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REVIEW ARTICLE

Clinical characteristics of thrombocytopenia in tropical diseases and management in resource-limited settings

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Abstract

Platelets play a central role in the pathogenesis of tropical infectious diseases. Infections such as malaria, dengue, and leptospirosis are often accompanied by thrombocytopenia. While the platelet count is typically monitored as a measure of thrombocytopenia, other platelet indices may better determine bleeding severity. Platelet dysfunction in these conditions requires a nuanced approach to management. Prophylactic platelet transfusions have shown limited efficacy in preventing hemorrhagic complications and carry additional risks. These include transfusion-transmitted infections, logistical challenges, and the high cost of platelet concentrates. Herein, we review current insights into platelet biology in major tropical infections, examine the varied mechanisms underlying thrombocytopenia in these conditions, and discuss the latest evidence on transfusion guidelines. We also propose evidence-based approaches to thrombocytopenia management and platelet transfusion. We aim to summarize approaches that may improve care for populations disproportionately affected by tropical infectious diseases in resource-limited settings.

KEYWORDS
dengue, malaria, platelets, resource-limited, thrombocytopenia

Essentials

- Thrombocytopenia is a common finding in several tropical diseases.
- Platelet function, rather than the absolute count, may better determine bleeding severity.
- Platelet indices, such as immature platelet fraction where available, may be more beneficial.
- Prophylactic platelet transfusions show little benefit, and trials are mostly limited to dengue.

1 | INTRODUCTION

Tropical infections continue to exert a substantial global health burden, particularly in resource-limited settings where they cause disproportionately high morbidity and mortality [1,2]. Thrombocytopenia is frequently encountered in these diseases and often precedes vascular leakage, organ dysfunction, or hemorrhagic complications. Recent evidence suggests that platelet function

extends beyond hemostasis, with antimicrobial effects also exhibited, which may be beneficial or counterproductive [3,4]. In malaria, for instance, platelets bind to parasitized erythrocytes and directly kill the parasite [5,6], while in dengue, platelet activation and apoptosis can worsen endothelial damage and drive extravasation of fluid into the interstitial space (plasma leakage). This contributes to multiorgan failure, bleeding risk, and mortality [7–10]. These observations highlight that platelet function, rather than absolute counts alone, may impact clinical outcomes [11]. Furthermore, unlike the malaria parasite, dengue virus can directly infect platelets and the platelet progenitors, megakaryocytes, in the bone marrow [12]. This leads to decreased platelet production and increased platelet destruction compared with malaria. These facts partly explain that while both malaria and dengue patients frequently have thrombocytopenia at presentation, life-threatening hemorrhage is considerably more common in dengue than in malaria.

Historically, prophylactic platelet transfusions have been employed in an attempt to prevent serious bleeding in diseases like dengue. However, recent data challenge their effectiveness in reducing hemorrhagic complications [13–15]. The shortcomings of this approach are particularly pressing in low-resource environments, where unnecessary transfusions deplete scarce blood products, risk transfusion-related complications, and strain already fragile healthcare systems. This underscores the urgent need for more evidence-based strategy that accounts for both quantitative and qualitative platelet defects while remaining feasible in resource-limited settings.

2 | PLATELETS AS ANTIMICROBIAL CELLS

Although platelets are historically known as mediators of hemostasis, recent research has suggested an array of antimicrobial functionalities (Figure 1). Platelets can bind and inactivate various pathogens, secrete cytokines, and shape the innate immune response [4,16]. By detecting pathogen-associated molecular patterns via Toll-like receptors (TLRs), Fc receptors, and other surface molecules, platelets not only mount local procoagulant responses but also secrete inflammatory mediators [17,18]. These immune-like properties can be witnessed in bacterial sepsis, in which platelets bind bacteria through Fc and complement receptors [19]. They are equally important in parasitic infections such as malaria, and in viral infections, including dengue and influenza [3].

One crucial feature of platelet antimicrobial activity is the direct physical interaction between platelets and microbes. For certain protozoan infections, notably *Plasmodium falciparum*, platelets attach to the parasitized erythrocytes using surface molecules like CD36, leading to parasite destruction [5,6]. In viruses such as dengue, platelets can recognize viral components via C-type lectin-like receptor 2 (CLEC-2), TLR4, or Fcγ receptors. This triggers a cascade of reactions that include cytokine release and microparticle generation [20,21]. Platelets also recruit leukocytes and coordinate their activation in local or systemic inflammatory responses through P-selectin expression [10].

Platelet granules house an array of antimicrobial peptides and chemokines such as platelet factor 4 (PF4). Originally known for its contribution to coagulation, PF4 also exhibits direct toxicity against *Plasmodium* parasites [5]. PF4 can also bind to microbial surfaces and recruit additional immune cells, thereby boosting pathogen clearance [22]. In dengue, PF4 has been implicated in viral propagation under some *in vitro* conditions, highlighting the complexity of platelet-pathogen interactions [23].

Platelets promote inflammation through the release of serotonin and cytokines such as interleukin-1β (IL-1β) and regulated upon activation, normal T cell expressed and secreted (RANTES) [24]. This secretory response can help recruit monocytes and neutrophils to sites of infection with subsequent phagocytosis, antigen presentation, microbiocidal activity, and further cytokine release [25]. Conversely, excessive platelet activation can lead to harmful outcomes such as microvascular thrombosis, endothelial barrier disruption, and cytokine storms [10]. Additionally, platelets express major histocompatibility complex class I molecules and costimulatory ligands [19]. Although they are anucleate, platelets can process and cross-present antigens to cytotoxic T cells under certain conditions, potentially influencing adaptive immunity [26,27].

In short, platelets are hypothesized to actively bind and clear pathogens, release microbicidal peptides, and shape both innate and adaptive immunity [28]. Yet, because many findings derive from animal models, further human studies are needed to clarify the extent of these antimicrobial properties. In tropical infections, this antimicrobial function is both vital and double-edged, as sustained platelet activation can also trigger widespread inflammation. This contributes to vascular leakage, organ injury, and thrombocytopenia.

3 | PLATELETS IN MALARIA

3.1 | How common is thrombocytopenia in malaria?

Malaria remains one of the most prevalent parasitic infections globally, primarily caused by *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* [29]. Thrombocytopenia is a characteristic laboratory finding affecting up to 85% of patients with acute malaria [30,31]. In fact, thrombocytopenia in acute febrile travelers returning from tropical regions has emerged as a highly sensitive clinical indicator for malaria diagnosis. Studies indicate that in febrile returning travelers, thrombocytopenia (platelet count $<150 \times 10^9$/L) has a diagnostic sensitivity of approximately 60% and a specificity of 70% to 88% [32,33]. Severe thrombocytopenia (platelet count $<50 \times 10^9$/L) is more commonly seen in severe *P. falciparum* infection than in infections with other species, with rates of 10% to 30% reported in the literature [34]. Severe thrombocytopenia correlates with higher parasitemia, organ failure, and mortality [35]. As thrombocytopenia is so ubiquitous, some clinicians in resource-limited settings use platelet counts as a supportive diagnostic indicator for malaria and a measure of severity, with moderate sensitivity but relatively high specificity [36,37].

