine output improved, capillary refilling time improved) fluid reduction should be done gradually as
 - 5-7 mL/kg/h for 2-4 hours
 - 3-5 mL/kg/h for 2-4 hours
 - 2-4 mL/kg/h for 2-4 hours
- Fluid should be stopped after 24-48 hours as per the clinical status of the patient

If there is no clinical improvement after IV fluid, hematocrit should be evaluated

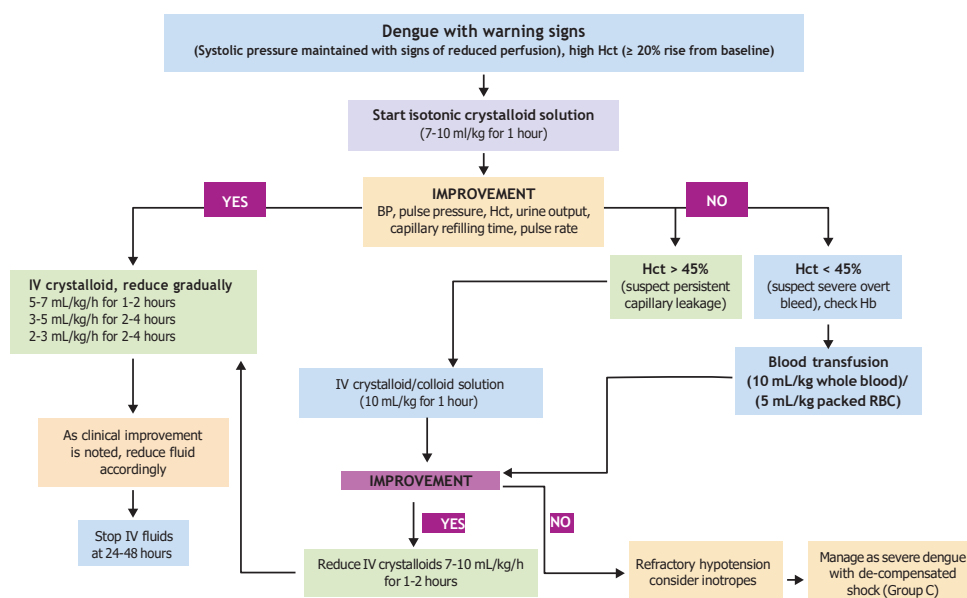
- If haematocrit remains >45%, give 2nd bolus (Crystalloid 10mL/kg) for 1hour. If there is no improvement after 2nd bolus, manage as Group C.
- If haematocrit falls to < 45%, suspect severe overt bleed and plan for blood transfusion. Give whole blood transfusion at 10ml/kg or packed RBC at 5ml/kg.

Monitoring of the patient

Temperature, Pulse, Respiratory rate, BP should be monitored until patient is out of critical phase:

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

Figure 11: Algorithms for hospital management for moderate dengue patients with warning signs:



Fluid therapy

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 hours. For example, in a child weighing 20 kg, the deficit of 5% is $50 \text{ ml/kg} \times 20 = 1000 \text{ ml}$. 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 hours in non-shock patients. The rate of infusion of this 2500 ml may be as shown below.

Rate of IV fluids in adults and children

	Children (ml/kg/hr)	Adult (ml/hr)
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.

Box 6: Rate of infusion in non-shock cases

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

- 100 ml/kg/day (4 ml/kg/hr) for first 10 kg body weight
- 50 ml /kg/day for next 10 kg body weight
- 20 ml/kg/day or subsequent kg body weight
- *For overweight/obese patients calculate normal maintenance fluid based on ideal body weight (IBW), using the following formula:
 - Female: $45.5 \text{ kg} + 0.91 (\text{height} - 152.4) \text{ cm}$
 - Male: $50.0 \text{ kg} + 0.91 (\text{height} - 152.4) \text{ cm}$ (20, 21)

Table 5: 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 kgs)	Volume of fluid to be given in 24 h	Rate of fluid (ml/hour)			
		R* 1	R* 2	R* 3	R* 4
10	1500	30	60	100	200
15	2000	45	90	150	300
20	2500	60	120	200	400
25	2850	75	150	250	500
30	3200	90	180	300	600
35	3550	105	210	350	700
40	3900	120	240	400	800
45	4250	135	270	450	900
50	4600	150	300	500	1000
55	4950	165	330	550	1100
60	5300	180	360	600	1200

Regimen 1- 3ml/kg/hr; 2 - 6ml/kg/hr; 3 -10ml/kg/hr, and 4- 20ml/kg/hr

- 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.

7.3.2 Management of Severe Dengue patients (Group C)

These patients are vulnerable and require urgent admission and management. Severe dengue has following characteristics

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

Principles of management of severe dengue:

- All patients to be stabilised and referred for admission to a hospital which has blood transfusion facilities.
- Judicious IV fluid resuscitation is essential and lifesaving.
- Prefer a crystalloid solution (0.9% NS or RL) sufficient to maintain an effective circulation during the period of plasma leakage (usually for 24–48 hours) and adjust fluid as per the patient status
- It's advised to obtain hematocrit level before starting fluid therapy; lack of haematocrit should not delay fluid management.
- Monitor vital signs every 5-30 min.
- Use IBW for overweight and obese patients while calculating fluid rates.
- Blood group of the patient to be investigated.

