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Integrated Clinical Management and Diagnostic Strategies for Dengue Fever: A Guideline-Based Approach Aligned with WHO Recommendations

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ABSTRACT

Dengue fever remains a major public health threat in endemic regions, with rising incidence due to urbanization, climate change, and expanding vector habitats. The World Health Organization (WHO) and national health authorities, including the Ministry of Health and Family Welfare (India), emphasize early detection, accurate diagnosis, and timely management as critical to reducing dengue-related morbidity and mortality. Current clinical care methods for dengue fever are outlined in this guideline-based study, focusing on patient classification and laboratory testing approaches. Serology using IgG ELISA and IgM is preferred in later stages. In early diagnosis, virological methods like NS1 antigen detection, RT-PCR, and viral isolation are used. Patients are divided into three classes—mild, moderate, and severe—based on WHO-recommended triage protocols. Each class requires a different treatment approach, which might include emergency fluid resuscitation or outpatient maintenance. Although several host-targeted therapies and direct-acting antivirals are under investigation, no specific antiviral drug is currently approved. The cornerstone of treatment is still supportive care, which includes antipyretics, fluid therapy, and careful monitoring of warning indicators and haemoglobin levels. The inclusion of patient education, community vector control, and adherence to WHO guidelines ensures a comprehensive approach to dengue management, especially in resource-limited settings.

Keywords: *Dengue fever, World Health Organization, fluid resuscitation, supportive care, antiviral therapy, vector control, national guidelines.*

1. INTRODUCTION

Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus, are the primary vectors of dengue, a flaviviral infection. More than 100 countries are impacted by the disease, which is thought to produce 390 million infections yearly, approximately 500,000 severe cases, and over 25,000 fatalities worldwide [1]. Dengue is a major public health concern, especially in Latin America, South-east Asia, and the Western Pacific. DENV (dengue virus) is a single-stranded positive RNA virus that can cause disease and is found in four antigenically different serotypes. Whereas a secondary infection raises the risk of severe dengue through antibody-dependent enhancement (ADE), a primary infection provides serotype-specific immunity [2][3].

Dengue can present clinically as a self-limiting feverish illness or as serious and potentially lethal complications. Classic symptoms include rash, nausea, vomiting, leukopenia, myalgia, arthralgia, acute headache (particularly retro-orbital pain), and abrupt onset of high-grade fever [2]. Patients may occasionally develop dengue haemorrhagic fever (DHF), which is typified by thrombocytopenia, plasma leakage, and bleeding symptoms such petechiae, gum bleeding, or hematemesis. Dengue shock syndrome (DSS), a more severe type, frequently necessitates special care since it can manifest with circulatory failure, hypotension, and multi-organ dysfunction [3][4]. Abdominal pain, frequent vomiting, mucosal bleeding, hepatomegaly, and an abrupt increase in haematocrit are warning symptoms that indicate the development of severe dengue [5].

There isn't a specific antiviral medication approved for treating dengue at present. Fluid resuscitation, careful observation for complications, and symptomatic administration of antipyretics like paracetamol (acetaminophen) are all part of the supportive care that is still provided [6]. Because of the danger of bleeding, non-steroidal anti-inflammatory drug (NSAID) use is generally discouraged. Preclinical and clinical trials have assessed several experimental medicines, including host-targeted treatments, monoclonal antibodies, direct-acting antivirals, and herbal formulations. However, a number of obstacles, such as the variety of dengue virus serotypes, the phenomena of antibody-dependent enhancement (ADE), and a lack of solid clinical trial data, have hindered the development of antiviral drugs [7][8].

This review aims to explore and critically analyse the pharmacological options investigated or used in dengue treatment, providing a structured overview of their mechanisms, outcomes, and current status in the drug development pipeline.

