Indian Journal of Pediatrics (February 2023) 90(2):168–177
https://doi.org/10.1007/s12098-022-04394-8

SPECIAL ARTICLE

Management of Dengue: An Updated Review

Anshula Tayal[1] · Sushil Kumar Kabra[1] · Rakesh Lodha[1]

Received: 23 September 2022 / Accepted: 25 October 2022 / Published online: 27 December 2022

Abstract
Dengue is an important public health problem with a wide clinical spectrum. The World Health Organization classifies dengue into probable dengue, dengue with warning signs, and severe dengue. Severe dengue, characterized by plasma leakage, severe bleeding, or organ impairment, entails significant morbidity and mortality if not treated timely. There are no definitive curative medications for dengue; management is supportive. Judicious fluid resuscitation during the critical phase of dengue is the cornerstone of management. Crystalloids are the initial fluid of choice. Prophylactic platelet transfusion is not recommended. Organ involvement in severe dengue should be carefully looked for and managed. Secondary hemophagocytic lymphohistiocytosis is a potentially fatal complication of dengue that needs to be recognized, as specific management with steroids or intravenous immunoglobulin may improve outcomes. Several compounds with anti-dengue potential are being studied; no anti-dengue drug is available so far.

Keywords Dengue · Shock · Management

Introduction

Dengue is a vector-borne infection caused by the dengue virus, a member of the Flaviviridae family. The virus is transmitted to humans by female mosquitoes of the species *Aedes aegypti*, less commonly *Aedes albopictus*, and a few other species. The dengue virus has 4 serotypes: DENV 1, 2, 3, and 4. Infection with one serotype renders lifelong immunity against that serotype. However, reinfection with a different serotype can occur. Secondary infection by another serotype increases the risk of developing severe dengue.

One modelling estimate places the global burden of dengue at 390 (95% credible interval 284–528) million infections per year, of which 96 (67–136) million manifest with varying levels of disease severity [1]. Case fatality rates (CFR) of approximately 1% have been reported for the World Health Organization (WHO) Southeast Asia region; in India, focal outbreaks away from urban areas have reported CFR of 3%–5% [2].

The WHO, in 1997, classified symptomatic dengue infections into three categories: undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF) [3]. DHF was classified into four grades based on severity; grades III and IV were defined as dengue shock syndrome (DSS) [3]. However, considerable overlap was seen among the entities, and difficulties in the use of this classification were reported [4]. An updated WHO guideline in 2009 classified dengue as probable dengue, dengue with warning signs, and severe dengue (Table 1) [2]. This classification also provided a severity grading and the potential to be used as a triage classification to help clinical decisions.

The Course of Dengue Illness—Implications in Management

There could be three phases of symptomatic dengue—febrile, critical, and recovery phase (Table 2) [2]. The majority will have only the febrile phase followed by the resolution of fever. Some children will develop the critical phase. However, it is difficult to predict the occurrence of the critical phase.

Depending on the clinical manifestations, patients may be classified into one of the following three management groups [2]:

Group A - can be managed at home.

✉ Rakesh Lodha
rlodha1661@gmail.com

[1] Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India

Table 1 Dengue case classification and levels of severity (WHO 2009 [2])

Dengue ± warning signs		*Severe dengue:* One or more of the following
Probable dengue	Warning signs	
Live in/travel to dengue-endemic area Fever and 2 of the following criteria: • Nausea, vomiting • Rash • Aches and pains • Tourniquet test positive • Leukopenia	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargement > 2 cm Laboratory: Increase in hematocrit (HCT) concurrent with rapid decrease in platelet count	**Severe plasma leakage** leading to: • Shock (DSS) • Fluid accumulation with respiratory distress **Severe bleeding** **Severe organ involvement** • Liver: AST or ALT ≥ 1000 • CNS: Impaired consciousness • Heart and other organs

ALT Alanine transaminase, *AST* Aspartate transaminase, *CNS* Central nervous system, *DSS* Dengue shock syndrome

Group B - needs in-hospital management.
Group C - needs emergency management (Table 3, Figs. 1 and 2).

Fluid Management in Severe Dengue

Dengue shock syndrome (DSS) is the most serious manifestation of dengue hemorrhagic fever characterized by a marked increase in vascular permeability.

The pulse pressure (difference between systolic and diastolic blood pressure) is an important determinant of the severity of plasma vascular leakage. Before overt shock develops, the diastolic BP starts rising and the pulse pressure narrows. According to WHO, DSS is characterized by a pulse pressure of less than 20 mmHg.

The mainstay of therapy for DSS is the rapid restoration of circulating plasma volume. There is a lack of consensus on the optimal choice of intravenous fluids. Historically, the management guidelines by WHO, first proposed in 1975, recommended initial volume replacement with crystalloid solutions, followed by colloids for patients with refractory shock. As DSS entails the leakage of small plasma proteins, colloid preparations with larger molecular weights may offer a theoretical advantage. Colloids stay in circulation longer and increase the colloid oncotic pressure, thus drawing extravasated fluid back into circulation. It has been proposed that much larger volumes of crystalloids need to be infused than colloids in order to achieve the same degree of resuscitation, and this may subsequently lead to fluid overload or pulmonary edema.

