Review Article

When Less is More: Can We Abandon Prophylactic Platelet Transfusion in Dengue Fever?

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Abstract

Dengue fever (DF) has several hematological manifestations including thrombocytopenia and increased bleeding risk. Prophylactic platelet transfusion—in the absence of major bleeding—is utilized in DF with thrombocytopenia with the intention of preventing hemorrhagic complications. However, prophylactic platelet transfusion in DF is neither standardized nor supported by clinical evidence. We conclude that risks, costs and poor resource utilization associated with prophylactic platelet transfusion in DF far outweigh any potential hematological benefit, and as such, should not constitute routine clinical practice.

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Introduction

Dengue fever (DF) is the most common mosquito-borne human viral illness worldwide, and has rapidly spread to reach hyper-endemic proportions in the urban tropics over the last quarter of a century.[1] With an estimated 2.5 billion people at risk and a global annual incidence of 50 million cases, DF has been identified as an example of a potential international public health emergency.[2]

In understanding the unique pathophysiology of DF, revisiting the terminology is a useful first step. DF refers to the acute self-limited form, which by itself does not account for the mortality seen in this illness.[3] Dengue Hemorrhagic Fever (DHF) is a complication which in contrast to other viral hemorrhagic fevers is not characterised by overt or dramatic hemorrhagic manifestations; rather, the hallmark increased capillary permeability leads to fluid shifts from intravascular to interstitial and serosal compartments.[3] The most severe form of DHF—with significant intravascular volume depletion, hemodynamic compromise and poor organ and tissue perfusion—is termed Dengue Shock Syndrome (DSS).[3] Although the more recent World Health Organization (WHO) classification system has grouped the various forms of this illness into Probable Dengue, Dengue with Warning Signs and Severe Dengue,[2] the classical terminology of DHF and DSS is still widely used today. The new WHO classification is more clinically relevant in its approach in assessing disease severity, triaging hospital admission and dengue case management, and covers disease manifestations beyond the DF/DHF/DSS classification.[2]

Methods

We reviewed the published clinical data on prophylactic platelet transfusion and the basis for transfusion thresholds in dengue and non-dengue settings. We critically analysed the risks and benefits of prophylactic platelet transfusion as it applies specifically to DF. We examined existing clinical practice guidelines on prophylactic platelet transfusion. We then provide an evidence-based assessment of the utility of prophylactic platelet transfusion in DF.

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Results

Prophylactic Platelet Transfusion

Platelets are a crucial component of hemostasis. Conditions that compromise the number and function of platelets confer increased risks of hemorrhage. Since Duke's initial 1910 description of patients with bleeding attributed to thrombocytopenia, and good response to whole blood transfusion,[4] it was not until the last 50 years or so that platelet transfusions emerged as an intervention against hemorrhage.[5] Platelet transfusion based solely on thrombocytopenia with the intent of preventing major bleeding (prophylactic platelet transfusion) is widely practised in various healthcare settings around the world. A 1992 study by the American Association of Blood Banks' Transfusion Practice Committee reported that over 70% of hospitals transfused platelets primarily for prophylaxis, with an arbitrary transfusion threshold of 20 x 10^9/L or higher in 80% of these hospitals.[6] This prophylactic platelet transfusion threshold can be traced to published data half a century ago, and was widely adopted for many years despite lack of clinical evidence that 20 x 10^9/L is the appropriate transfusion threshold.[7]

