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Position paper on the management of antithrombotic therapy in patients with dengue

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Dengue is endemic in more than 100 countries, primarily affecting tropical and subtropical regions, including Argentina. Between epidemiological weeks (EW) 1 and 47 of 2024, the Region of the Americas reported a cumulative incidence of 1,327 cases per 100,000 inhabitants, representing a 197% increase compared with 2023. By EW47, 160 cases (0.3%) were classified as severe dengue, with 45 deaths (case fatality rate [CFR]: 0.084%). In Argentina, sustained viral circulation has been documented since 2023, including during winter months, particularly in the northeastern region. During the 2024 season, the cumulative incidence reached 1,203 cases per 100,000 population, more than threefold higher than in 2022–2023. The Northwest (NOA) region reported the highest incidence (2,533 per 100,000), followed by the Northeast (NEA, 1,645) and Central region (1,098). Although incidence was lower in the Central region, it accounted for the majority of absolute cases (58.7%). Overall, 1,604 cases met severity criteria and 408 deaths were recorded (CFR: 0.07%). Thrombocytopenia was observed in 25–90% of patients, with platelet counts below 20,000/mm^3 in approximately half of severe cases. This position paper, based on real-world clinical experience at the main dengue referral center in Salta Province, Argentina, addresses the management of antiplatelet and anticoagulant therapies in dengue patients with thrombocytopenia. The recommendations aim to provide guidance for clinicians managing cardiovascular comorbidities during dengue outbreaks in endemic regions. The current paper focuses on the indicated therapeutic use of antiplatelet- and anticoagulant treatment in dengue patients experiencing thrombocytopenia.

KEYWORDS

antithrombotic therapy, clinical management, dengue, statement, thrombocytopenia

Introduction

Dengue is considered one of the most common vector-borne diseases worldwide, with a transmission rate that has increased more than eightfold over the past two decades.

During the 2024–2025 season (EW 31/2024 to EW 49/2024), 13,922 suspected cases were reported to the Argentinean National Health Surveillance System (SNVS 2.0), of

which 272 were confirmed. Among these, 197 had no travel history, while the remainder were linked to international travel or organ transplantation (1–3).

This highly infectious disease is an arboviral infection transmitted by *Aedes aegypti* mosquitoes that affects millions of people worldwide each year. The causative agent is the dengue virus (DENV), which exists in four human serotypes (DENV-1 to DENV-4) (4–9). The pathogenesis begins when the virus enters the bloodstream, infecting key cells such as endothelial cells, macrophages, and monocytes. This triggers an immune response with the release of multiple inflammatory mediators. Although the response aims to control viral replication, it significantly influences the clinical spectrum of the disease.

Most cases present with mild to moderate symptoms. Up to 5% of patients may progress to severe disease (4). While the underlying mechanisms remain incompletely understood, immune-mediated activation leading to excessive cytokine expression (10) has been proposed as a major contributor to two key findings in critically ill patients: increased vascular permeability (11), which can result in shock, and thrombocytopenia (12) with coagulopathy, which predisposes to bleeding. Risk factors for severe disease include prior infection with a different serotype (13, 14), viral genotypes associated with more efficient replication (15–17), specific genetic polymorphisms (18), and comorbidities such as diabetes, obesity, and cardiovascular disease. The World Health Organization recommends close monitoring and prompt hospitalization of patients with warning signs or risk of severe dengue to reduce mortality (5). Thrombocytopenia (decreased production, immune destruction), endothelial alterations, platelet dysfunction, coagulation factors, and hepatic dysfunction in terms of their impact on anticoagulant metabolism, which together affect the risk of bleeding under antithrombotic therapy.

This position paper which is based on the experience from Argentina during the dengue epidemic in 2024 aims to provide an updated review of the diagnosis and management of patients with severe dengue in the intensive care unit, with a focus on antithrombotic therapy.