2. LABORATORY DIAGNOSIS AND DIAGNOSTIC TESTS

An accurate and effective opinion of dengue is critical for clinical care (i.e., early discovery of severe cases, case evidence, and discrimination opinion with other contagious conditions), surveillance, outbreak control, etiology, disquisition, vaccine development, and clinical trials. By relating the contagion, viral nucleic acid, antibodies, antigens or a combination of these, laboratory individual procedures can corroborate dengue contagion infection. The contagion remains in serum, tube, circulating blood cells, and other organs for around four to five days following the onset of the sickness. Viral insulation, nucleic acid analysis, or antigen discovery can all be used to diagnose the infection beforehand in the illness. As the acute period of infection draws to a close, serology is the recommended individual system [9][10].

2.1 Considerations in the choice of diagnostic methods

2.1.1 Clinical management

A dengue virus infection can cause a wide range of symptoms, many of which are vague. A diagnosis made only on the basis of clinical symptoms is therefore unreliable. Given that some patients have rapid progression from mild to severe disease, and occasionally even death, early laboratory confirmation of clinical diagnosis may be beneficial. Early intervention could save lives. Viral RNA identification using nucleic acid amplification tests (NAAT), virus isolation in cell culture, or viral antigen detection using ELISA or other fast assays can all be used to identify dengue infections before day five of illness during the febrile stage. Typically, only labs with the required facilities and technological know-how can isolate viruses in cell culture. Blood samples should be kept chilled or frozen for virus culture in order to maintain the virus's vitality while being transported from the patient to the lab. In cell cultures, dengue virus isolation and identification usually take a few days. It is possible to identify dengue virus RNA within 24 to 48 hours by employing nucleic acid detection methods that exhibit remarkable performance features. These tests, however, call for costly tools and chemicals, and they must be carried out by qualified specialists who adhere to quality control protocols to prevent contamination. Now that they are commercially available, NS1 antigen detection kits can be used in labs with little equipment and get results in a matter of hours.

Table 2.1 Summary of operating characteristics and comparative costs of dengue diagnostic methods

Diagnostic methods	**Diagnosis of acute infection**	**Time to results**	**Specimen**	**Time of collection after onset of symptoms**	**Facilities**	**cost**
Viral isolation and serotype identification	confirmed	1–2 weeks	Whole blood, serum, tissues	1–5 days	Mosquito or cell culture facilities, BSL-2/BSL-3a laboratory fluorescence microscope or molecular biology equipment	$$$
Nucleic acid detection	confirmed	1 or 2 days	Tissues, whole blood serum, palsma	1-5 days	BSL-2 laboratory, equipment for molecular biology	$$$
Antigen detection	Not yet determined confirmed	1 day > 1 day	Serum Tissue for immuno-chemistry	1–6 days NA	ELISA facilities Facilities for histology	$$ $$$
IgG (paired sera) by ELISA, HI or neutralization test	confirmed	7 Days or more	Serum, plasma, whole blood	Acute sera, 1–5 days; convalescent after 15 days	ELISA facilities BSL-2 laboratory for neutralization assay	$
IgM ELISA	Probable	1–2 days	Serum, plasma, whole blood	After 5 days	ELISA facilities	$
IgM rapid test		30 minutes			No additional supplies	

a requirement may vary according to each country’s national policies.

Dengue viruses and antigens leave the circulation after day five, along with the development of certain antibodies. Some individuals may have NS1 antigen for a few days after defervescence. Dengue serologic testing is more widely available in dengue-endemic countries than virological testing. Immunoglobulins do not require shipment because they are stable at tropical room temperatures.

Serology offers a more flexible specimen collection schedule than viral isolation or RNA detection because it allows for the evaluation of an antibody response by comparing samples obtained during the acute phase of illness with those obtained weeks or months later. IgM ELISA assays are less accurate in diagnosing certain secondary infections because there may be little to no detectable dengue IgM response. Within an hour, rapid test results can be available. However, one should exercise caution when depending on quick testing to diagnose dengue infections because reference laboratories have not yet evaluated the performance of all commercial assays [11].