Randomized controlled trials (RCT) in the late 1990s–early 2000s in Vietnamese children with DSS demonstrated faster recovery of hemodynamic parameters in the colloid group compared to crystalloids [5, 6]. A few years later, another RCT in a similar population found no significant difference between colloids and crystalloids in the requirement for rescue colloids. Improvement in hematocrit

Table 2 The course of dengue illness

Phase	Clinical manifestations	Challenges
Febrile phase	• Usually lasts 2–7 d • Sudden onset high-grade fever, facial flushing, erythematous skin rash, body ache, myalgia, arthralgia, headache • Mild hemorrhagic manifestations - petechiae, mucosal bleeds • Tender hepatomegaly • Progressive leukopenia	Dehydration High fever may cause neurological disturbances/febrile seizures
Critical phase	• Usually lasts 24–48 h • Starts around time of defervescence • Progressive leukopenia, thrombocytopenia • Plasma leakage (pleural effusion, ascites) • Rise in HCT (may fall in severe bleeds)	• Hypovolemic shock • Cardiogenic shock (myocardial dysfunction) • Severe organ impairment • Metabolic acidosis • Disseminated intravascular coagulation
Recovery phase	• The next 48–72 h • Gradual resorption of extravascular compartment fluid • Improvement in general wellbeing, appetite • Diuresis • Rash - "isles of white in the sea of red" • Generalized pruritus • Bradycardia	Fluid overload if excessive fluids have been infused, pulmonary edema, congestive cardiac failure

HCT Hematocrit

Table 3 Outline of current management protocol

Management group	Principles of treatment
Group A	Oral fluids, paracetamol (avoid NSAIDs), explain danger signs
Group B without warning signs	Oral fluids; if not tolerated, intravenous fluids for 24–48 h (0.9% saline or Ringer lactate) at maintenance rate Clinical and laboratory parameter monitoring
With warning signs	Baseline HCT, isotonic fluids: 5–7 mL/kg/h for 1–2 h; 3–5 mL/kg/h for 2–4 h; 2–3 mL/kg/h till patient is able to take orally adequately Increase or decrease fluid rate based on serial HCT Clinical and laboratory parameter monitoring
Group C	Judicious fluid resuscitation (Figs. 1 and 2) Treatment of bleeding manifestations Glycemic control Discontinue intravenous fluids once hemodynamics stabilize

HCT Hematocrit, *NSAID* Non steroidal anti-inflammatory drug

and initial recovery occurred later in the Ringer's lactate group, but there were no differences in all other measures of treatment response. Also, more adverse reactions were noted in the dextran recipients [7].

To summarize, while no clear clinical benefit has been demonstrated with either of these, adverse effects with colloids have been a cause of concern; *crystalloids are, therefore, the initial choice of resuscitation fluids in DSS.* The fluids should be titrated based on the clinical monitoring and serial hematocrit values.

Normal (0.9%) saline and Ringer's lactate have been the crystalloids of choice in dengue fluid resuscitation. Normal saline may be chosen for initial resuscitation in a patient with/without hyponatremia and with normal chloride levels (95–105 mmol/L). If the patient has hyperchloremia, hyperchloremic acidosis, or hypernatremia, Ringer's lactate may be a better choice [2].

Transfusion of Blood Products

A common question that baffles the healthcare personnel managing dengue patients is whether or not to transfuse platelet products to a given dengue patient. Most dengue epidemics in the country see an exponential rise in the demand for platelet concentrates threatening the existing platelet inventory. A single-center study from AIIMS, New Delhi in the 2013 Dengue epidemic in India showed that a total of 1750 random donor platelet units (RDPs) and 114 single donor platelet (SDP) units were transfused to 531 patients; of which, 23.2% transfusions were found to be inappropriate [8]. Moreover, bleeding tendencies often do not correlate with platelet counts, and may also occur in children with normal platelet counts [9]. This highlights the need for clarifying the indications for platelet transfusions in thrombocytopenic dengue patients without any overt bleeding, with minor bleeds, or with major bleeds.

Several causes have been implicated in causing thrombocytopenia in dengue.

- Bone marrow suppression with attenuation of megakaryocyte maturation.
- Peripheral destruction of platelets through activation of complement cascade, antibody-mediated destruction and phagocytosis.