- Blood transfusion should be given to patients with established severe bleeding, or suspected severe bleeding (fall in Hct) with unexplained hypotension.

Intravenous fluid therapy during the critical period

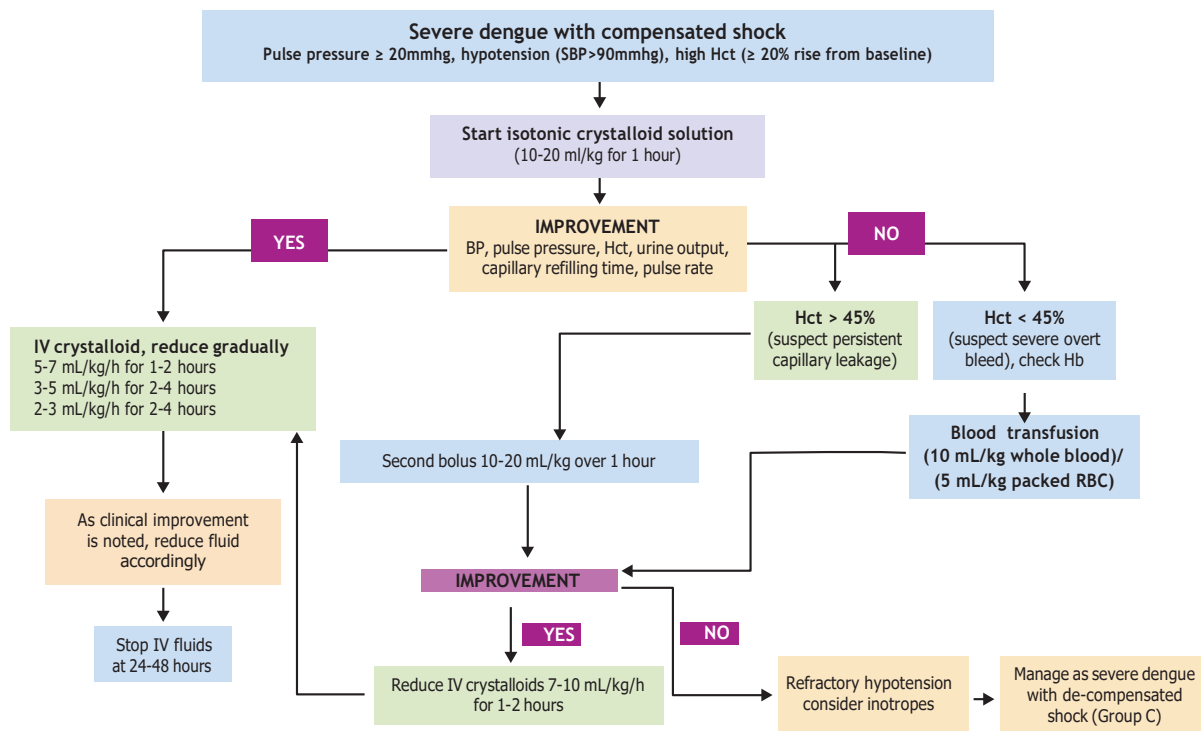
- Isotonic crystalloid solutions should be used throughout the critical period except in the very young infants <6 months of age in whom 0.45% sodium chloride may be used.
- Hyper-oncotic colloid solutions (osmolarity of >300 mOsm/l) such as dextran 40 or starch solutions may be used in patients with massive plasma leakage, and those not responding to the maximum volume of crystalloid. Iso-oncotic colloid solutions such as plasma and hemacel may not be as effective.
- The duration of intravenous fluid therapy should not exceed 24 to 48 hours for those with shock. However, for those patients who do not have shock, the duration of intravenous fluid therapy may have to be longer but not more than 60 to 72 hours. 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 intravenous therapy has begun.
- Always check for the signs of fluid overload.
- 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.

Management of compensated shock

The action plan for treating patients with compensated shock is as shown in algorithm below:

- Start intravenous fluid resuscitation with isotonic crystalloid solutions at 10-20ml/kg/ hour over one hour.
- Reassess the patient's condition (vital signs, capillary refill time, haematocrit, urine output)
- If the patient's condition improves, intravenous fluids should be gradually reduced to 7–10 ml/kg/hr for 1–2 hours, then to 5–7 ml/kg/hr for 1-2 hours, then to 3–5 ml/kg/hr for 2-4 hours, then 2-3 ml/kg/h for 2-3 hours and then further depending on haemodynamic status, which can be maintained for up to 24–48 hours.
- If patient is not clinically improved (i.e. shock persists), check the haematocrit after the first bolus. If the haematocrit increases or is still high (>45%), repeat a second bolus of crystalloid solution at 10ml/kg/hr for one hour. After this second bolus, if there is improvement, reduce the rate to 7–10 ml/ kg/hr for 1–2 hours, and then continue to reduce as above.
- If haematocrit decreases compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. Give whole blood transfusion at 10ml/kg or packed RBC at 5ml/kg.

