JSTMU Journal of Shifa Tameer-e-Millat University

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REVIEW ARTICLE

Dengue - A comprehensive review detailing regional prevalence, clinical aspects and novel treatment

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Author`s Contribution

[1] Conceptualization, manuscript writing

[2-5] Manuscript writing, editing

[3] Figures Illustrations

Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Article information

Submission date: 25-09-2024

Acceptance date: 21-11-2024

Publication date: 31-12-2024

Cite this article as *Saqib M, Munawar A, Sarha, Malik HH, Malik HH. Dengue- A comprehensive review detailing regional prevalence, clinical aspects and novel treatment. JSTMU. 2024; 7(2):196-201.*

A B S T R A C T

Dengue fever poses a grave health risk to the majority of the urban population in humid and temperate regions. The virus has four serologic variants where secondary infection by heterozygous serotype can lead to antibody-dependent enhancement, also a limitation of the proposed vaccine Dengvaxia. Classically presented as an acute self-limiting febrile illness its diagnosis is concluded by reverse transcription polymerase chain reaction and NS1 antigens as gold standard. Current treatment modalities are limited to pain and fluid management. The targeted antiviral therapies for viral genome, fusion and entry, replication, and halting immunological cascade are still under clinical investigations and population trials. This article aims to detail the pathognomic pathway, clinical picture, and regional burden of the dengue virus to narrow down and associate it with modern treatment modalities. The search engines used were PubMed, Google Scholar, and Scopus, and the data was compiled in three months.

Keywords: *Dengue virus (DENV); NS proteins; Dengue shock syndrome*

Introduction

Dengue is an acute self-limiting arboviral infection guilty of shifting a whole plethora of global diseases, and economic, and environmental burdens on its preventive and treatment modalities by health services.[1] particularly with its 3-5 yearly cyclic epidemic outbursts claiming a ten-fold increase in the case incidence within the past two decades.[2]

Epidemiology: In the year 2023, the World Health Organization (WHO) reported a post-COVID upsurge in dengue reporting a historic record high of five million newly diagnosed cases with a death toll of five thousand patients, among which nearly 4 million cases were reported in central and southern American territories only.[3] The National Institute of Health (NIH) Pakistan; despite proclaiming a major lack of surveillance tools; gave the stats accounting for approximately 53,000 cases with more than 200 deaths in the year 2021; 79,000 cases with 150 deaths in 2022 and roughly more than 2500 confirmed cases with 62 deaths reported till September 2023 soon

after traditional peak dengue season.[4] The regional prevalence, manually estimated by weekly Integrated Disease Surveillance and Response (IDSR) Reports published by NIH, Islamabad is shown in Figure 1.

Conducive factors include unplanned urbanization and industrialization on a massive scale, global climate shifts, circulation of heterozygous variants, fragile health infrastructure, and implemented policies leading to poor communication with stakeholders with a resultant lack of proper awareness, behavior assessments, inadequate diagnostic and management resources and ultimate practical steps towards control of the endemic.[5]

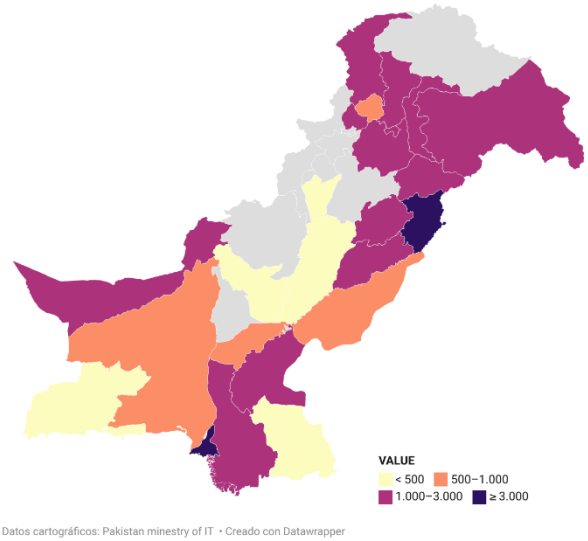

Figure 1: The prevalence of dengue in Pakistan, a conclusive estimate of the year 2023.

