Chapter 6
The Critically Ill Patient with Abnormal Platelet Count

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Abnormal platelet counts are a common finding in critically ill patients. Whereas thrombocytopenia, defined as a platelet count less than $150*10^9$/L, affects 13–60 % of Intensive Care Unit (ICU) patients [1] and has been extensively studied, the occurrence of thrombocytosis (platelet counts $>400*10^9$/L) is observed less frequently and has not been studied to the same extent.

In this chapter, the main causes of thrombocytopenia and thrombocytosis in critically ill patients will be illustrated, and their implications on morbidity and mortality will be discussed. Due to its importance in the ICU setting, a section in this chapter will be dedicated to heparin-induced thrombocytopenia (HIT).

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6.1 Thrombocytopenia: A Classification

Before addressing the issues related to "true" thrombocytopenia, pseudo (or spurious) thrombocytopenia must be defined. In some conditions such as liver diseases, neoplasia, autoimmune disease, or in healthy subjects, antibodies mediated by anticoagulants such as EDTA are responsible for platelet clumping, which, not being detected by cell counters, will lead to falsely low platelet counts [2]. Pseudothrombocytopenia is not clinically significant and is diagnosed by microscopic examination of the blood smear (Fig. 6.1) and by repeating the whole blood count in tubes with a different anticoagulant (heparin- or citrate-based solutions).

"True" thrombocytopenia, to a variable degree, affects all types of ICU patients in all parts of the world; adult medical ICU patients are mostly affected, but it is also observed in surgical and pediatric patients. These observations underlie the comment made by R.I. Parker in his recent review [1] that thrombocytopenia in ICU patients is "a truly universal occurrence."

Although a threshold value of $150*10^9$/L is generally accepted to indicate thrombocytopenia, stable platelet counts between 150 and $100*10^9$/L are not necessarily considered pathological. Moreover, it is now recognized that the risk of clinically spontaneous bleeding is significantly high when platelet counts fall below $20–10*10^9$/L [3].

The two main mechanisms responsible for thrombocytopenia are reduced production and increased destruction of platelets; less frequently, a reduced platelet count may also be due to sequestration and hemodilution [1, 2].

Table 6.1 summarizes the main classification criteria for thrombocytopenia, the most frequent pathological mechanisms and the associated clinical conditions. The table does not include causes of thrombocytopenia in pregnancy and postpartum, since these conditions go beyond the scope of this chapter.

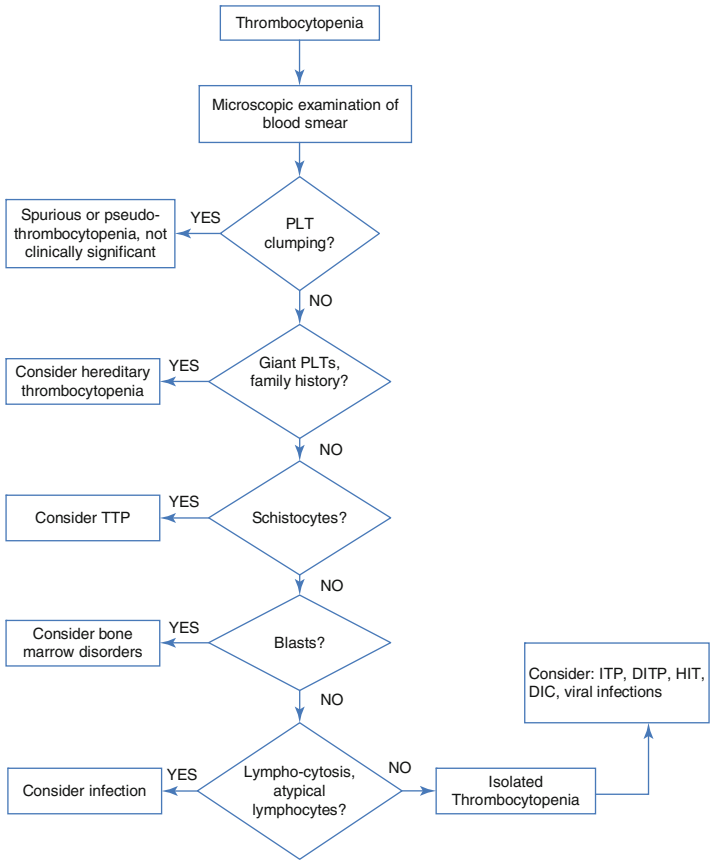

Fig. 6.1 Diagnostic algorithm based on blood smear (Adapted from Stasi [3])

