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Platelet Transfusions for Patients with Consumptive Thrombocytopenias

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Background: Consumptive thrombocytopenia (CT) is a pathophysiologic finding shared by a number of disorders and manifesting as an acute or subacute decrease in platelet count – sometimes to an extremely low level. In some CTs, the concomitant aggregation of activated platelets can promote arterial or venous thrombosis and lead to ischemic organ dysfunction. Thus, when caring for patients affected by CTs, it can be challenging to balance the benefits of platelet transfusions (PTs) with their thrombogenic risks.

As randomized clinical trials (RCTs) in this area are sparse and often impractical, decisions about when to transfuse platelets are frequently guided by observational studies and expert opinions. This review will focus on four specific CTs: (1) disseminated intravascular coagulation (DIC), (2) heparin-induced thrombocytopenia (HIT), (3) immune thrombocytopenic purpura (ITP), and (4) thrombotic thrombocytopenic purpura (TTP).

Pathophysiology: The pathophysiology of CTs is remarkably heterogeneous, as is summarized by Table 1. Regardless of the diverse mechanisms involved, however, platelet consumption in these disorders can be associated with bleeding risks that are, to varying degrees, offset by the hypercoagulable state (for DIC) or platelet activation (more apparent for TTP and HIT) which have created the primary problem. Platelet activation, moreover, plays a direct role in the thrombogenic process and may be fueled by PTs.

Table 1: Pathophysiology of Selected CTs[1-4]

Disorder	Pathophysiology (and Thrombogenic Risk)
DIC	Systemic activation of coagulation system with consumptive coagulopathy plus hyperfibrinolysis (intravascular fibrin generation causes thrombosis of small- and medium-sized vessels with risk for eventual organ dysfunction)
HIT	Antibodies to PF4/heparin complexes crosslink Fcγ receptors on platelets leading to platelet activation plus thrombin generation (thromboembolic complications occur in up to 50% of affected patients)
ITP	Autoantibodies plus cytotoxic T cells directed against platelet antigens leading to accelerated platelet destruction (a substantial minority of patients have anti-phospholipid antibodies which are independently associated with thrombosis)
TTP	Congenital or acquired ADAMTS13 deficiency leading to reduced cleavage of VWF multimers and formation of microvascular platelet thrombi (renal and neurologic impairment is a result of micro-thrombi within small vessels)

Legend: PF4 = Platelet factor 4; VWF = von Willebrand factor

Key Points

- Consumptive thrombocytopenia, with its diverse etiologies and concomitant risks of bleeding and thrombosis, represents a unique clinical dilemma with respect to platelet transfusion decision-making (which must be tailored to individual patients).
- In patients with DIC, prophylactic and therapeutic platelet transfusions have been proposed to maintain platelet counts above 20 x 10^9 and 50 x 10^9 cells/L, respectively, depending on the presence and/or severity of bleeding.
- There is no proven benefit of platelet transfusions in consumptive platelet disorders, while, in patients with TTP and HIT, platelet transfusions may increase the odds of arterial thrombosis and overall mortality.

Indications for Platelet Transfusions: Recent guidelines from AABB recommend prophylactic PTs for hospitalized adult patients with chemotherapy-induced hypoproliferative thrombocytopenia when platelet counts fall below 10 x 10^9 cells/L.[5] This is a strong recommendation supported by moderate-quality evidence. Other recommendations are weak and based on evidence of low to very low quality. For instance, prophylactic PTs should be considered for patients undergoing central venous catheter (CVC) placement with platelet counts below 20 x 10^9 cells/L and diagnostic lumbar punctures or elective nonneuraxial surgeries with platelet counts below 50 x 10^9 cells/L.[5]