Virus and Vector: Dengue virus (DENV) is an enveloped, positively polar, single-stranded RNA virus;[6] belonging to the genus flavivirus; carried by the globally widespread female Aedes aegypti mosquitoes alongside less effectual vector Aedes albopictus mosquitoes which are more prevalent in North American and European regions.[7] These vectors are capable of parallel vertical transmission and nurture in the hot and humid climate of tropical, subtropical, and temperate regions majorly targeting dense urban and sub-urban populations which constitute about 3 billion of the world's total population.[2,5] The virus has 4 antigenically distinctive serotypes detected on reverse transcription - PCR (RT -PCR) and enzyme-linked immunosorbent assay (ELISA) amongst which DENV 1-3 are more predominant in humans with a small proportion of sylvatic strains whereas DENV 4 is utterly confined to primates.[8] Serotype DENV 5 has been reported only once in India in 2015 and has never been reported again since then. These serotypes have further genotype strains which are classified based on their geographical epidemic prospects, regionalizing Southeast Asia, the Indian Subcontinent, Thailand, Central, and South Pacific regions of America and Africa.[1,7]

With 65-70% of homologous genomes, all the variants have the identical competence to cause the full spectrum of disease,[1] still Laboratory identification of each serotype holds a clinical significance as primary infection provides post-recovery life-long immunity against re-infection of the similar antigen to the patient but in case of secondary infection with different serotype the risk or severity of complications is higher owing to transient heterozygous immunity.[8,9]

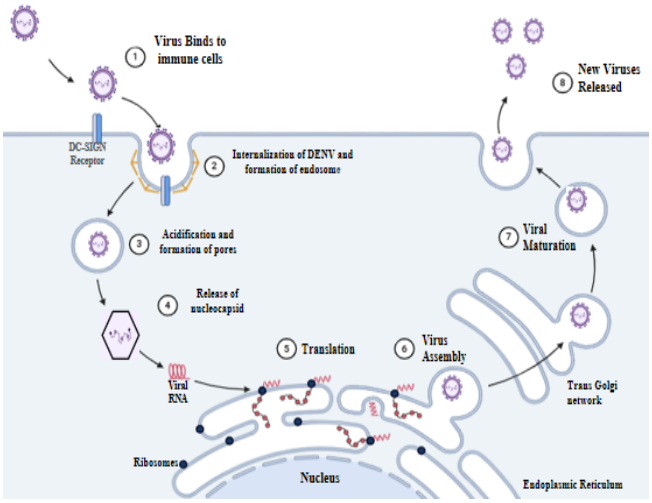

Figure 2: Step-by-step configuration of dengue life cycle in the host.[10]

Pathophysiology: As soon as the vector bites and inoculates the virus in the skin it undergoes internalization by immature dendritic and mono-nuclear immune cells including splenic macrophages and Langerhans cells. DENV attaches on the surface of the immune cells where adhesion proteins particularly Fc and dendritic cell-specific inter-cellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) play a pivotal role.[11] Post-infection lifelong immunity is retained as the monocyte acquires the ability to neutralize antibodies however in the case of heterozygous serotypes they lead to Fc receptor-mediated antibody-dependent enhancement (ADE) where immune

complexes are facilitated which leads to the synergism of the old and new serotypes alongside host cells leading to severe clinical manifestations due to a massive viral output. Till now it is considered the most valid study model of pathognomic pathway.[8,9,12]

Post attachment the virus enters the cell cytoplasm by endocytosis via endosomes, inside the endosomes the acidic pH transforms its architecture forming hairpin-like hydrophobic fusion loop peptide spikes which can tear the endosomes to form pores and release the nucleocapsid.[11] Further in the cytoplasm the viral genome binds to the endoplasmic reticulum for translation of proteins while altering the milieu to manipulate the organelles' micro-environment to favor the spread. Newly formed virions are assembled by the viral structural protein NS2A and are transported to the cytoplasm via a secretory pathway. The newly replicated viral titers go to the circulation leading to viremia while the immune cells alert the lymphatics., step by step illustrated in Figure 2. It leads to the activation of cross-reactive and regulatory T cells, meanwhile promoting the release of cytokines and chemokines by persuading the interleukin, tumor necrosing factors, and interferons.[6,9,11]

On the other hand, it gives rise to DENV antibodies cross-reacting against plasmin, endotheliocytes and platelets simultaneously leading to endothelial dysfunction and blood coagulation disorders which are in particular strengthened by bone marrow suppression and hepatocytic necrosis adding onto the platelet consumption. On the other hand, the overt transmission of cytokines and chemokines post viral opsonization, formation of antibody complexes and disruption of endothelial glycocalyx with degradation of sialic acid by NS1 viral structural protein shall be taken into account for contributing to fragility of the vascular integrity. This further leads to microvascular leakage and angioedema which leads to severe clinical symptoms requiring intensive supportive care.[12]