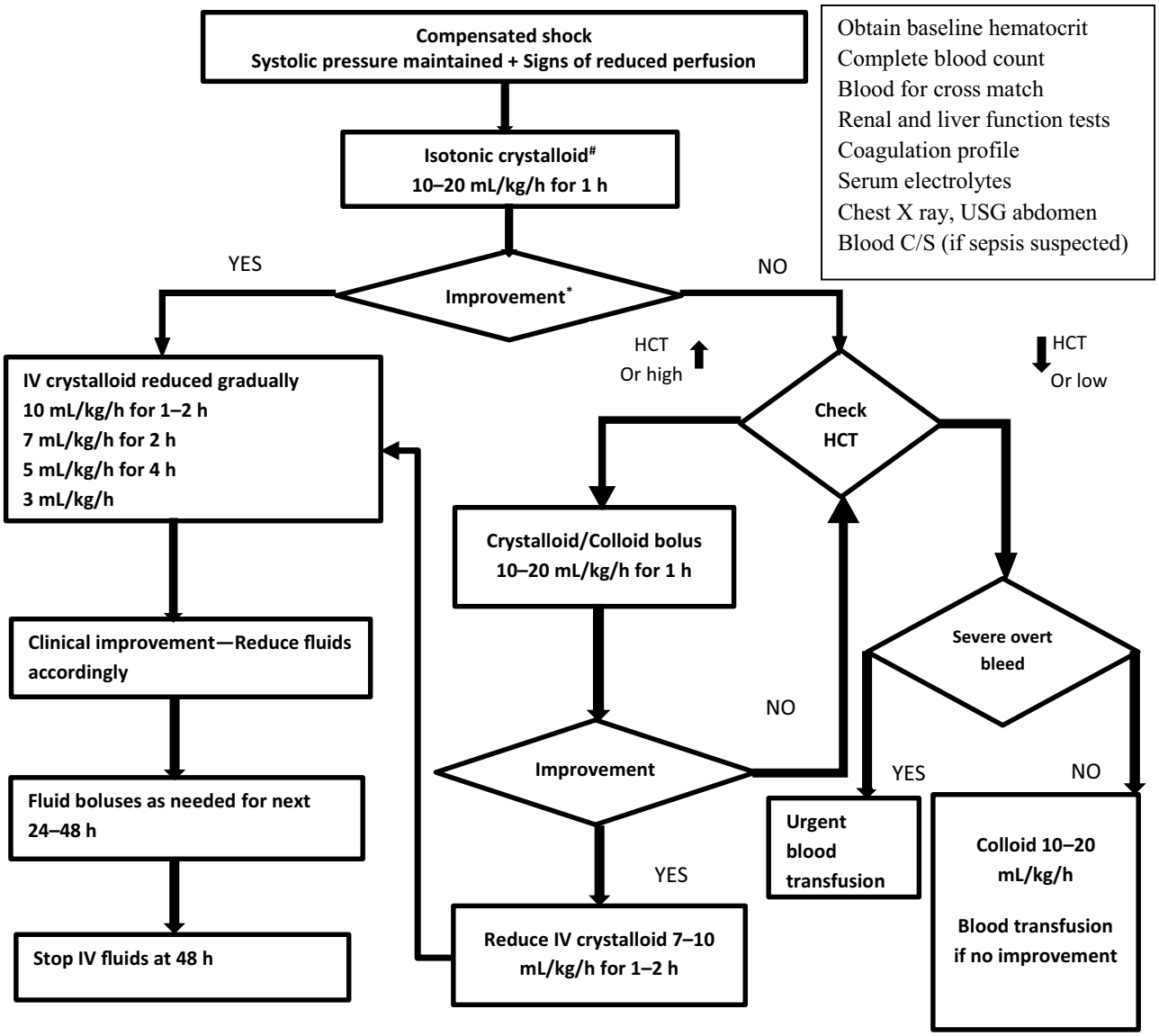
Several other factors contribute to the bleeding tendencies in dengue patients including platelet dysfunction, coagulopathy, and vasculopathy.

(a) *Prophylactic platelet transfusion*

Several studies in adult dengue patients have shown that prophylactic platelet transfusion had no significant benefit over supportive care alone, and it did not prevent bleeding or hasten platelet recovery [10, 11]. The existing evidence suggests no role of prophylactic platelet transfusion in adult dengue patients with thrombocytopenia, but no active bleed. More robust evidence is needed for pediatric dengue patients and patients with severe dengue. Many units consider transfusing platelets once the count is less than 10000/mm^3.