Data from randomized clinical trials suggest that a decrease in platelets counts of up to 10 x 10^9/L may be tolerated without the need for prophylactic platelet transfusion in the absence of major bleeding.[8-10] In acute leukemic patients with chemotherapy-induced thrombocytopenia, major bleeding rates (any bleeding more than petechial, mucosal or retinal bleeding) were no different with prophylactic platelet transfusion thresholds of 10 x 10^9/L (21.5%) and 20 x 10^9/L (20%).[10] In another study involving patients with acute myeloid leukemia, the rates of mild to severe blood loss was the same in groups with 10 x 10^9/L and 20 x 10^9/L platelet transfusion thresholds.[8] Data also suggest that platelet counts even less than 10 x 10^9/L may be well tolerated without the need for prophylactic platelet transfusion, provided additional bleeding risks (significant coagulopathy, sepsis, anatomic aberrations, platelet function impairments) are absent: a single centre prospective analysis of 98 patients (2147 patient study days) demonstrated major bleeding in 1.39% (30/2147) of study days when platelet counts were <10 x 10^9/L; in 2.3% (50/2147) of study days when platelet counts were 10-20 x10^9/L, and in 5.4% (117/2147) of study days in patients with platelet counts >20 x 10^9/L.[11] In the absence of additional bleeding risk factors, major hemorrhage was noted in 0.51% (11/2147) of study days when platelet counts were greater than or equal to 10 x 10^9/L. Following the introduction of a stringent prophylactic platelet transfusion policy with a trigger of <10 x 10^9/L for stable patients, a 36% reduction in platelet transfusion was observed when compared with a transfusion trigger of 20x10^9/L (P <0.02), demonstrating the safety and cost-benefit of a transfusion trigger of <10 x 10^9/L in the absence of active bleeding and additional bleeding risks such as fever (>38^{0}C) or sepsis.

The British Committee for Standards in Hematology (BCSH), in its most recent guidelines on platelet transfusion, states that a threshold of 10 x 10^9/L is as safe as higher levels for patients without additional bleeding risk factors such as sepsis, concurrent use of antibiotics or other abnormalities of hemostasis[12] (Agency for Healthcare Research and Quality (AHRQ) grade A, level Ib evidence).

Singapore's clinical practice guidelines recommend prophylactic platelet transfusion at a trigger of 10 x 10^9/L for patients with impaired bone marrow function in the absence of additional bleeding risk factors (grade B, level 1+ evidence).[13] These guidelines also recommend prophylactic platelet transfusion in patients with impaired bone marrow function when platelet counts are less than 20 x 10^9/L in the presence of additional bleeding risk factors, or when there is a rapid decline in platelet count (grade C, level 2+ evidence).[13]

Available evidence suggests that an even lower platelet level may be safe in certain circumstances. Within the BCSH guidelines, a platelet transfusion threshold of 5 x 10^9/L is identified for patients without any bleeding risk factors if alloimmunisation leading to platelet refractoriness is a concern (AHRQ grade B, level IIa). A stringent transfusion threshold of 5 x 10^9/L was supported in a prospective analysis of 102 patients with acute leukemia, where 31 major bleeding episodes were observed at platelet counts of 1 x 10^9/L to 65 x 10^9/L, with most occurring in the presence of additional bleeding risk factors. Major bleeding occurred in 1.9% of study days with platelet counts equal to or less than 10 x 10^9/L, and in 0.07% of study days when platelet counts were 10-20 x10^9/L; the low prophylactic platelet transfusion threshold of 5 x 10^9/L was proven safe in the absence of additional bleeding risks such as new hemorrhagic manifestations or fever (>38^{0}C).[14] Data is limited on withholding prophylactic platelet transfusion in platelet counts less than 5 x 10^9/L.

There is also increasing interest in the strategy of therapeutic-only versus prophylactic platelet transfusions. The disparity in the relationship between platelet count and bleeding risk[15] has led to re-evaluating the need for platelet transfusion prophylaxis in otherwise stable patients. The trial of prophylaxis versus no-prophylaxis platelet transfusions (TOPPS), a randomized controlled study based in the United Kingdom, is designed to determine whether a therapeutic transfusion policy is as effective and safe as a prophylactic policy using a trigger of 10 x 10^9/L in hematologic patients.[16] Due to close in late 2011, the TOPPS study is expected to provide further insight into the safety of a therapeutic-only

platelet transfusion strategy.