Clinical Spectra

Risk Factors: Dengue fever is also known as dandy fever and bone-breaking fever due to its ability to cause intense body aches. As densely populated urban areas foster more conducive exposure to the vector so all age groups are prone to the infection however children and young adults have a higher number of cases due to outdoor exposures.[2,5] The complication risk and subsequent mortality rate are higher in patients above 60 years of age due to frailty of immune system and vascular integrity.[6]

The most alarming high-risk group includes pregnant females particularly in the third trimester as maternal anti-DENV antibodies can cross the placental barriers and may lead to preterm birth or fetal death; any other systemic congenital anomaly in case of survival has not been identified as yet.[13] The vector propagation peaks in mid-summer and moon-soon season. Unwarranted climate shifts may also lead to increased incidence as one remarkable example is the floods in the region of Punjab and Sindh in 2022 when there was expansion in marshy areas leading to the augmentation of disease spread even in the fall and winter seasons, meanwhile, co-occurrence of COVID led to missed diagnosis and relevant in time aid.[2]

Symptoms: Most dengue cases are asymptomatic and, though it reduces the health service burden transiently, the formation of ADE complexes makes the patient prone to more intensive secondary infection.[12] The viral incubation period may vary from a couple of days to a couple of weeks followed by an illness period of 3-7 days. This illness period has a panel of three phases: febrile, critical, and recovery.[14]

Febrile phase: The febrile phase has a characteristic high-grade fever of 101-105°F with a biphasic or saddle-back pattern; where the body temperature spikes a day then remits for another and keeps following the pattern with chills and malaise. In children, there is a risk of associated febrile convulsions as well.[14] Severe gastrointestinal symptoms which include nausea and bouts of propulsive vomiting with other systemic symptoms like arthralgia and myalgia are more often accompanied. During this phase, there may also be acute retro-orbital pain which is a characteristic feature of acute illness. On examination rash, skin flushing and petechiae may be found with a positive tourniquet test. Persistence of this phase beyond 3-4 days may lead to palpable lymphadenopathy and hepatomegaly.[15] Most patient recovers post-febrile phase however if during the defervescence the complication ensues and the increasing viral titer leads to microvascular leakage, this marks the advent of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). It is a critical phase that requires immediate hospitalization.[6,12]

Critical phase: The critical phase subsides in 48-72 hours but it warrants crucial medical care. Due to poor

perfusion and decreased intra-vascular fluid volume, the patient can go into shock which is clinically demarcated by the characteristic rapid and weak pulse pressure which happens due to an increase in diastolic and sustained systolic pressure. Immediate fluid resuscitation is advised in this case but with the caution of not leading the patient into respiratory distress. The other early symptoms are intense abdominal pain with vomiting, lethargy, and significant but non-characteristic mucosal or petechial bleeding. The children are at a lower threshold of developing DSS.[14]

Contrary to this adults have a high risk of hemorrhages with altered live hemostasis and resultant lower platelet count; exhibiting menorrhagia, bleeding from gums, epixtasis, and rare intracranial and intra-abdominal bleeds. Systemic manifestations include bradycardia and arrhythmia; transient painless visual impairments; generalized seizure, encephalopathy, and neuropathy, acute renal failure with micro-hematuria and rhabdomyolysis and rare acute liver failure.[15,16]

Recovery Phase: Precise supportive care may help in complete remission of the symptoms in 1-2 weeks with an even quicker resolution of microvascular injuries within 2-3 days. Failure of complete recovery may be due to comorbidities like peptic ulcer, metabolic or coagulation disorders, or already compromised hepato-renal biomachinery. There is a high risk of bacterial super-infections as well due to altered immune status.[14] This phase demands limited physical activity as there is a high chance of ensuing fibromyalgia, lethargy, visual impairment, and dizziness accompanied by headache.[15]

Laboratory Investigations: During the epidemic season, any case with the aforementioned symptoms marks it as a candidate for further lab investigation. These are divided into three modalities including:

1. Serum biochemistry
2. Indirect Method: Qualitative detection of dengue antibodies
3. Direct Method; Virus isolation and nucleic acid detection