An increase of four times or more in antibody levels in paired samples is indicative of an acute or recent flavivirus infection, according to IgG ELISA or the haemagglutination inhibition (HI) test. However, awaiting the convalescent serum to be obtained at the patient's discharge simply yields a retrospective outcome and is not particularly helpful for diagnosis or clinical care.

3. MANAGEMENT OF DENGUE FEVER

The prevalence of dengue fever (DF) is high in older children, adolescents, and adults. The patient typically has a biphasic fever, leukopenia, thrombocytopenia, rashes, myalgias, and arthralgias in addition to a strong headache. While DF might be although benign, break-bone fever can be a debilitating illness that causes severe headaches, myalgia, and polyarthralgia, especially in adults. Massive epistaxis, hypermenorrhoea, and gastrointestinal bleeding are examples of haemorrhages that might occasionally happen.

3.1 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:

Typically, a person with clinical training in diagnosing and identifying dengue warning signs should do triage.

• Patients who have moderate to severe dengue should be sent immediately to a qualified nurse or medical assistant in the emergency department.

• The following criteria ought to be evaluated:

• The duration of the fever

• The existence of warning indicators

• High-risk groups (co-morbidities and co-infections);

• Tourniquet test;

• Vital indicators, including temperature, pulse rate, respiration rate, and blood pressure;

• Peripheral perfusion, as determined by capillary refill time, pulse volume, and extremity colour;

• CBC recommendations, including platelet count and haematocrit;

• All patients exhibiting warning signs

• Every patient who has a fever lasting more than three days

3.2 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

3.2.1 Management of Mild dengue patient (Group A)

The outpatient department should provide the following instructions to patients and their families. Educate people on warning signals and how to report them if they develop.

1. Educate people on warning signals and how to report them if they develop.

• 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. Advise avoiding fizzy drinks and consuming enough oral fluids (coconut juice or ORS).

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.Ifthe 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.

3.2.2 Management of Moderate Dengue patients (Group B)

High-risk groups and those exhibiting warning signs are identified from among patients with moderately unwell dengue.

A clinical strategy for treating patients with mild dengue

• Should be admitted for in-hospital management.

• If the investigation's findings are available right away, a baseline haematocrit (hct) test must to be carried out prior to beginning fluid therapy.

• Paying close attention to any warning signs and symptoms is crucial.

• Blood sugar level and other laboratory tests should be done.

• Encourage oral fluids. If not tolerated, start IV 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.

• When calculating fluids for patients who are overweight or obese, consider their ideal body weight.

• To maintain excellent perfusion and urine output of roughly 0.5 ml/kg/hour, an adequate intravenous fluid volume may be needed.

• Preferred isotonic crystalloid fluid: 0.9% NS or RL

• Give7-10ml / kg crystalloid solution (Hartmann′s or 0.9% NSS) in 1 h.

• Clinical progress should be evaluated on an hourly basis.

• If patient condition 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

• After 24 to 48 hours, fluid should be discontinued based on the patient's clinical situation.

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

3.2.3 Management of Severe Dengue patients (Group C)

These patients need to be admitted and managed immediately since they are vulnerable. Severe dengue has following characteristics

• Severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress

• Severe haemorrhages

• severe organ dysfunction, such as encephalopathy, encephalitis, cardiomyopathy, liver damage, or renal impairment

• 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.

• Choose a crystalloid solution (0.9% NS or RL) that will keep the circulation going during the plasma leakage phase (typically 24 to 48 hours) and adjust the fluid according to the patient's condition.

• It's advised to obtain haematocrit 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 [12][13].

4. PHARMACOLOGICAL TREATMENT

4.1 DIRECT-ACTING ANTIVIRAL AGENTS (DAAS)

Direct-acting antivirals (DAAs) aim to inhibit specific stages of the dengue virus (DENV) life cycle, including viral entry, genome replication, protein processing, and virus assembly [9].