The Relationship between Platelet Counts and Hemorrhage in Dengue

The mechanisms of hemorrhage in dengue are multi-factorial and incompletely understood. It is not, however, solely attributed to thrombocytopenia. Studies have demonstrated that the presence or degree of thrombocytopenia alone is not associated with increased bleeding risks in dengue.

In a prospective analysis of children with DSS,[17] only modest increase in prothrombin time (PT) and partial thromboplastin time (PTT) was noted. The plasma concentration of anticoagulants protein C, S and antithrombin III were noted to decrease with increasing severity of shock, likely due to increased capillary leakage. Increased levels of thrombomodulin, tissue factor and plasminogen activator inhibitor type 1 (PAI-1) were observed, with thrombomodulin levels increasing with severity of shock, and PAI-1 levels increasing with severity of bleeding. Direct activation of fibrinolysis by the dengue virus has been implicated, a process that distinguishes hemorrhage in dengue from that seen in classic disseminated intravascular coagulopathy.

In a prospective analysis of 114 children with DSS[18] in which 24 patients had severe bleeding and 92 patients had no bleeding, there was no significant difference in lowest platelet counts between the group with significant hemorrhage (median lowest platelet count 17 x 10^9/L; range 7.0-90.0) and the group with mild or no hemorrhage (median lowest platelet count 22 x 10^9/L; range 5.3-99.5). Similarly, PT and PTT were not significantly different between the 2 groups, nor was liver failure or renal failure. Prolonged duration of shock (Odds Ration (OR), 2.11; 95% Confidence Interval (CI), 1.13 to 3.92; P = 0.019) and low-normal hematocrit at time of shock (OR, 0.72; 95% CI, 0.55 to 0.95; P = 0.020)—suggesting blood loss in addition to capillary leakage—were the strongest predictors of hemorrhage in DHF/DSS.

The presence of fever is viewed as an additional risk factor for bleeding in the presence of severe thrombocytopenia. Severe thrombocytopenia in dengue occurs around the tail end of the febrile period; therefore it may be argued that fever, which is usually absent, or present only for 48-72 hours when platelet counts reach below 10-20 x 10^9/L, does not translate into significant, sustained additional bleeding risks.

The lack of association between bleeding severity and degree of thrombocytopenia has been demonstrated in numerous other examples, including a prospective analysis in which bleeding scores were not related to platelet counts, suggesting instead that vascular alteration and platelet activation seen in dengue infection—a separate, underlying process—was responsible for bleeding as well as thrombocytopenia.[19] In a retrospective cohort analysis of 256 patients admitted to hospital with dengue in Singapore, the incidence of clinical bleeding was 6% among patients with platelet count >150 x 10^9/L, 12% among patients with platelet count of 100-149 x 10^9/L, 11% among patients with platelet count of 80-99 x 10^9/L, 10% among patients with platelet count of 50-79 x 10^9/L, 11% among patients with platelet count of 20-49 x 10^9/L, 13% among patients with platelet count of 10-19 x 10^9/L, and 0% among patients with platelet count <10 x 10^9/L (P = 0.22), demonstrating no significant relationship between clinical bleeding and platelet counts.[20]

The majority of randomized controlled clinical trials involving prophylactic platelet transfusion have been conducted in hematology-oncology patients. There is a lack of corresponding randomized controlled trial data to address prophylactic platelet transfusion in dengue populations. Patient characteristics between leukemia and chemotherapy induced thrombocytopenic patients and dengue patients are invariably different, potentially confounding applicability of data from one group to the other. While both groups are expected to be susceptible to similar bleeding risk factors, the presence, duration and severity of these risk factors may vary between the two groups. Leukemia patients may have lower body temperature recordings than their dengue counterparts, potentially adding to the risk of bleeding in the latter, though it should be noted that fever and thrombocytopenia in dengue usually overlap only for 1 to 3 days. Prolonged fever, either due to severe dengue hepatitis or secondary bacterial infection, may increase bleeding risks in dengue patients when accompanied by severe thrombocytopenia. Conversely, dengue patients have otherwise healthy bone marrow, a much shorter duration of thrombocytopenia, and as a population, tend to be younger than their leukemia counterparts. Invasive fungal infections, fungemia and bacterial infections related to infected endovascular devices or neutropenia may confer higher bleeding risk in the hematology-oncology population. These factors may translate to a potentially lower risk of bleeding in the dengue group when stratified by platelet counts in the absence of uncorrected hemodynamic compromise, DHF and severe dengue.