It should always be remembered that in a significant number of cases, thrombocytopenia is due to multiple factors, such as for example in sepsis.

The diagnostic workup for thrombocytopenia must include, in addition to laboratory tests discussed in this chapter, a family

Table 6.1 Causes of thrombocytopenia

Main classification criteria	Pathological mechanism	Examples of clinical conditions	References
Decreased production	Primary bone-marrow failure	Myelodisplastic disorders, Fanconi's anemia, congenital amegakaryocytic thrombocytopenia	[4–7]
	Secondary bone-marrow failure	Sepsis, severe idiopathic aplastic anemia, severe malnutrition	[8]
	Infiltration of bone marrow due to neoplastic diseases	Acute leukemia, widespread marrow metastases	[9]
	Infiltration of bone marrow due to storage disorders	Gaucher's disease	[10]
	Drug-related marrow suppression	Chemotherapy, other drugs	[11]
	Marrow failure due to radiation therapy	Internal radiation, external radiation	[12]
Enhanced destruction	Nonimmune: mechanical	Intravascular devices such as central venous catheters, intraaortic balloon pump	[13]
	Nonimmune: microangiopathic	Thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), subacute bacterial endocarditis (SBE), vasculitis	[14, 15]
	Nonimmune: platelet aggregation	Drugs	[11]
	Immune: platelet specific auto-antibodies	Immune thrombocytopenic purpura (ITP)	[16]
	Immune: immune complexes	Autoimmune disorders	[17]

	Immune: cell-mediated	Hypersplenism, hemophagocytic lymphohistiocytosis	[18]
	Immune: platelet-specific allo-antibodies	Posttransfusion purpura	[19]
	Immune: Drugs	Drug related immune thrombocytopenia: antiepileptics, gold compunds, vancomycin, thiazides, quinine/quinidine	[11]
	Immune: Heparin-induced	Heparin-Induced Thrombocytopenia (HIT)	[20]
	Immune: sepsis	Sepsis	[8]
Sequestration	Congestive splenomegaly	Portal hypertension leads to the redistribution of platelets from the circulating pool to the splenic pool	[21]
Hemodilution	Secondary to fluid infusion in case of massive hemorrhage	Transfusion of platelet-poor blood products, infusion of colloids and crystalloids	[22]

history for thrombocytopenia, the evaluation of its "dynamics," meaning if it is a new finding, if it is chronic or whether it has a relapsing presentation. Information on bleeding episodes is also very important, as is the history of concomitant diseases such as infections, tumors, or autoimmune diseases. Finally, it is of paramount importance to collect the history related to recent medication (heparin, antibiotics) and blood transfusion since especially for hospitalized patients, drug-induced thrombocytopenia (DITP) is among the most common causes of low platelet counts. Since the aim of this chapter is to discuss thrombocytopenia in critically ill patients, it goes without saying that it is challenging to understand this condition in these patients also because a complete history may be difficult to obtain.

Whereas by definition, the Whole Blood Count is the basic laboratory test for diagnosing thrombocytopenia, the microscopic examination of the blood smear gives additional, important information on the pathogenetic mechanism involved [3]. Figure 6.1 illustrates an algorithm that guides the hematologist in the diagnosis of isolated thrombocytopenia. Other tests employed in the diagnosis of the causes of thrombocytopenia are liver and renal function tests, coagulation tests including D-dimers, lactate dehydrogenase, and bone marrow aspirate and biopsy.

Platelet antibody assays and other tests such as reticulated platelets have a limited specificity and therefore their use is debatable [16].

