A Rational Approach to the Diagnosis and Management of Thrombocytopenia in the Hospitalized Patient

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Thrombocytopenia is one of the most common reasons for inpatient hematology consultations. The main challenges in the management of hospitalized patients with thrombocytopenia are to identify the underlying cause and to recognize when urgent interventions are required. Examination of the blood film is essential in the investigation of any patient with thrombocytopenia, and the context in which thrombocytopenia occurred, its severity, timing, and association with bleeding are important clues to the diagnosis. Evidence from randomized trials provides some guidance on the use of platelet transfusions for patients with chemotherapy-induced thrombocytopenia; however, recommendations for non-oncology patients are based largely on expert opinion. Thrombocytopenia does not protect against thrombosis and antithrombotic therapy is often required for patients despite very low platelet counts and as a general rule, antithrombotic therapy should not be withheld because of thrombocytopenia alone. In this article normal platelet homeostasis and the epidemiology of thrombocytopenia in hospitalized patients are reviewed. We provide a practical approach to the investigation and management of this common problem and discuss contentious issues including when to use platelet transfusions and how to manage antithrombotic therapy in the setting of thrombocytopenia.
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The number of circulating platelets is normally tightly regulated. Pathological processes and certain physiological conditions may result in the development of thrombocytopenia. Thrombocytopenia is a common problem among hospitalized patients, and the diagnosis and treatment are directed at the underlying cause; however, nonspecific interventions aimed at raising the platelet count may be required when thrombocytopenia becomes severe or when additional risk factors for bleeding are present. In this review we provide a practical approach to thrombocytopenia in the hospitalized patient, including a discussion about when to use platelet transfusions and how to manage concomitant antithrombotic therapy.

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NORMAL PLATELET HOMEOSTASIS

Platelets are anucleate cells that are involved in the process of primary hemostasis. They are attracted to sites of vessel wall injury initially through interactions between platelet glycoprotein IbIX and von Willebrand factor and subsequently through platelet agglutination mediated by fibrinogen binding to platelet glycoprotein IIbIIIa. Ultimately, platelets become activated in a highly regulated manner that results in the exposure of phospholipid surfaces, the release of procoagulant proteins, and the formation of a localized clot. In conditions of thrombocytopenia, this process may be impaired resulting in an increased risk of bleeding.

Regulation of Platelet Number

The number of circulating platelets is a function of the rate of platelet production by megakaryocytes balanced against the rate of platelet removal after their 7- to 10-day lifespan and normal platelet pooling in the spleen.[1] Platelet production is tightly regulated by the hormone thrombopoietin (TPO), which is secreted by the liver at a constant rate (constitutive secretion) and

Table 1. Physiological Causes of Thrombocytopenia

	Typical Platelet Count	Mechanisms
Pseudothrombocytopenia	70×10^9/L	EDTA-dependent platelet antibodies, which cause platelet clumping in vitro
Incidental thrombocytopenia of pregnancy	Nadir of 70×10^9/L occurring late in pregnancy	Uncertain
Surgery	Platelet counts between 50 and 150×10^9/L between 1 and 4 days after major surgery	Dilution, consumption
Massive transfusion	Thrombocytopenia worsens with the number of RBC units transfused; platelets less than $<50 \times 10^9$/L may occur after 20 RBC units transfused within 24 hours	Dilution, consumption

Abbreviations: EDTA, ethylenediaminetetraacetic acid; RBC, red blood cells.

acts on hematopoietic progenitor cells, bone marrow megakaryocytes, and platelets by binding to its receptor c-Mpl.[2–5] Binding of TPO to c-Mpl leads to the differentiation of hematopoietic progenitor cells down the megakaryocyte lineage, maturation of megakaryocytes, and ultimately increased platelet production. Once TPO is bound to c-Mpl, it is internalized, degraded, and removed from the circulation. Levels of free TPO are therefore controlled by the number of circulating platelets and the megakaryocyte mass: when platelet levels and megakaryocyte numbers are low, free TPO levels are high and more platelets are produced; when platelet levels are high, circulating TPO levels are reduced.[6] Although the processes of platelet production, destruction, and pooling are complex, platelet counts within individuals appear to remain remarkably constant over time.[7] The baseline platelet count is therefore a key piece of information in the evaluation of patients with thrombocytopenia.