Figure 12: Algorithm for management of Severe Dengue with compensated shock.



Management of Decompensated shock

Patients with decompensated/hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is as shown in the algorithm below:

- Initiate intravenous fluid resuscitation with crystalloid or colloid solution (if available) at 20 ml/kg as a bolus given over 15 minutes
- If the patient's condition improves, give a crystalloid/colloid infusion of 10 ml/ kg/hr for one hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, and to 2–3 ml/kg/hr or less, which can be maintained for up to 24–48 hours
- If shock persists, review the haematocrit. If the haematocrit increases or is still high (>45%), repeat a second bolus of crystalloid solution at 10-20 ml/kg over 15-30 minutes. After this second bolus, if there is improvement, reduce the rate to 7–10 ml/ kg/hr for 1–2 hours, and then continue to gradual reduction of fluid as mentioned above. Upto three rapid boluses may be given.
- If haematocrit decreases compared to the initial reference haematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. Give whole blood transfusion at 10ml/kg or packed RBC at 5ml/kg.
- If the shock is refractory
 - Use of inotropes should be considered.
 - Determine cardiogenic shock, septic shock
 - Evaluate metabolic cause and organ dysfunction
 - Evaluate concomitant medical conditions and stabilize the baseline condition
 - Evaluate persistent acidosis and risk of (hidden) hemorrhage and treat accordingly

- If needed, administer additional boluses of hydrating solution (crystalloid or colloid) over the next 24 hours; the speed and volume of each bolus will depend on clinical response;
- Manage patient, preferably in ICU

Figure 13: Algorithm for management of severe dengue with decompensated shock.

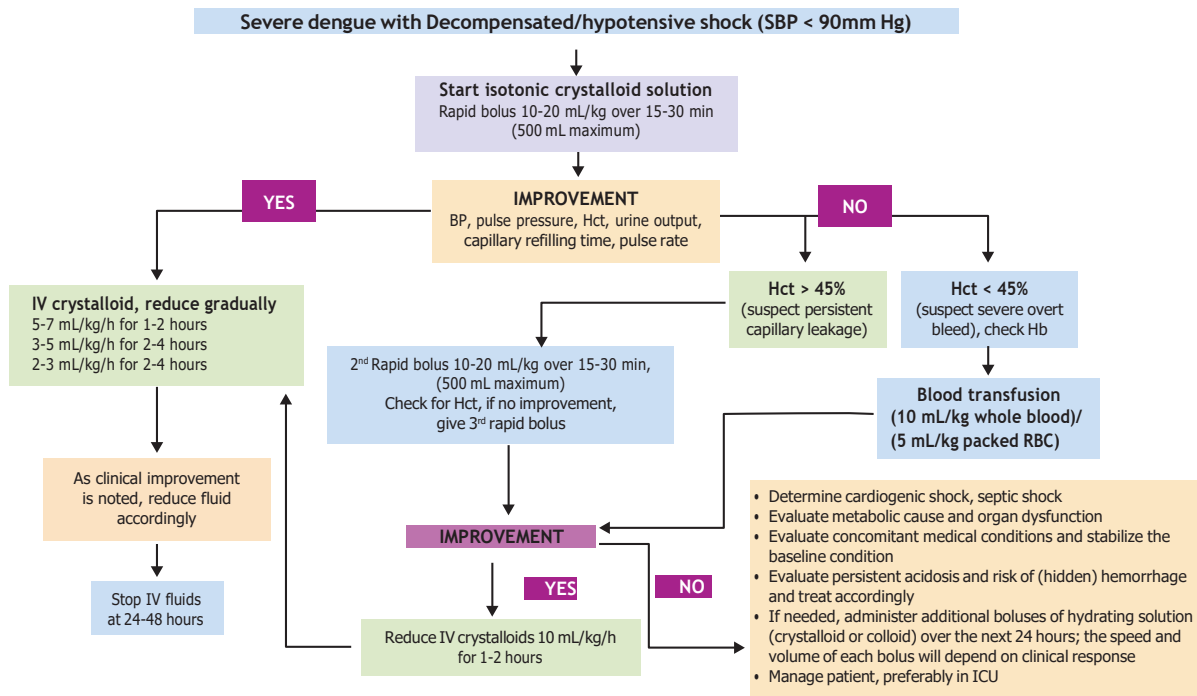


Table 7: Requirement of fluid based on ideal body weight

Ideal body weight (Kgs)	Maintenance (ml)	M +5% deficit (ml)	Ideal body weight (kgs)	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

Platelet transfusion is not recommended for thrombocytopenia (no prophylaxis platelet transfusion). It may be considered in adults with underlying hypertension and thrombocytopenia less than 10 000 cell/mm³.

Box 7: When to stop intravenous fluid therapy

Intravenous fluids should be reduced or discontinued when any of the following signs are present.

- Normal blood pressure, pulse and peripheral perfusion;
- Decrease in hematocrit
- Apyrexia (without the use of antipyretics) for more than 24–48 hours;
- Resolving bowel/abdominal symptoms;
- Improving urine output.
- Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary oedema and other complications such as thrombophlebitis.

