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Literature Review

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Navigating the Therapeutic Dilemma: Safety and Efficacy of Antiplatelet, Anticoagulation and Statin Therapy in Dengue Hemorrhagic Fever, a Case-Based Literature Review

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ABSTRACT

Dengue hemorrhagic fever presents as a management challenge in patients requiring concurrent dual antiplatelet therapy (DAPT), anticoagulation and statins. Similar scenarios are profuse in endemic regions like Kandy, Sri Lanka. We present two cases of Dengue Hemorrhagic Fever (DHF) in similar context which was managed based on thorough literature review which suggests that, while DAPT and anticoagulation may need to be discontinued in severe thrombocytopenia, statins can often be safely continued under close monitoring. We highlight the advanced management guidelines for similar complex clinical scenarios that need to balance thrombotic and bleeding risks, as in DHF. Local guidelines which address specific similar context are lacking and this narrative review highlights the need to develop evidence-based recommendations.

Keywords: Anti platelet and Statin therapy, Dengue hemorrhagic fever, Stent thrombosis

INTRODUCTION

In Sri Lanka, Dengue is one of the main challenges, particularly in endemic regions like Kandy. We see many cases of dengue in individuals with high-cardiovascular risk. Existing guidelines on dengue management (Supplement 1), primarily focus on the general management of the disease and its direct complications and fail to address contexts in which patients are on antiplatelet therapy and anticoagulation when having DHF, leaving clinicians in a dilemma. This review focuses on the safety of DAPT, anticoagulation and statins in similar context of DHF and offer insights into best practices based on advanced literature search (based on 35 highly matching articles) due to the unavailability of specific guidelines.

CASE PRESENTATION

Case 1: DHF in a patient who underwent recent (3 months back) percutaneous coronary intervention (PCI)

A 36-year-old male who underwent PCI with drug eluting stents (DES) placement following ST Elevation Myocardial Intervention (STEMI), on DAPT and Statins, presented with fever with arthro-

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myalgia and retro-orbital headache and tested positive for Dengue NS1 antigen and managed according to guidelines and clinical course shown in Figure 1. The patient recovered fully without complications.

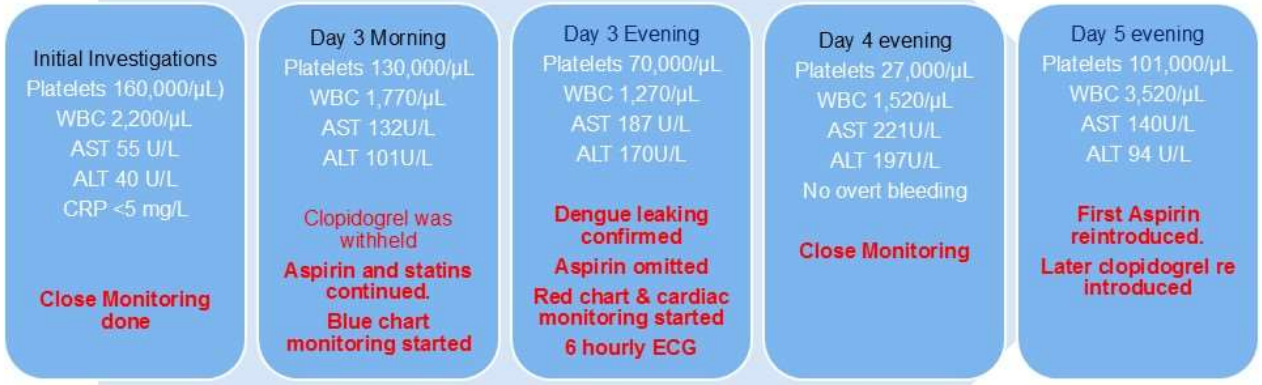

Figure 1: Clinical progression of case 1

Case 2: Non-ST elevated myocardial infarction (NSTEMI) in a Patient with Dengue Fever

A 52-year-old male with ischemic heart disease (IHD), on long-term aspirin and atorvastatin therapy, presented with vertigo. While being evaluated for vertigo, he developed NSTEMI [New ECG changes with rising Troponin I 450 ng/L (<20 ng/L) on Day 3 after admission] and was initiated on subcutaneous low molecular weight heparin (LMWH) and DAPT. On day four, he developed high spiking fevers and later confirmed to have dengue fever. Clinical course shown in Figure 2. After a gradual recovery the patient was discharged safely without complications.