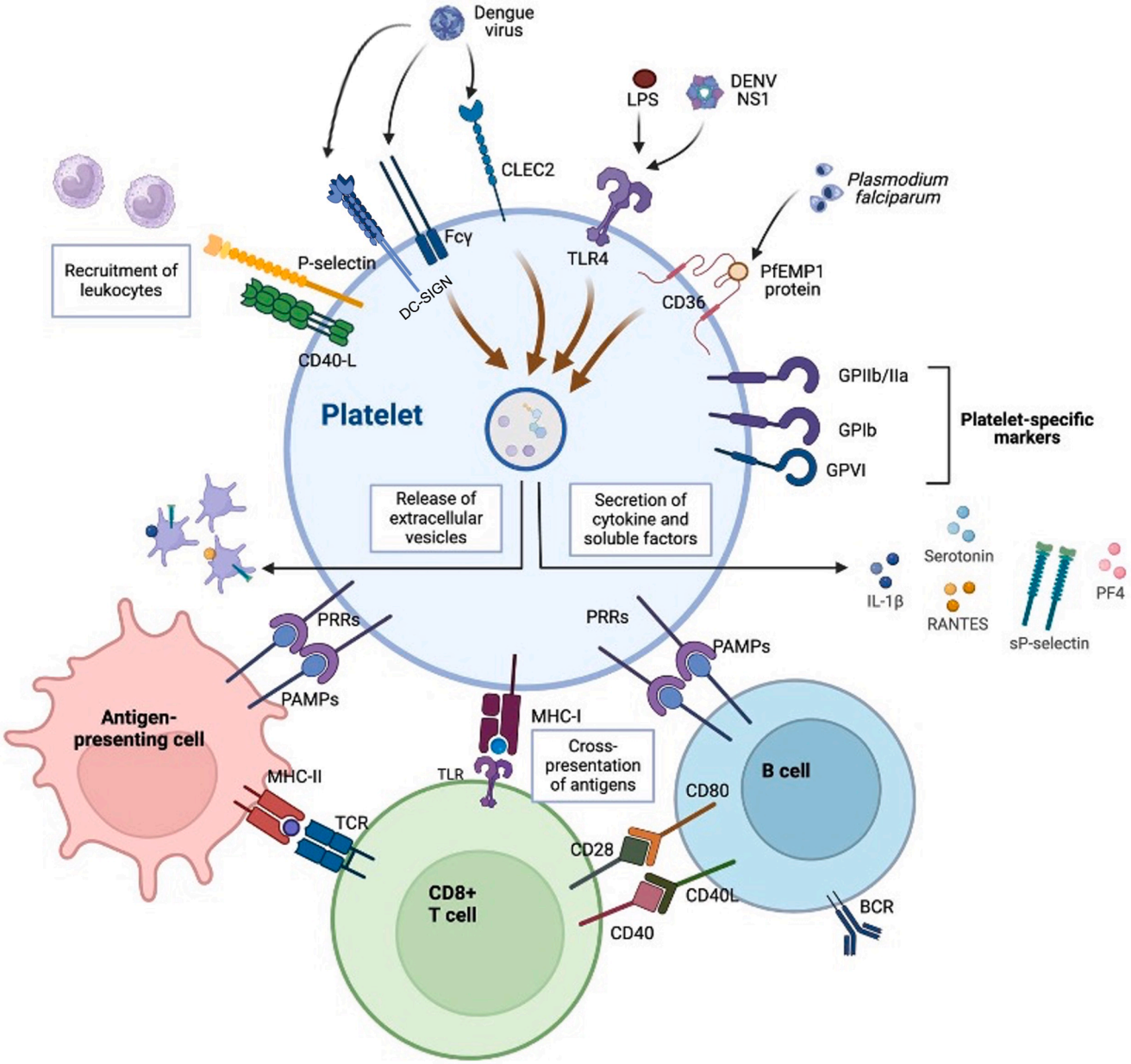

FIGURE 1 Platelets as antimicrobial cells. Platelets, traditionally recognized for their role in hemostasis, also possess diverse antimicrobial functions. They contain granules rich in host-defense peptides and receptors that detect pathogens. Platelets recognize microbial components via Toll-like receptors (TLRs), Fc receptors, and C-type lectin-like receptor 2 (CLEC-2). This triggers cytokine release, microparticle generation, and procoagulant activity. They bind pathogens directly, as seen in malaria, where they attach to *Plasmodium falciparum*-infected erythrocytes, leading to parasite destruction. In dengue, platelets interact with viral components, modulating immune responses through platelet factor 4 (PF4) and inflammatory cytokines like interleukin (IL)-1β. Beyond direct pathogen clearance, platelets recruit immune cells, enhance phagocytosis, and induce neutrophil extracellular traps (NETs) to entrap microbes. They also support antigen presentation where they cross-present antigens via major histocompatibility complex class I (MHC-I) to cytotoxic T cells. BCR, B-cell receptor; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; DENV, dengue virus; GP, glycoprotein; LPS, lipopolysaccharide; NS1, nonstructural protein 1; PAMP, pathogen-associated molecular pattern; PfEMP1, *P. falciparum* erythrocyte membrane protein 1; PRR, pattern recognition receptor; RANTES, regulated upon activation, normal T cell expressed and secreted; sP-selectin, soluble P-selectin. Figure made with BioRender.

In a meta-analysis of severe non-*P. falciparum* malaria (predominantly *P. vivax* and *P. knowlesi*), 47% of patients developed severe thrombocytopenia (platelet count $<50 \times 10^9$/L) and 20% had profound thrombocytopenia (platelet count $<20 \times 10^9$/L) [38]. Worsening thrombocytopenia was associated with increased morbidity, with an estimated mortality rate of 11% in those with

severe/profound thrombocytopenia. Although severe thrombocytopenia is not part of the current World Health Organization (WHO) criteria for severe malaria, clinicians should remain vigilant to profound thrombocytopenia in malaria as a potential marker of adverse outcomes.

3.2 | Mechanisms of thrombocytopenia

Multiple pathophysiological mechanisms contribute to platelet depletion in malaria (Figure 2). Parasites and parasite-derived antigens can directly activate platelets, triggering platelet-platelet clumping [39]. Immune complexes containing malarial antigens can opsonize platelets, thereby promoting platelet phagocytosis by splenic macrophages, particularly in severe cases of both *P. falciparum* and *P. vivax* malaria [40]. Bone marrow function may be transiently suppressed or show dysmegakaryopoiesis during infection, reducing platelet production [41]. There is also evidence for complement activation on platelets and intravascular microthrombi formation, which further accelerates platelet clearance [42].

