How to approach thrombocytopenia

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Thrombocytopenia is a common hematologic finding with variable clinical expression. A low platelet count may be the initial manifestation of infections such as HIV and hepatitis C virus or it may reflect the activity of life-threatening disorders such as the thrombotic microangiopathies. A correct identification of the causes of thrombocytopenia is crucial for the appropriate management of these patients. In this review, we present a systematic evaluation of adults with thrombocytopenia. The approach is clearly different between outpatients, who are frequently asymptomatic and in whom we can sometimes indulge in sophisticated and relatively lengthy investigations, and the dramatic presentation of acute thrombocytopenia in the emergency department or in the intensive care unit, which requires immediate intervention and for which only a few diagnostic tests are available. A brief discussion of the most common etiologies seen in both settings is provided.

Introduction

Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution. Results of the third US National Health and Nutrition Examination Survey (NHANES III) support the traditional value of 150×10^9/L as the lower limit of normal.[1] However, platelet counts between 100 and 150×10^9/L do not necessarily indicate disease if they have been stable for more than 6 months,[2] and the adoption of a cutoff value of 100×10^9/L may be more appropriate to identify a pathologic condition.[3] Furthermore, it is now appreciated that in many non-Western countries, the lower threshold of the normal platelet count is lower than 150×10^9/L.[3]

The relevance of thrombocytopenia in the individual patient is variable and depends on the clinical presentation. Because platelets play an essential role in preserving vessel wall integrity, thrombocytopenia is associated with a defect of primary hemostasis. Clinically significant spontaneous bleeding does not usually occur until the platelet count is less than $10\text{-}20 \times 10^9$/L. However, the presence of thrombocytopenia can aggravate surgical or traumatic bleeding or prevent the administration of effective treatment for several conditions (eg, antiviral therapy for chronic hepatitis C virus infection or cancer chemotherapy). In other situations, a low platelet count is the only initial manifestation of an underlying disorder that poses greater risks than thrombocytopenia itself (eg, HIV infection or myelodysplastic syndromes) or is an important marker of disease activity (eg, thrombotic microangiopathies). Establishing the cause of thrombocytopenia has obvious clinical repercussions, but is sometimes quite challenging. This is particularly the case for hospitalized patients, in whom thrombocytopenia appears frequently in the background of a multisystem disorder and may be determined by multiple mechanisms. Conversely, in the outpatient setting, thrombocytopenia is often isolated and asymptomatic, and the diagnosis of the specific cause is usually straightforward (Table 1). Thrombocytopenia in pregnancy deserves special consideration because of the possible consequences on the fetus. A structured approach to the diagnosis of thrombocytopenia involves an integration of clinical findings and appropriate support from the laboratory and other medical disciplines.

Mechanisms of thrombocytopenia

The major mechanisms for a reduced platelet count are decreased production and increased destruction of platelets. Typical examples of the former are the BM failure syndromes (eg, aplastic anaemia, myelodysplastic syndromes, and chemotherapy-induced thrombocytopenia), whereas increased destruction is seen in conditions such as disseminated intravascular coagulation (DIC) and the thrombotic microangiopathies. Two less common mechanisms are platelet sequestration and hemodilution. Platelet sequestration is seen in congestive splenomegaly due to portal hypertension and is characterized by redistribution of platelets from the circulating pool to the splenic pool.[4] Hemodilution is seen in patients who have suffered a massive hemorrhage and have received colloids, crystalloids, and platelet-poor blood products.

It is now known that in many cases of thrombocytopenia, such as primary immune thrombocytopenia (ITP) and hepatitis C virus infection, multiple mechanisms may contribute to the development of thrombocytopenia.