DISCUSSION

Pathophysiology of thrombocytopenia and bleeding risk in DHF

Thrombocytopenia in dengue fever occurs due to multiple mechanisms, including direct viral effects, immune-mediated destruction of platelets, and increased platelet clearance. The dengue virus (DENV) can directly infect hematopoietic progenitors and megakaryocytes, resulting in impaired platelet syntheses in the bone marrow (1,2). Moreover, the immune response to DENV may destroy platelets through mechanisms such as thrombophagocytosis, where activated monocytes engulf platelets, a process exacerbated by elevated levels of tumor necrosis factor-alpha (TNF-α) (3). Enhanced platelet clearance is also a factor, with VWF binding to platelets and subsequent desialylation (Platelet desialylation is a process that removes sialic acids from the surface of platelets, which can lead to platelet destruction) and removal from circulation (4). Serotonin, released from mast cells, has also been described as increasing platelet activation and clearance during DENV infection (5). (Summarized on Figure 3)

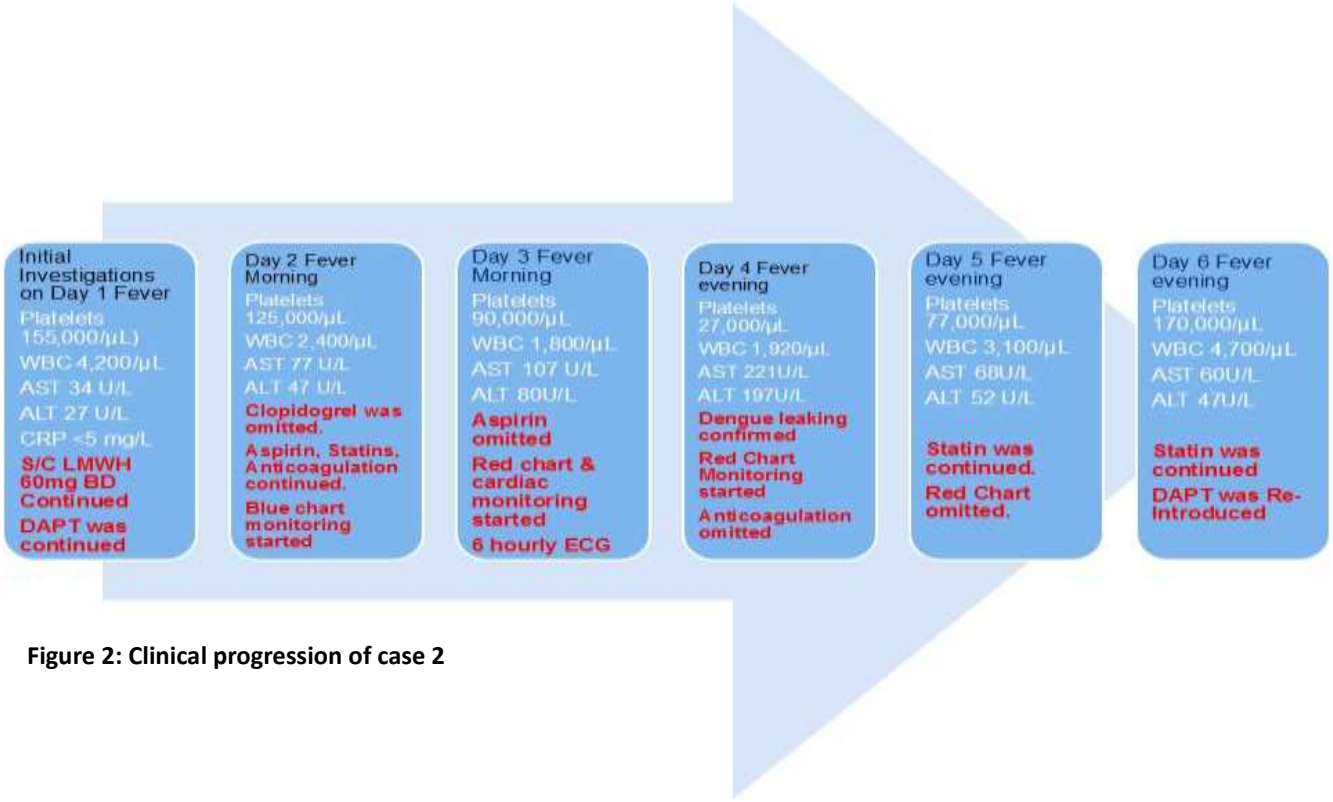

Figure 2: Clinical progression of case 2

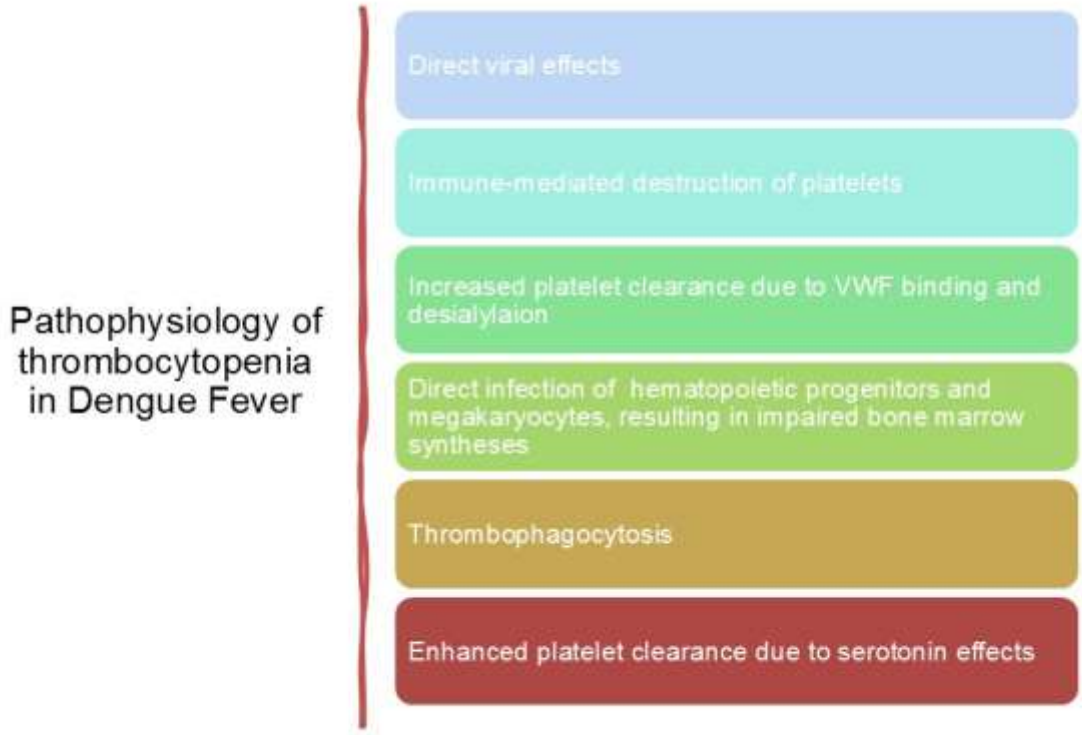

Figure 3: Pathophysiological mechanisms of thrombocytopenia in Dengue Fever

Comparison analysis between the risks and benefits of single-anti-platelet-therapy (SAPT) and DAPT