Before describing the clinical conditions associated with thrombocytopenia, the importance of the rate of decline in platelet counts must be pointed out. When a constant, slow reduction in platelet number is observed with minimum (nadir) counts falling below $20*10^9$/L, a DITP due to marrow inhibition is the probable cause. On the other hand, when there is a fast rate of decline (24–48 h) in platelet numbers, an immune mechanism is suspected. A variable rate in platelet reduction is suggestive of consumptive coagulopathy [1].

6.1.1 *Thrombocytopenia Due to Reduced Production*

Thrombocytopenia caused by bone marrow suppression may be due to acquired or congenital conditions. In the latter category are comprised Fanconi's anemia, congenital amegakaryocytic thrombocytopenia, thrombocytopenia, and absent radii syndrome; a comprehensive review of these clinical conditions has been recently published by Parikh and Bessler [4]. The inherited bone marrow failure syndromes are genetic disorders affecting blood cell lineages. They are characterized by a wide spectrum of symptoms ranging from aplastic anemia to symptoms related to the suppression of one or two cell lines. Congenital amegakaryocytic thrombocytopenia is an inherited bone marrow failure syndrome usually diagnosed at birth, and characterized by insufficient production of megakaryocytes due to a defect in the thrombopoietin receptor [5].

Acquired bone marrow failure is often due to myelodysplastic syndromes, a heterogeneous group of clonal bone marrow disorders characterized by ineffective hematopoiesis, morphological and functional abnormalities of hematopoietic cells, and increased risk of malignant transformation. The prevalence of thrombocytopenia in these diseases varies from 40 to 65 % [6], and together with platelet dysfunction, is responsible for the increased hemorrhagic risk in these patients.

Sepsis is a condition affecting a significant number of patients admitted to hospitals; a recent review reports that in the USA, 2 % of patients corresponding to 750,000 per year are septic, half of which are admitted to ICUs [8]. Clinical signs of sepsis are diverse and depend on the microorganism, site of original infection, and health condition of the patient. Thrombocytopenia in sepsis is a common finding and severe forms of sepsis are associated with coagulation disorders that can lead to disseminated intravascular coagulation (DIC).

Thrombocytopenia can also be caused by drugs that suppress the bone marrow, and in particular megakaryocyte proliferation and maturation. Whereas antimetabolytes, cytotoxic drugs, and alkylating agents exert a toxic effect on all bone marrow cell lines, some antibiotics such as linezolid, may cause a selective suppression of platelet cell lines [11].

Other causes of thrombocytopenia due to decreased production (Table 6.1) are storage disorders [10], infiltration of bone marrow due to neoplastic diseases [9] and radiation therapy [12].

Thrombocytopenia due to reduced production is not a frequent cause of admission to the ICUs, since it is more often preexistent.

6.1.2 Thrombocytopenia Due to Enhanced Destruction or Consumption

6.1.2.1 Thrombocytopenia Due to Enhanced Destruction: Nonimmune Mechanisms

Medical devices such as mechanical heart valves, left-ventricular assistance devices, and aortic balloon pumps may be responsible for the destruction of platelets. In a study on 1,302 patients who underwent percutaneous coronary intervention (PCI) with baseline normal platelet counts ($\geq 150*10^9$/L), 3.1 % developed post-PCI thrombocytopenia. Multivariate analysis showed that the use of intra-aortic balloon pump was an independent predictor of thrombocytopenia, with an odds ratio of 2.8, confidence intervals 1.1–6.8, $p=0.024$. Post-PCI thrombocytopenia was significantly associated with major adverse cardiovascular events at 6 months (hazard ratio 2.7, CI 1.3–5.5, $p=0.0069$) [13].

Microangiopathic processes such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) may be

responsible for thrombocytopenia due to enhanced platelet destruction.