Role of history taking and physical examination

Taking a thorough medical history can provide invaluable information and greatly facilitate diagnosis. Aspects of particular relevance that should be investigated include the presence of a family history of thrombocytopenia (it is not infrequent to diagnose congenital thrombocytopenia in adults); the temporal profile of the thrombocytopenia or of the bleeding manifestations (new onset, chronic, or relapsing); disease history, with particular reference to autoimmune disorders, infections, or malignancies; pregnancy status in premenopausal woman; recent medications and vaccinations; recent travels (eg, malaria, rickettsiosis, dengue fever); recent transfusions; recent organ transplantation; ingestion of alcohol and quinine-containing beverages; dietary habits; and risk factors for retroviral infections and viral hepatitis. A history of recurrent, symptomatic thrombocytopenia with platelet counts returning to normal within days, even in the absence of specific treatment, should prompt investigation of a drug-induced thrombocytopenia. The bleeding history does not help in diagnosing the nature of the thrombocytopenia, but gives important clues about its duration and defines its clinical phenotype. Collecting a detailed medical history is not always possible, the

Table 1. Clinical scenarios and most common causes of thrombocytopenia

Outpatient	Inpatient			Pregnancy/postpartum
	Multisystem illness/ICU	Cardiac patient		
ITP	Infections	HIT		GT
DITP	TTP/HUS	Cardiac bypass		ITP
Infections	DITP	GPIIb/IIIa inhibitors		HELLP syndrome
HIV	DIC	Other DITP		Preeclampsia
Hepatitis C virus	Liver disease	Dilutional		Abruptio placentae
Helicobacter pylori	HIT			TTP/HUS
CMV	MAS			
Other recent viral infections	BM disorders			
Connective tissue disorders	CIT			
Systemic lupus erythematosus				
Rheumatoid arthritis				
Antiphospholipid syndrome				
Vaccinations				
Myelodysplastic syndromes				
Congenital thrombocytopenia				
Common variable immunodeficiency				

TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; MAS, macrophage activation syndrome (including hemophagocytic syndrome); CIT, chemotherapy-induced thrombocytopenia; HELLP, hemolysis, elevated liver enzymes, and low platelets.

typical situation being the unconscious patient with severe thrombocytopenia in the intensive care unit (ICU). However, in such cases, thrombocytopenia is almost always an acute event and the disease history and exposure to medications (eg, heparin and antibiotics) immediately preceding the development of thrombocytopenia should be available in the patient's notes.

Physical examination should focus on the location and severity of bleeding risk and other abnormalities that can help in the diagnosis of the thrombocytopenia, such as the presence of organomegaly or skeletal abnormalities. Patients with thrombocytopenia typically experience mucocutaneous bleeding. The presence of joint or extensive soft tissue bleeding suggests the presence of coagulation abnormalities, such as occurs in DIC. The presence of an ischemic limb of skin necrosis should raise suspicion of heparin-induced thrombocytopenia (HIT).

Role of the laboratory

Step 1: Observation of the peripheral blood smear
In the era of genomic medicine and widespread molecular testing, examination of the peripheral blood film still remains the most important investigation guiding our diagnostic approach to thrombocytopenia (Figure 1). All 3 blood cell lineages should be assessed carefully (Table 2). From a practical perspective, when we are investigating thrombocytopenia in a critically ill patient, the immediate information we need to obtain is whether it is thrombotic microangiopathy (as shown by RBC fragmentation) or acute leukemia (blasts). Even a short delay in making these diagnoses may prove fatal for the patient if appropriate treatment is not initiated promptly.

Step 2: Additional investigations
Bearing in mind that thrombocytopenia can be the end result of pathogenetic mechanisms that are not mutually exclusive and that, particularly in the acute care setting, multiple potential causes of thrombocytopenia can be identified, a basic laboratory evaluation should include liver and renal function tests, a clotting screen with D-dimers, and measurement of lactate dehydrogenase.

Second-tier investigations should be prompted by clinical findings and the results of the peripheral blood smear. There is no single hematologic or biochemical test that is conclusive for a given mechanism of thrombocytopenia. If the etiology of the thrombocytopenia is unclear, a BM aspirate and biopsy should be performed to rule out a primary BM disorder. Reticulated platelets or the equivalent immature platelet fraction can help in discriminating between thrombocytopenia due to BM failure (low percentages) and hyperdestructive thrombocytopenia (high percentages),[5,6] although the specificity of these tests has not been validated prospectively. Limited evidence suggests that plasma glycocalicin and thrombopoietin levels can increase the specificity of reticulated platelets in thrombocytopenia due to increased platelet destruction.[7] The most common specific etiologies and associated investigations are discussed in the next sections.

Isolated thrombocytopenia
In the context of this review, we define isolated thrombocytopenia as a low platelet count in the absence of abnormalities of RBC and WBC lineages and no signs or symptoms of systemic illness.