SAPT with aspirin, is a vital long-term therapy following MI to lower the risk of recurrence and other complications. DAPT involves aspirin and a P2Y12 inhibitor (such as clopidogrel, prasugrel, or ticagrelor) to reduce the risk of thrombosis in patients with cardiovascular conditions and is commonly prescribed after procedures like PCI with stent placement or after myocardial infarctions (MIs) (9,6,7). Studies have shown that while SAPT can improve neurological outcomes in patients with non-cardioembolic mild stroke and thrombocytopenia without increasing hemorrhage risk, DAPT does not yield additional benefits but is found to significantly increase the risk of gastrointestinal bleeding (OR=2.837, 95%CI: 1.311-6.136, P<0.01) (8). But in acute MIs, DAPT has shown a trend towards better outcomes compared to SAPT, but this difference was not statistically significant, and bleeding events were comparable (2,3,7,8). A meta-analysis found that thrombocytopenic patients on DAPT following PCI experienced a significantly higher rate of major bleeding events (OR: 1.67, 95% CI: 1.42–1.97; P = 0.00001) and intra-cranial bleeding (OR: 1.78, 95% CI: 1.30–2.43; P = 0.0003) (4,9). In many cases, SAPT may be a safer alternative for thrombocytopenic patients, particularly those at higher risk of bleeding complications, as in DHF (2,7). Although, aspirin is indicated for secondary prevention in patients with established cardiovascular disease, but its role in primary prevention is still debated due to the risk of major bleeding (5,10). In patients with a high risk of bleeding, including those with a history of gastrointestinal bleeding or those undergoing high-risk surgical procedures, the use of aspirin may be contraindicated. Improper management of aspirin in the perioperative context can lead to an increased risk of either thrombotic or hemorrhagic events, signifying the patient-based, individualized approach (6,7,1112) . The clinical decision to start or continue aspirin therapy in thrombocytopenic patients should be guided by platelet count thresholds. General recommendations derived from the literature reviews suggest that a platelet count above 100,000/µL is safe for initiation of aspirin therapy, while counts below this threshold significantly increase the risk of bleeding (which might be affected by Acetylsalicylic acid (ASA) sensitivity patterns as well) (8-10,13-15).

Research indicates that early discontinuation of clopidogrel within the first 30 days post-PCI is associated with a 35.4% incidence of stent thrombosis (ST), which decreases to 11.7% if discontinued within 180 days. Unplanned discontinuation of DAPT increases and poses a significant risk of major adverse cardiac events, with an adjusted hazard ratio of 7.65 within the first three months post-PCI. Patients with a high atherothrombotic risk exhibit a higher incidence of ST (8.7% vs. 4.0% in lower-risk patients) (14-18). Discontinuation beyond one month after stenting correlates with increased ST risk, particularly in patients with DES. While some studies suggest that discontinuation may be safe after 12-24 months in low-risk patients, it mandates a meticulous approach to weigh the risk of ST against the potential for bleeding, particularly in thrombocytopenic patients as in the case of dengue fever (16-20).

Recommendations on Anticoagulation in thrombocytopenia

The administration of LMWH in thrombocytopenic patients must be meticulously handled to balance the risk of bleed with the need for effective anticoagulation. In cases of acute VTE, full therapeutic doses of LMWH are recommended for patients with platelet counts ≥50,000/µL, while a 50% dose reduction is suggested for counts between 30,000 and 50,000/µL. For patients with platelet counts below 30,000/µL, LMWH should be discontinued, and alternative interventions such as IVC filters or platelet transfusions should be considered (8, 9,13,14). Similar guidelines apply to non-acute venous thrombo-embolism (VTE) cases, with adjustments made based on platelet counts to minimize bleeding risk while maintaining adequate anticoagulation, as in our case. In cardiology, anticoagulation in thrombocytopenic patients requires careful consideration. For example, a platelet count of <25,000/µL typically necessitates avoiding anticoagulation, while a half-dose of LMWH is suggested for counts between 25,000 and 50,000/µL (11,12, 21,22) These guidelines provide a framework for managing thrombocytopenia in

patients requiring concurrent anticoagulation, but the variation in individual responses and the potential for complications such as heparin-induced thrombocytopenia (HIT) mandate very careful monitoring (13, 23). We need further research to refine these recommendations.

Recommendations of statin therapy in the context of DHF

Statin therapy, particularly in the context dengue hepatitis, requires a careful evaluation. While concerns about statin-induced hepatotoxicity are prevalent, evidence suggests that a mild increase in liver enzymes often does not mandate discontinuation of therapy. Statins are very rarely associated with clinically significant liver injury, with only a small number of documented cases despite common and widespread use (24). Studies indicate that in many patients with elevated liver enzymes, statin therapy can be safely continued, with some cases showing spontaneous resolution of liver enzyme elevations (25). The PITCH study demonstrated that statin therapy led to significant reductions in liver enzymes in patients with mild to moderate elevations, supporting the continued use of statins in this population (26).