4.1.1 Balapiravir

Balapiravir is a nucleoside analog originally developed for hepatitis C. It targets the NS5 RNA-dependent RNA polymerase of dengue virus. In Phase II trials, balapiravir was administered at 1500 mg twice daily in patients with dengue; however, it failed to significantly reduce viremia or improve clinical outcomes, and its use was associated with transient lymphopenia, raising concerns about safety [7].

4.1.2 JNJ-A07

JNJ-A07 is a novel NS4B inhibitor with broad activity across DENV serotypes. Preclinical studies have demonstrated that it significantly reduces viral replication and protects mice against lethal DENV challenge. It interferes with the formation of the viral replication complex and is currently under evaluation in early-phase human clinical trials [14].

4.1.3 ST-148

ST-148 is a small-molecule capsid inhibitor that disrupts DENV capsid protein interactions essential for viral assembly. It has shown potent antiviral activity in vitro and protective effects in mouse models. However, it remains in the preclinical stage, and human data are not yet available [15].

4.1.4 AT-752

AT-752 is an oral guanosine nucleotide analog prodrug that inhibits the NS5 polymerase. Its active metabolite, AT-9010, impairs viral RNA synthesis. In murine models, AT-752 demonstrated reduced viremia and improved survival. Phase I/II trials are ongoing to assess its safety and antiviral efficacy in humans [16].

4.1.5 NITD Compounds

Several nucleotide analogues developed by the Novartis Institute for Tropical Diseases (NITD) have demonstrated inhibition of NS4B and NS5 proteins in vitro. However, development of lead compounds was discontinued due to suboptimal pharmacokinetics and safety profiles [17].

4.2 HOST-DIRECTED THERAPIES

Host-directed therapies aim to modulate the host cellular environment to inhibit viral replication or mitigate immune-mediated damage caused by dengue virus (DENV). Unlike direct-acting antivirals, these therapies target host pathways or molecules that the virus exploits during its life cycle. This approach offers potential advantages, such as reduced likelihood of resistance and broader efficacy across DENV serotypes. However, concerns remain regarding off-target effects and host toxicity.

4.2.1 Celgosivir

Celgosivir is an oral prodrug of castanospermine that inhibits host α-glucosidase I, impairing the proper folding of viral envelope glycoproteins. It was evaluated in the CELADEN Phase 1b trial at a dose of 400 mg daily. Although celgosivir was safe and well-tolerated, it did not significantly reduce viremia or improve clinical outcomes [7]. Despite limited clinical efficacy, it demonstrated antiviral activity in preclinical models and remains a reference compound in host-directed antiviral research.

4.2.2 Ivermectin

Originally developed as an antiparasitic agent, ivermectin inhibits the importin α/β-mediated nuclear transport of viral proteins. In vitro studies showed antiviral effects against DENV, and a randomized trial found reduced NS1 antigenemia in ivermectin-treated patients. However, there was no significant impact on viremia or symptom duration, and larger trials are required to confirm its clinical utility [19].

4.2.3 Statins

Statins, particularly lovastatin, have been explored for their potential to interfere with DENV replication by disrupting cholesterol-dependent pathways critical for viral assembly. In a randomized controlled trial in Vietnam, lovastatin did not demonstrate significant antiviral or clinical benefit, although it was well tolerated [20].

4.2.4 Chloroquine

Chloroquine, an antimalarial drug with immunomodulatory properties, has been studied for dengue treatment due to its ability to inhibit endosomal acidification and interfere with viral entry. However, Chloroquine is currently not advised for dengue, though, as clinical trials have not consistently demonstrated benefits [21].

4.2.5 Doxycycline

Doxycycline, a tetracycline-class antibiotic, has shown immunomodulatory and antiviral activity in vitro by interfering with the NS2B-NS3 protease complex. Preliminary studies reported faster platelet recovery and shorter duration of illness, but more robust evidence is needed from larger clinical trials [22].