Development of the recommendations

The recommendations presented in this Position Paper were developed through an expert consensus process supported by a comprehensive review of the literature. Searches were conducted in major medical databases to identify guidelines, observational studies, case series, and case reports addressing cardiovascular involvement in dengue infection and the management of thrombocytopenia. Given the limited and low-level evidence specific to dengue, additional information was extrapolated from studies evaluating thrombocytopenia in other infectious and systemic diseases. The available evidence was critically reviewed and discussed within the Department of Internal Medicine at Hospital Papa Francisco, the main referral center for dengue in Salta Province. Final recommendations were agreed upon by consensus and reflect the extensive clinical experience derived from the management of a large number of dengue patients in this setting.

Disease characteristics and the situation in the Province of Salta

From an epidemiological perspective, the province of Salta holds particular relevance due to the endemic presence of vector-borne diseases such as Dengue, Zika, and Chikungunya, as well as other diseases like Hantavirus. These diseases have significant public health implications. Arbovirus surveillance is conducted within the framework of Integrated Surveillance of Acute Undifferentiated Febrile Syndrome (AUFS) and specific case definitions for each arbovirus. Notifications are reported through the National Health Surveillance System.

Between October 1st, 2023 (EW40) and June 29th, 2024 (EW26), 37,175 notifications were recorded for patients evaluated with a presumptive diagnosis of AUFS potentially linked to mosquito-borne diseases. Among these, 33,442 cases of dengue were confirmed, representing a cumulative incidence of 1,758 per 100,000 population, and 333 cases of Chikungunya were confirmed, with a cumulative incidence of 23 per 100,000 population. These data reflect a high disease burden, particularly for dengue, highlighting a significant outbreak in the region. In contrast, the incidence of Chikungunya remained relatively low.

Dengue: trend analysis

Epidemiological curve analysis revealed that dengue cases emerged early in the 2023/2024 season. Using a moving average to smooth weekly fluctuations, a peak was observed in EW15, with 3,637 cases reported that week (1). A subsequent decline in weekly cases was noted thereafter. The onset of the outbreak coincided with regional climatic conditions—high temperatures and rainfall—favoring the proliferation of the Aedes aegypti vector.

Cumulative data for 2024 show:

- A 1.6-fold increase in cases compared to 2023.
- A 5.7-fold increase compared to the average of the past five years.

This trend underscores a sustained increase in dengue incidence in the province, reflecting intensified viral circulation and likely increased exposure of the population to the vector. The five-year trend, as illustrated in Figure 5, shows a marked increase in dengue cases, potentially associated with factors such as climate change (higher temperatures, prolonged rainy seasons), urbanization, and low population immunity to circulating serotypes.

In the Capital Department, where Hospital Papa Francisco served as a referral center for dengue patients, 14,640 confirmed cases were recorded, corresponding to an incidence of 2,332 per 100,000 inhabitants (2).

Demographic characteristics

A general trend toward higher incidence among younger age groups was observed, with rates decreasing progressively with age. Children under 10 and adults over 70 consistently exhibited the lowest rates. While incidence was similar between sexes across most age groups, females aged 30–39 showed slightly higher rates.

Circulating serotypes

Two dengue virus serotypes were identified during the outbreak: DENV-1 and DENV-2, with co-circulation of both serotypes over several epidemiological weeks. The distribution showed a higher prevalence of DENV-1 (64.53%), followed by DENV-2 (35.22%). Less than 1% of cases were associated with DENV-3 or DENV-4.

Mortality

During the period of enhanced surveillance, 33 dengue-related deaths were recorded in Salta Province (2). Most deaths occurred among adults aged 20–49 years (16 deaths, 48%) and elderly individuals over 70 years (9 deaths, 27%). There were 3 deaths among children aged 0–9 years (9%), and no fatalities were reported among adolescents aged 10–19. The overall case fatality rate (CFR) for the province was 1.3 per 1,000 cases, reflecting a relatively low mortality rate despite the high case burden, though significant variations were observed among departments. The Capital Department recorded the highest number of deaths (14 deaths; 42% of the total) with a CFR of 1.0 per 1,000 cases.