(b) *Platelet transfusion in patients with minor and major bleeds*

A preliminary study on 74 dengue patients with thrombocytopenia-related bleeding showed that although platelet transfusion increased the absolute platelet count by 50%–100%, it had no significant impact on clinical bleeding and did not improve clot strength as assessed by thromboelastography (TEG) [12]. Another study on adult dengue patients with thrombocytopenia and no or mild bleeding showed that platelet transfusion neither prevented progression to severe bleeding nor reduced time to cessation of bleeding and was rather associated with severe adverse reactions [13]. Currently,



*Colloid is preferred if child already received boluses of crystalloid

#Reassess the child's clinical condition, vital signs, pulse volume, capillary refill time, and temperature of extremities

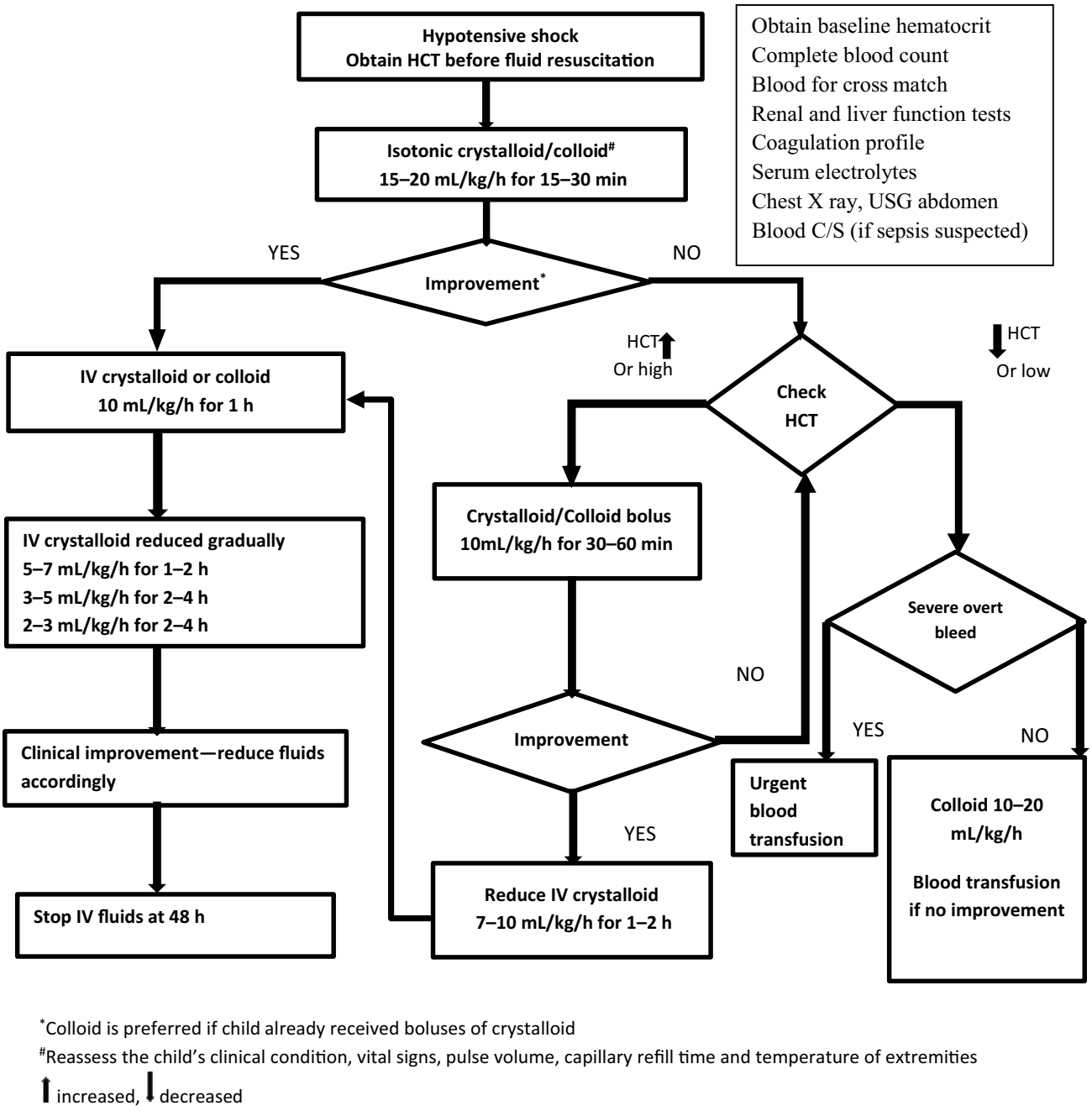
↑ increased, ↓ decreased

Fig. 1 Algorithm for management of compensated shock. *HCT* Hematocrit, *IV* Intravenous. (Adapted from: Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. New ed. Geneva, Switzerland: WHO 2009 [2])

there is inadequate evidence to prove or disprove the benefit of platelet transfusion in dengue patients with bleeding [14]. However, most units do transfuse platelets if the patient has acute severe mucosal bleed, which is not controlled with supportive care.

Immature Platelet Fraction (IPF)

IPF is a measure of the reticulated platelets in peripheral blood. Analogous to the reticulocyte count for red blood cells, IPF reflects bone marrow recovery. Hence, an



*Colloid is preferred if child already received boluses of crystalloid

#Reassess the child's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities

↑ increased, ↓ decreased

Fig. 2 Algorithm for management of uncompensated shock. *HCT* Hematocrit, *IV* Intravenous. (Adapted from: Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. New ed. Geneva, Switzerland: WHO 2009 [2])

elevated IPF indicates an increased rate of thrombopoiesis in the marrow. The freshly released platelets are larger in size and physiologically more efficient than mature platelets. A cutoff IPF level of ≥ 10% predicts platelet recovery within the next 72 h [15].