Box 8: Indication of platelet transfusion

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

7.4 Management of severe haemorrhage

- Source of bleeding should be identified as soon as possible and efforts to stop the bleeding to be initiated immediately.
- 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, it should be replaced immediately. 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.
- In gastrointestinal bleeding, H-2 antagonists and proton pump inhibitors can be 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.

7.5 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 diuresis are usually observed.
- **Intravenous fluid should be discontinued.**
 - i. In patients with pleural or pericardial effusion and ascites, fluid overload may occur and diuretic therapy may be necessary to prevent pulmonary oedema.
 - ii. Hypokalemia may be present due to stress and diuresis and should be corrected with potassium-rich fruits or supplements.

- iii. Bradycardia is commonly found and requires intense monitoring for possible rare complications such as heart block or ventricular premature contraction (VPC).
- iv. Convalescence rash is found in 20%–30% of patients.

Signs of recovery

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

7.6 Management of complications

7.6.1 Fluid overload

Clinical manifestations:

- Early signs and symptoms include puffy eyelids, distended abdomen (ascites), mild dyspnoea.
- Late signs and symptoms include all of the above, along with moderate to severe respiratory distress, which are also an early sign of interstitial pulmonary oedema. Restlessness/agitation and confusion are also seen.
- These patients may require ventilatory support soon. If the intravascular volume is inadequate or the blood pressure is unstable, check the ABCS (Acidosis, Bleeding, Calcium (Na+ & K+), Sugar) 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 effusion or ascitic fluid aspiration may be indicated and can be life-saving in cases with severe respiratory distress and failure of other measures. 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.

Management of fluid overload

- Review the total intravenous fluid therapy and clinical course, and check and correct for ABCS (Acidosis, Bleeding, Calcium (Na+ & K+), Sugar). 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). Fluid may be effective (osmolarity = 308 mosmole) and the upper limit is 50ml/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 to 30 minutes of infusion, administer IV 1 mg/kg/dose of furosemide and continue with dextran infusion until completion. Intravenous fluid should be reduced to as low as 1 ml/kg/h until discontinuation when haematocrit decreases to baseline or below (with clinical improvement).
- 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 minutes 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).

7.6.2 Encephalopathy

Severe dengue patients sometimes present with manifestations of central nervous system (CNS) involvement, such as convulsion and/or coma.

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 end up by 30 degrees.
 - Early endotracheal intubation should be considered to avoid hypercarbia and protect the airway.

- May consider steroid to reduce ICP and dexamethasone 0.15 mg/kg/dose IV to be administered every 6–8 hours.
- Decrease ammonia production by the following measures:
 - Give lactulose 5–10 ml every six hours 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. In the hospital and are started at a rate of 5-10 ml/kg over one hour. Recommended glucose infusion rate is between 4–6 mg/kg/hour.
- Correct acid-base and electrolyte imbalance, e.g. correct hypo/hyponatremia, hypo/hyperkalemia, hypocalcemia 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.

Chapter 8

SPECIAL CONDITIONS IN DENGUE FEVER

8.1 Management of Dengue in High-risk groups (Co-morbidities and Co-infections)

Various conditions like pregnancy, pediatric age group, hypertension, diabetes, thyroid diseases, hepatitis, heart diseases and renal diseases are considered as risk factors of severe manifestations in dengue.

8.1.1 Management of dengue in pregnancy

Dengue infection in pregnancy carries the risk of severe bleeding, fetal complications, low birth weight and premature birth. Risk of vertical transmission of infection from mother to child is high if the mother is having severe viremia during around the time of labor. As pregnancy is a hypervolumic state, pleural effusion, ascites, hypotension may manifest easily among them when infected with dengue. Strict vital monitoring, frequent platelet count and coagulation profile testing should be done. Fulminant hepatic failure, ARDS and Acute Renal failure in pregnancy may be associated with dengue infection. Fluid overload due to management in dengue may occur and may lead to pulmonary edema. Thus management of pregnant female's infection with dengue should be done carefully to reduce morbidity and mortality in mother as well as fetus.

8.1.2 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 severe dengue with shock among neonates and infants. Close observation, symptomatic and supportive treatment are the mainstay of management.

b. Management of dengue in infants

- **Management of dengue in infants without warning signs**

Oral rehydration should be encouraged with oral rehydration solution (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 in infants with warning signs**

When the infant has dengue with warning signs, he/she should be admitted immediately and intravenous fluid therapy should be initiated. 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 hours in most of the patients.

c. Management of infants with severe dengue

Treatment of shock: 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 analyzed separately. The child should be managed in PICU. (for more details, refer chapter 'Dengue in Children'.

8.1.3 Management of Dengue in Co-morbidities

a. Dengue viral hepatitis

Some patient may have impairment of liver function due to dengue viral infection. The AST/ALT level may be very high along with prolongation of prothrombin time. Hepatic complication is commonly associated with pre-existing conditions like chronic viral hepatitis, liver cirrhosis and hepatomegaly. Patient may also develop hepatic encephalopathy due to acute liver failure. Risk of severe GI bleeding is also present which may lead to shock. Thus 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 CAD, hypertension, diabetic and valvular heart disease. Management of shock with IV fluid in such case is sometime difficult due to myocardial dysfunction. Patient may develop pulmonary oedema due to improper fluid management.