Clinical manifestations

Dengue virus infection may present asymptomatically or as a systemic, dynamic illness with a wide clinical spectrum that, in severe cases, can progress to death. Clinically, the disease evolves through three phases: febrile, critical, and recovery (Figure 1).

Febrile phase – This stage is characterized by the sudden onset of high fever (39–40 °C), severe headache, asthenia, myalgia, arthralgia, retro-orbital pain, and rash (present in approximately 50% of cases, typically maculopapular and involving the face, trunk, and extremities). The febrile phase generally lasts 2–7 days. At this stage, dengue can be difficult to distinguish from other acute febrile illnesses. In most patients, symptoms gradually improve with a return to baseline health (5, 19).

Critical phase – This phase typically begins once the fever subsides and is defined by plasma leakage, fluid accumulation, respiratory distress, and severe bleeding. Careful monitoring is required to identify warning signs that may signal progression to severe dengue and demand urgent medical intervention. Warning signs include severe abdominal pain, persistent vomiting, tachypnea, gingival bleeding, profound fatigue, and hematemesis or melena. Other severe manifestations include hemorrhage and dysfunction of vital organs such as the heart, lungs, kidneys, liver, and central nervous system (4, 19).

Recovery phase – Patients who survive the critical phase experience a gradual reabsorption of extravasated fluids, leading to progressive clinical improvement over 48–72 hours (4, 5).

According to the most recent World Health Organization (WHO) classification (2009), dengue severity is stratified into three categories:

A. Dengue without warning signs.
B. Dengue with warning signs.
C. Severe dengue (5).

Severe dengue is defined by one or more of the following: (1) shock or respiratory distress, (2) severe bleeding, and (3) severe organ impairment. Patients with secondary infections are at increased risk of severe outcomes. Coexisting conditions that further increase the risk of severe dengue include pregnancy, diabetes, hypertension, extremes of age (<1 year or >60 years), hemolytic anemia, chronic renal or hepatic failure, asthma, chronic obstructive pulmonary disease, and use of anticoagulant therapy (4, 19, 20).

The differential diagnosis of dengue includes other infectious diseases such as malaria, leptospirosis, typhoid fever, and viral infections including Zika and Chikungunya, due to overlapping clinical features. Dengue, Zika, and Chikungunya share the same mosquito vector and several clinical manifestations. Serological testing and polymerase chain reaction (PCR) assays for dengue virus infection are required to establish a definitive diagnosis (20, 21).

Dengue fever may cause significant organ dysfunction, most notably involving the coagulation system, cardiovascular system, pulmonary system, and central nervous system, among others.

Thrombocytopenia

Thrombocytopenia (TP) exposes patients to hemorrhagic complications and represents a major limiting factor for the use of antithrombotic therapies, including anticoagulants, antiplatelet agents, and fibrinolytics. Antiplatelet therapy in patients with acute coronary syndromes (ACS) and thrombocytopenia poses a particular challenge for physicians, as these patients are simultaneously at increased risk of bleeding and paradoxically at risk of ischemic events (22). Unfortunately, no current clinical guidelines or consensus statements provide clear recommendations for the management of this cohort. In this context, we review the available evidence and provide expert opinion regarding future directions and therapeutic strategies for this patient population.