Platelet Micro-particles

Micro-particles (MPs) are small cell-derived phospholipid membrane vesicles. Platelet micro-particles (PMPs) are derived from activated platelets and function like platelets. A preliminary study from India showed significantly elevated

PMP levels in dengue patients with thrombocytopenia without bleeding, as compared to those with bleeding manifestations [16]. This raised the assumption that these patients may be protected due to the procoagulant effect of PMPs; PMPs may serve as a biomarker to decide prophylactic platelet transfusion.

Other Interventions for Bleeding in Dengue Patients

A study on 25 children with dengue hemorrhagic fever grade II–III with active bleeding showed short-term control of bleeding with recombinant factor VIIa (rFVIIa), but no overall benefit [17]. While intravenous anti-D globulin has shown some benefit in improving the platelet counts in dengue, evidence is insufficient to suggest benefit with intravenous immunoglobulin (IVIg), interleukin-1 (IL-1), or tranexamic acid [14].

Role of Corticosteroids

There have been discussions on the role of corticosteroids in dengue shock syndrome and the possibility of preventing progression to severe illness if given early in the course; however, there is no evidence to support either of these [18–20].

Expanded Dengue Syndrome (EDS)

The EDS refers to dengue cases with multi-organ involvement—cardiovascular, gastrointestinal, renal, respiratory, and hematological as highlighted in Table 4 [21].

Table 4 Expanded dengue syndrome [adapted from Ref. [21]]

Organ system	Manifestations
Cardiac	Bradyarrhythmias: Sinus bradycardia, atrioventricular block, sinoatrial exit block Tachyarrhythmias: Sinus tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation Myocarditis Pericarditis, pericardial effusion
Gastrointestinal	Acute liver failure, acalculous cholecystitis, acute pancreatitis, bleeding gastric ulcers, abdominal compartment syndrome
Renal	Acute kidney injury
Respiratory	Acute respiratory distress syndrome, pneumonitis, bronchiolitis, pulmonary hemorrhages (pleural effusion is considered a sign of plasma leakage, and not EDS)
Hematological	Aplastic anemia, thrombotic thrombocytopenic purpura
Neurological [22]	Dengue encephalopathy, encephalitis Intracranial hemorrhage Immune-mediated syndromes: Acute transverse myelitis, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica Neuromuscular: Guillain–Barré syndrome (GBS), transient muscle dysfunctions, rhabdomyolysis Neuroophthalmic complications

EDS Expanded dengue syndrome

Management of Complications

Cardiac Complications

Dengue patients with myocarditis and cardiogenic shock need extremely careful fluid resuscitation followed by early initiation of inotropic agents, as these are at high risk of developing congestive cardiac failure and pulmonary edema.

Hepatitis and Liver Failure

The dengue virus has a direct cytopathic effect on hepatocytes causing their apoptosis. Additionally, immune-mediated hepatocyte injury, cytokine storm, and hypoperfusion also contribute to liver injury in DHF. This may manifest as hepatomegaly, jaundice, elevated transaminases, and acute liver failure (ALF) [22]. Management is similar to that of ALF due to other causes.

Acute Kidney Injury

Hypoperfusion, rhabdomyolysis, and hemolysis, apart from the direct effects of DENV and immune-mediated injury may lead to renal impairment in dengue. Management comprises judicious fluid management to target a urine output > 0.5 mL/kg/h and early renal replacement therapy when indicated. Continuous venovenous hemofiltration (CVVH) is the preferred modality [2].

Respiratory Complications

Pleural tap is best avoided in dengue; rarely, therapeutic pleural fluid drainage may be needed in situations where massive pleural effusion leads to an inability to ventilate the child. Children with refractory shock have to be intubated

and mechanically ventilated. Few children may develop ARDS; lung protective ventilation should be initiated in this setting.

Neurological Complications

DENV has the ability to cause neural injury by direct invasion and by antibody-dependent enhancement. Management remains supportive in form of adequate hydration, monitoring of consciousness, airway protection, anti-seizure medications in case of seizures, and anti-raised intracranial pressure measures if clinically indicated. Intravenous immunoglobulin (IVIg) may be useful in post-dengue GBS. Pulsed steroids may be helpful in immune-mediated complications like ADEM; however, data are insufficient [23].