It is important to note that the above recommendations do not apply directly to patients affected by CTs. The indications for prophylactic PTs for patients with CTs remain unclear due to the lack of strong evidence; most important is treating the underlying cause of platelet consumption. Platelet counts are expected to recover rapidly after: (1) appropriate antimicrobial therapy in patients with sepsis-triggered DIC, (2) initiating plasmapheresis in patients with TTP, (3) discontinuing heparin in patients with HIT, and (4) administering corticosteroids and/or intravenous immunoglobulin in patients with ITP. Thus,

thrombocytopenia constitutes a temporary problem in the majority of these cases and prophylactic PTs probably can be safely withheld (with the possible exception of DIC, as is discussed in the following paragraph) – especially when the platelet counts are $\geq$ 10 x 10^9 cells/L. It is uncertain whether it is necessary, when treating patients suffering from these conditions, to target platelet counts of at least 20 x 10^9 cells/L before CVC placement (or higher for other invasive procedures). In emergent settings, however, this often is a moot point, as it is not uncommon for patients to be transfused with platelets before the consumptive process is even recognized.

DIC probably promotes the most severe and prolonged consumption of platelets and coagulation factors; thus, both prophylactic and therapeutic PTs have been widely used during its management.[1,6] A recent international consensus[1] suggests administering prophylactic PTs to maintain platelet counts $\geq$ 20 x10^9 cells/L in DIC patients without bleeding or thromboses. It also emphasizes the importance of tailoring PTs for individual patients. For example, in DIC patients with major bleeding, it seems reasonable to maintain platelet counts $\geq$ 50 x 10^9 cells/L.[1] These recommendations are based on expert opinions, while one small RCT in this setting (albeit published over 30 years ago) suggests no impact of PTs on patient survival or coagulation testing results.[7]

For patients with HIT, ITP, and TTP experiencing active bleeding, therapeutic PTs are not absolutely contraindicated. The dose should be adjusted empirically based on the grade of bleeding, with close monitoring for thromboembolic complications in HIT and TTP patients.[2-4]

Efficacy and Safety of Platelet Transfusions: The efficacy of PTs can be measured by the grade, frequency, and duration of bleeding, although these indicators are difficult to assess in retrospective, observational studies. For other important outcomes, such as patient survival, the underlying disease may have a more direct impact than the PTs.

The suspicion that PTs augment thrombotic risks in TTP and HIT has found support in a recent study of thousands of cases from the Nationwide Inpatient Sample Database.[6,8] After observing that PTs were frequently administered to hospitalized patients with TTP, HIT, and ITP (with PT incidence rates of 10.1%, 7.1% and 25.8%, respectively), the authors noted that the transfused patients were more likely to have bleeding events than their non-transfused counterparts, perhaps due not so much to lack of efficacy of PTs as to confounding by indication. PTs also were associated with significantly increased odds of arterial thrombosis and mortality in TTP and HIT patients after adjusting for demographics and clinical severity and acuity.[6] No significant thromboembolic associations were found for ITP patients. Despite the intrinsic limitations of database research, the study provides a panoramic view of the practice of PTs in DIC, HIT, and TTP and heightens concerns for risks associated with PTs, especially for patients with TTP and HIT.

Table 2: Platelet Transfusions for Selected CTs

Disorder	Platelet Transfusion Considerations
DIC	Consider prophylactic PTs for plt ct < 20,000 x 10^9/L*
HIT	Do not transfuse plts prophylactically* PTs may increase risk for arterial thrombosis and death
ITP	Do not transfuse plts prophylactically* PTs do not appear to worsen pt outcome
TTP	Do not transfuse plts prophylactically* PTs may increase risk for arterial thrombosis and death

*Note: When considering the need for therapeutic PTs, the decision-making process should in general mirror what is applied to non-CT patients but take into account the additional risk for adverse outcomes in HIT and TTP.
Legend: ct = count; plt = platelet.

Conclusion: Platelet consumptive disorders are heterogeneous in their pathophysiology as well as with respect to their risks for bleeding and thrombosis. PTs should be reserved for such patients who are experiencing severe bleeding, or administered prophylactically in selected DIC patients. The dose should be tailored to individual patient needs based on careful evaluation, andclose monitoring for thromboembolic events is warranted.

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