The use of statins in DHF, particularly in cases with hepatitis, has taken attention due to their potential antiviral effects and cardiovascular benefits. Statins such as atorvastatin and lovastatin have shown significant reductions in dengue virus titers in vitro, suggesting a direct antiviral effect independent of cholesterol levels in some studies (27). Ongoing RCTs are assessing the safety and efficacy of lovastatin in adult dengue patients, focusing on potential benefits in disease progression (28). Additionally, statins are known to reduce cardiovascular risks, even in patients with liver disease, where they are safe and effective (29). The use of statins in patients with MASLD (metabolic dysfunction -ssociated steatotic liver disease) has been associated with a lower risk of cardiovascular disease, highlighting their protective cardiovascular effects (30).

Therapeutic dilemma met in our cases

In cases of severe thrombocytopenia, the continuation of DAPT can lead to life-threatening hemorrhages, while discontinuation raises concerns about ST in patients with recent coronary stenting (31). DHF complicates the use of anticoagulants and continuous monitoring of platelet counts is crucial, especially in patients transitioning from anticoagulation to recovery from DHF, as evidenced by cases where patients developed chronic immune thrombocytopenic purpura post-DHF (32,33). The management should be individualized. For example, in cases of concurrent infections, such as endocarditis, careful adjustment of anticoagulant therapy is essential. In critical cases, such as pregnant women with DHF, urgent interventions may be required, including cesarean sections and blood and platelet transfusions, necessitating rapid decision-making in anticoagulation management (34,35).

In Case 1, Aspirin was not discontinued despite the patient's thrombocytopenia and elevated liver enzymes and discontinuing it in a post-PCI patient with a DES poses a high risk of in-stent thrombosis, especially within the critical first six months. Clopidogrel was withheld temporarily when platelet counts began to decline and approach 130,000/mcl, given its additive bleeding risk when combined with aspirin and it was reintroduced only after significant platelet recovery.

In Case 2, DAPT was temporarily discontinued as platelet counts dropped significantly (Closer to 90,000/mcL). However, it was reintroduced gradually as the platelet count began to recover (Closer to 170,000/mcL). This approach balances the prevention of recurrent cardiovascular events against the risk of hemorrhagic complications in dengue. Anticoagulation with enoxaparin was discontinued after three days upon confirmed dengue fever and significant thrombocytopenia and the decision to stop was guided by dynamic bleeding risk assessments and clinical monitoring. In both cases statin therapy was continued cautiously despite liver enzyme elevation with close monitoring not to exceed upper limits as statins are critical in acute coronary syndrome (ACS) and post-PCI settings.

The management of antiplatelet, statin, and anticoagulation therapy in dengue fever with cardiovascular comorbidities requires a dynamic balance between bleeding and thrombotic risks. In

our cases, decisions were guided by clinical evolution, platelet counts, liver function and cardiology input. Frequent monitoring, including platelet trends, cardiac biomarkers and bleeding assessments, played a crucial role in optimizing outcomes while mitigating complications.

CONCLUSION

Our review highlights the importance of a cautious, individualized approach when managing DHF while balancing the risk versus benefit. Although converting DAPT to SAPT and then discontinuing SAPT and Anticoagulation at some point in DHF may be necessary. Statin therapy can often be continued safely with close monitoring. Local guidelines should be developed considering evidence-based recommendations in this regard to improve the ultimate outcome.

Abbreviations

DHF: Dengue Hemorrhagic Fever
DENV: Dengue Virus
DAPT: Dual Antiplatelet Therapy
SAPT: Single Antiplatelet Therapy
PCI: Percutaneous Coronary Intervention
DES: Drug-Eluting Stent
IHD: Ischaemic Heart Disease
MI: Myocardial Infarction
VTE: Venous Thromboembolism
ST: Stent Thrombosis

Author declaration

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Authors' contributions:
Conceptualization and Design: NMMR; Data Collection and Patient Care: NMMR, IKJ, NA; Literature Review: NMMR, JFS; Manuscript Writing: NMMR Critical Review and Editing: NMMR, IKJ, NA, JFS.

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All data generated during this study are included in this published article.

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