A distinctive aspect of malaria is the reported interaction of platelets with infected red blood cells. Platelet binding to parasitized erythrocytes can deliver PF4 into the parasite, leading to parasite death [6,43]. However, this beneficial antimicrobial activity may come at the cost of platelet consumption [43]. Persistent platelet activation often leads to an 'exhausted' phenotype and possibly shortened platelet lifespan [44]. Additionally, in severe *P. falciparum* infections, platelets bind to *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) expressed on infected erythrocytes [43]. This binding leads to platelet aggregation and consumption, a process that, while aiding parasite clearance, can result in microvascular obstruction [45].

3.3 | Clinical correlates of thrombocytopenia

From a clinical perspective, thrombocytopenia in malaria can serve as a marker of disease severity. Patients with platelet counts $<50 \times 10^9$/L are more likely to develop severe complications, such as cerebral malaria and acute renal failure [11,34]. However, severe hemorrhage remains relatively rare in malaria even at low platelet counts [45]. Instead, microvascular ischemia due to platelet aggregates in cerebral or renal vasculature is a more pressing concern [46].

Plasma coagulation abnormalities are increasingly encountered in acute malaria. Patients may exhibit prolongation of prothrombin time/international normalized ratio and activated partial thromboplastin time (aPTT) with hypofibrinogenemia and elevated D-dimer, reflecting activation of coagulation and secondary fibrinolysis [47]. A meta-analysis estimates disseminated intravascular coagulation (DIC) occurs in around 11% to 12% of malaria cases overall and is more prevalent in severe and fatal cases [48]. Yet, it is suggested that only around 5% to 10% of DIC is associated with bleeding [49].

Management of thrombocytopenia in malaria typically revolves around effective antimalarial therapies such as artemisinin-based combination treatments. This leads to parasite clearance and subsequent platelet recovery [22]. Although platelet transfusions are often deemed unnecessary, whole blood transfusion may be beneficial in improving survival, particularly in those with impaired consciousness or hyperlactatemia [50]. However, further evidence is needed to refine these recommendations. In resource-limited settings, supportive care and monitoring remain critical, including vigilance for signs of end-organ damage [37]. Overall, thrombocytopenia itself rarely demands direct intervention in malaria. Instead, it is a significant indicator of disease severity and a reminder of the delicate immunologic balance in these patients.

4 | PLATELETS IN DENGUE

4.1 | How common is thrombocytopenia in dengue?

Dengue is a mosquito-borne viral infection caused by 4 major serotypes of dengue virus (DENV-1 through DENV-4), with a fifth serotype described more recently [51]. Dengue has a broad clinical spectrum ranging from asymptomatic or mild febrile illness to dengue hemorrhagic fever and dengue shock syndrome [52]. Thrombocytopenia is a nearly universal finding in symptomatic dengue and has historically been used to help identify at-risk patients [53]. In many cohorts, platelet counts begin to plummet around day 3 to 5 of illness. Platelet count can reach as low as 20×10^9/L in severe cases [53].

4.2 | Mechanisms for thrombocytopenia

The mechanisms that drive thrombocytopenia in dengue are multifactorial and there remains some ambiguity behind the pathophysiology (Figure 3). Dengue virus can directly infect or bind to platelets through receptors such as dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), TLR4, or CLEC-2, leading to platelet activation and apoptosis [54]. Dengue virus activates platelets which leads to caspase-1 activation, IL-1β release, and platelet apoptosis, accelerating their clearance and contributing to thrombocytopenia [55]. Antibody-dependent enhancement can exacerbate platelet destruction when nonneutralizing antibodies bind to new DENV serotypes, promoting platelet phagocytosis via Fcγ receptors [56]. Complement activation also plays a role, with C3 deposition on platelets accelerating their clearance [19,57].

Additionally, dengue may alter megakaryopoiesis by infecting hematopoietic progenitors in the bone marrow. The precise mechanism of DENV-induced bone marrow suppression remains unclear. As well as its direct effects on megakaryopoiesis [12], dengue may indirectly stifle platelet production via the release of proinflammatory cytokines [58]. The pronounced inflammatory environment triggers widespread platelet activation. This results in the formation of platelet-leukocyte aggregates, microparticle release, and ultimately cell death [10]. Microvascular thrombosis may also

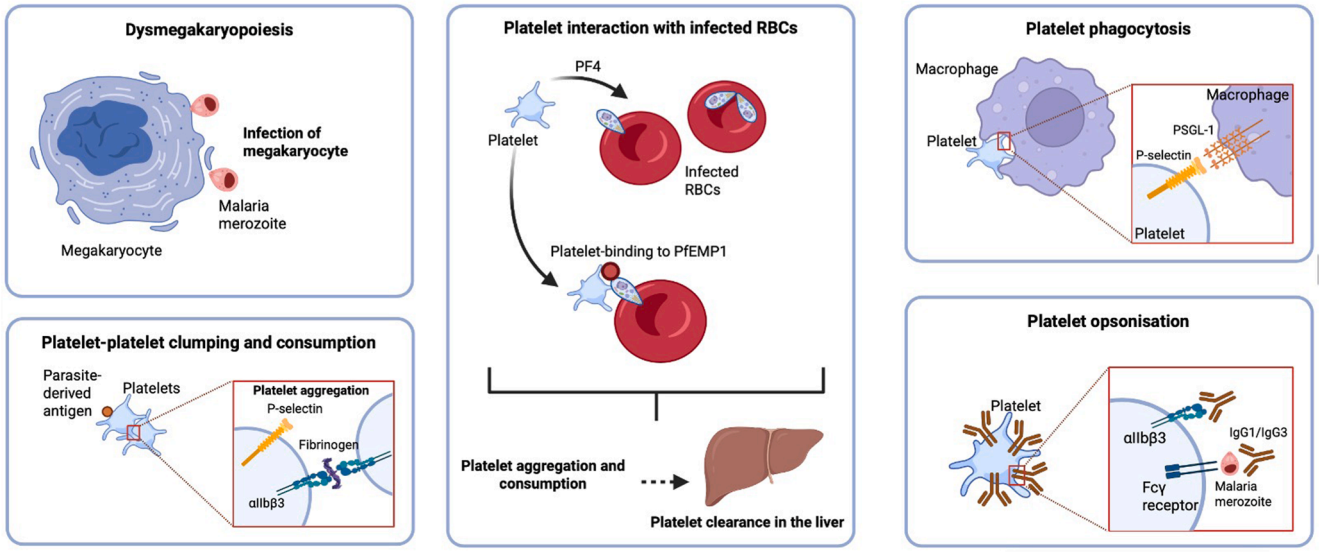

FIGURE 2 Mechanisms of thrombocytopenia in malaria. Malaria-induced thrombocytopenia results from multiple mechanisms. This includes direct platelet activation, immune-mediated destruction, and impaired production. Parasite antigens trigger platelet aggregation and consumption while immune complexes opsonize platelets for splenic clearance. Bone marrow suppression and dysmegakaryopoiesis further reduce platelet production. Complement activation accelerates platelet clearance. A unique feature of malaria is platelet interaction with infected erythrocytes. Platelets bind *Plasmodium falciparum*-infected red blood cells (RBCs), delivering platelet factor 4 (PF4) to kill the parasite but at the cost of platelet depletion. Platelet aggregation via *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) contributes to microvascular obstruction. Additionally, splenic macrophages may phagocytose platelets, particularly in severe *P. falciparum* and *P. vivax* infections. PSGL-1, P-selectin glycoprotein ligand-1. Figure made with BioRender.