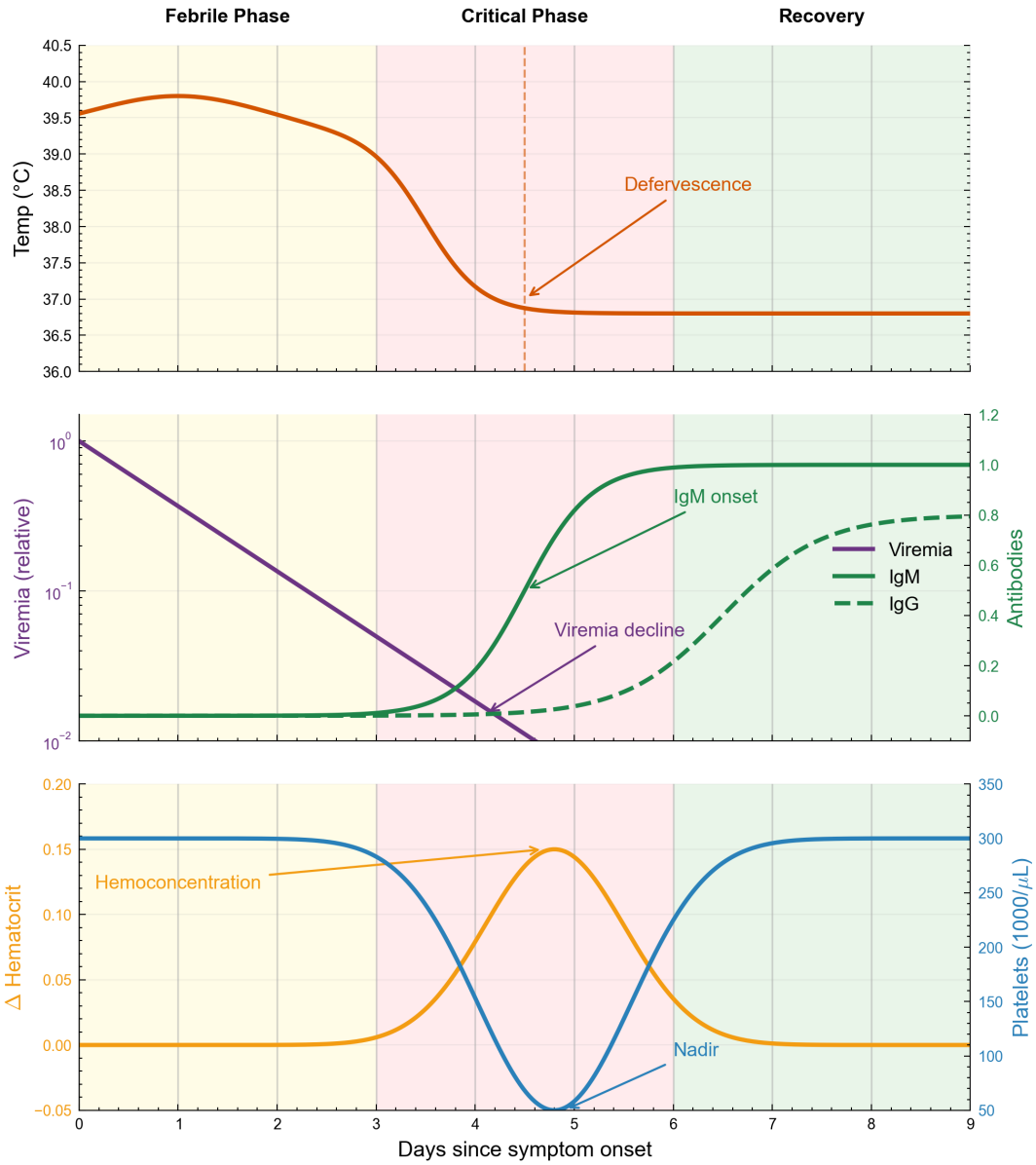

FIGURE 1
Clinical phases of dengue disease. Adapted from WCL Yip (1980) and subsequently modified by Hung NT, Lum LCS, and Tan LH.

Thrombocytopenia is a common finding and one of the warning signs of dengue virus infection. Platelet depletion is clinically significant, as it may lead to other severe manifestations of dengue. Understanding the molecular mechanisms underlying thrombocytopenia in dengue infection remains challenging due to the multifactorial nature of dengue virus–host interactions and the dynamic course of the disease. Platelet counts reflect the balance between platelet production and platelet consumption or clearance. Both megakaryopoiesis and thrombopoiesis—two interdependent processes in platelet production—are impaired during dengue infection. Conversely, platelet clearance via activation, apoptosis, and phagocytosis is increased. Collectively, these abnormalities contribute to dengue-associated thrombocytopenia.

Research focused on the molecular events of dengue-mediated thrombocytopenia holds significant promise but requires further investigation. The application of novel biomarkers, such as the measurement of immature platelet fraction, may facilitate disease monitoring and improve clinical decision-making.