A low platelet count during a routine evaluation in an otherwise asymptomatic person is a relatively common reason for referrals to hospital outpatient clinics by general practitioners. Nevertheless, patients with severe thrombocytopenia can present to the emergency department with mucocutaneous bleeding or internal hemorrhage. Isolated thrombocytopenia has a limited differential diagnosis (Table 1). The 2 most prevalent etiologies are ITP and drug-induced thrombocytopenia (DITP).

ITP
Although ITP is the most common cause of isolated thrombocytopenia, there are no tests sensitive or specific enough to confirm this diagnosis, which remains one of exclusion. There is no consensus on the set of investigations to perform, and practice varies greatly not only from country to country, but also from center to center within the same country. There is little doubt that local resources may play a relevant role in the choice of investigations. In my current practice, I follow the recommendations set forth in the
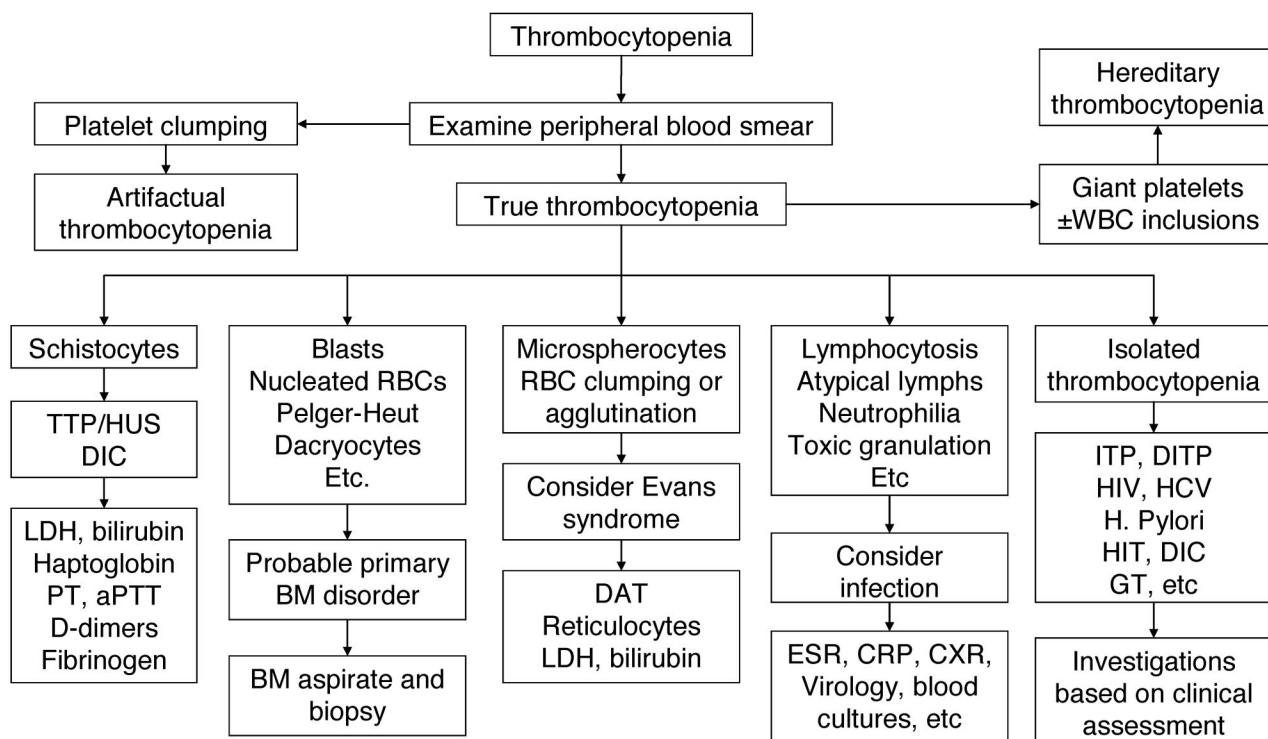
Figure 1. Algorithm for workup of thrombocytopenia based on observation of the peripheral blood film. TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