The biochemical markers get deranged in the early febrile phase and a complete blood count (CBC) may be considered as an effective indicative tool. There is atypical lymphocytosis with thrombocytopenia and leukopenia. A remarkable decrease in neutrophils and platelet count may be considered a bankable sign. Meanwhile, due to altered liver hemostatic status, there is increased prothrombin time and transaminases with decreased levels of fibrinogen indicative of higher bleeding tendency.[9] Avidin Biotin Complex IgM Antibody Capture ELISA (ABC MAC-ELISA) helps to detect IgM antibodies in the early convalescing phase. At high viral titer, IgG antibodies become obvious as well which may persist for a year or maybe a lifetime.[8] IgG/IgM ratios are considered to be comparable to the earlier in practice haemagglutination-inhibition test. However, these tests are not distinctive.[9]

For discerning the DENV from Zika virus or chikungunya viral RNA detection is done via polymerase chain reaction (PCR) and nucleic acid amplification tests (NAAT). NAAT gives results within 24-48 hours of virus inoculation but these tests require expensive machinery and are not done in routine.[17] As an alternative commercially available rapid antigen dengue detection test particularly NS1 antigen detection is gaining massive popularity due to ease of access, affordability, and authenticity. Duo kits with both NS1 and IgG/IgM detection are gaining market momentum as well. NS 1 stays in the blood for up to 7-10 days.[8]

Treatment: According to the revised WHO guidelines (2012) dengue is classified as:

I. Dengue without warning signs
II. Dengue with warning signs
III. Severe dengue[14]

This classification helps to organize respective treatment modalities. These regimens are designed as a mode of supportive care as no particular anti-viral drug has been postulated to be considered as a targeted therapy.

Dengue without warning signs: If the DENV NS1 antigen is detected but the patient has no symptoms of stable hematocrit in an early stage with routine urine passage habits then it is recommended to detain the patient for a few hours for monitoring and discharge. The patient is advised to maintain complete bed rest, and oral hydration with four hourly intakes of acetaminophen not exceeding 4 grams per day, in children dosage is adjusted likewise.[18] The patient is strictly advised in writing to have a regular follow-up ideally daily for hematocrit (Hct) and physical monitoring. Complete counseling regarding immediate contact with the hospital in case of the appearance of warning signs must be provided.[19]

Dengue with warning signs: High-risk cohorts like pregnant women and patients with mucosal bleeding, gastrointestinal symptoms like vomiting, palpable lymphadenopathy, and hepatomegaly are considered for referral to in-patient care.[13] Intravenous isotonic solutions like 0.9% Ringer solution are administered with continuous monitoring of serum Hct.[18] In case of Hct rise the fluid resuscitation gets more intensive however it is proportionately reduced in case of a fall in Hct and regaining of pulse pressure indicating plasma volume recovery after vascular leakage.[12] Adequate urination after every 4-6 hours is another relevant sign of recovery. Alongside hemostatic monitoring, it is imperative to carry on hepatic and renal function tests daily.[19] The patient may be discharged from the hospital in case of no respiratory symptoms, waning of symptoms, gradual rise in platelets, and no respiratory distress.

Severe dengue: Severe dengue has the following two presentations**.** Dengue shock syndrome; is treated by continuous intravenous crystalloids followed by colloids in case of failure to improve under Hct monitoring and hepato-renal function tests.[18] Dengue hemorrhagic fever: in case of uncontrolled bleeding fresh whole blood or packed red cells are administered under continuous CBC monitoring.[16]

Vaccination: To prevent the secondary infection caused by all four serotypes in ages nine and above CYD-TDV (Dengvaxia) vaccine is considered to be effective. It is a live attenuated chimeric vaccine to be administered at 0, 6, and 12 months. The limiting factor is that it may cause severe symptoms in disease-naive recipients most probably due to ADE. Other side effects include generalized headache, myalgia, and anaphylactic reactions.[12,20]

Conclusion

Dubbed as the most neglected tropical disease, dengue is targeting nearly half of the world's population. It affects the immunity status and vasculoendothelial integrity leading to a plethora of illness symptoms ranging from mild myalgia and lethargy to high-grade fever with chills which may complicate as intensive bleeding or even shock.[14] With the advent of accessible and rapid antigen detection it is easier to pinpoint diagnosis at an early stage leading to time medical management. The therapeutic modality resorts to symptomatic care only and lacks definitive treatment aiming for guaranteed recovery. Similarly, the vaccine designed so far can be administered to a limited patient cohort who already had an episode of dengue. The current drug development aims to target the different viral genomic structures. However, no decisive milestone has been achieved so far due to the requirement of high-resolution molecular studies, the complex interplay between virus and host immune cells, and the phenomenon of ADE.[12] The novel drug groups under clinical trials and development are summarized as follows:

1. Small antiviral molecule inhibitor: They have classical targets i.e. NS3 protease (6), NS3 helicase, NS4B, and NS5 halting the viral replication process.

a) Sinefungin, a SAM (S-adenosyl-L-methionine) analogue targets proteases effectively but is limited by poor cellular permeability.[6]

b) Ribavirin, a synthetic guanosine analogue had considerable anti-DENV activity but failed to act as an effective drug.[20]

c) Fleximers: flexible nucleoside analogs target NS5, a promising drug candidate with a seemingly low resistance ratio. Effective against yellow fever, Zika virus, and ichikungunya.[20,21]

2. Nucleoside analogue Inhibitors: Alters DENV enzymatic pathway leading to disrupted genome metabolism and synthesis which then blocks the viral replication, Balapiravir went under clinical investigation but failed to meet the requirements.[22]

3. Non-Nucleoside Inhibitors: They cause allosteric inhibition of viral replication against the hepatitis C virus and have shown a limited but considerable conformational change to DENV.[20]

4. Tetracycline: Molecular docking via combinatorial computational demonstrated doxycycline leading conformational change via hydrophobic interactions blocking viral fusion to the plasma membrane and ultimately inhibiting its entry.[23] This led to various trials amongst which the latest one was reported from India where doxycycline given twice for five days led to a remarkable reduction in inflammatory cytokines.[24]

Hence, the government authorities must take stern action regarding the unplanned expansion of cities and towns, develop effective surveillance strategies, and take measures to control vector propagation before the peak season in case of any calamity,[5] tailored interventions

should be done in case of risk assessment, proper health infrastructure including labs and in-patient hospital facilities should be improved, the attitude health care staff should be evaluated and addressed accordingly.[2]