Physiological Influences on Platelet Count Number

In a population study of 12,142 individuals enrolled in the Third National Health and Nutrition Examination Survey (NHANES III), females had a slightly higher platelet count than males and blacks had a slightly higher platelet count than whites after controlling for environmental covariates.[7] Other studies with less adjustment for confounding have shown that platelet counts tend to be lower in blacks,[8,9] and data from five population-based cohorts in the United States enrolling more than 30,000 individuals showed that the platelet count level was similar between groups.[10] In summary, if platelet count is influenced by gender and/or ethnicity, these influences are small and generally do not account for reductions in platelet count levels that are below the normal reference range.

However, certain physiological conditions may cause platelet counts to register below the lower limit of normal, including platelet clumping in vitro, incidental thrombocytopenia of pregnancy, and hemodilution (Table 1). Pseudothrombocytopenia is a laboratory artifact that results from platelet clumping due to naturally occurring ethylenediaminetetraacetic acid (EDTA)-dependent platelet antibodies.[11] Examination of the blood film confirms the diagnosis, and a repeat sample using a different anticoagulant or collected at 37°C resolves the issue for most patients. Pseudothrombocytopenia has no clinical significance in vivo. During pregnancy, 6% of women will develop incidental (or gestational) thrombocytopenia of unknown cause, accounting for approximately 75% of all thrombocytopenias presenting in pregnancy.[12] Platelet counts may decrease to as low as 70×10^9/L in this condition, which must be differentiated from pathological disorders such as pregnancy-related hypertensive disorders and pregnancy-associated immune thrombocytopenia (ITP).[13]

EPIDEMIOLOGY OF THROMBOCYTOPENIA IN HOSPITALIZED PATIENTS

Incidence and Prevalence

Thrombocytopenia, typically defined as a platelet count less than 150×10^9/L, is a common occurrence in hospitalized patients. In a registry of more than 64,000 patients admitted to hospital with non-ST segment elevation acute coronary syndromes, 6.8% of patients had baseline thrombocytopenia and 13% devel-

oped thrombocytopenia during their hospital stay.[14] In another study of 2,420 hospitalized medical patients receiving heparin for at least 4 days, 36% developed thrombocytopenia.[15] A systematic review of 6,894 critically ill patients reported that thrombocytopenia was present in 8% to 68% of patients on admission to the intensive care unit (ICU) and developed in 13% to 44% of patients during their ICU stay.[16]

Major surgery is another common cause of thrombocytopenia in the hospitalized patient. After major surgery, platelet counts typically decline quickly and reach their nadir within 1 to 4 days due to consumption and dilution.[17] In a study of 581 patients who underwent cardiac surgery with cardiopulmonary bypass, thrombocytopenia occurred in 56.3% of patients within 10 days of surgery.[18] Similar decreases in the platelet counts were observed in patients undergoing abdominal, vascular, or major trauma surgery, although the nadir was reached earlier and platelet count recovery was faster following abdominal surgery.[19]

Thrombocytopenia is also expected following massive transfusion due to hemodilution. In a retrospective study (n = 39 trauma patients), of the four patients who received 20 or more red blood cell (RBC)-containing products, three (75%) developed a platelet count less than 50×10^9/L compared to none who received fewer than 20 RBC units.[20] These expected patterns of platelet count fall and rise after surgery or massive transfusion are important to recognize because deviations, especially late-onset thrombocytopenia, may signal dangerous pathological disorders such as heparin-induced thrombocytopenia (HIT).[21]