Hemophagocytic Lymphohistiocytosis (HLH)

Secondary HLH is a potentially fatal complication of dengue characterized by a hyperinflammatory state due to the uncontrolled proliferation of activated lymphocytes and the production of proinflammatory cytokines. Although the clinical features may be overlapping, some features that could suggest HLH in a dengue patient include persistent fever, persistent thrombocytopenia beyond 10 d, hyperferritinemia, and elevated lactate dehydrogenase (LDH) levels [24]. Bone marrow aspiration is not mandatory for diagnosis. Treatment with IVIg and/or corticosteroids has been shown to lead to improved outcomes [25]. Early recognition is imperative for a favorable outcome. Higher incidence of liver dysfunction and ARDS, increased requirement for invasive ventilation, and longer duration of ICU stay have been observed in dengue patients who develop HLH [26]. Soluble interleukin-2 receptor levels may act as a potential biomarker for dengue HLH [26].

Predictive Factors for Severe Dengue

Progression to severe dengue is a feared complication and currently, there is no biomarker proven to reliably predict this progression. Several biomarkers like red blood cell micro-particles, serum chymase levels and matrix metalloproteinases (MMP-2 and MMP-9) have been shown to predict this distinction [16, 27, 28]. Clinical features observed to have a positive association with severe dengue include lethargy, persistent vomiting, abdominal pain, diarrhea, hepatomegaly, severe bleeding, pleural effusion, and ascites [29]. Significantly high ALT and AST, hypoproteinemia, hypoalbuminemia, proteinuria, and elevated creatine kinase (CK), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) have been seen to be positively associated with severe dengue [29]. Cytokines interleukin (IL)-10, IL-8, sVCAM-1, and IP-10 have also been shown to be positively associated with severity [29].

Dengue and SARS-CoV-2 Co-infection

In the face of the ongoing coronavirus disease 2019 (COVID-19) pandemic, co-infection with dengue virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a significant health concern and speculation over a possibly more severe course. Indeed, patients co-infected with the two viruses have been shown to have severe disease, higher rate of ICU admission, and greater mortality [30, 31]. This has been attributed to similar pathophysiology of the two viruses for causing cytokine storms, capillary leakage, thrombocytopenia, and coagulopathy; during a co-infection, both the viruses either synergistically or individually cause multi-organ damage [32].

Anti-dengue Drugs

There is no antiviral drug currently approved for the treatment of dengue. However, several potentially efficacious anti-DENV drugs are currently being tested in humans and are at various stages of development. The DENV genome encodes three structural proteins—envelope (E), membrane (M) and capsid (C) and seven non-structural proteins—NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5.

The dengue viral proteins most commonly being studied as potential therapeutic targets include the E protein, NS3pro/NS2B protease, NS3 helicase, NS5 methyltransferase, and RNA-dependent RNA polymerase of NS5 [33].

The dengue virus utilizes several host proteins for its entry, translation, and replication in the host cells. These host proteins such as proteases, kinases, and glucosidases are also potential targets for anti-DENV drugs [33]. In addition, numerous compounds of natural origin, for instance, flavonoids obtained from various plant sources (quercetin, quercitrin, rutin, oroxylin A), curcumin, alpha-mangostin, mangiferin, etc. have been shown to be active against DENV [33–35].

In vitro and in vivo studies in mice models by an Indian group have demonstrated the potential anti-dengue activity of *Cocculus hirsutus*; further studies are underway [36]. Compounds derived from marine micro-organisms, e.g., *Streptomyces gougerotii* GT and *Microbulbifer variabilis* C-03 have been found to have anti-DENV activity. Over the past few years, synthetic nucleoside-based compounds have been developed as possible DENV treatment.

Table 5 Live, attenuated vaccines for dengue

Vaccine/Candidate vaccine	Description	Efficacy/Immune response	Current status
Dengvaxia (CYD-TDV)	Live, attenuated, chimeric, tetravalent vaccine built on a yellow fever 17D backbone Developed by Sanofi Pasteur	Vaccine efficacy against confirmed dengue pooled across 2 trials was 59.2% in the year following the primary series (per protocol analysis) During this initial time period, pooled vaccine efficacy against severe dengue was 79.1% [https://www.who.int/news-room/questions-and-answers/item/dengue-vaccines]	Phase 3 trials completed Marketed in some countries
TAK-003	Tetravalent dengue vaccine candidate, based on a live, attenuated dengue serotype 2 virus, which provides the genetic "backbone" for all four vaccine viruses. Developed by Takeda	Primary efficacy data from part 1 of the TIDES trial showed an overall efficacy to be over 80% [41]. Cumulative efficacy after 3 y of vaccination is 62% (95% CI 56.6–66.7) against virologically confirmed dengue (VCD) and 83.6% (76.8–88.4) against hospitalized VCD [42]	Currently undergoing phase 3 trials; demonstrated efficacy regardless of serostatus before immunization
TVOO3/TV005	Live, attenuated tetravalent vaccine developed using recombinant DNA technology by the US NIH's National Institute of Allergy and Infectious Diseases (NIAID)	A single dose of the vaccine has been shown to induce immune response against all four serotypes in 70%–90% of flavivirus-naive recipients [43]	Currently undergoing phase 2 trials

Certain drugs currently approved for other diseases, e.g., chloroquine, prednisolone, lovastatin, ivermectin, and ribavirin are also being studied for potential anti-DENV effects, but studies have not demonstrated benefit so far [37].