Prophylactic Platelet Transfusions in Dengue

In an analysis of pediatric DSS, patients who received prophylactic platelet transfusions were compared with an equal number who did not. There was no significant difference in occurrence of hemorrhage between the two groups (P = 0.136); however, length of hospitalisation and

development of pulmonary edema were significantly higher in the prophylactic platelet transfusion group (P <0.05). [21]

In a retrospective cohort analysis of 256 patients with DF in Singapore whose platelet counts were <20 x 10^9/L without major bleeding, 188 patients received prophylactic platelet transfusion. Clinically significant bleeding occurred in transfused (1/188) and non-transfused (2/68) patients, with no significant difference in rates of bleeding (P = 0.17). The median time to platelet count >50 x 10^9/L was similar in the transfused and non-transfused groups (3 days; OR, 1.05; 95% CI, 0.79–1.39; P = 0.59).[20]

In dengue, even more so than in other conditions where prophylactic platelet transfusions are administered, the quantifiable increases and improvements in platelet counts and other coagulation parameters are transient at best. In DSS patients who underwent prophylactic platelet transfusion, platelet counts, prothrombin time ratio (PTR), and PTT returned to pre-transfusion values in less than 5 hours,[21] demonstrating the lack of sustained hemostatic benefit of prophylactic platelet transfusions in DF, which translates into lack of clinical efficacy as an intervention which happens to target a parameter – platelet counts – which is not the implicated culprit of major bleeding in dengue.

Risks of Platelet Transfusion

Platelet transfusion, whether pooled random-donor platelet concentrates or single-donor apheresis platelets, carries with it a variety of risks including alloimmunisation and platelet refractoriness, allergic reactions, febrile non-hemolytic reactions, bacterial sepsis and less commonly, transfusion associated acute lung injury, viral and parasitic infections.[22-29] Platelet transfusion-related pulmonary edema from volume overload has been reported in DF,[21] which is not surprising considering the unpredictable and poorly understood fluid shifts that occur in this illness. It is estimated that 1 in 1000 to 3000 platelet units are contaminated with bacteria which can result in transfusion associated sepsis in recipients, resulting in life-threatening sepsis in 1 in 100,000 recipients and immediate fatal outcomes in 1 in 500,000 recipients.[22] Transfusion-related bacterial sepsis is the second most frequent cause of transfusion-related deaths in the United States, accounting for 46 (17%) of 277 reported transfusion deaths during 1990-1998.[22] Platelets carry an added risk of bacterial contamination due to room temperature storage for up to 5 days, compared with other blood products which are stored at refrigeration or frozen temperatures. Furthermore, pooled platelets carry a higher risk for viral and bacterial infections than red blood cell transfusions, as platelets are typically pooled from 4 to 8 donors.[23] Despite the introduction of bacterial testing in recent years, transfusion-associated sepsis continues to occur. This risk is thought to be under-recognised and under-reported: a survey of US infectious disease consultants revealed that only 36% of participants were aware of bacterial contamination of platelet transfusion being one of the most common risks to platelet recipients.[22]