References

1. Poltep K, Phadungsombat J, Nakayama EE, Kosoltanapiwat N, Hanboonkunupakarn B, Wiriyarat W, et al. Genetic diversity of dengue virus in clinical specimens from Bangkok, Thailand, during 2018–2020: co-circulation of all four serotypes with multiple genotypes and/or clades. Trop Med Infect Dis. 2021 Sep 4;6(3):162. DOI: https://doi.org/10.3390/tropicalmed6030162
2. Akram MI, Akram W, Qayyoum MA, Rana AA, Yasin M, Saddiq B. Vector indices and metrological factors associated with dengue fever outbreak in Punjab, Pakistan. Environ Dev Sustain. 2023; 25(9):9839-50. DOI: https://doi.org/10.1007/s10668-022-02462-9
3. Haider N, Asaduzzaman M, Hasan MN, Rahman M, Sharif AR, Ashrafi SA, et al. Bangladesh's 2023 Dengue outbreak–age/gender-related disparity in morbidity and mortality and geographic variability of epidemic burdens. Int J Infect Dis. 2023; 136:1-4. DOI: https://doi.org/10.1016/j.ijid.2023.08.026
4. Mumtaz Z, Zia S, Saif R, Farhan Ul Haque M, Yousaf MZ. Evolutionary patterns and heterogeneity of Dengue Virus serotypes in Pakistan. J Evol Biol. 2024; 37(8):915-25. DOI: https://doi.org/10.1093/jeb/voae076
5. Malik HA, Abid F, Wahiddin MR, Waqas A. Modeling of internal and external factors affecting a complex dengue network. Chaos, Solitons & Fractals. 2021; 144:110694. DOI: https://doi.org/10.1016/j.chaos.2021.110694
6. Roy SK, Bhattacharjee S. Dengue virus: epidemiology, biology, and disease aetiology. Can J Microbiol. 2021; 67(10):687-702. DOI: https://doi.org/10.1139/cjm-2020-0572.
7. Gutierrez JA, Laneri K, Aparicio JP, Sibona GJ. Meteorological indicators of dengue epidemics in non-endemic Northwest Argentina. Infect Dis Model. 2022; 7(4):823-34. DOI: https://doi.org/10.1016/j.idm.2022.10.004
8. Shu PY, Chen LK, Chang SF, Su CL, Chien LJ, Chin C, et al. Dengue virus serotyping based on envelope and membrane and nonstructural protein NS1 serotype-specific capture immunoglobulin M enzyme-linked immunosorbent assays. J Clin Microbiol. 2004; 42(6):2489-94. DOI: https://doi.org/10.1128/JCM.42.6.2489-2494.2004
9. Zerfu B, Kassa T, Legesse M. Epidemiology, biology, pathogenesis, clinical manifestations, and diagnosis of dengue virus infection, and its trend in Ethiopia: a comprehensive literature review. Trop Med Health. 2023; 51(1):11. DOI: https://doi.org/10.1186/s41182-023-00504-0
10. Lee MF, Wu YS, Poh CL. Molecular mechanisms of antiviral agents against dengue virus. Viruses. 2023; 15(3):705. DOI: https://doi.org/10.3390/v15030705.
11. King CA, Wegman AD, Endy TP. Mobilization and activation of the innate immune response to dengue virus. Front Cell Infect Microbiol. 2020; 10:574417. DOI: https://doi.org/10.3389/fcimb.2020.574417.
12. Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunol. 2017; 151(3):261-9. DOI: https://doi.org/10.1111/imm.12748.
13. Mulik V, Dad N, Buhmaid S. Dengue in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2021; 261:205-10. DOI: https://doi.org/10.1016/j.ejogrb.2021.04.035.
14. Htun TP, Xiong Z, Pang J. Clinical signs and symptoms associated with WHO severe dengue classification: a systematic review and meta-analysis. Emerg Microbes Infect. 2021; 10(1):1116-28. DOI: https://doi.org/10.1080/22221751.2021.1935327.
15. Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. Lancet. 2019; 393(10169):350-63. DOI: https://doi.org/10.1016/S0140-6736(18)32560-1.
16. Chaturvedi UC, Nagar R. Dengue and dengue haemorrhagic fever: Indian perspective. J Biosci 2008; 33(4):429-41. DOI: https://doi.org/10.1007/s12038-008-0062-3.
17. Chen PK, Chang JH, Ke LY, Kao JK, Chen CH, Yang RC, et al. Advanced detection method for dengue NS1 protein using ultrasensitive ELISA with thio-NAD cycling. Viruses. 2023; 15(9):1894. DOI: https://doi.org/10.3390/v15091894.
18. Madanayake PM, Jayawardena AE, Wijekoon SL, Perera N, Wanigasuriya JK. Fluid requirement in adult dengue haemorrhagic fever patients during the critical phase of the illness: an observational study. BMC Infec Dis. 2021; 21:1-9. DOI: https://doi.org/10.1186/s12879-021-05971-6.
19. Prapty CN, Rahmat R, Araf Y, Shounak SK, Rahaman TI, Hosen MJ, et al. SARS-CoV-2 and dengue virus co-infection: epidemiology, pathogenesis, diagnosis, treatment, and management. Rev Med Virol. 2023; 33(1):e2340. DOI: https://doi.org/10.1002/rmv.2340.
20. Obi JO, Gutiérrez-Barbosa H, Chua JV, Deredge DJ. Current trends and limitations in dengue antiviral research. Trop Med Infect Dis. 2021; 6(4):180. DOI: https://doi.org/10.3390/tropicalmed6040180.
21. Lim SP, Noble CG, Shi PY. The dengue virus NS5 protein is a target for drug discovery. Antiviral Res. 2015; 119:57-67. DOI: https://doi.org/10.1016/j.antiviral.2015.04.010.
22. Chen YL, Abdul Ghafar N, Karuna R, Fu Y, Lim SP, Schul W, et al. Activation of peripheral blood mononuclear cells by dengue virus infection depotentiates balapiravir. J Virolog. 2014; 88(3):1740-7. DOI: https://doi.org/10.1128/JVI.02841-13.
23. Yang JM, Chen YF, Tu YY, Yen KR, Yang YL. Combinatorial computational approaches to identify tetracycline derivatives as flavivirus inhibitors. PLoS One. 2007; 2(5):e428. DOI: https://doi.org/10.1371/journal.pone.0000428.
24. Kumar BV, Kamboj K, Pannu AK, Yadav AK, Bhatia M, Saroch A. Role of doxycycline in the treatment of dengue infection: An open-label, randomized, controlled, pilot trial. Asian Pac J Trop Dis. 2024; 17(4):160-5. DOI: https://doi.org/10.4103/1995-7645.391777