It is suggested that alternative medicines be avoided in absence of evidence; there is potential for harm as well.

Anti-dengue Vaccines

The development of an anti-dengue vaccine is an urgent priority owing to the lack of a specific anti-viral treatment against dengue. Currently, five types of dengue vaccines are under development—live, attenuated virus vaccines, inactivated virus vaccines, recombinant subunit vaccines, viral-vector vaccines, and DNA vaccines. The ones furthest along in development include the live, attenuated vaccines—CYD-TDV, TAK-003, and TV003/005 (Table 5). The vaccine candidates from other classes are in various stages of development [38].

CYD-TDV, brand name "*Dengvaxia*", is currently the only marketed dengue vaccine. The WHO has approved Dengvaxia for the age group 9–45 y, living in a dengue-endemic region and having had laboratory-confirmed DENV infection in past. Dengvaxia has been reported to increase the risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals), due to the phenomenon of antibody-dependent enhancement (ADE) [39]. Hence, prevaccination screening for past dengue infection is recommended [40]. Dengvaxia is currently not licensed in India.

Future Research Questions

While relentless research over the past few decades has greatly improved the outcomes of dengue, many pertinent questions still remain unanswered. It is still difficult for clinicians to predict the progression to severe illness and there is a need to identify reliable biomarkers that could predict this progression. There is no clear guideline on the cutoff for prophylactic platelet transfusion. So far, there is no definite cure for dengue and the management is only supportive; hence, the development of effective vaccines and anti-dengue drugs is the need of the hour.

Authors' Contributions AT, SKK, and RL contributed to the review and prepared the manuscript. RL will act as the guarantor for this paper.

Declarations

Conflict of Interest None.