occur due to direct injury of the endothelium by the release of endotoxin and pronounced levels of inflammatory cytokines [59]. Finally, there remains uncertainty as to whether platelets are directly infected by dengue. Dengue antibodies have previously been found on the surface of platelets in infected patients [60,61]. However, there is no conclusive evidence that DENV can undergo active replication in purified platelet samples from patients infected with the virus [62]. The uncertainty in the immunopathogenesis of DENV

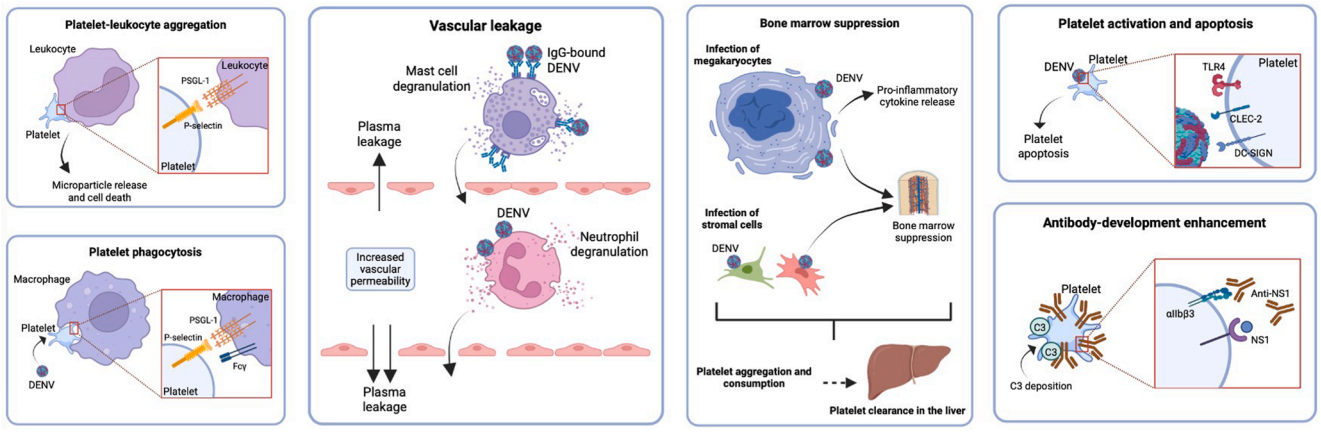

FIGURE 3 Mechanisms of thrombocytopenia in dengue. Dengue-associated thrombocytopenia is multifactorial. Mechanisms include direct viral interactions, immune-mediated destruction, and impaired platelet production. Dengue virus (DENV) binds to platelets via dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), Toll-like receptor 4 (TLR4), or C-type lectin-like receptor 2 (CLEC-2), which triggers activation and apoptosis. Antibody-dependent enhancement (ADE) exacerbates platelet clearance by promoting Fcγ receptor-mediated phagocytosis while complement activation accelerates their destruction through C3 deposition. Endothelial dysfunction, which increases vascular permeability, also plays a role. At the same time, widespread platelet activation leads to microparticle release, platelet-leukocyte aggregation, and apoptosis. DENV may also affect megakaryopoiesis, which possibly suppresses bone marrow function through direct damage or inflammatory cytokine storms. Although dengue antibodies have been found on platelets, evidence of active viral replication within platelets remains inconclusive. NS1, nonstructural protein 1; PSGL-1, P-selectin glycoprotein ligand-1. Figure made with BioRender

underscores the need for further research to elucidate the role of platelets in this process [63].

The mechanism linking dengue-associated plasma leakage to thrombocytopenia is complex and involves multiple pathways. This includes endothelial dysfunction, platelet activation, and immune responses [64–67]. An imbalance in angiopoietins, with increased angiopoietin-2 and decreased angiopoietin-1, disrupts vascular integrity, promoting plasma leakage in severe dengue [68].

4.3 | Clinical correlates of thrombocytopenia

Thrombocytopenia is a clinically important marker in dengue. A sustained drop in platelet count correlates with progression from dengue fever to dengue hemorrhagic fever and shock [53]. Bleeding manifestations in dengue can range from petechiae and ecchymoses to life-threatening gastrointestinal or intracranial hemorrhages. Furthermore, platelet count may not perfectly predict bleeding risk [69].

The tourniquet test is a simple, low-cost procedure in which a blood pressure cuff is inflated on the arm to induce petechiae, thereby revealing capillary fragility. It was included in the WHO 1997 guidelines for the diagnosis of dengue. However, the test lacks the sensitivity and specificity needed to reliably distinguish between dengue fever and dengue hemorrhagic fever or to separate dengue from other febrile illnesses. As a result, the WHO introduced a revised classification in 2009 that excluded the tourniquet test [70]. However, this inexpensive test may serve as a practical diagnostic aid in rural clinics located in dengue-endemic tropical regions. While a positive result should trigger careful monitoring or prompt referral to a hospital, a negative result does not conclusively rule out dengue infection.

Plasma coagulopathy in dengue is multifactorial; hepatic synthetic impairment, endothelial glycocalyx injury, and enhanced fibrinolysis all contribute to this coagulopathy [71]. The most consistent laboratory pattern is a prolonged aPTT with reduced fibrinogen. The prothrombin time/international normalized ratio may also be deranged, and D-dimer frequently increases [72]. Notably, several contemporary studies associate aPTT prolongation with bleeding risk, supporting its inclusion among severity markers [71,73].

Clinical management largely involves vigilant monitoring of platelet counts and hematocrit, the elevation of which indicates plasma leakage [74–76]. Fluid resuscitation is essential in preventing or treating shock. The use of prophylactic platelet transfusions, once a widely practiced strategy, has been called into question by randomized trials showing no significant decrease in bleeding complications [13]. Identifying biomarkers such as the immature platelet fraction may help pinpoint when thrombocytopenia is genuinely threatening or merely reflective of intense platelet turnover [77,78]. As with malaria, the resolution of dengue viremia is associated with the spontaneous recovery of platelet counts [13]. However, unlike malaria, where antiparasitic treatment directly targets the pathogen, dengue management relies on supportive care. We expand on both transfusion and platelet indices later in this review.

5 | PLATELET ABNORMALITIES IN OTHER TROPICAL DISEASES

Beyond malaria and dengue, other tropical diseases are less well-studied (Table). A variety of pathogens encountered in tropical regions can induce significant platelet abnormalities, including both quantitative and qualitative changes. Leptospirosis, caused by *Leptospira interrogans*, often arises in areas with poor water and sanitation infrastructure. While most patients experience mild-to-moderate thrombocytopenia, which is often less pronounced than that in severe malaria or dengue, alveolar hemorrhage and mucosal bleeding can still occur [79]. In a study of 374 patients with severe leptospirosis, thrombocytopenia (platelet count $<100 \times 10^9$/L) was found in 200 patients (53.5%), with 107 patients (29.3%) having a platelet count $<50 \times 10^9$/L [80]. Research suggests that the severity of bleeding does not always correlate strictly with platelet count. Rather, platelet 'exhaustion' and increased platelet-leukocyte aggregates appear to damage the microvasculature, particularly in the lungs [79]. There is also evidence that platelet dysfunction may be mediated through increased von Willebrand factor-platelet binding and subsequent activation and clearance of platelets [81].