International Consensus Report on the investigation and management of ITP (Table 3),[8] although admittedly some of these recommendations are based on poor evidence. I also request an ultrasound of the abdomen (to rule out the occasional initial manifestation of chronic liver disease with hypersplenism and the presence of enlarged abdominal-pelvic lymph nodes) and a chest X-ray (to rule out "silent" mediastinal lymphadenopathy and "silent" tuberculosis). Antiplatelet Ab assays are not very sensitive, although their specificity approaches 90%. They may be useful in differentiating ITP from DITP. The role of the BM biopsy and aspirate in patients with isolated thrombocytopenia remains controversial. The International Consensus Report panel recommends performing these investigations in patients more than 60 years of age, because isolated thrombocytopenia may be the initial abnormality of a myelodysplastic syndrome. Conversely, the updated ASH guidelines for immune thrombocytopenia suggest that BM studies are not necessary in patients of any age in whom physical examination, complete blood count, and examination of the peripheral blood smear do not suggest etiologies other than ITP.[9]

DITP

The list of drugs associated with thrombocytopenia is an ever-increasing one (www.ouhsc.edu/platelets). Because of its peculiar pathogenesis and clinical course, HIT will be discussed separately. The pathophysiologic mechanism of DITP is the development of drug-dependent Abs against new epitopes of platelet glycoproteins created by their interaction with the drug. Patients with DITP usually present with moderate to severe thrombocytopenia and bleeding manifestations of varying degrees of severity. The decrease of the platelet count typically occurs within 2-3 days (sometimes a few hours) of taking a drug that has been taken previously or 1-3 weeks after starting a new drug. When the drug is

stopped, the thrombocytopenia usually resolves in 5-10 days after drug withdrawal. Clinically, DITP can be easily confused with ITP and only an accurate history collection can help in the diagnostic process.[10] If the patient has recently taken a medication for the first time, a diagnosis of DITP should be considered. DITP should also be suspected when patients have recurrent episodes of thrombocytopenia with prompt recovery. Sometimes the diagnosis is very challenging because the substance causing the thrombocytopenia is not a drug, but a food or beverage, such as walnuts,[11] cow's milk,[12] cranberry juice,[13] tonic water (which contains quinine), and certain herbal remedies.[14]

The diagnosis of DITP is mostly empirical, being based on platelet recovery after discontinuation of the drug or after abstaining from certain foods or beverages. Laboratory diagnosis involves the demonstration of drug-dependent antiplatelet Abs by methods such as flow cytometry, platelet immunofluorescence test, ELISA, and immunoprecipitation-Western blotting.

Thrombocytopenia in the hospitalized patient

Thrombocytopenia may complicate the course of the hospital stay of patients with a variety of medical and surgical problems. In one study, thrombocytopenia was observed in approximately 1% of adult inpatients in an acute care hospital.[15] However, less than 30% of these patients presented with bleeding manifestations. As expected, thrombocytopenia is much more common in ICUs, where it is found in in 8%-68% of patients on admission, and in 13%-44% of patients during the stay in the unit.[16] Many potential etiologies are often concomitant in the acute care setting (eg, sepsis, DIC, drugs, and cardiac bypass surgery), and it is not always possible to elucidate the cause of the thrombocytopenia. However, because of its frequency, consideration should always be given to

Table 2. Morphologic aspects of the peripheral blood smear of particular relevance to the diagnosis of thrombocytopenia

Platelets
  Platelet clumping
    Platelet clumping caused by EDTA-dependent platelet autoantibodies is a common cause of artifactual thrombocytopenia. It occurs in about 1 in 1000 normal adults and is not associated with bleeding or thrombosis.
  Platelet size and granularity
    Consistently large platelets suggest hereditary macrothrombocytopenia. Large platelets with a gray color on Wright-Giemsa stain define the gray platelet syndrome, an autosomal-dominant macrothrombocytopenia associated with bleeding tendency due to absent or greatly reduced α-granules.
    In thrombocytopenia due to peripheral destruction, large platelets or giant platelets are often seen in addition to platelets of normal size.
    When thrombocytopenia is due to reduced platelet production (eg, after chemotherapy), platelets are of normal size. In myelodysplastic syndromes, platelets have variable size (giant platelets may be seen) and are frequently hypogranular. In Wiskott-Aldrich syndrome, and X-linked thrombocytopenia, both caused by mutations of the WAS gene, platelets are small.