Thrombocytopenia as a Predictor of Bleeding

Surprisingly, the relationship between thrombocytopenia and bleeding has not been well characterized. Early studies in patients with leukemia suggested that the bleeding risk is proportional to the degree of thrombocytopenia beyond a certain threshold[22]; more recent evidence derives from platelet transfusion trials. A randomized controlled trial (RCT) evaluating different platelet transfusion doses in patients with chemotherapy-associated thrombocytopenia suggested that major bleeding was mostly restricted to patients with a platelet count of 5×10^9/L or less.[23] Another RCT was stopped early because of an excess of major bleeding events in the low-dose platelet transfusion group.[24] In a systematic review of RCTs evaluating different platelet transfusion thresholds, rates of bleeding were similar in patients with a platelet transfusion threshold of 10×10^9/L or 20×10^9/L.[25] Thus, in oncology patients, only very severe thrombocytopenia, for example, a platelet count below 10×10^9/L (and maybe $<5 \times 10^9$/L), is associated with an increased risk of bleeding.

Very few studies have examined the relationship between thrombocytopenia and bleeding in non-oncology patients. For example, in patients with ITP, observational data suggest that bleeding rarely occurs with platelet counts above 30×10^9/L,[26] and evidence-based guidelines suggest that platelet-raising therapies are generally not necessary when platelet counts are above 20 to 30×10^9/L.[27] In critically ill patients, a systematic review of the epidemiology of thrombocytopenia identified only one study that used multivariable analysis to examine the association with bleeding, and found no association.[28] It seems apparent that, in addition to the absolute platelet count number, patient-specific characteristics are likely to be important modifiers of the relationship between thrombocytopenia and bleeding, especially for critically ill and surgical patients who have complex comorbidities, frequently require invasive procedures, and have variable causes for thrombocytopenia.[29] Additional studies in this area are needed.

Thrombocytopenia as a Predictor of Death

In almost all patient populations, the presence of thrombocytopenia appears to be an ominous sign. In patients receiving heparin-based anticoagulation in the hospital, thrombocytopenia was a weak predictor of the composite of mortality and rehospitalization at 6 months (hazard ratio = 0. 80; 95% confidence interval [CI], 0. 65–0. 98).[30] In patients with acute coronary syndrome, the development of thrombocytopenia—irrespective of the cause (HIT [0. 3%], glycoprotein IIb/IIIa associated thrombocytopenia [0. 6%] or other thrombocytopenia [0. 7%])—was associated with higher rates of major bleeding, recurrent infarction, stroke, and in-hospital death.[31] In critically ill patients, the presence of thrombocytopenia was found to be an independent predictor of death in hospital (odds ratio [OR], 2. 1–26. 2) and in the ICU (OR, 3. 1–4. 2) across six observational studies (N = 6,894).[16]

Association Between Thrombocytopenia and Thrombosis

Not only does thrombocytopenia not protect against the development of thrombosis, in some circumstances it may be associated with an increased risk.[32] Examples are the antiphospholipid antibody syndrome (APS), HIT, and disseminated intravascular coagulation (DIC).

In retrospective cohort studies, patients with APS who had thrombocytopenia had similar rates of venous and arterial thromboembolic events compared to APS patients with normal platelet counts, suggesting that thrombocytopenia offered no protection.[33,34] In a retrospective analysis of 408 patients with HIT, severity of thrombocytopenia correlated with an increased risk of thrombosis; patients with more than 90% decrease in platelet count had the highest risk (OR, 8. 79 [95% CI, 2. 26–34. 17]).[35] DIC is characterized by uncontrolled thrombin generation, resulting in depletion of coagulation factors and fibrin and platelet deposition in the