Ebola virus disease (EVD), caused by a Filovirus, is notorious for its hemorrhagic manifestations and shock in advanced cases. Thrombocytopenia tends to be moderate rather than profound in EVD. In a study of 150 patients with EVD, thrombocytopenia (platelet count $<150 \times 10^9$/L) was present in 47 (45%) individuals, with severe thrombocytopenia (platelet count $<50 \times 10^9$/L) only in 3 (2.9%) [82]. Platelets in Ebola may lose their normal aggregatory responses or become hyperactivated in a sporadic, dysregulated manner, culminating in DIC and multiple organ failure [83]. Treatment typically revolves around aggressive supportive care. The use of prophylactic platelet transfusions has not been investigated in EVD.

In Chagas disease, caused by *Trypanosoma cruzi*, overt thrombocytopenia is less common, yet chronic platelet activation can drive low-grade inflammation. Over time, this persistent activation contributes to microvascular damage and myocardial fibrosis, which may result in the development of chronic cardiomyopathy [84]. While antiparasitic treatments are available that directly target the pathogen, a deeper understanding of platelet-mediated damage may lead to future adjunct therapies aimed at reducing vascular injury and endotheliopathy.

Additional neglected tropical diseases reveal parallel patterns of platelet involvement. Leishmaniasis, for example, manifests in cutaneous, mucocutaneous, or visceral forms. In visceral leishmaniasis, splenomegaly is common, and mild thrombocytopenia may develop due to sequestration and immune-mediated destruction [85]. The delicate balance between beneficial immune activity and pathological inflammation remains an area of active investigation. Additionally, the correlations between thrombocytopenia and parasite index remains to be fully elucidated [85].

TABLE Summary of platelet abnormalities in tropical diseases.

Infection	Key platelet abnormalities	Mechanisms	Clinical manifestations	Typical platelet threshold for transfusion	Notes / special considerations
Malaria (*P. falciparum*, *P. vivax*)	- Thrombocytopenia in up to 90% of hospitalized cases - Platelet dysfunction (microthrombi in severe forms) - PF4-mediated parasite killing	- Direct parasite/antigen activation of platelets - Immune complex opsonization - Splenic sequestration	- Microvascular ischemia (cerebral malaria) - Acute renal failure - Rare severe bleeding	Typically avoid prophylaxis; transfuse if bleeding is severe	- Use prophylactic transfusion cautiously; watch for coagulopathy
Dengue (DENV-1 to DENV-5)	- Marked thrombocytopenia (down to 20 $\times$ 10^9/L) - Platelet activation, apoptosis - 'Capillary leak' risk	- Direct virus–platelet binding (eg, TLR4, CLEC-2) - Antibody-dependent enhancement - Complement-mediated destruction	- Petechiae, ecchymoses - Hemorrhagic fever - Shock due to plasma leakage, not always bleeding driven	Avoid prophylaxis; transfuse if bleeding is severe	- Prophylactic transfusions generally not recommended - Fluid resuscitation crucial; IPF can guide recovery
Leptospirosis (*L. interrogans*)	- Mild-moderate thrombocytopenia - Platelet dysfunction (platelet-leukocyte aggregates) - Alveolar hemorrhage	- Immune-driven platelet 'exhaustion' - Microvascular endothelial injury - Possibly complement activation	- Pulmonary hemorrhage - Mucosal bleeding - Multiorgan involvement in severe cases	Typically avoid prophylaxis; transfuse if alveolar bleeding is severe	- Watch for alveolar hemorrhage even at moderate counts
Ebola (Filoviridae)	- Moderate thrombocytopenia - Profound platelet dysfunction - DIC in severe cases	- Virus-induced dysregulation of coagulation - Endothelial damage & cytokine storm	- Severe hemorrhage - Shock - Multiorgan failure	No fixed threshold; transfuse only if overt bleeding and other supportive measures fail	- Resource constraints hamper transfusion in outbreaks - Investigational therapies, aggressive support needed
Chagas (*T. cruzi*)	- Often mild thrombocytopenia - Persistent platelet activation in chronic disease	- Low-grade inflammation - Microvascular endothelial injury	- Chronic cardiomyopathy - Cardiac fibrosis	Typically not indicated for prophylaxis (platelet count often not severely low)	- Management centered on antiparasitics & supportive care - Platelet involvement is more chronic/inflammatory
Leishmaniasis (*L. donovani*, etc.)	- Mild thrombocytopenia (esp. visceral forms) - Splenic sequestration - ?Immune complex formation	- Possible platelet–parasite binding - Splenomegaly fosters sequestration - Platelet–monocyte cooperation in clearing parasites	- Minimal bleeding risk unless advanced disease - Potential endothelial dysfunction	Rarely needed unless actively bleeding	- Focus on antileishmanial therapy - Platelet activation can be beneficial or harmful depending on disease stage

CLEC-2, C-type lectin-like receptor 2; DENV, dengue virus; DIC, disseminated intravascular coagulation; IPF, immature platelet fraction; PF4, platelet factor 4; TLR4, Toll-like receptor 4.

6 | LABORATORY INDICES AND TRIAGE IN RESOURCE-LIMITED SETTINGS

In many low-resource settings, platelet counts alone are relied upon to assess hematological status due to limited laboratory infrastructure. However, one emerging area of interest is the use of platelet indices that can offer a more nuanced understanding of platelet production and consumption. Measurements like the immature platelet fraction (IPF) show promise for predicting disease progression and forecasting platelet recovery. In one study, higher IPF% was associated with severe dengue compared with nonsevere dengue on days 3 to 5 of illness [78]. Rising IPF% may act as an early marker of thrombocytopenia recovery [77]. Thus, an increase in IPF% points to responsive marrow and may support safer postponement of platelet transfusions if there is no major bleeding [86]. Other parameters such as mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) have also been associated with severe malaria and leptospirosis [30,87,88]. Although MPV, PDW, and PCT can be obtained from standard 3-part differential counters, IPF typically requires more advanced cell counters that may not be available in rural centers. In such situations, simpler scoring systems are being explored for dengue [89,90] and malaria [32], but these currently have low statistical power and remain to be validated for routine bedside use.