WBCs
  Leukemic cells
    Malignant hematological disorders (leukemias and lymphomas) are often associated with thrombocytopenia, which is almost never an isolated finding.
  Other abnormalities of WBCs, including leukocyte inclusions
    A constellation of nonspecific abnormalities of WBCs are common to many conditions (eg, neutrophilia, lymphocytosis, leukopenia, etc) and may be associated with thrombocytopenia. The presence of hypolobulated neutrophils (Pelger-Huët anomaly) suggests a myelodysplastic syndrome. Dark coarse granules (toxic granulations) found in neutrophils suggest sepsis. Atypical lymphocytes suggest viral infection. The presence of WBC inclusions ((Döhle-like bodies)) should be investigated carefully when platelets are mostly large (MYH9-related congenital macrothrombocytopenia).

RBCs
  Schistocytes
    The presence of RBC fragments known as schistocytes is indicative of a thrombotic microangiopathy (TTP/HUS) or DIC.
  Size and other morphological features
    Microspherocytes may suggest Evans syndrome, but may also be present along with shistocytes in thrombotic microangiopathies. Macrocytosis (and hypersegmentation of neutrophils) suggest vitamin B12 or folate deficiency. Dacryocytes (teardrop-shaped cells) suggest myelofibrosis. Nucleated RBCs suggest hemolytic anemia, myelofibrosis, or an infiltrative process of the BM.
  Parasites
    The presence of intracellular parasites (eg, in malaria) is diagnostic of infection.

DITP. The frequency of DITP in critically ill patients is approximately 20%. Antibiotics in this setting are a frequent etiology.[17,18] Tests for the detection of drug-dependent antiplatelet Abs are not widely available, are time-consuming, and are not sensitive enough to be incorporated in a diagnostic algorithm for the urgent management of patients with severe thrombocytopenia. The decision to discontinue a potential causative drug in such cases should rely solely on clinical criteria.[19]

Heparin-induced thrombocytopenia
HIT occurs in 0.5%-5% of heparin-treated subjects, depending on the patient population studied.[20] It should be suspected in any patient who, while on heparin therapy, has a $\geq 50\%$ decrease in platelet count compared with baseline or a total platelet count of $< 100 \times 10^9$/L with normal baseline counts. Thrombocytopenia is usually moderate, with median platelet counts ranging from 50-80 $\times 10^9$/L and nadir counts rarely below 20 $\times 10^9$/L. Clinical manifestations may include venous or arterial thrombosis, necrotic skin lesions at heparin injection sites, or acute systemic reactions subsequent to IV heparin bolus administration. At present, it is not possible to predict which patients will develop these complications. However, HIT is relatively rare in the ICU, where it accounts for fewer than 1% of cases of thrombocytopenia.[21]

HIT typically develops after exposure to heparin for 5-10 days. Earlier onset of HIT (sometimes a few hours after the first heparin administration) occurs in approximately 30% of cases. These patients have a history of exposure to heparin in the prior 3 months, thereby developing Abs against the heparin-PF4 complex. Less commonly (in 10%-15% of cases), HIT has a delayed onset, occurring several days after all heparin has been stopped.

HIT is often a clinical emergency, and on such occasions, the presumptive diagnosis has to be based solely on clinical findings. There is simply no time to wait for the results of heparin-PF4 Ab testing. In addition, these Abs can also be present in heparin-treated patients who do not have a clinical syndrome of HIT. Clinicians can be supported in their choices by clinical scoring systems based on the pretest probability of HIT, such as the one known as the "4Ts": Thrombocytopenia, Thrombosis, Timing, and other causes of Thrombocytopenia (Table 4).[22] In patients with strongly suspected HIT, heparin therapy should be stopped and an alternative anticoagulant be administered until the results of a confirmatory test are available. Although the gold standard for diagnostic tests for HIT is the ^{14}C-serotonin release assay, this is available in only a few comprehensive centers. Commercial enzyme immunoassays are widely available and very sensitive ($> 90\%$), but are not very

Table 3. Basic laboratory evaluation of patients with suspected ITP according to the International Consensus Report

Complete blood count and reticulocyte count
Peripheral blood film
Quantitative Ig level measurement
BM examination (in patients older than 60 y)
Blood group (Rh)
Direct antiglobulin test
*Helicobacter pylori**
HIV*
HCV*

Adapted from Provan et al.[8]
*Recommended by the majority of the panel for adult patients regardless of geographic locale.