TTP is characterized by microvascular platelet clumping, which leads to thrombocytopenia and microangiopathic hemolytic anemia. Common findings are "broken" erythrocytes or schistocytes (see algorithm reported in Fig. 6.1), neurological disorders, renal failure, and fever [14]. The disease is due to a congenital or acquired deficiency in ADAMTS13, a metalloprotease which cleaves von Willebrand factor. ADAMTS13 deficiency is responsible for microvascular thrombosis and thrombocytopenia. Plasma exchange is the optimal therapy, and its effectiveness is probably due to the removal of anti-ADAMTS13 autoantibodies and large von Willebrand factor multimers.

HUS is similar to TTP in that microvascular thrombosis, thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, and altered mental status are common features. However, ADAMTS13 is normal and the disease is generally due to endothelial cell damage caused by a toxin produced by pathogenic strains of *Escherichia* or *Shigella*. In HUS, thrombocytopenia is usually not severe but dialysis may be required to treat renal insufficiency [23].

DIC does not occur as an isolated event but is practically always associated with an underlying condition such as tissue damage (trauma, burns, hemolytic transfusion reaction, acute transplant rejection), neoplasia, systemic infection, obstetric conditions (abruption placentae, placenta previa, amniotic fluid embolism), and other clinical conditions such as shock, cardiac arrest, and aortic aneurysm. DIC is the result of an overstimulation of the coagulation system and its clinical presentation varies from severe hemorrhage to thrombosis (or both simultaneously). Thrombocytopenia, abnormal prothrombin time and activated partial thromboplastin time (PT and aPTT), decreased fibrinogen and elevated fibrinogen degradation products are common laboratory features of DIC. DIC-associated mortality is mostly due to

the original disease, which is complicated by hemorrhage or thrombosis. Multiorgan dysfunction syndrome is a frequent consequence of DIC and is due to hemorrhagic or thrombotic events in liver, heart, kidneys, central nervous system, and lungs [15].

The main therapeutic goal in DIC is that of treating the underlying condition. As far as transfusion of blood products is concerned, there has been a lot of debate on its benefit and potential harm; generally, platelet counts should be kept more than $20*10^9$/L in presence of mild bleeding and more than $50*10^9$/L when there is active bleeding. Plasma or cryoprecipitate should be considered when bleeding is associated with low fibrinogen levels. The aim of fibrinogen replacement is to maintain levels more than 100 mg/dl to prevent or treat bleeding [24].

6.1.2.2 Thrombocytopenia Due to Enhanced Destruction: Immune Mechanisms (Except HIT)

In addition to Heparin-Induced Thrombocytopenia (HIT) which will be discussed in the following section, primary Immune Thrombocytopenia (ITP), post-transfusion purpura (PTP), and drugs may lead to immune platelet destruction.

ITP is an acquired disorder mediated by immunological mechanism, characterized by low platelet counts in the absence of any possible known cause of thrombocytopenia. It affects children and adults (with a slight prevalence in women) and symptoms range from massive bleeding (gastrointestinal, skin–mucosal, and intracranial) to minimal bruising or only alterations in whole blood count. Evaluation of the blood smear is important in the diagnosis of ITP (Fig. 6.1) and antiplatelet antibody assays are not routinely performed due to the low specificity of this test. Adult ITP is treated with corticosteroids or IVIg and platelet transfusions are recommended only for emergency cases in presence of active bleeding [16].

PTP is a rare complication of transfusion occurring 7–10 days after a red blood cell or platelet transfusion and is characterized by a dramatic fall in platelet count reaching a nadir less than $10*10^9$/L. Thrombocytopenia is caused by platelet alloantibodies in the recipient which at first destroy the transfused platelets, but successively also react with self-platelets. PTP is managed by administering IVIg or if available, compatible platelets (usually HPA-1a negative) [19].

Drug-induced thrombocytopenia (DITP) may either be caused by drugs suppressing bone marrow (see previous section) or by drugs eliciting diverse types of antibodies. Table 6.2 summarizes the main types of antibodies implicated in DITP [11]. DITP may be hard to diagnose in critically ill patients, since thrombocytopenia may become evident several days after the beginning of therapy, and has to be distinguished from other causes of thrombocytopenia.