There remains a risk of acquiring viral infection via platelet transfusion although this has been reduced significantly by enhanced screening and testing methods. The risk of acquiring Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV) following transfusion is currently very low in most developed countries.[23-28] For instance, some estimates report the risk of HIV-1 infection from transfusion to be about 1 in 493,000 donor units (95% CI, 202,000 to 2,778,000); for HTLV, 1 in 641,000 (256,000 to 2,000,000); for HCV, 1 in 103,000 (28,000 to 288,000); and for HBV, 1 in 63,000 (31,000 to 147,000).[28] With the advent of nucleic acid technology (NAT) in blood supply screening in 1999, the risk of transfusion-transmitted HBV is estimated to be 1 in 282,000 to 1 in 357,000; 0.03-0.5 in 1,000,000 for HCV and 1 in 1.5 million to 1 in 4.3 million for HIV.[30] Nevertheless, reports of transmission of HBV as well as HIV (as recently as 2007) via NAT-negative units serve as humbling reminders that zero risk has not yet been achieved.[30] The presence of leukocytes in platelet products also increases the risk of cell-associated viral infections, most commonly Cytomegalovirus, Epstein-Barr Virus, Human Herpes Virus type 6, and Human T- Lymphotrophic Virus (HTLV) I and II. In economically under-developed countries where the majority of dengue occurs, one cannot expect the same NAT-driven safety standards in pathogen transmission, which makes stringent transfusion recommendations that much more important.

The presence of leukocytes in platelet preparations is largely responsible for febrile non-hemolytic transfusion reactions via generation of cytokines, which occurs in an estimated 30% to 40% of platelet transfusion recipients.[27] Alloimmunisation, as well as non-immune causes, may result in platelet refractoriness and future platelet transfusion complications. Platelet transfusion can also cause significant hypotension in patient on angiotensin converting enzyme inhibitors by generation of large amounts of bradykinin by filtration of platelet concentrates through a negatively charged filter.[31]

In the US, it is estimated that a single unit of packed red blood cells has an acquisition cost of US$200, which translates to an actual cost of US$1600 to US$2400 once all direct, indirect and variable costs along with the increased costs to any one patient's hospital stay as a result of a transfusion-associated morbidity have been factored in. The acquisition cost for a unit of apheresed platelets is over US$500; applying the packed red-cell cost formula,

the actual cost of platelet transfusion becomes considerably higher than the aforementioned figures.[29] Using pharmaco-economic models, examples of massive healthcare savings by even modest reduction in transfusions have been demonstrated: in a US cardiothoracic surgery setting, savings from single unit reductions in transfusions per case leads to annual savings of US$480,000 to US$720,000 (when performing 300 cases of cardiothoracic cases per year) to US$1,120,000 to US$1,680,000 (when performing 700 cases per year).[32]

Conclusion

Prophylactic platelet transfusion criteria in dengue have not been clearly defined as standard practice guidelines or as recommendations stemming from randomized clinical trials. As a result, a wide variety of transfusion triggers can be observed in clinical practice.

Singapore's Clinical Practice Guidelines recommend prophylactic platelet transfusion in patients with impaired bone marrow function at transfusion triggers of 20 x 10^9/L and 10 x 10^9/L respectively depending on the presence or absence of additional bleeding factors.[13] In this context, it should be noted that dengue patients have preserved bone marrow function as opposed to their hematology and oncology counterparts. The guidelines further recommend prophylactic platelet transfusion in patients with DF "who experience a rapid fall in platelet count or in the presence of prolonged clotting times"[13] (no assigned grade or level of evidence). This recommendation cites two retrospective single-institution studies.[33,34] The first, a pediatric study based on 1986 WHO criteria (not currently utilized), found no statistical significance between platelet count and bleeding risk, and the occurrence of bleeding was not correlated with platelet counts (P = 0.207). The authors noted that "patients with marked thrombocytopenia did not bleed but those with moderate thrombocytopenia had acute bleeding" suggesting additional bleeding risk factors are at play. Furthermore, this was a study that utilized platelet transfusions therapeutically—for patients with active bleeding—rather than prophylactically.[33] The second study cited in the guideline recommendation also noted the absence of significant correlation between bleeding and thrombocytopenia in dengue; the study authors noted that inappropriate platelet transfusion was a major concern.[34] These factors may limit the quality and strength of recommendations of Singapore's clinical practice guidelines on prophylactic platelet transfusion in dengue.