4.2.6 Vitamins and Immunomodulators

Trials involving vitamin D and vitamin E have investigated their roles in modulating immune responses and reducing disease severity. Some studies suggest improved platelet recovery and reduced liver enzyme elevation, but data are inconsistent [23]. Similarly, interferon therapy and siRNA-based approaches targeting host-virus interactions are in early experimental stages, with no approved therapeutic applications yet.

4.3 SUPPORTIVE THERAPY

Supportive therapy remains the cornerstone of dengue management, as no specific antiviral treatment is yet approved. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and diclofenac are contraindicated due to the risk of gastrointestinal bleeding and platelet dysfunction [6]. Oral rehydration therapy is essential in mild cases, while intravenous fluid resuscitation is required in moderate to severe cases to manage plasma leakage and prevent shock [5]. Close monitoring of haematocrit, platelet counts, and warning signs is critical during the critical phase of the illness.

Antipyretics, particularly paracetamol (acetaminophen), are used to manage fever and pain. The recommended dose is 500–1000 mg every 6 hours in adults (maximum 4 g/day), and 10–15 mg/kg every 4–6 hours in children (maximum 60 mg/kg/day) [6]. Oral rehydration solutions (ORS) are vital in cases with mild dehydration, especially in children, with a dosing guideline of 50–100 mL/kg over 4 hours [24].

In patients with moderate to severe disease presenting with plasma leakage or impending shock, intravenous fluids such as isotonic crystalloids (e.g., Ringer's lactate or normal saline) are used for resuscitation, typically starting at 5–7 mL/kg/hour and adjusted based on haematocrit, urine output, and clinical signs [1].

5. NON-PHARMACOLOGICAL APPROACHES

Non-pharmacological management forms the foundation of dengue treatment, especially in the absence of approved antiviral therapies. These approaches aim to prevent complications, support physiological stability, and ensure timely recognition of disease progression. Effective implementation of supportive care and patient monitoring has been shown to significantly reduce dengue-related morbidity and mortality.

5.1 Hemodynamic and Laboratory Monitoring

Frequent monitoring of haematocrit, platelet count, and clinical warning signs is vital, particularly during the critical phase (typically days 3–7 of illness). An increase in haematocrit ≥20% with concurrent platelet decline may indicate plasma leakage and impending shock [6]. Serial measurements—every 4–6 hours in unstable patients—help determine the need for fluid adjustment or escalation to colloids in case of persistent hypotension [19][6].

5.2 Rest and Symptom Management

Physical rest during febrile and critical phases helps reduce metabolic demand and cardiovascular stress. Patients should avoid strenuous activity, which may increase the risk of bleeding. Fever and pain are managed with tepid sponging and acetaminophen, avoiding NSAIDs due to bleeding risk [24].

5.3 Patient Education and Home-Based Care

In outpatient settings, patients and caregivers must be educated about the signs of disease progression, including bleeding, persistent vomiting, abdominal pain, and altered consciousness. Patients should be advised to maintain oral intake, monitor urine output, and seek medical attention promptly if warning signs develop. Written instructions and daily follow-up during days 3–7 of illness are recommended [24][25].

5.4 Prevention of Nosocomial and Vector Transmission

In hospitalized patients, mosquito nets and repellents help prevent nosocomial transmission of dengue virus, particularly to non-immune individuals. Community-based vector control strategies, though beyond the scope of individual treatment, contribute significantly to broader public health impact.

6. DENGUE VACCINES

DENGVAXIA

The live-attenuated chimeric tetravalent dengue vaccine Dengvaxia is based on the 17D backbone of yellow fever. People between the ages of 9 and 45 who have a history of confirmed DENV infection are advised to take Dengvaxia by the WHO. Dengvaxia holds licenses in 20 nations. Only those with a confirmed history of DENV infection are advised to use Dengvaxia, as the vaccine's manufacturer, Sanofi Pasteur, warned that recipients who have never had DENV before but receive the vaccine may be at risk of developing severe dengue if they do. In May 2019, Dengvaxia received FDA approval for use in children and adolescents ages 9–16 who reside in dengue-endemic areas and have a history of laboratory-confirmed DENV infection. Many dengue vaccine candidates are now in clinical trials. Phase 3 trials are currently evaluating two tetravalent vaccination candidates that have been live-attenuated.