- **Dengue in coronary artery diseases (CAD) and heart failure:**

Management of dengue in CAD is challenging as these patients are already on antiplatelet agents which may lead to severe bleeding unless stopped. Cardiac ischemia or electrolyte disturbances should be frequently reassessed. Patient may develop congestive or biventricular heart failure and hence fluid management is challenging. Thus, patients who are on anti-platelet or anticoagulant medications should be carefully monitored. The anti-platelets agent such as aspirin and other anti-platelet 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 is also associated with high risk of fluid overload due to plasma leakage in dengue fever, thus to avoid further deterioration of the patient's state, it's critical to recognize early indicators of fluid overload. 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 is hemodynamically stable.

c. **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, hyperglycemia may occur which may require insulin therapy for better management. Before starting the treatment, a reference hematocrit level must be determined and fluid replacement should be done with caution and under the supervision of a doctor in hospital.

d. **Renal involvement:**

- **Dengue associated renal disease:**

Acute Tubular Necrosis (ATN) may develop during severe dengue as a result of shock and may complicate to acute kidney injury (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 is essential to assess renal involvement. Microscopic-macroscopic hematuria should be evaluated along with other investigations like blood urea, creatinine, serum electrolyte, eGFR, and bicarbonate. 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, a high prevalence of dengue-induced AKI and its link to a subsequent risk of renal impairment has been observed. The level of renal recovery varies depending on the criteria utilized, with the majority of AKI survivors attaining less than 25% of their baseline serum creatinine. This data suggests that dengue patients with AKI deserve a careful and long-term medical follow-up, especially under nephrology care.

- **Dengue in Chronic Kidney Disease**
Dengue patients may develop severe dengue in the presence of diabetic nephropathy, hypertensive nephropathy, connective tissue disorders and other preexisting chronic diseases. A multidisciplinary approach with collaboration between physician and nephrologist is needed to decide for fluid therapy, renal replacement therapy and medications.

e. **CNS involvement:**

Altered sensorium may develop in dengue patient due to various conditions like shock, electrolyte imbalance (due to persistent vomiting), fluid overload (dilutional hyponatremia or other electrolyte imbalance), hypoglycemia, 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.

8.1.4 Management of DENGUE with co-infections

In countries with dengue as an endemic disease, healthcare 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 these infections may exist in dengue cases. All these illnesses exhibit non-specific 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 healthcare workers. The management of dengue is more challenging and difficult with co-infections like HIV, TB, Malaria, Chikungunya, Enteric fever and *Leptospira* as it may lead to severe dengue. Thus, a high index of suspicion will be required to identify dengue co-infections.

- **TB:** Patients may develop breathlessness and massive hemoptysis in Pulmonary Tuberculosis. These patients 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.
- **HIV:** Dengue patients may have severe complications like shock, hemorrhage, significant bleeding and organ involvement among HIV and AIDS patients. Outcome of dengue infection is poor amongst severely immune compromised patients those who have opportunistic infection and very low CD4 count. Multi-organ 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.
- **Malaria:** Malaria is also a common co-infection in dengue as it is prevalent across India and transmission also coincides during the same period/season. Malaria should be excluded in the initial phase only as it has its specific

management. Antimalarial treatment should be started as soon as possible to prevent complication and better outcome during co-infection.

- **Chikungunya:** It is also reported that in some geographical area both 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, Chikungunya should be investigated. 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
- **Enteric Fever:** Water borne diseases like typhoid fever and gastroenteritis are common during monsoon season along with dengue outbreak. In the initial phase of dengue infection, coinfection with enteric fever may lead to serious complications and can precipitate severe dengue. In strong suspicion, blood culture for salmonella typhi should be sent for confirmation as widal test may not be positive before 2nd week of fever. Most Salmonella typhi and Salmonella paratyphi isolates are susceptible to azithromycin and third-generation cephalosporins.
- **Bacterial infections:** Few patients with dengue cases experience a secondary bacterial infection usually community acquired pneumonia (CAP). In such cases, empirical 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.
- **Scrub Typhus:** Scrub typhus and dengue are two major causes of acute febrile illness and may co-exist together. Scrub typhus usually presents with sudden onset of 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 blanches 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.
- **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/post monsoon, the possibility of coinfection should be considered. The recommended treatment of choice for Rickettsial disease are doxycycline and azithromycin.