We currently lack the benefit of randomized control trails to clearly define prophylactic platelet transfusion thresholds in dengue. Until such data become available, we are forced to scientifically analyse the best available data in dengue patients including several well conducted prospective studies and retrospective analyses, and extrapolate other applicable findings from non-dengue settings such as acute leukemia patients, where a larger collective database and

Table 1. World Health Organization Bleeding Categories

Bleeding Grade	Features
Grade 1	-Mucocutaneous hemorrhage (oral blood blisters) -Petechiae (lesions <2 mm in size) -Purpura (lesions <2.54 cm (1inch diameter) -Ecchymosis (lesions <10 cm in size) -Oropharyngeal bleeding -Conjunctival bleeding -Epistaxis <1 hour in duration and not requiring intervention -Abnormal vaginal bleeding (nonmenstrual) with spotting (< 2 pads per day)
Grade 2 (Does not require red cell transfusion)	-Ecchymosis (lesions >10 cm in size) -Hematoma -Epistaxis >1 hour in duration or packing required -Retinal hemorrhage without visual impairment -Abnormal vaginal bleeding (not normal menses) using >2 pads/day -Melena, hematemesis, hemoptysis, hematuria, hematochezia -Bleeding from invasive sites, musculoskeletal bleeding
Grade 3 (Requiring red cell transfusion specifically for support of bleeding within 24 hours of onset)	-Melena -Hematemesis -Hemoptysis -Hematuria−including intermittent gross bleeding without clots -Abnormal vaginal bleeding -Hematochezia -Epistaxis -Oropharyngeal -Bleeding from invasive sites, musculoskeletal bleeding, or soft tissue bleeding
Grade 4	-Debilitating bleeding including retinal bleeding with visual field deficit -Nonfatal central nervous system (CNS) bleeding with neurologic signs and symptoms -Fatal bleeding from any source

Data from Heddle NM et al[35] and Miller AB et al[36]

analyses including randomized controlled trials have indeed addressed the issue of prophylactic platelet transfusion.

Based on the evidence summarised herein, we propose that prophylactic platelet transfusion in dengue patients may be safely withheld for platelet counts as low as 5 x 10^9/L in the absence of additional bleeding risk factors such as prolonged high fever (as seen in dengue patients with severe hepatitis and secondary bacterial infections), sepsis, vascular compromise, anatomic aberrations, significant coagulopathy, uncorrected hemodynamic instability, DHF and severe dengue.

We propose that, in the absence of such additional bleeding risk factors, platelet transfusion in dengue should be reserved for patients with major bleeding (Grade 2 and above in WHO bleeding scale, see Table 1). Careful observation without platelet transfusion is warranted in stable dengue patients with only minor 'dry' bleeding such as petechiae, ecchymoses and minor 'wet' bleeding such as mucosal oozing (WHO bleeding scale Grade 1, see Table 1). Factors that contribute to increased risk of bleeding such as those mentioned above may warrant higher platelet transfusion triggers based on astute clinical judgment.

In summary, the authors are of the opinion that prophylactic platelet transfusion in stable dengue patients without additional bleeding risk factors may be avoided without compromising patient safety. More importantly, prophylactic platelet transfusion, when viewed as an intervention not supported by best available clinical evidence, confers added risks to patients via adverse events including alloimmunisation, platelet refractoriness, allergic reactions, transmitted bacterial and viral infections, acute lung injury and hemolysis to name a few. Furthermore, significant healthcare costs—both direct and indirect—as well as unnecessary usage of a precious transfusion commodity may be avoided by adhering to stringent platelet transfusion policies while actually improving patient safety and outcomes.

Attempting to increase platelet counts via transfusion in the absence of major bleeding has not conferred protective benefits from bleeding in dengue. Rather, early recognition of dengue, especially severe dengue and DHF, with prompt correction of hemodynamic parameters, remains the cornerstone of avoiding hemorrhage and ensuring good clinical outcomes.

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