Other causes of thrombocytopenia include platelet sequestration and hemodilution. Thrombocytopenia is a common feature of liver cirrhosis and is attributable to portal hypertension with sequestration of platelets in the enlarged spleen [21].

In massive transfusion, defined as the transfusion of one blood volume in 24 h, coagulation abnormalities are almost always present and are in part due to hemodilutional thrombocytopenia. However, coagulopathy associated with massive transfusion has many additional components, among which are coagulation factor dilution, hypothermia, type of solutions used for volume replacement, and DIC [22].

6.1.2.3 Clinical Significance of Thrombocytopenia in Critically Ill Patients

Hui and coworkers published a review in 2011 [25] aimed at better understanding the clinical role of thrombocytopenia in critically ill patients. It analyzed 24 studies for a total of 6,894

Table 6.2 Antibodies and mechanisms implicated immune drug-induced thrombocytopenia

Type of antibody (Ab)	Mechanism and features	Main drugs
Drug-dependent Ab	"Classic" mechanism: severe thrombocytopenia occurs 5–10 days after beginning of new drug, which binds to platelet glycoproteins (IIb/IIIa, or IbIX). Abs bind to glycoproteins and sensitized platelets are eliminated by the reticuloendothelial system, resulting in severe thrombocytopenia. Abs react with glycoproteins only when the drug is present.	Quinine
Hapten-induced Ab	Drug acts like a hapten, i.e., small molecules that elicit an immune response when linked to larger carrier molecule. Abs will bind to the platelet membrane glycoproteins only when the hapten (drug) is covalently linked to them.	Penicillin
Fiban-dependent Ab	Drugs bind to glycoprotein IIb/IIIa and may form a neo-epitope: autoantibodies are either preexistent and therefore naturally occurring, or may be stimulated by exposure. Thrombocytopenia occurs after a few hours from beginning of therapy.	Tirofiban and eptifibatide
Fab-binding monoclonal Ab	Abciximab is a Fab fragment monoclonal antibody which reacts with glycoprotein IIIa, preventing fibrinogen binding. Thrombocytopenia associated with this drug is due to naturally occurring antibodies which recognize the murine portions of the monoclonal Ab.	Abciximab

Drug-induced autoantibody formation	Some drugs may elicit autoantibodies which do not require the presence of the drug to bind to platelet antigens. Thrombocytopenia can therefore persist after the drug is no longer administered.	Gold, L-dopa, procainamide, sulphonamides, alemtuzumab
Immune complexes	Heparin-induced Thrombocytopenia (see following chapter)	Heparin
Anti-megakaryocyte Abs	Some platelet Abs in addition to binding to circulating platelets may also react with megakaryocytes, thus inhibiting platelet production.	Eptifibatide, quinine

Based on data from Arnold et al. [11]

patients; whereas 8.3–67.4 % of patients had low platelet counts at admission, the proportion of patients which developed thrombocytopenia during their stay in the ICU ranged from 13 to 44 %. Major risk factors for the development of thrombocytopenia were high illness severity, organ dysfunction, sepsis, and renal failure. The review was unable to show convincing evidence for an association between thrombocytopenia and bleeding, but multivariate analysis conducted by six studies indicated that thrombocytopenia was an independent predictor of mortality. This finding is confirmed by Stansbury and coworkers [26] in their study on the prognostic significance of platelet counts in the first 24 h after severe injury.

6.2 Heparin-Induced Thrombocytopenia (HIT)

Critically ill patients are often suspected of having HIT, because both thrombocytopenia and heparin treatment are common in the ICU setting. Nevertheless, a recent study demonstrated that the diagnosis of HIT was confirmed in only 0.5 % of these patients [27].

Heparin-Induced Thrombocytopenia (HIT) is a particular type of drug-induced thrombocytopenia that is associated with a prothrombotic condition, despite a low circulating platelet count. Although this disorder may occur with any molecular-weight heparin, the incidence of HIT is higher with unfractionated heparin compared to low-molecular-weight heparin [28, 29]. Other risk factors are host-related, with the female sex more affected than the male [30] and the surgical population more affected than the medical [31].