Chapter 9

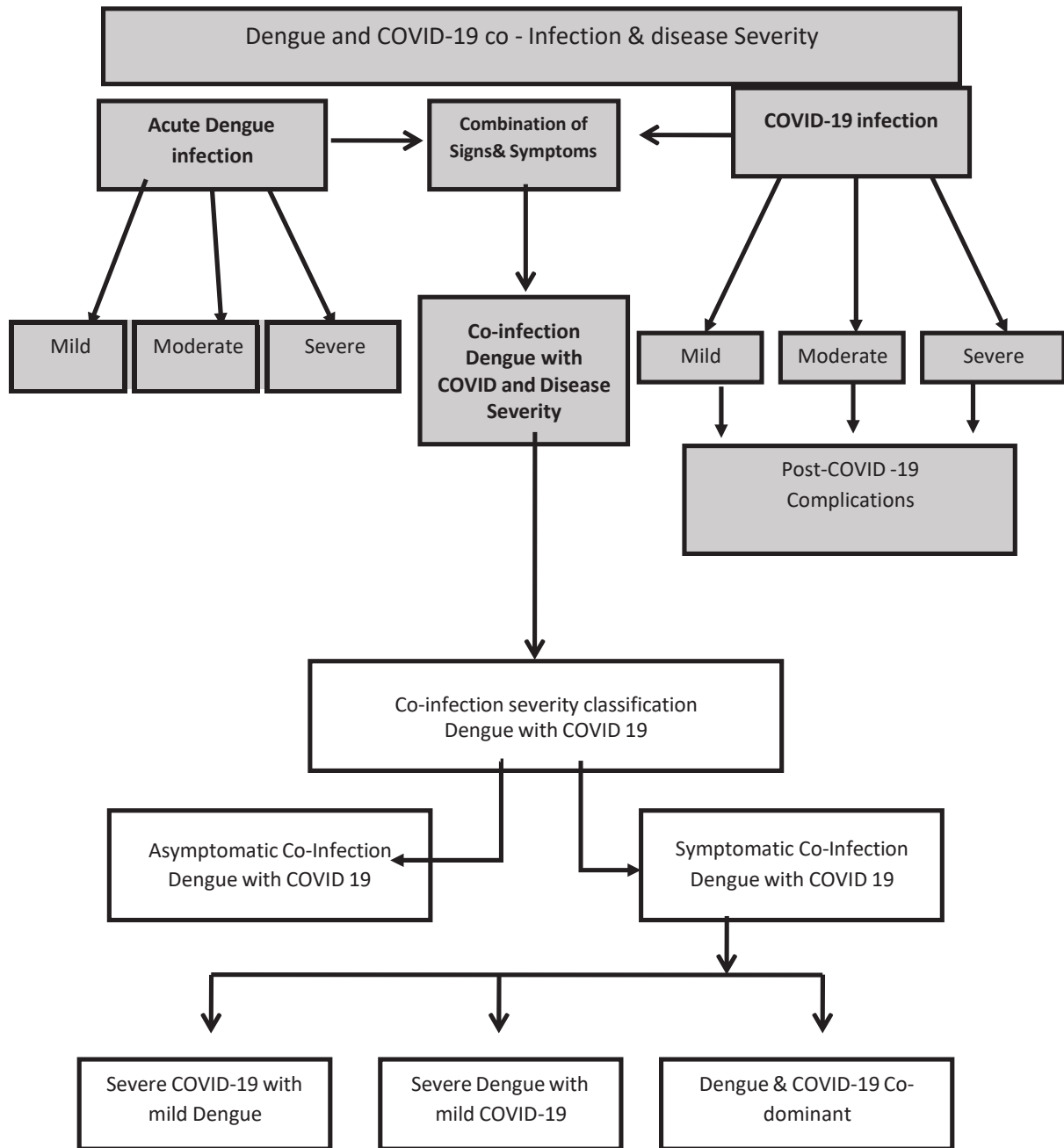
MANAGEMENT OF DENGUE AND COVID-19 CO-INFECTION

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 healthcare 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 healthcare workers. Thus, a high index of suspicion will be required to identify dengue and COVID-19 co-infections.

9.1 Case classification of co-infection (COVID-19 & Dengue)

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

Figure 14: Case classification of co-infection Dengue and COVID-19



9.2 Case classification of co-infection:

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

1. Asymptomatic Co-infection:

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

2a. COVID-19 predominant (P-CVD):

A case having cough, fever, shortness of breath, having X-ray changes and/or CT changes suggestive of COVID-19 and has signs and symptoms of mild or moderate dengue fever.

2b. Dengue predominant (P-DVD):

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

2c. Co-dominant Co-infection of COVID-19 and Dengue (CD-CI):

Concurrent manifestation of respiratory symptoms cough, sore throat, shortness of breath and typical dengue symptoms such as headache, retro-orbital pain and joint pain associated with nausea vomiting or pain abdomen. Both infections may have severe manifestations.

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

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

Treatment

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

In the eventuality of a patient being simultaneously infected with more than one virus (co-infection), the diagnostic challenge is further compounded. The following typical and specific clinical features might help in the categorical clinical diagnosis of a case. The treatment mainly dependent on severity or predominant infection either dengue or COVID-19.

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

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

At the same time, all secondary and tertiary level hospitals should be prepared to manage severe dengue and COVID-19 cases. Consider development and implementation of protocols for clinical management of acute febrile illness, based on a scenario of co-infection of arboviral diseases, COVID-19 and other respiratory viruses (e.g., influenza).