Table 4. The 4Ts pretest probability of heparin-induced thrombocytopenia

4Ts	Points* 2	1	0
Thrombocytopenia	Platelet count decrease > 50% and platelet nadir > 20 × 10⁹/L	Platelet count decrease 30-50% or platelet nadir 10-19 × 10⁹/L	Platelet count decrease < 30% or platelet nadir < 10 × 10⁹/L
Timing of platelet count decrease	Clear onset between d 5 and 10 or platelet decrease ≤ 1 d (prior heparin exposure within 30 d)	Consistent with d 5-10 decrease, but not clear (eg, missing platelet counts); onset after d 10; or decrease ≤ 1 d (prior heparin exposure 30-100 d ago)	Platelet count decrease < 4 d without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing erythematous) skin lesions; Suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Pretest probability score: 6-8, high; 4-5, intermediate; 0-3, low. Adapted from Lo et al.[22]
*0, 1, or 2 for each category with a maximum possible score of 8.

specific. However, a positive ELISA with high optical density values can improve the accuracy and specificity of the diagnosis.[23]

DIC

DIC is a consumptive coagulopathy complicating several diseases. It is characterized by activation of intravascular coagulation with microvascular thrombi formation, thrombocytopenia, depletion of clotting factors, variable bleeding complications, and end-organ damage. DIC can develop acutely or present with a chronic course. The International Society on Thrombosis and Haemostasis (ISTH) further recommends classifying DIC as overt (decompensated hemostatic system) or non-overt (compensated coagulopathy).[24]

Acute DIC is commonly seen in severe sepsis and septic shock, after trauma (especially neurotrauma), after surgery, as an obstetric complication (eg, abruptio placentae, amniotic fluid embolism, and preeclampsia), after ABO-incompatible blood transfusion, and as a complication of acute promyelocytic leukemia. Consumptive coagulopathy in these cases is severe and leads to bleeding manifestations (eg, mucocutaneous bleeding and blood oozing from wound sites) and frequent organ damage (eg, renal and hepatic damage). There is no single laboratory test for accurate and precise diagnosis of DIC. The ISTH committee has proposed a scoring system using the parameters reported in Table 5,[24] in which a score ≥ 5 is consistent with overt DIC. Chronic DIC is more frequently observed in solid tumors and in large aortic aneurysms, usually with few obvious clinical or laboratory indications of the presence of DIC. Fibrinogen levels may be slightly decreased, within the reference range, or even increased. Platelets may be moderately low or normal and D-dimer levels are modestly elevated.

Thrombocytopenia in the cardiac patient

Several mechanisms can induce thrombocytopenia in patients undergoing open heart surgery. Cardiopulmonary bypass may result in mechani-

cal destruction of platelets, hemodilution in the bypass circuit, and drug-induced platelet destruction. More rare causes include sepsis, intra-aortic balloon pumping, and posttransfusion purpura. The nadir platelet count is typically seen on the second or third day after surgery, with a rapid platelet count recovery thereafter.

Severe thrombocytopenia is observed in 0.1%-2% of patients after exposure to GPIIb/IIIa inhibitors (eg, abciximab, tirofiban, or eptifibatide) during percutaneous coronary intervention. The peculiarity of this DITP is its rapid onset, usually within a few hours after surgery. This phenomenon has been attributed to the presence of naturally occurring Abs against neoepitopes exposed by alteration of the GPIIb/IIIa molecule.[25] In typical cases, thrombocytopenia resolves within 10 days. Delayed development of thrombocytopenia 3-6 days after treatment with abciximab has been described in a few patients.[26] The mechanism of the thrombocytopenia in these cases is the production of Abs against murine peptide sequences of abciximab, which react with other target epitopes on abciximab-coated platelets.