Thrombocytopenia can generally be graded according to severity (Table 1). While the risk of bleeding may increase even in mild thrombocytopenia, a platelet count $<100 \times 10^9$/L is considered clinically relevant and warrants proactive measures to mitigate bleeding risk.

TABLE 1 Classification of thrombocytopenia.

Grade	Platelet count (x10^9/L)
1	75–<100
2	50–<75
3	25–<50
4	<25

Discussion with recommendations

We recommend the following general approach to all antithrombotic regimens in patients with dengue and thrombocytopenia (23–26):

1. Reassess the indication for antithrombotic therapy, regardless of the degree of TP.
2. Evaluate ongoing thrombotic and hemorrhagic risks by identifying patient-specific risk factors.
3. Anticipate the expected duration of TP.
4. Formulate a clear management plan for antithrombotic therapy, with frequent reassessment according to the treatment strategy, TP kinetics, and potential complications or comorbidities.
5. Consider resuming antithrombotic therapy once platelet counts are consistently above the threshold deemed safe for full dose therapy.

Strategies to minimize bleeding risk in patients with significant thrombocytopenia include:

- Avoiding nonsteroidal anti-inflammatory drugs (NSAIDs).
- Avoiding glycoprotein IIb/IIIa inhibitors.
- Using proton pump inhibitors unless contraindicated.
- Preferring low-dose aspirin (<100 mg/day).
- Avoiding triple antithrombotic therapy in patients already receiving long-term anticoagulation.
- For patients undergoing percutaneous coronary intervention (PCI):

  o Prefer the radial over the femoral approach.

  o Restrict dual antiplatelet therapy (DAPT) to one-month post-stenting.

  o Favor second-generation drug-eluting stents over bare-metal stents.

Anticoagulant therapy

When platelet counts are >50 × 10^9/L (i.e., grade 1–2 TP), therapeutic-dose anticoagulation, whether oral or parenteral, appears to be safe, as the risk of bleeding increases substantially when platelet counts fall below 50 × 10^9/L. However, it remains unclear whether different thresholds below 50 × 10^9/L, differentially impact safety and efficacy.

In patients with atrial fibrillation (AF) and grade 1–2 TP, we recommend continuing current anticoagulation without dose adjustment, extrapolating from safety data on venous thrombosis, as no specific evidence is available. Anticoagulant dosing should be evaluated on a case-by-case basis if additional bleeding risk factors are present. Full-dose anticoagulation should not be used in patients with grade 3–4 TP.

In selected patients with mechanical heart valves and stable platelet counts between 40–50 × 10^9/L lasting weeks to months, we recommend considering vitamin K antagonists (VKAs) with close monitoring of both platelet counts and the international normalized ratio (INR), targeting 2.0. This recommendation reflects the high risk of prosthetic valve thrombosis and systemic embolism (8.6% per year) associated with withholding anticoagulation in this population. Direct oral anticoagulants (DOACs) are strictly contraindicated in patients with mechanical heart valves, regardless of AF status.

Several cohort studies have demonstrated that venous thrombosis frequently recurs shortly after platelet recovery in patients who do not resume anticoagulation. Therefore, among patients in whom anticoagulation is withheld or reduced during TP, we recommend resuming full-dose anticoagulation as soon as platelet counts permit, provided the indication persists.

Recommendations for anticoagulant therapy in patients with dengue and TP

Grade 1–2 TP

i. Therapeutic-dose oral or parenteral anticoagulation should be maintained according to approved indications, following individualized assessment of bleeding and thrombotic risk.

ii. In patients with unstable grade 1–2 TP and acute venous thrombosis, low-molecular-weight heparin (LMWH) should be preferred over DOACs or VKAs.

iii. In patients with unstable grade 1–2 TP and AF or mechanical heart valves, LMWH may be considered as a short-term bridging strategy.