Specific therapeutic options and their use in cases with co-infection:

Fluid Therapy: Fluid therapy to be given in co-infection cases depends on the hemodynamic status of patient and degree of severity. One may follow the fluid chart given above for clinical management of dengue fever for most co-infection cases. It is only in the presence of Severe Acute Respiratory Illness (SARI) with COVID-19 that we need to be careful with aggressive fluid administration as it may lead to worsening of oxygenation and in such a scenario Point of care ultrasound (POCUS) guided fluids based on inferior vena cava diameter (IVC) 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.

LMWH: LMWH is being used and has been included in the guidelines for the management of moderate to severe COVID-19 cases as it is associated with increased thrombosis. LMWH is indicated in moderate to severe category; however, careful monitoring is required by D-dimer estimation and when the platelet count falls below 1,00,000/mm³, 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 5 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 national guidelines of COVID 19

Chapter 10

MANAGEMENT OF DENGUE CASES AT PRIMARY HEALTH CARE LEVEL AND REFERRAL

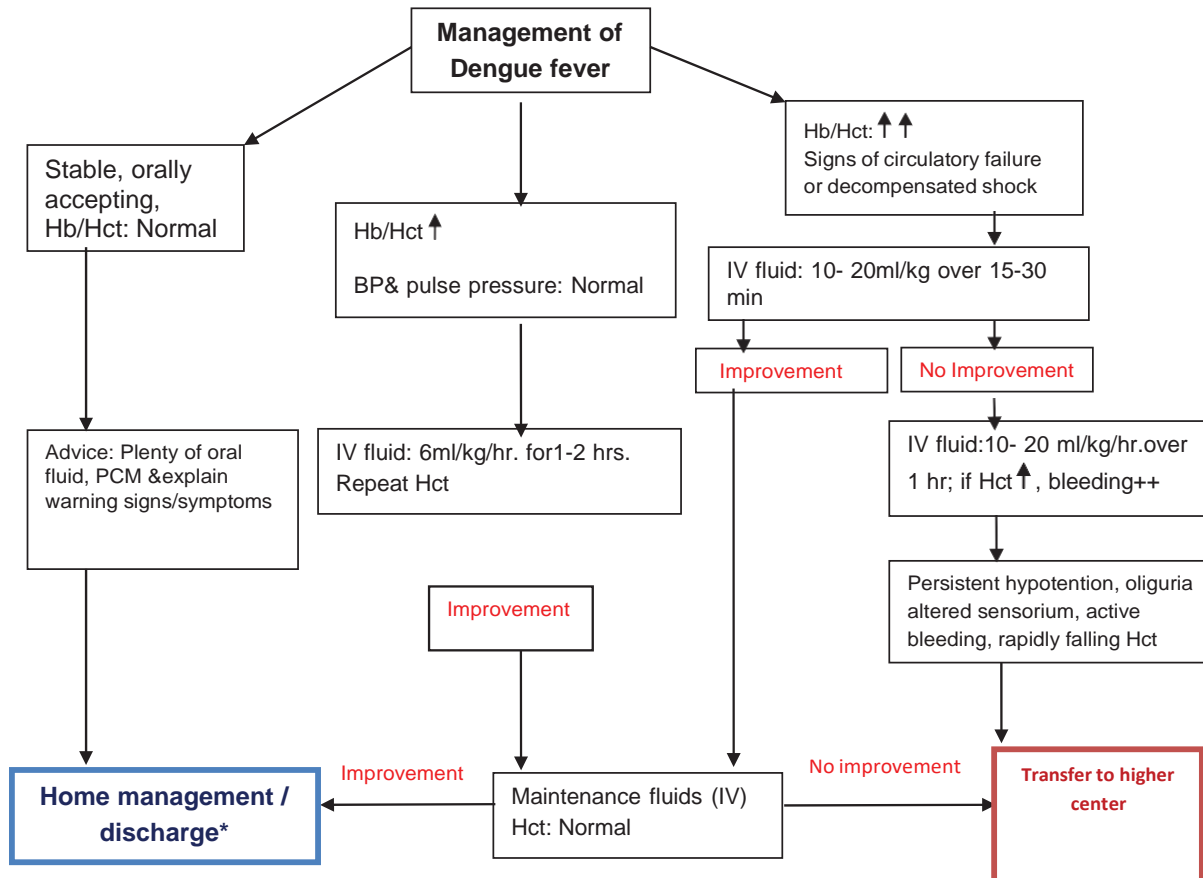
Dengue was earlier known as an urban disease. However, due to man-made, environmental, societal changes and improper water storage practices, the vector *Aedes aegypti* has also invaded rural areas. Frequent movement of the population has also helped in introduction of the virus in rural areas, leading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

10.1 Diagnosis of Dengue cases: See chapter 7

NOTE: Inform the District Vector Borne disease (VBD) officer for taking public health measures in the affected area to prevent further spread of the disease.

10.2 Management and referral of Dengue cases at Primary Health Centre (PHC) level

In the PHC, the following guidelines have to be followed for management of dengue cases and for referral of severe/complicated cases to higher centre:



*Patient should be advised to come for follow-up after 24h for evaluation. 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
- Persistent vomiting, not passing urine for 12 hr.
- Decreased urinary output
- Restlessness
- Seizure
- Excessive crying (young infants),
- Altered sensorium and behavioral changes
- Severe persistent headache
- Cold clammy skin
- Sudden drop in temperature.