District and provincial laboratories may struggle to deliver more than a basic platelet count and often lack reliable coagulation testing because of gaps in equipment, quality systems, and workforce training. [91] The WHO Model List of Essential *In Vitro* Diagnostics explicitly prioritizes tests such as platelet count and core coagulation assays for routine care and emergencies. It encourages countries to integrate them into national essential diagnostics lists to guide procurement and investment [92]. The advanced platelet indices discussed in this review require analyzer capabilities and validated methods that are not yet universally available. We therefore encourage programs that pair stepwise laboratory quality improvement/accreditation (Strengthening Laboratory Management Towards Accreditation/Strengthening Laboratory Quality Improvement Process Towards Accreditation) with focused hemostasis training through regional training centers and participation in external quality assessment to build durable capacity for platelet and coagulation testing [93].

7 | MANAGEMENT OF THROMBOCYTOPENIA IN RESOURCE-LIMITED SETTINGS: WHEN DO WE NEED PLATELET TRANSFUSIONS?

Management of thrombocytopenia in a tropical setting typically begins with evaluating whether the patient has signs of hemodynamic instability or severe organ involvement and whether easily testable factors such as hematocrit (in dengue) or parasite load (in malaria) can guide evaluation of the risk of complications (Figure 4). Physical findings such as gum bleeding, petechiae, or rapid respiratory decompensation should trigger urgent assessment. Even when laboratory infrastructure is limited, rapid diagnostic tests for malaria and respiratory auscultation for possible alveolar involvement in leptospirosis can help distinguish urgent cases. Clinicians rely on serial clinical observation if platelet transfusions are not available or the facility is unable to measure IPF to gauge marrow responsiveness. Basic interventions, such as compressive measures for local bleeding, intravenous fluids for shock, and oxygen supplementation or vasopressor support can also avert severe complications. The use of platelet transfusions to manage thrombocytopenia in tropical infections has been debated for decades.

7.1 | Potential advantages of platelet transfusion

One of the clearest arguments for platelet transfusions continues to be the prevention or treatment of active bleeding, particularly in settings where mucosal or gastrointestinal hemorrhage can rapidly deteriorate. A second key benefit is that platelets help maintain endothelial integrity by providing direct support to the vascular wall. Under inflammatory conditions, platelets adhere to sites of endothelial damage and release protective factors like sphingosine-1-phosphate and angiopoietin-1, which help seal endothelial junctions [76]. In diseases like dengue, the phenomenon of plasma leakage is a leading cause of morbidity. Thus, in theory, restoring platelet levels through transfusion could boost endothelial integrity, reducing capillary leak [76].

7.2 | Potential disadvantages of platelet transfusion

Clinicians should be mindful of the thrombotic risk associated with platelet transfusion. Several cohorts, albeit outside of the context of tropical diseases, report higher rates of venous and arterial thrombosis and mortality after platelet transfusion, plausibly mediated by infusion of activated platelets and procoagulant platelet-derived microparticles [94,95]. Thrombosis induced or promoted by platelet transfusion has long been a concern for patients with consumptive thrombocytopenia in particular conditions such as thrombotic thrombocytopenic purpura. However, higher rates of thrombotic events after platelet transfusion have also been observed in a broad range of conditions, including those with infectious causes [95]. Platelet transfusion has a number of associated inflammatory sequelae through the release of inflammatory mediators, chemokines, cytokines, and microparticles [96]. Microparticles are prothrombotic and are known to be increased in malaria, particularly severe cerebral malaria [97]. Of note, platelet microparticles from platelet transfusion were noted to remain in circulation far longer than ones derived from a cerebral malaria rabbit model [98]. 'Fueling the fire' with platelet transfusion may therefore promote thrombosis.

Concerns regarding the proinflammatory nature of transfused platelets also motivate restraint. Platelet concentrates typically contain cytokines, chemokines, and microparticles that can amplify

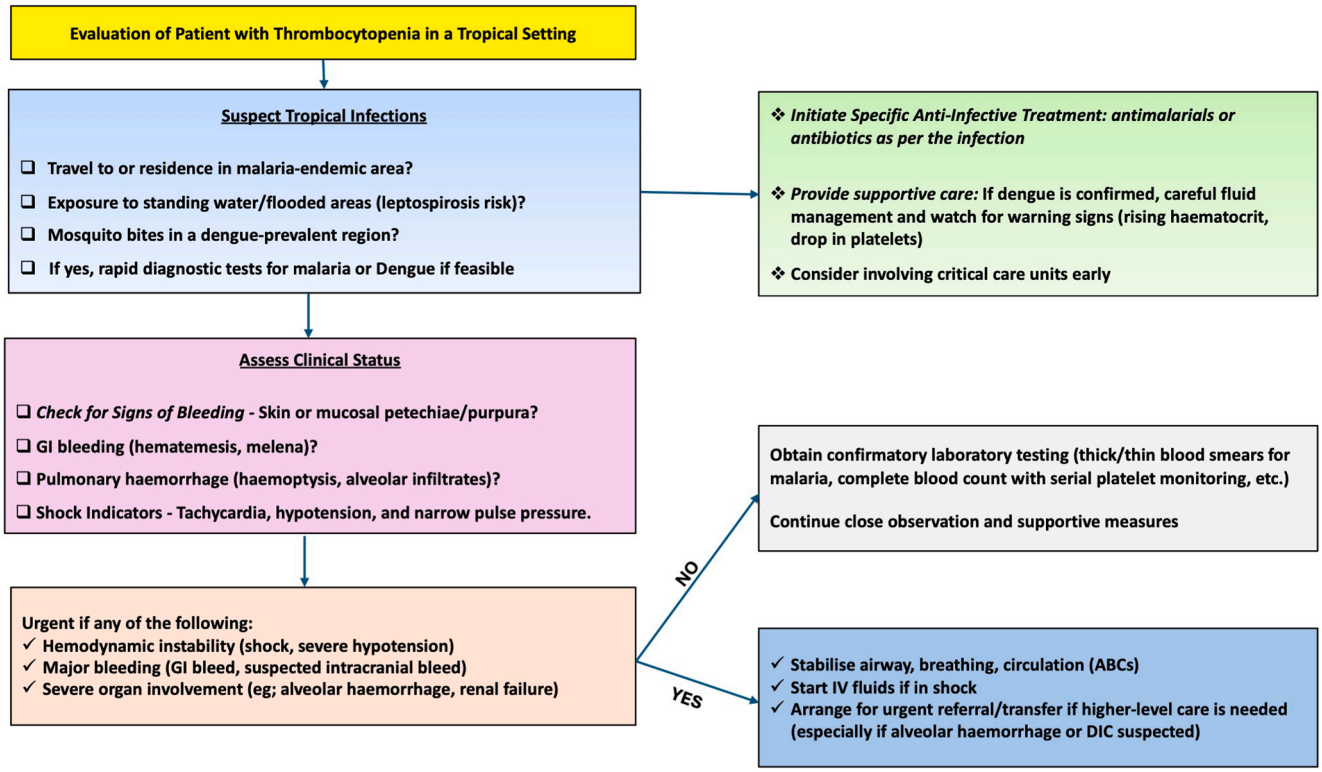

FIGURE 4 Evaluation of a patient with thrombocytopenia in a tropical setting. A structured diagnostic approach beginning with clinical history to identify epidemiological risk factors (eg, malaria, dengue, leptospirosis) and bedside assessment for bleeding or shock. Laboratory confirmation (thick/thin blood films, full blood count) guides management. Patients with hemodynamic instability, major bleeding, or severe organ involvement require immediate stabilization and urgent referral for higher-level care. DIC, disseminated intravascular coagulation; GI, gastrointestinal; IV, intravenous.