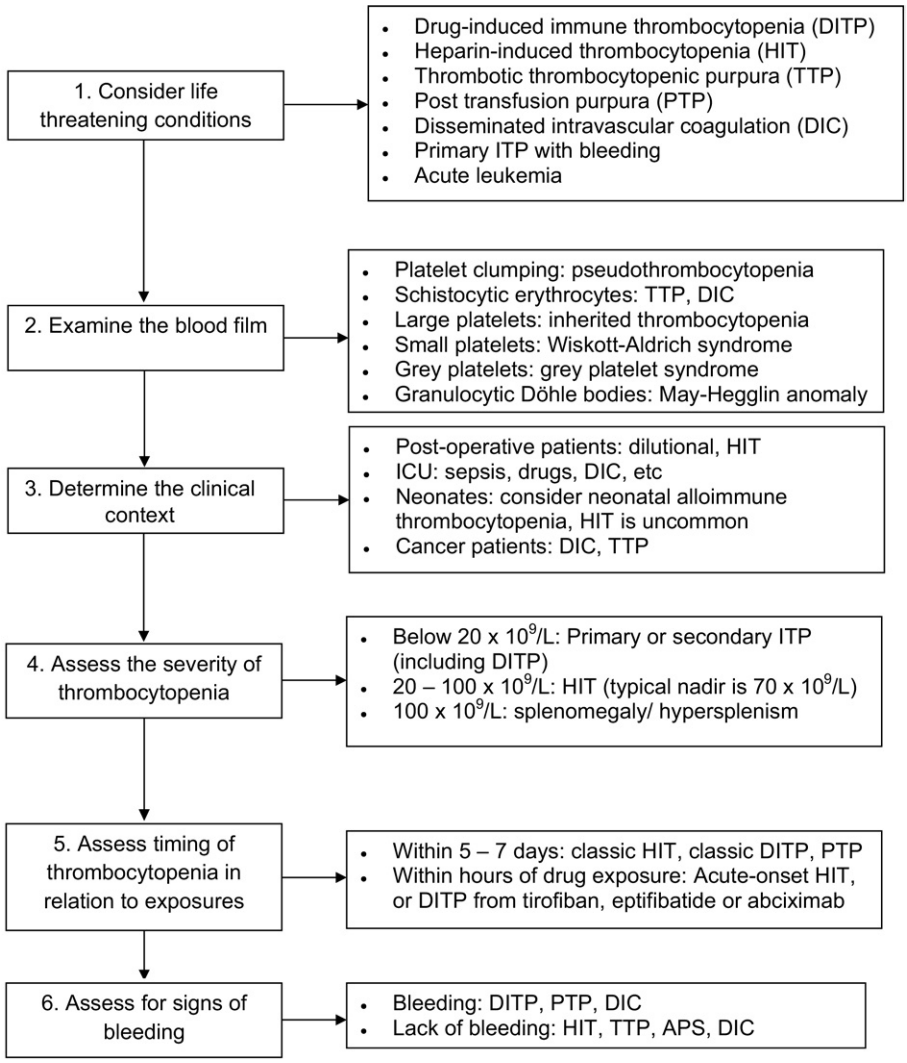

Figure 1. Rational approach to the diagnosis of thrombocytopenia in the hospitalized patient. ICU, intensive care unit.

microcirculation producing hypofibrinogenemia and thrombocytopenia. DIC can present with bleeding and/or thrombotic manifestations despite moderate to severe thrombocytopenia.[36]

APPROACH TO THE DIAGNOSIS OF THROMBOCYTOPENIC DISORDERS

The differential diagnosis of thrombocytopenia in the hospitalized patient is wide and a detailed description of each of the causes of thrombocytopenia is beyond the scope of this article. A conventional mechanistic approach to thrombocytopenia is to consider causes of decreased platelet production, increased platelet destruction, or increased splenic sequestration. In the following section we present a symptoms-based approach that may prove to be more practical (Figure 1).

Consider Life-Threatening Conditions

Even before any investigations are initiated, life-threatening causes of thrombocytopenia should be considered, including HIT; drug-induced immune thrombocytopenia (DITP), especially due to vancomycin[37] or piperacillin[38] exposure in hospitalized patients; post-transfusion purpura (PTP); DIC; thrombotic thrombocytopenic purpura (TTP); ITP with severe hemorrhage; and acute leukemia.

Examination of the Blood Film

Examination of the blood film is mandatory to exclude pseudothrombocytopenia and to identify concomitant morphologic changes in erythrocytes—such as schistocytes in TTP and DIC; and white blood cells—such as granulocyte Döhle bodies in hereditary thrombocytopenia.