Two types of HIT are described with different clinical features. Type 1 HIT is likely induced by a nonimmune mechanism, with circulating platelet clumping in the presence of heparin and their sequestration in the spleen. The consequent thrombocytopenia develops usually in 2–3 days after starting

heparin, is mild and resolves spontaneously with no thrombotic or hemorrhagic complications. Unlike the former, Type 2 HIT is an immunomediated disorder, in which the anticoagulant binds to Platelet Factor 4 (PF4), a protein released from activated platelets, and triggers the development of specific antibodies [32]. The macromolecular complex constituted by the antibody and heparin-PF4 binds a specific receptor on the platelet surface leading to further platelet activation [33] and to thrombin generation [34]. Activated platelets are cleared from circulation with consequent thrombocytopenia and a paradoxical enhanced risk for arterial and especially venous thrombosis.

Different laboratory methods are available to identify the presence of HIT antibodies:

- Functional assays with the HIT patient serum activating normal platelets in the presence of heparin
- Antigen assays to detect the binding of HIT antibodies to their target heparin/PF4

Functional assays are more specific for clinically relevant antibodies, but require specialized personnel, so antigen assays are the most widely used [35].

A typical feature of Type 2 HIT is the reduction of more than 50 % in the platelet count, leading to a moderate thrombocytopenia with a median platelet nadir of 50–60*10^9/L; unlike other drug-mediated thrombocytopenias, a platelet number less than 20*10^9/L is very uncommon. In naïve patients, the typical onset of thrombocytopenia is 5–14 days after the beginning of heparin exposure; in patients treated in the past 3 months, it may occur early within 24 h (early onset). Seldom platelet counts begin to fall after more than 15 days from the beginning of heparin treatment, sometimes after heparin discontinuation with a delay onset [36].

When HIT is strongly suspected, any heparin treatment (even exposure to heparin flushes or lines washing procedure) must be discontinued and replaced with another anticoagulant, for example, direct thrombin or activated FX inhibitors [37]. In a

few days, platelet count returns to normal values or to pretreatment values.

Actual guidelines suggest a clinical evaluation with a scoring system to test the likelihood of the disorder [38, 39]. The most widely used is the 4 T's score, based on clinical traits of HIT such as the degree of thrombocytopenia, the timing of the onset, the presence of a new or enlarged thrombosis, and an eventual different cause of platelet count decrease, as is shown in Table 6.3 [38].

With a low score (≤3), HIT can be excluded without any laboratory assay and the heparin treatment may be continued; if the score is moderate or high (4–6), all heparin exposure should be discontinued to avoid HIT complications and an alternative anticoagulant should be chosen [40]. Recently, two new methods have been proposed for assessing the clinical probability of HIT in the early management of patients suspected of having HIT [41, 42] but they need further validation. Whichever method is used, a careful evaluation is necessary in HIT exclusion or confirmation in order to prevent bleeding risks in thrombocytopenic patients.

6.3 Thrombocytosis in Critically Ill Patients

Elevated platelet counts (>400*10^9/L) are not a common finding among critically ill patients and contrary to thrombocytopenia, thrombocytosis in hospitalized patients has not been investigated at great length. From the etiological point of view, thrombocytosis may be classified as primary or secondary. Whereas the former group includes myeloproliferative or myelodysplastic syndromes, the latter may be either secondary or paraneoplastic. In the ICU patient, the main underlying clinical conditions responsible for thrombocytosis are infection, trauma, splenectomy, hemolysis, bleeding, and drugs such as antifungals, amoxicillin/clavunate, enoxaparin [43]. Two

Table 6.3 The 4 T's score (adapted from [38])