Grade 3 TP

i. DOACs and VKAs should not be used for venous thromboembolism (VTE) or AF.

ii. LMWH at prophylactic doses or with a 50% reduction of therapeutic dosing may be considered in acute VTE, after carefully balancing bleeding and thrombotic risks.

iii. In patients with AF and expected short TP duration, ongoing anticoagulation should be withheld unless the patient is at very high thrombotic risk or has dengue-related risk factors.

iv. A 50% reduction in therapeutic LMWH dosing with close platelet monitoring may be considered in patients with

stable grade 3 TP lasting weeks to months and very high thrombotic risk.

v. In patients with stable platelet counts of 40–50 × 10^9/L and a mechanical valve, in our experience, VKAs may be considered with a target INR of 2.0.

vi. In patients with mechanical valves and platelet counts of 25–40 × 10^9/L or unstable INR, a 50% reduction in therapeutic LMWH dosing may be considered.

Grade 4 TP

We recommend discontinuing anticoagulants for all indications.

Anticoagulation at appropriate dosing should be resumed as soon as platelet counts allow.

Antiplatelet therapy

Single antiplatelet therapy in secondary prevention

a. Grade 1 TP: We recommend maintaining SAPT with low-dose aspirin.

b. Grade 2 TP: We recommend maintaining SAPT with low-dose aspirin, provided the patient has no additional major bleeding risk factors.

c. Grade 3 TP: SAPT with low-dose aspirin should be continued only if there are additional cardiovascular thrombotic risk factors.

d. Grade 4 TP: We recommend temporarily discontinuing SAPT, irrespective of thrombotic risk level.

e. If discontinued, SAPT should be resumed as soon as platelet counts reach ≥25-50 × 10^9/L, depending on thrombotic risk.

Low-dose aspirin in primary prevention

a. Grade 1 TP: We recommend maintaining low-dose aspirin therapy when indicated, unless other bleeding risk factors are present.

b. Grade ≥2 TP: We recommend discontinuing aspirin therapy and resuming it once platelet counts are ≥75 × 10^9/L.

Antiplatelet therapy in acute coronary syndrome and post-percutaneous coronary intervention

a. Grades 1–4 TP: Intravenous antiplatelet agents (P2Y12 inhibitors) are not recommended.

b. Grade 1 TP: Dual antiplatelet therapy (DAPT) with clopidogrel is recommended in patients with ACS within the past 12 months, unless high thrombotic risk factors are present without significant additional bleeding risks.

c. Grades 2–4 TP: DAPT with ticagrelor or prasugrel is not recommended.

d. Grade 2 TP: DAPT with clopidogrel is recommended.

e. Grades 1–2 TP: Consider shortening the duration of DAPT and switching to SAPT following PCI with a modern drug-eluting stent—up to 6 months after ACS, or up to 3 months if no recent ACS has occurred. This decision should be individualized in consensus with the treating interventional cardiologist.

f. Grade 3 TP: We recommend SAPT with low-dose aspirin in all scenarios where thrombotic risk is not high. DAPT with clopidogrel may be considered only in cases of very high thrombotic risk occurring within the previous 3 months. Coronary intervention should be avoided if possible.

g. Grade 4 TP: Both DAPT and SAPT should be discontinued, except in cases of very high thrombotic risk where SAPT with low-dose aspirin may be justified if platelet counts are >10 × 10^9/L. Coronary intervention should be avoided.

Conclusion

The management of antithrombotic therapy in dengue should be individualized, dynamic, and based on the severity of dengue, thrombotic risk, and clinical evolution, in the absence of specific international guidelines.

This position paper was developed based on the clinical experience gained during the most recent dengue epidemic in Argentina, a scenario for which robust scientific evidence remains scarce. The document provides practical guidance derived from real-world management of patients exposed to the dual challenges of dengue infection and antithrombotic therapy. Its recommendations are of particular relevance to cardiologists and other clinicians who routinely prescribe antiplatelet and anticoagulant agents. By integrating local expertise with current international evidence, this work aims to support safer and more informed decision-making in a context of growing epidemiological importance.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

RL: Writing – review & editing, Writing – original draft. DN: Writing – original draft, Writing – review & editing.

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