Determine the Clinical Context

The clinical context will help focus the differential diagnosis, including recent surgery (dilution, consumption), ICU admission (sepsis, DIC), underlying malignancy (DIC, TTP), liver disease (cirrhosis, splenomegaly, infection), and age (neonatal alloim-

Table 2. Summary of Platelet Transfusion Triggers From Published Guidelines[56–59]

Indication	Platelet Transfusion Trigger
Surgical patients	50×10^9/L
Cardiac surgery with CPB	50×10^9/L or reserved for bleeding
Liver transplantation	50×10^9/L
Surgical and obstetric patients with microvascular bleeding	50×10^9/L
Surgery with a low risk of bleeding	50×10^9/L
HELLP syndrome requiring cesarean section	50×10^9 /L
HELLP syndrome requiring vaginal delivery	30×10^9/L
Spinal anesthesia	50×10^9/L
Epidural anesthesia	80×10^9/L
Ophthalmologic and CNS surgery	100×10^9/L
Massive transfusion	50×10^9/L
Multiple trauma or CNS injury	100×10^9/L
Disseminated intravascular coagulation	50×10^9/L or reserved for bleeding
Autoimmune thrombocytopenia	Reserved for serious bleeding

Abbreviations: CPB, cardiopulomonary bypass; HELLP, hemolysis elevated liver enzymes low platelets; CNS, central nervous system.

mune thrombocytopenia occurs in newborns, HIT is uncommon in children[39]).

Assess Severity and Timing of Thrombocytopenia

The severity of thrombocytopenia and its timing in relation to exposure to drugs or to blood transfusions are important clues to the diagnosis. Platelet counts below 20×10^9/L are typical in DITP[40]; platelets are usually 20 to 100×10^9/L in HIT[41]; approximately 100×10^9/L in patients with splenomegaly[42]; and mildly to moderately reduced in sepsis.[43,44] Sepsis may cause thrombocytopenia from a number of mechanisms, including anti-platelet antibodies,[45] consumption,[46] and bone marrow suppression.[47] Immune-mediated platelet disorders, including classic HIT and PTP, typically occur 5 to 10 days following exposure to heparin or RBC transfusion, respectively; DITP may show a similar pattern, or may occur rapidly, even within hours of the first exposure to certain drugs such as tirofiban, eptifibatide, or abciximab or after re-exposure to other drugs including heparin when platelet-reactive antibodies are already present.[40]

Assess for Signs of Bleeding

Finally, bleeding symptoms frequently occur in patients with DITP, whereas bleeding is rare in HIT[48] and TTP,[49] even when platelet counts drop to very low levels.

MANAGEMENT OF THROMBOCYTOPENIA IN HOSPITALIZED PATIENTS

The management of thrombocytopenia is largely directed towards treating the underlying cause. However, two questions require careful consideration when evaluating the bleeding risk: (1) *When should platelet transfusions be used?* and (2) *How should antithrombotic agents be administered?*

Platelet Transfusion Therapy

Most of the evidence for platelet transfusion therapy derives from studies conducted in patients with chemotherapy-induced thrombocytopenia. In those patients, three randomized trials[50–52] enrolling 492 patients showed no difference in bleeding with a prophylactic platelet transfusion trigger of 10×10^9/L or 20×10^9/L.[25] Based on these data, a platelet trigger of 10×10^9/L has been generally adopted for prophylactic platelet transfusions in stable hematology/oncology patients.[53] Ongoing trials in this population are examining the safety of therapeutic (given because of bleeding and thrombocytopenia) or prophylactic platelet transfusions (given because of thrombocytopenia only).[54]

High-quality evidence is lacking to guide platelet transfusion practice in non-oncology patients. In one retrospective study in the ICU examining 76 platelet transfusions administered to 27 patients, the threshold platelet count was 33×10^9/L for prophylactic transfusions, 46×10^9/L for planned invasive procedures, and 51×10^9/L for the treatment of bleeding.[55] The platelet count increased by a median of 14×10^9/L after one platelet transfusion. Published guidelines recommend a platelet count trigger of 50×10^9/L for patients with DIC or massive transfusion, and 50 to 100×10^9/L for patients in whom an invasive procedure is planned, depending on the procedure (Table 2). These recommendations are generally based on expert opin-

ion and clinical experience.[56–59] Observational data suggest that platelet transfusions are overused.[60]