	Points = 2	Points = 1	Points = 0
Thrombocytopenia	>50 % platelet fall *and* Platelet nadir ≥20*10^9/L	50 % fall or Platelet nadir 10–19*10^9/L	<30 % fall or Platelet nadir <10*10^9/L
Timing of platelet count fall	Clear onset between day 5 and 10 or Platelet fall ≤1 day (if heparin exposure within past 30 days)	Consistent with immunization but not clear (e.g., missing platelet counts) or Onset of thrombocytopenia after day 10 or Fall ≤1day if heparin exposure 30–100 days ago	Platelet count fall ≤4 days (without recent heparin exposure)
Thrombosis (or other sequelaes, e.g., skin lesions)	New thrombosis (confirmed); Skin necrosis; Acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; Erythematous skin lesions; Suspected thrombosis not yet proven	None
Other causes of thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

other main conditions leading to thrombocytosis are familial (hereditary), due to a mutation responsible for an increase in the production of thrombopoietin [44], and essential thrombocythemia, a condition which may eventually lead to myelofibrosis or leukemia.

Differential diagnosis between primary and secondary thrombocytosis is not always straightforward in the ICU setting. Generally speaking, if thrombocytosis occurs during the stay in an ICU, it is most probably of secondary nature. However, if the patient is admitted urgently and no previous whole blood count is available, hematological consultation and further testing (e.g., *JAK2*) might be useful for the characterization of thrombocytosis [43]. For patients affected by secondary thrombocytosis, risk of thrombotic or hemorrhagic complications is <2 %, irrespective of platelet count.

As far as therapy is concerned, there is no threshold above which platelet removal by apheresis or antiaggregation therapy should be initiated. Risk of thrombosis in these patients must consider associated clinical conditions such as sepsis, trauma, and rheumatic disease, which themselves predispose to venous clot formation. Platelet apheresis is able to reduce platelet counts significantly and is used primarily in patients with myeloproliferative diseases in which either a thrombotic or bleeding event has occurred. Aspirin is administered in thrombocytosis (both primary and secondary) patients who have had a thrombotic event.

References

1. Parker RI (2012) Etiology and significance of thrombocytopenia in critically ill patients. Crit Care Clin 28:399–411
2. Rice TW, Wheeler AP (2009) Coagulopathy in critically ill patients. Part 1: Platelet disorders. Chest 136:1622–1630
3. Stasi R (2012) How to approach thrombocytopenia. Hematology 2012: 191–197

4. Parik S, Bessler M (2012) Recent insights into inherited bone marrow failure syndromes. Curr Opin Pediatr 24:23–32
5. Ballmaier M, Germeshausen M (2009) Advances in the understanding of congenital amegakaryocytic thrombocytopenia. Br J Hematol 146:3–16
6. Kantarjian H, Giles F, List A et al (2007) The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer 109(9): 1705–1714
7. Cazzola M, Malcovati L, Invernizzi R (2011) Myelodysplastic/myeloproliferative neoplasms. Hematology 2011:264–272
8. Finfer SR, Vincent JL (2013) Severe sepsis and septic shock. NEJM 369(9):840–851
9. Kwaan HC (2007) Thrombosis and bleeding complications in malignant hematologic disorders. Hematology 2007:151–157
10. Grabowski GA (2012) Gaucher disease and other storage disorders. Hematology 2012:13–18
11. Arnold DM, Nazi I, Warkentin TE et al (2013) Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev 27(3):137–145
12. Mac Manus M, Lamborn K, Khan W (1997) Radiotherapy-associated neutropenia and thrombocytopenia: analysis of risk factors and development of a predictive model. Blood 89(7):2303–2310
13. Shenoy C, Orshaw P, Devarakonda S et al (2009) Occurrence, predictors, and outcomes of post-percutaneous coronary intervention thrombocytopenia in an unselected population. J Interven Cardiol 22:156–162
14. Fontana S, Kremer Hovinga JA, Lammle B et al (2006) Treatment of thrombotic thrombocytopenic purpura. Vox Sanguinis 90:245–254
15. Kitchens CS (2009) Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). Hematology 2009:240–246
16. Provan D, Stasi R, Newland AC et al (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 115(2):168–186
17. McKenzie CGH, Guo L, Freedman J et al (2013) Cellular immune dysfunction in immune thrombocytopenia (ITP). Br J Haemat 163:10–23
18. Usmani NG, Woda A, Newburger PE (2013) Advances in understanding the pathogenesis of HLH. Br J Haemat 161:609–622
19. Rozman P (2002) Platelet antigens. The role of human platelet alloantigens (HPA) in blood transfusion and transplantation. Transplant Immunol 10:165–181
20. Warkentin TE, Sheppard JA, Heels-Ansdell D et al (2013) Heparin-induced thrombocytopenia in medical surgical critical illness. Chest 144(3): 848–858
21. Peck-Radosavljevic M (2001) Hypersplenism. Eur J Gastroenterol Hepatol 13:317–323