Also follow Chart for volume replacement algorithm

Chapter 11

NURSING CARE IN ADMITTED CASES

Nursing care plays an important role for management of Dengue cases. Patients of dengue cases who are hospitalized require intensive monitoring of vital parameter and improvement and deterioration during fluid management.

A) Basic nursing care of Dengue patients to hospitals includes

- Close observation and intensive monitoring of vitals including sensorium, 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 hemorrhage **and other bleeding manifestations** and immediate referral

B) Watch for warning signs & symptoms

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

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

C) Management of common problems in dengue patients:

- High-grade fever: Tepid sponging, Tablet paracetamol & encourage intake of plenty of oral fluids
- Abdominal pain: Severe abdominal pain may be a warning symptom of severe complication, so remain vigilant and inform the treating doctor, estimate & record the amount if blood loss is present, monitor vitals and inform the doctor.
- Plasma leakage: Monitor vitals, hematocrit and fluid input/output, encourage oral intake if possible and start IV fluid as per instructions
- Shock or impending shock: Monitor vitals, hematocrit, sensorium and fluid input/output, start IV fluid/inotropes as per instructions
- Decreased urine output: First rule out catheter blockage by palpating the bladder. Flush the catheter if blocked. Continue monitoring vitals, fluid input/output and inform the doctor.
- Respiratory distress: Check oxygen saturation and administer oxygen via face mask or nasal catheter if SpO₂ <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 fluid input/output monitoring during the recovery phase.

D) Providing Health education & motivation

- Motivational behavior change talks must be given to attendants of patients and patients if they are fully conscious. The contents should include:
 - Common breeding sites of *Aedes* mosquitoes and adoption of strategy of search and destroy the breeding sites.
 - Use of personal protection measures against mosquito bite
 - Recognition of dangerous signs & early health seeking behavior

CRITERIA FOR ADMISSION OF A DENGUE PATIENT TO A 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 >2cm)
 - 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. Coagulopathy
8. Patient living alone or far from a health facility and without any reliable means of transport

DISCHARGE OF DENGUE PATIENT FROM HOSPITAL

Signs of recovery of dengue 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 hematocrit at baseline level.
- Convalescent confluent petechiae rash or itching, especially on the extremities.

Criteria for discharging patients

- Absence of fever for at least 24 hours without the use of anti-pyretic agent.
- Signs of recovery
- A minimum of 2–3 days have elapsed after recovery from shock.
- No respiratory distress from pleural effusion/ascites.
- Platelet count of more than 50,000/mm³.

PLATELET PRODUCTS

1. **Random donor platelets (RDP):** the platelets are prepared from whole blood. Depending upon the preparation methods they can be classified as PRP Platelets and buffy coat reduced platelets. Either of these platelet products have a volume of 40-50 ml, platelet content of 5.5×10^{10} and shelf life of 5 days. These whole blood derived platelet concentrates are expected to raise the platelet count by 5-7 thousand in an adult and 20 thousand in pediatric patients.
2. **Buffy coat pooled platelets (BCPP):** Pooled buffy coat platelet concentrates are derived from four donations of whole blood (Obtained from the Buffy Coat of ABO identical donors re-suspended in plasma or additive solutions). BCPP has a volume of 160-200 ml, with platelet content of ranging from 2.5 to 4.4×10^{11} per product.
3. **Single donor aphaeresis (SDP):** are collected by a variety of aphaeresis systems, using different protocols. A single donation procedure may yield one to three therapeutic doses and the donation may be split between two or three bags, depending on counts. SDP prepared are leukocyte reduced however in some aphaeresis systems filtration may be required for leucocyte depletion. For SDP Collection Donor are tested for platelet counts, TTI markers and blood group before collection. The average volume for SDP is 200-300 ml, yield or platelet content of 3×10^{11} per bag and is thus equal to 5-6 RDP. Thus it also often regarded as the jumbo pack. SDPs are expected to increase a patient's platelets count by 30-50000/ul. BCPP serves as an alternative choice of SDP in case of emergency.
 - a. Compatibility testing not required for platelet concentrates. Although platelet concentrates from donors of the identical ABO group and the patient can have the components of choice and should be used as far as is possible. However, administration of non identical ABO platelet transfusions are also an acceptable transfusion practice in particular, when platelet concentrates are in short supply.
 - b. Similarly, RhD-negative platelet concentrates should be given, where possible, to RhD-negative patients, particularly to women who have not reached the menopause. If RhD-positive platelets are transfused to RhD-negative woman of childbearing potential, it is recommended that anti-D should be given. A dose of 300 IU of anti-D should be sufficient to cover six SDP or 30 RDP RhD - positive platelets within a 6-week period.
 - c. Standard Dose for adults is 5-6 units of Random Donor Platelets or One unit of Aphaeresis platelets. For Neonates/ Infants the dose of the platelets should be 10-15ml/kg of body weight.

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