Anticoagulation and Antiplatelet Therapy in Patients With Thrombocytopenia

While thrombocytopenia can increase the risk of bleeding, it does not protect against thrombosis. Antithrombotic therapy (anticoagulants or antiplatelet agents) is often necessary in hospitalized patients despite concomitant thrombocytopenia, and thrombocytopenia (unless very severe) is generally not a reason to withhold antithrombotic therapy.

Common indications for anticoagulation in hospitalized thrombocytopenic patients include prevention or treatment of venous thromboembolism, stroke prevention in atrial fibrillation or flutter, or prevention of thrombosis of mechanical heart valves. Antiplatelet agents are indicated for primary or secondary prevention of cardiac disease, stroke, and peripheral vascular disease. In a prospective study of 416 oncology patients with central venous catheters (81. 2% of whom had any thrombocytopenia [$<50 \times 10^9$/L] and 53. 2% of whom had severe thrombocytopenia [$<10 \times 10^9$/L]), 16 patients (3.5%) had severe bleeding events, including three fatal intracerebral hemorrhages.[61] Antithrombotic prophylaxis had been given to 2 of the 16 patients with severe bleeding and none of the three patients with fatal bleeding. In a small case series, no major bleeding events were observed among 10 patients with chemotherapy-induced thrombocytopenia and a platelet count $<20 \times 10^9$/L receiving anticoagulation for venous thrombosis treatment or prophylaxis, although one patient developed small retinal hemorrhages and coffee ground hematemesis.[62] Observational data from patients with ITP suggest that bleeding rarely occurs with platelet counts above $20–30 \times 10^9$/L.[26] Based on these data, we propose that anticoagulation is likely to be safe for most patients with platelet counts above 30×10^9/L. Higher platelet count thresholds may be necessary when therapeutic doses of anticoagulation are required or when the bleeding risk is high.

The need for anticoagulation despite thrombocytopenia is most compelling in patients with a high risk of thrombosis. For example, thrombocytopenia in APS may indicate increased disease activity and increased thrombotic potential; thus aggressive antithrombotic therapy is warranted.[63] In patients with HIT, therapeutic doses of a non-heparin anticoagulant are indicated despite the presence of thrombocytopenia[64]; and in patients with DIC where thrombosis predominates, anticoagulation with heparin, while controversial, has been recommended.[65]

One strategy for managing the risk of bleeding in patients with thrombocytopenia is to increase the platelet count where possible. For patients with ITP, corticosteroids or intravenous immune globulin can increase the platelet count temporarily and TPO receptor agonists, rituximab, or splenectomy may be considered when long-term antithrombotic therapy is indicated.[27] Using a similar strategy, TPO receptor agonists have been used in patients with hepatitis C–related cirrhosis and thrombocytopenia to allow for the administration of interferon-based treatments, which are known to cause worsening thrombocytopenia.[66] Lowering the intensity of warfarin anticoagulation to reduce bleeding risk is inadequate for secondary prevention of thrombotic events and generally should be avoided.[67] Overall, the management of antithrombotic therapy in patients with thrombocytopenia requires individualized assessments of the risk of bleeding and the risk of thrombosis. Patient preference is an important consideration.[68]

CONCLUSION

In summary, thrombocytopenia is a frequent finding in hospitalized patients. Life-threatening causes should be considered initially and examination of the blood film is important to exclude spurious (eg, pseudothrombocytopenia) or serious causes (eg, TTP). The timing of the platelet count fall in relation to drug exposure or RBC transfusion, the severity of thrombocytopenia, and the presence or absence of bleeding symptoms provide clues to the underlying cause. Platelet transfusions should be considered in the event of serious bleeding and thrombocytopenia alone is not a contraindication to antithrombotic therapy; however, the risks and benefits of these interventions must be weighed carefully.

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