There were no recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding the use of vaccines to prevent dengue prior to Dengvaxia's FDA approval. According to the ACIP guidelines in this report, children ages 9 to 16 who reside in dengue-endemic areas and have a history of DENV infection should take Dengvaxia. In areas where DENV infection is endemic, these guidelines are meant to help laboratory professionals and public health practitioners develop and test immunization programs [26].

TVDV (tetravalent DNA vaccine)

This tetravalent DNA vaccine, which is now undergoing phase I and animal testing, is used in conjunction with vaxfectin as an adjuvant. It is based on sequences that code for the prM and E proteins. TVDV with adjuvant was discovered to have a better safety profile and to efficiently elicit a robust T-cell IFNγ response against dengue. Rhesus monkeys were vaccinated with a combination of TVDV, tetravalent pure formalin-inactivated virus (TPIV), and tetra-live attenuated virus (TLAV) to evaluate effectiveness. TVDV/TVDV/TLAV-immunized monkeys showed moderate protection, but TPIV/TLAV-immunized monkeys showed no signs of viremia at all. Furthermore, TVDV with Vaxfectin adjuvant elicits an anti-dengue T-cell IFNγ response with the highest level of safety, according to findings from phase 1 clinical trials [27].

D1ME100

This DNA vaccine expresses dengue viral antigens, including prM and 92% of the envelope (E) genes, which are critical for inducing an immune response. The purpose of this vaccination is to produce cellular and humoral (antibody-mediated) protection to the dengue virus. Anti-dengue antibodies can be successfully induced in animal models by D1ME100. D1ME100 may be a useful vaccine because it has been shown to elicit a robust antibody response in mice when administered intradermally. Despite its promise, D1ME100 has difficulties reaching high immunogenicity, just as other DNA vaccines. Its efficacy can be increased by employing highly effective promoters, investigating different delivery systems, co-immunization with adjuvants, and introducing immunostimulatory motifs [27].

7. CONCLUSION

Despite substantial advancements in understanding dengue virus pathogenesis and immune responses, a safe and effective antiviral therapy remains unavailable. Dengue continues to pose a major global health threat, particularly in tropical and subtropical regions, with rising incidence driven by urbanization, climate change, and expanding vector habitats. Supportive therapy remains the mainstay of clinical management, focusing on fluid resuscitation, careful monitoring, and symptomatic treatment. While these approaches have proven effective in reducing mortality, they do not address the underlying viral replication or disease progression.

Emerging pharmacological strategies—including direct-acting antivirals (DAAs), host-directed therapies, Immunotherapeutics such as monoclonal antibodies, and repurposed agents—show promise in preclinical and early clinical trials. However, progress has been hampered by several factors: the genetic and antigenic diversity of DENV serotypes, the risk of antibody-dependent enhancement (ADE), limited predictive value of animal models, and the scarcity of large-scale, well-controlled human trials.

Monoclonal antibodies offer targeted neutralization but face challenges in cross-serotype efficacy and cost. Host-targeted agents may reduce the emergence of resistance but risk off-target effects and toxicity. Meanwhile, novel drug delivery systems and combination therapies could enhance bioavailability and therapeutic outcomes, yet require rigorous validation. Non-pharmacological interventions such as fluid management, education, and vector control remain indispensable components of an integrated care approach.

Future research should prioritize multi-serotype coverage, long-term safety evaluation, and scalable interventions suited for resource-limited settings. Collaborative international efforts, public–private partnerships, and continued funding are vital to translate laboratory findings into clinically viable treatments. Ultimately, a multipronged strategy combining antivirals, immunotherapies, vaccines, and effective public health measures will be essential to reduce the global burden of dengue.

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