inflammatory cascades [4]. In dengue, an already heightened cytokine environment could theoretically worsen with transfusions, and in malaria, excessive platelet activation has been implicated in microvascular thrombosis and cerebral complications [8,46]. Another major pitfall is that prophylactic transfusions can sometimes aggravate fluid overload in dengue, where precise fluid management is crucial for balancing management of shock and respiratory compromise. Resource constraints form an added disincentive to use prophylactic transfusions in low-income regions. Platelet concentrates require specialized storage, continuous agitation, and screening for transfusion-transmitted infections, all of which can be logistically challenging during large outbreaks or in rural areas [37,99]. Indeed, platelet transfusions carry a greater risk of infection and death compared with transfusion of other blood products [71].

7.3 | Clinical studies of platelet transfusion in tropical disease

Clinical trials of platelet transfusion in tropical diseases have primarily studied patients with dengue, and to date, have failed to demonstrate significant benefit from transfusion. A multicenter, open-label, randomized study in 372 adults with dengue and profound thrombocytopenia (platelet count $<20 \times 10^9$/L) found no reduction in bleeding complications in participants receiving prophylactic platelet transfusions compared with those receiving supportive care alone [13]. In this trial, platelet counts did not differ significantly beyond day 2 after transfusion, and prophylaxis was associated with adverse events, including transfusion-related acute lung injury and fluid overload. Another prospective study of 158 patients with dengue and poor platelet recovery (defined as platelet count $<20 \times 10^9$/L on day 2 of infection) reported an increased likelihood of bleeding following prophylactic platelet transfusion [14]. A smaller randomized study of 87 patients with dengue and a platelet count of $<30 \times 10^9$/L allocated participants to supportive care or platelet transfusion, with no impact on bleeding observed [100]. Similarly, a large retrospective study of 788 patients with dengue and a platelet count $<20 \times 10^9$/L, of which 486 received prophylactic platelet transfusion, found no impact on bleeding or mortality [15]. Thrombocytopenia arising from various tropical infections often reflects ongoing platelet consumption or destruction [81,82]. It is therefore possible that newly transfused platelets are similarly destroyed or sequestered, and the net hemostatic benefit may be minimal. Given the absence of clinical trials in other tropical diseases, the role of platelet transfusion remains even less certain.

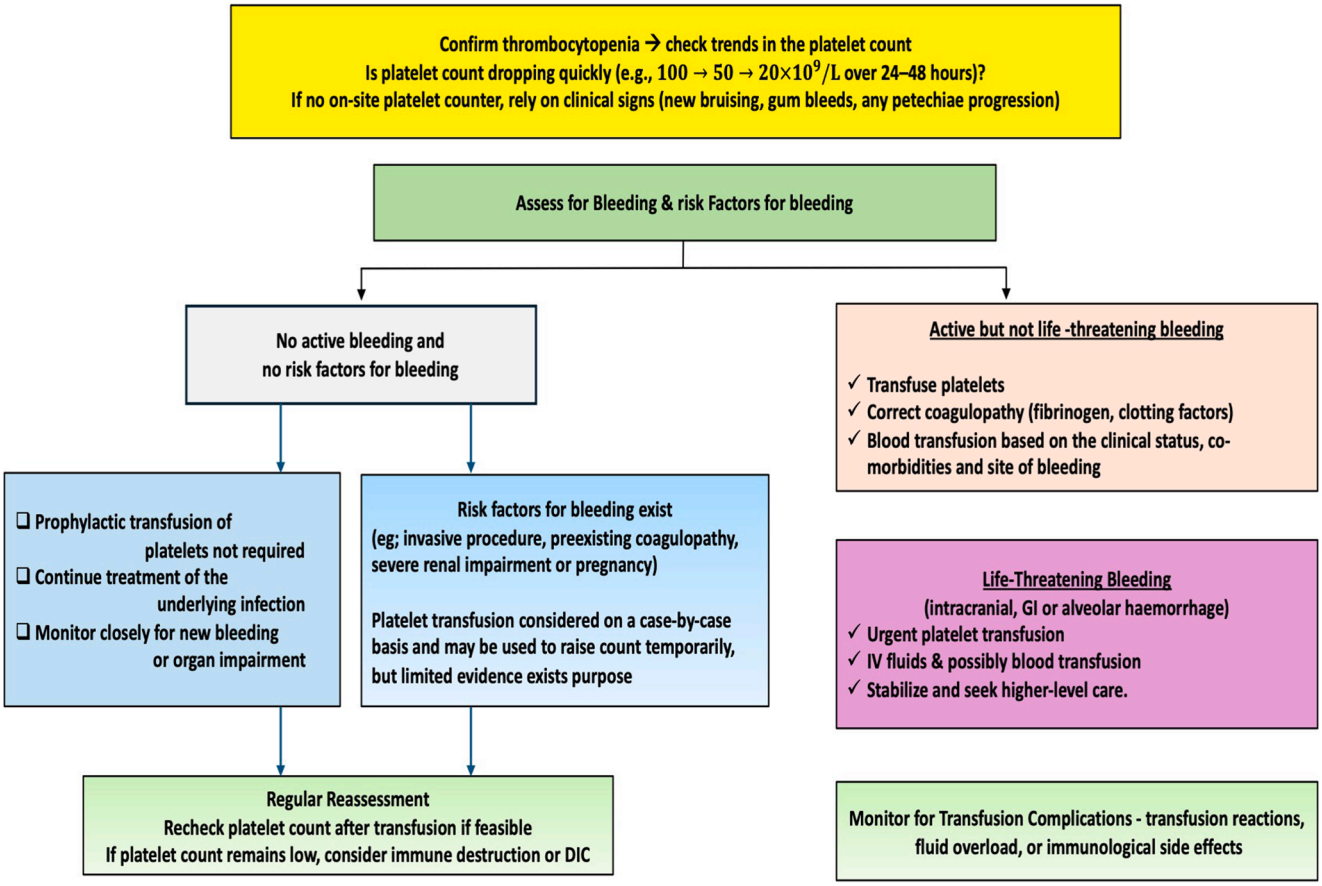

FIGURE 5 Algorithm for platelet transfusion and bleeding management in thrombocytopenia. Prophylactic transfusion is generally avoided without bleeding risk factors. Platelet support is individualized for active bleeding or invasive procedures. Urgent platelet and blood transfusions are indicated for life-threatening hemorrhage. Ongoing monitoring for transfusion-related complications and reassessment of platelet trends are emphasized. DIC, disseminated intravascular coagulation; GI, gastrointestinal; IV, intravenous.

7.4 | When should we consider platelet transfusion?