References

1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496:504–7.
2. World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control. New Ed. Geneva: World Health Organization; 2009. PMID: 23762963.
3. World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment, prevention, and control. 2nd ed. Geneva: World Health Organization; 1997. Available at: https://apps.who.int/iris/bitstream/handle/10665/41988/9241545003_eng.pdf?sequence=1&isAllowed=y. Accessed on 12 Nov 2022.
4. Bandyopadhyay S, Lum LCS, Kroeger A. Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever. Trop Med Int Health. 2006;11:1238–55.
5. Dung NM, Day NP, Tam DT, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999;29:787–94.
6. Ngo NT, Cao XT, Kneen R, et al. Acute Management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001;32:204–13.
7. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353:877–89.
8. Chaurasia R, Zaman S, Chatterjee K, Das B. Retrospective review of platelet transfusion practices during 2013 dengue epidemic of Delhi. India Transfus Med Hemother. 2015;42:227–31.
9. Pothapregada S, Kamalakannan B, Thulasingam M. Role of platelet transfusion in children with bleeding in dengue fever. J Vector Borne Dis. 2015;52:304–8.
10. Lye DC, Archuleta S, Syed-Omar SF, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. Lancet. 2017;389:1611–8.
11. Prashantha B, Varun S, Sharat D, et al. Prophyactic platelet transfusion in stable dengue fever patients: is it really necessary? Indian J Hematol Blood Transfus. 2014;30:126–9.
12. Sundar V, Bhaskar E. Effect of platelet transfusion on clot strength in dengue fever with thrombocytopenia related bleeding: a thromboelastography-based study. Transfus Med Hemother. 2019;46:457–60.
13. Khan Assir MZ, Kamran U, Ahmad HI, et al. Effectiveness of platelet transfusion in dengue fever: a randomized controlled trial. Transfus Med Hemother. 2013;40:362–8.
14. Rajapakse S, de Silva NL, Weeratunga P, Rodrigo C, Fernando SD. Prophylactic and therapeutic interventions for bleeding in dengue: a systematic review. Trans R Soc Trop Med Hyg. 2017;111:433–9.
15. Chuansumrit A, Apiwattanakul N, Sirachainan N, et al. The use of immature platelet fraction to predict time to platelet recovery in patients with dengue infection. Paediatr Int Child Health. 2020;40:124–8.
16. Patil R, Bajpai S, Ghosh K, Shetty S. Microparticles as prognostic biomarkers in dengue virus infection. Acta Trop. 2018;181:21–4.
17. Chuansumrit A, Wangruangsatid S, Lektrakul Y, et al. Control of bleeding in children with dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. Blood Coagul Fibrinolysis. 2005;16:549–55.
18. Nguyen TH, Nguyen TH, Vu TT, et al. Corticosteroids for dengue - why don't they work? PLoS Negl Trop Dis. 2013;7:e2592.
19. Tam DT, Ngoc TV, Tien NT, et al. Effects of short-course oral corticosteroid therapy in early dengue infection in Vietnamese patients: a randomized, placebo- controlled trial. Clin Infect Dis. 2012;55:1216–24.
20. Zhang F, Kramer CV. Corticosteroids for dengue infection. Cochrane Database Syst Rev. 2014;2014:CD003488.
21. World Health Organization- Regional Office for South-East Asia. Comprehensive Guidelines for Prevention and Treatment of Dengue and Dengue Hemorrhagic Fever. Revised and expanded edition. WHO, SEARO. 2011. Available at: https://apps.who.int/iris/rest/bitstreams/909932/retrieve. Accessed on 20 Sept 2022.
22. Leowattana W, Leowattana T. Dengue hemorrhagic fever and the liver. World J Hepatol. 2021;13:1968–76.
23. Carod-Artal FJ, Wichmann O, Farrar J, Gascón J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12:906–19.
24. Giang HTN, Banno K, Minh LHN, et al. Dengue hemophagocytic syndrome: a systematic review and meta-analysis on epidemiology, clinical signs, outcomes, and risk factors. Rev Med Virol. 2018;28:e2005.
25. Wan Jamaludin WF, Periyasamy P, Wan Mat WR, Abdul Wahid SF. Dengue infection associated hemophagocytic syndrome: therapeutic interventions and outcome. J Clin Virol. 2015;69:91–5.
26. Singh D, Raghunathan V, Dhaliwal M, Rastogi N, Chadha R, Yadav SP. Soluble interleukin-2 receptor level as a marker of hemophagocytic lymphohistiocytosis in children with severe dengue. Front Pediatr. 2021;9:721857.
27. Rathore APS, Senanayake M, Athapathu AS, et al. Serum chymase levels correlate with severe dengue warning signs and clinical fluid accumulation in hospitalized pediatric patients. Sci Rep. 2020;10:11856.
28. Sivasubramanian S, Mohandas S, Gopalan V, et al. Serum levels of matrix metalloproteinases as prognostic markers for severe dengue with plasma leakage. Exp Mol Pathol. 2022;128:104821.
29. Yuan K, Chen Y, Zhong M, Lin Y, Liu L. Risk and predictive factors for severe dengue infection: a systematic review and meta-analysis. PLoS ONE. 2022;17:e0267186.
30. Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Wangdi K. Clinical features and outcomes of COVID-19 and dengue co-infection: a systematic review. BMC Infect Dis. 2021;21:729.
31. El-Qushayri AE, Kamel AMA, Reda A, Ghozy S. Does dengue and COVID-19 co-infection have worse outcomes? A systematic review of current evidence. Rev Med Virol. 2022;32:e2339.
32. Prapty CNBS, Rahmat R, Araf Y, et al. SARS-CoV-2 and dengue virus co-infection: epidemiology, pathogenesis, diagnosis, treatment, and management. Rev Med Virol. 2022. https://doi.org/10.1002/rmv.2340.
33. Dighe SN, Ekwudu O, Dua K, Chellappan DK, Katavic PL, Collet TA. Recent update on anti-dengue drug discovery. Eur J Med Chem. 2019;176:431–55.
34. Kalaimathi K, Rani JMJ, Vijayakumar S, et al. Anti-dengue potential of mangiferin: intricate network of dengue to human genes. Rev Bras Farmacogn. 2022;32:410–20.
35. Ratanakomol T, Roytrakul S, Wikan N, Smith DR. Oroxylin A shows limited antiviral activity towards dengue virus. BMC Res Notes. 2022;15:154.
36. Shukla R, Rajpoot RK, Poddar A, et al. *Cocculus hirsutus*-Derived Phytopharmaceutical drug has potent anti-dengue activity. Front Microbiol. 2021;12:746110.
37. Beesetti H, Khanna N, Swaminathan S. Investigational drugs in early development for treating dengue infection. Expert Opin Investig Drugs. 2016;25:1059–69.
38. Wang WH, Urbina AN, Lin CY, et al. Targets and strategies for vaccine development against dengue viruses. Biomed Pharmacother. 2021;144:112304.
39. Halstead SB. Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age. Vaccine. 2017;35:6355–8.

40. Dengue vaccine. WHO position paper, September 2018 - recommendations. Vaccine. 2019;37:4848–9.
41. Biswal S, Reynales H, Saez-Llorens X, et al. TIDES Study Group. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. N Engl J Med. 2019;381:2009–19.
42. Rivera L, Biswal S, Sáez-Llorens X, et al. Three-year efficacy and safety of Takeda's dengue vaccine candidate (TAK-003). Clin Infect Dis. 2022;75:107–17.
43. Kirkpatrick BD, Durbin AP, Pierce KK, et al. Robust and balanced immune responses to all 4 dengue virus serotypes following administration of a single dose of a live attenuated tetravalent dengue vaccine to healthy, flavivirus-naive adults. J Infect Dis. 2015;212:702–10.