22. Hardy JF, de Moorloose P, Samama M (2004) Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. Can J Anesth 51(4):293–310
23. Thiele T, Selleng K, Selleng S et al (2013) Thrombocytopenia in the Intensive Care Unit – diagnostic approach and management. Semin Hematol 50(3):239–250
24. Dunn AL (2009) Disseminated intravascular coagulopathy. In: Hillyer CD, Shaz BH, Zimring JC, Abshire TC (eds) Transfusion Medicine and hemostasis: clinical and laboratory aspects. Elsevier, Burlington/London
25. Hui P, Cook DJ, Lim W et al (2011) The frequency and clinical significance of thrombocytopenia complicating critical illness. Chest 139(2): 271–278
26. Stansbury LG, Hess AS, Thompson K et al (2013) The clinical significance of platelet counts in the first 24 hours after severe injury. Transfusion 53(4):783–789
27. Trehel-Tursis V, Louvain-Quintard V, Zarrouki Y et al (2012) Clinical and biologic features of patients suspected or confirmed to have heparin-induced thrombocytopenia in a cardiothoracic surgical ICU. Chest 142(4):837–844
28. Warkentin TE, Levine MN, Hirsch J et al (1995) Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330–1335
29. Martel N, Lee J, Wells PS (2005) Risk for heparin-induced thrombocytopenia with unfractionated and low molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 106:2710–2715
30. Warkentin TE, Sheppard JAI, Sigoin CS et al (2006) Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 108:2937–2941
31. Chong BH (2003) Heparin induced thrombocytopenia. J Thromb Haemost 1:1471–1478
32. Amiral J, Bridey F, Dreyfus M et al (1992) Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 68:95–96
33. Newman PM, Chong BH (2000) Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4–heparin antibodies to platelets and the resultant platelet activation. Blood 96: 182–187
34. Tardy-Poncet B, Piot M, Chapelle C et al (2009) Thrombin generation and heparin-induced thrombocytopenia. J Thromb Haemost 7:1474–1481
35. Greinacher A, Warkentin TE (2006) Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. Thromb Res 118:165–176

36. Warkentin TE (2002) Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. Recommendations of the College of American Pathologists. Arch Pathol Lab Med 126:1415–1423
37. Backhoul T, Greinacher A (2012) Recent advances in the diagnosis and treatment of heparin-induced thrombocytopenia. Ther Adv Hematol 314:237–251
38. Linkins LA, Dans AL, Moores LK et al (2012) Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: America College of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest 141:e495S–e530S
39. Watson H, Davidson S, Keeling D (2012) Guidelines on the diagnosis and management of heparin induced thrombocytopenia: second edition. Br J Haematol. doi:10.1111/bjh.12059
40. Lo GK, Juhl D, Warkentin TE et al (2006) Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. JTH 4:759–765
41. Cuker A, Arepally G, Crowther MA et al (2010) The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost 8:2642–2650
42. Messmore HL, Fabbrini N, Bird NL et al (2011) Simple scoring system for early management of heparin-induced thrombocytopenia. Clin Appl Thromb Hemost 17:197–201
43. Powner DJ, Hoots WK (2008) Thrombocytosis in the NICU. Neurocrit Care 8:471–475
44. Vannucchi A, Barbui T (2007) Thrombocytosis and thrombosis. Hematology 2007:363–370