The WHO guidelines for dengue recommend avoiding routine prophylactic transfusions unless there is significant active bleeding or a clear necessity due to impending high-risk procedures [101]. Clinicians should transfuse platelets primarily for individuals with established hemorrhage (Figure 5). This stance reflects increasing recognition that a purely numeric platelet threshold is insufficient. The presence or absence of actual bleeding or major risk factors should guide therapy.

Across other tropical infections considered in this review, the evidence guiding platelet transfusion is sparse and largely observational, with no high-quality trials to define universal thresholds or clear net benefit. Consequently, decisions should be individualized based on active clinically relevant bleeding or clearly imminent high-risk procedures. Prophylactic transfusion for isolated thrombocytopenia is generally discouraged. Instead, clinicians should prioritize definitive antimicrobial or antiparasitic therapy and fluid and organ support.

In general, transfusion should be considered for those with active bleeding [102]. This involves active mucosal bleeding, persistent epistaxis, hematemesis, or melena, together with hemodynamic instability or organ compromise. Suspecting severe complications is particularly vital in tropical settings; alveolar hemorrhage in leptospirosis may present with hemoptysis or acute respiratory distress, cerebral malaria is suggested by altered mental status or seizures, and a narrow pulse pressure in dengue is often an early indicator of shock [45,79,101,103]. If transfusion is selected, the British Society for Haematology recommends maintaining the platelet count >50 $\times$ 10^9/L in cases of severe bleeding [104].

A watchful waiting strategy is therefore often employed in the absence of signs of severe bleeding or severe thrombocytopenia (platelet count <20 $\times$ 10^9/L) combined with other aggravating factors, and ongoing management with careful escalation revolves around daily or twice-daily monitoring of clinical parameters, alongside laboratory measures when feasible (Figure 6). Detecting alveolar hemorrhage early in leptospirosis or neurological changes in malaria can be lifesaving, as the clinician can escalate therapy promptly. This may involve, where available, referral to a higher-tier facility,

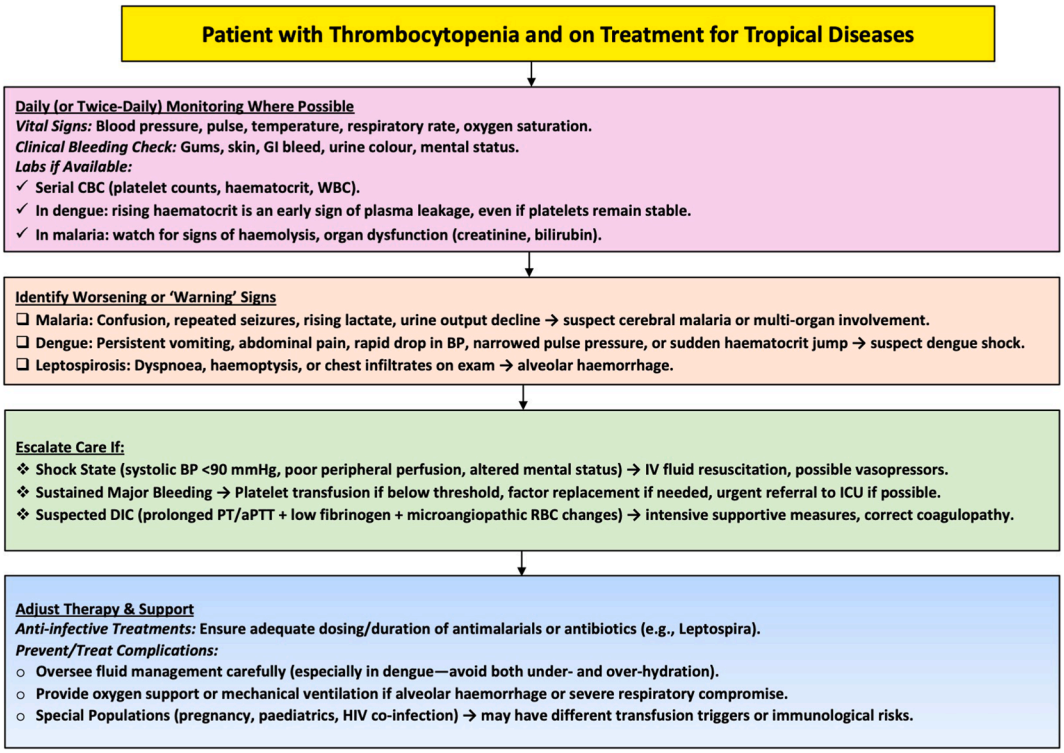

FIGURE 6 Management of a patient with thrombocytopenia receiving treatment for tropical infections. Monitoring recommendations for vital signs, hematologic parameters and warning signs of disease progression (eg, dengue shock, cerebral malaria, leptospiral pulmonary hemorrhage). Guidance is provided on escalation of care in shock or disseminated intravascular coagulation as well as adjustments to antimicrobial therapy, fluid management, and supportive measures. aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; DIC, disseminated intravascular coagulation; ICU, intensive care unit; PT, prothrombin time; WBC, white blood cell.

beginning mechanical ventilation, or addressing coagulopathy with additional blood products. The presence of DIC may also require that fibrinogen and other coagulation factors be simultaneously corrected [105]. The usefulness of antifibrinolytics such as tranexamic acid remains ambiguous in tropical infections [106]. One study found that intravenous tranexamic acid did not confer significant benefit over supportive care in dengue and may even correlate with adverse outcomes [107]. Antifibrinolytics cannot therefore be universally recommended.

Ultimately, platelet transfusions have a narrow but critical role in tropical infections complicated by thrombocytopenia. They can be lifesaving where significant hemorrhage is ongoing or imminent or where procedures must be performed in high-risk patients with very low platelet counts. Prophylactic use in stable patients is increasingly discouraged due to adverse effects, limited resources, and sparse evidence of efficacy. Consideration of special populations such as pregnant women or those in refractory shock is warranted. Sound judgment rooted in clinical signs of bleeding risk, appropriate triage for complications such as cerebral malaria or respiratory compromise, and essential supportive measures guides these decisions more reliably than fixed count thresholds. Expanding platelet indices and laboratory performance may help refine transfusion practices. Though for many resource-poor hospitals, the current emphasis remains on determining if platelet transfusion is truly necessary and ensuring alternative supportive therapies are optimized. Recognizing early when shock or organ failure mandates escalation to advanced care also remains crucial.

8 | CONCLUSION

Platelets play a vital yet double-edged role across a range of tropical infections. Their involvement extends well beyond hemostasis, encompassing immune modulation, endothelial integrity, and microvascular function. While prophylactic platelet transfusions were once considered a protective measure, evidence increasingly shows little benefit in preventing bleeding and, in some circumstances, they may exacerbate inflammation or resource shortages. Instead, early identification of platelet dysfunction and hyperdestruction, supported by platelet indices, can guide more judicious use of transfusions alongside targeted antimicrobials and comprehensive supportive care. This approach not only improves clinical outcomes for patients but also reduces the burden on limited healthcare resources in tropical regions.

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RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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