HIT is an important cause of thrombocytopenia in patients undergoing cardiac surgery. It occurs in 1%-3% of patients receiving heparin beyond the first postoperative week[27] and in 10% of patients after ventricular assist device implantation.[28] Extreme caution should be used in the interpretation of the assays for HIT because of the high proportion of false positives. In fact, in the first 10 days after cardiac surgery, 25%-70% of patients develop a positive immunoassay for heparin-PF4 Abs and 4%-20% have an abnormal serotonin release assay.[27]

Thrombocytopenia in pregnancy

Platelet counts < 150 × 10⁹/L have been reported in 6%-15% of women at the end of pregnancy, but counts < 100 × 10⁹/L are

Table 5. Diagnostic score for the diagnosis of overt DIC

Parameter	Points 0	1	2	3
Platelet count	> 100 × 10⁹/L	< 100 × 10⁹/L	< 50 × 10⁹/L	
Elevated fibrin degradation products	No increase		Moderate increase	Strong increase
Prothrombin time at upper limit of reference range	< 3 s	> 3 s	> 6 s	
Fibrinogen level	> 1 g/L	< 1 g/L		

An overall score of 5 or more is compatible with overt DIC. A score less than 5 is suggestive of non-overt/low-grade DIC. Adapted from Taylor et al.[24]

observed in only 1% of women.[29] The most common causes of thrombocytopenia are gestational thrombocytopenia (GT; 70%), preeclampsia (21%), and ITP (3%).[30]

GT is seen in the mid-second to third trimester of pregnancy and is supposed to represent the extreme variation of the physiologic decrease of the platelet count that is observed during pregnancy.[29] There is no clearly defined minimum value of the platelet count in GT, but counts $< 70 \times 10^9$/L should raise suspicion of an alternative diagnosis. There are no confirmatory laboratory tests of GT and the diagnosis remains one of exclusion. To support a diagnosis of GT, women should have no past history of thrombocytopenia (except during a previous pregnancy), and the thrombocytopenia should resolve spontaneously within 1-2 months after delivery. Furthermore, the fetus/newborn baby should have not suffered from thrombocytopenia.

ITP occurs in 1-2 in 1000 pregnancies, but is the most common cause of isolated thrombocytopenia in the first and early second trimesters.[31] Approximately one-third of cases are first diagnosed during pregnancy, whereas two-thirds are in patients with preexisting disease. There are variable reports of exacerbation of ITP during pregnancy or in the postpartum period. Approximately half of patients with a prior diagnosis of ITP experience a mild decline in platelet count progressively during pregnancy. Differentiating ITP from GT is clinically relevant, because pregnancies in women with ITP may be complicated by severe neonatal thrombocytopenia in 9%-15% of cases, with a risk of neonatal intracranial hemorrhage of 1%-2%.[32] In women with no history of ITP, platelet counts below 100×10^9/L early in pregnancy and declining as gestation progresses are more consistent with ITP than with GT. The situation becomes more complicated if a low platelet count is detected during the third trimester. Again, there are no clear lower limits of the platelet count in GT, and there is a "hazy" platelet count range between 50 and 70×10^9/L in which the diagnosis remains uncertain. From a clinical perspective, knowing the exact diagnosis at that stage of pregnancy changes little in the management of the pregnancy, although consideration will be given to the possible thrombocytopenia of the neonate. Whenever the platelet count is $< 50 \times 10^9$/L in the absence of obstetric complications, the diagnosis should be ITP by default. As always in medicine, results need to be interpreted in the clinical context.

Conclusions

A low platelet count can result from a wide range of conditions and may be determined by multiple mechanisms. Prompt recognition of the cause of thrombocytopenia is often crucial for the correct management of patients, as in acute promyelocytic leukemia, heparin-induced thrombocytopenia, or thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. The initial approach to determining the cause of thrombocytopenia is based on the patient's history of underlying diseases and drug treatments, on physical examination, and on careful examination of the peripheral blood smear. The 2 most common causes of a low platelet count in the absence of other hematologic abnormalities and no evidence of a multisystem disease are ITP and DITP. The most common cause of a low platelet count in pregnancy is GT. In hospitalized and critically ill patients, the diagnosis of thrombocytopenia is often challenging due to the presence of several potential etiologies, including drugs and infections. Examination of the BM with aspiration and biopsy is warranted in patients with severe or worsening thrombocytopenia of unexplained nature. Thrombocyto-penia in pregnancy deserves special consideration because of the possible consequences on the fetus.

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References

1. Cheng CK, Chan J, Cembrowski GS, van Assendelft OW. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. *Lab Hematol*. 2004;10:(1)42-53.
2. Stasi R, Amadori S, Osborn J, Newland AC, Provan D. Long-term outcome of otherwise healthy individuals with incidentally discovered borderline thrombocytopenia. *PLoS Med*. 2006;3(3):e24.
3. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-2393.
4. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. *J Clin Invest*. 1966;45(5):645-657.
5. Pons I, Monteagudo M, Lucchetti G, et al. Correlation between immature platelet fraction and reticulated platelets. Usefulness in the etiology diagnosis of thrombocytopenia. *Eur J Haematol*. 2010;85(2):158-163.
6. Monteagudo M, Amengual MJ, Munoz L, Soler JA, Roig I, Tolosa C. Reticulated platelets as a screening test to identify thrombocytopenia aetiology. *QJM*. 2008;101(7):549-555.
7. Kurata Y, Hayashi S, Kiyoi T, et al. Diagnostic value of tests for reticulated platelets, plasma glycocalicin, and thrombopoietin levels for discriminating between hyperdestructive and hypoplastic thrombocytopenia. *Am J Clin Pathol*. 2001;115(5): 656-664.
8. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186.
9. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207.
10. Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol*. 2003;122(6):966-974.
11. Achterbergh R, Vermeer HJ, Curtis BR, et al. Thrombocytopenia in a nutshell. *Lancet*. 2012;379(9817):776.
12. Caffrey EA, Sladen GE, Isaacs PE, Clark KG. Thrombocytopenia caused by cow's milk. *Lancet*. 1981;2(8241):316.
13. Davies JK, Ahktar N, Ranasinge E. A juicy problem. *Lancet*. 2001;358(9299):2126.

14. Royer DJ, George JN, Terrell DR. Thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. *Eur J Haematol*. 2010;84(5):421-429.

15. Teo CP, Kueh YK. Incidence of thrombocytopenia in an acute care hospital. *Ann Acad Med Singapore*. 1989;18(4):379-381.

16. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest*. 2011;139(2): 271-278.

17. Von Drygalski A, Curtis BR, Bougie DW, et al. Vancomycin-induced immune thrombocytopenia. *N Engl J Med*. 2007;356(9): 904-910.

18. Rousan TA, Aldoss IT, Cowley BD Jr, et al. Recurrent acute thrombocytopenia in the hospitalized patient: sepsis, DIC, HIT, or antibiotic-induced thrombocytopenia. *Am J Hematol*. 2010; 85(1):71-74.

19. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. *Hematology Am Soc Hematol Educ Program*. 2009;2009:153-158.

20. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood.* 2005;106(8): 2710-2715.

21. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. *Crit Care Clin*. 2011;27(4):805-823.

22. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4(4):759-765.

23. Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? *Am J Hematol*. 2007;82(12):1037-1043.

24. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327-1330.

25. Bougie DW, Wilker PR, Wuitschick ED, et al. Acute thrombocytopenia after treatment with tirofiban or eptifibatide is associated with antibodies specific for ligand-occupied GPIIb/IIIa. *Blood.* 2002;100(6):2071-2076.

26. Curtis BR, Divgi A, Garritty M, Aster RH. Delayed thrombocytopenia after treatment with abciximab: a distinct clinical entity associated with the immune response to the drug. *J Thromb Haemost*. 2004;2(6):985-992.

27. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg*. 2003;76(6):2121-2131.

28. Warkentin TE, Greinacher A, Koster A. Heparin-induced thrombocytopenia in patients with ventricular assist devices: are new prevention strategies required? *Ann Thorac Surg*. 2009;87(5):1633-1640.

29. Boehlen F, Hohlfeld P, Extermann P, Perneger TV, de Moerloose P. Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol*. 2000;95(1):29-33.

30. Bockenstedt PL. Thrombocytopenia in pregnancy. *Hematol Oncol Clin North Am*. 2011;25(2):293-310.

31. McCrae KR. Thrombocytopenia in pregnancy. *Hematology Am Soc Hematol Educ Program*. 2010;2010:397-402.

32. Gill KK, Kelton JG. Management of idiopathic thrombocytopenic purpura in pregnancy. *Semin Hematol*. 2000;37(3):275-289.