How I Treat

How I evaluate and treat thrombocytopenia in the intensive care unit patient

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Abstract

Multiple causes (pseudothrombocytopenia; hemodilution; increased consumption; decreased production; increased sequestration; immune-mediated destruction of platelets) alone or in combination make thrombocytopenia very common in intensive care unit (ICU) patients. Persisting thrombocytopenia in critically ill patients is associated with increased mortality but not causative. Identification of the underlying cause is key for management decisions in the individual patient. While in patients with impaired platelet production, or increased platelet destruction, platelet transfusion might be indicated, this could be deleterious in patients with increased intravascular platelet activation. Sepsis and trauma are the most common reasons of thrombocytopenia in the ICU. In these patients, treatment of the underlying disease will also increase the platelet count. Heparin-induced thrombocytopenia requires alternative anticoagulation in therapeutic dose and immune thrombocytopenia immunomodulatory treatment. Thrombocytopenia with symptomatic bleeding ≥WHO grade 2 or planned invasive procedures are established indications for platelet transfusions, while the evidence for a benefit of prophylactic platelet transfusions is low and controversial. If the platelet count does not increase after transfusion of two fresh ABO blood group identical platelet concentrates (therapeutic units), ongoing platelet consumption and high-titer anti-human leukocyte antigen (HLA) class I antibodies should be considered. The latter requires transfusion of HLA compatible platelet concentrates.
Introduction

Thrombocytopenia is generally defined as platelet counts <150x10⁹/L and represents a common laboratory finding in intensive care unit (ICU) patients. Up to 50% of patients present with thrombocytopenia at some time point of their ICU stay, and 5-20% develop severe thrombocytopenia, defined as platelet counts <50x10⁹/L.¹⁻³ Normally, the platelet count in the peripheral blood is controlled by complex interactions regulating platelet production in the bone marrow, platelet pooling in the liver and spleen, and their elimination in the reticuloendothelial system,⁴⁻⁵ which then feeds back into thrombopoietin regulation.⁶ The platelet count is rather constant in an individual person.⁷ In critically ill patients, however, these mechanisms can fail, which results in disturbance of the balance between platelet production, platelet pooling, and platelet consumption. Thrombocytopenia should be seen as a sensitive marker for considerable alteration of normal physiology. This is most likely the reason for the consistent finding that a low platelet count is associated with an increased risk for mortality in critically ill patients.⁸⁻¹⁵ For example, in a prospective observational study that analyzed 257 patients who stayed longer than two weeks in the ICU, 138 patients (54%) presented with thrombocytopenia of <150x10⁹/L on day 4 after ICU admission. They had a higher mortality than the non-thrombocytopenic patients (33% vs. 16%; p <0.05).⁸ While in most patients the platelet count returned to normal in the second week, for 51 of the 257 patients, thrombocytopenia remained on day 14; these patients had the highest mortality (66% vs. 16%; p<0.05).⁸

The mechanisms contributing to thrombocytopenia in the ICU include the following: 1.) pseudothrombocytopenia, 2.) hemodilution, 3.) platelet consumption, 4.) decreased platelet production 5.) increased sequestration of platelets, and 6.) immune-mediated destruction of platelets.¹⁶ In the individual thrombocytopenic ICU patient, often more than one of these mechanisms is responsible for the low platelet count, e.g., thrombocytopenia in sepsis results from decreased production as well as increased consumption and destruction of
platelets.\textsuperscript{17,18} (e.g. by hemolysins).\textsuperscript{19} Table 1 correlates these mechanisms with potential underlying diseases in typical ICU patients.

A crucial step for successful treatment of thrombocytopenia in the critically ill is to identify the underlying cause(s) of the low platelet count, as management differs substantially depending on the underlying disease. While in patients with impaired platelet production, or increased platelet consumption/destruction, platelet transfusion might be indicated, this could be deleterious in patients with increased intravascular platelet activation like in heparin-induced thrombocytopenia (HIT) or thrombotic thrombocytopenic purpura (TTP),\textsuperscript{20,21} and possibly in certain prothrombotic forms of disseminated intravascular coagulopathy (DIC). In the following we will discuss different causes for thrombocytopenia and the implications on patient management, using illustrative patient cases.

As with any complex disease, a detailed history and careful physical examination are key to achieving the right diagnosis. Supported by a few laboratory tests, interpretation of these data within the specific clinical context often enables diagnosis. In case of unexpected thrombocytopenia, the first question should be whether the patient is really thrombocytopenic.

**Case 1: Pseudothrombocytopenia**

*Scenario*

A 67-year-old male patient who suffered from acute coronary syndrome (ACS) received emergency percutaneous coronary intervention with implantation of several stents, one of them in the left main coronary artery, followed by therapeutic dose anticoagulation with unfractionated heparin (UFH) plus platelet inhibition with aspirin, clopidogrel, and eptifibatide (all in standard doses). Six hours post-intervention, the platelet count had dropped from $270 \times 10^9$/L (pre-procedure) to $6 \times 10^9$/L (in ethylenediaminetetraacetic acid [EDTA]-anticoagulated blood as well as in citrated blood), and the patient was admitted
to the ICU due to the anticipated risk of major bleeding, although he did not show overt bleeding symptoms.

Management

The case raises several management issues: Should all antiplatelet drugs, including eptifibatide, be stopped? Should heparin be stopped? Should platelets be transfused to prevent bleeding? Should tranexamic acid be given prophylactically? As physical examination revealed no bleeding signs, immediate review of the blood film was requested, which showed large platelet aggregates, confirming the diagnosis of eptifibatide-induced pseudothrombocytopenia. The patient was transferred back to the cardiology ward for ongoing standard post-stenting treatment.

Comment

Pseudothrombocytopenia is a laboratory artifact usually caused by in vitro platelet agglutination in EDTA-anticoagulated blood. These platelet aggregates can not be recognized by automated cell counters, thus underestimating the true platelet count. Naturally-occurring immunoglobulin class M antibodies directed against epitopes on platelet glycoprotein (GP) IIbIIIa, which are expressed upon calcium chelation by EDTA,\textsuperscript{22,23} cause in vitro platelet clumping, and spurious thrombocytopenia. In most cases, the diagnosis is confirmed by measuring normal platelet counts in citrated blood. However, during treatment with GPIIbIIIa antagonists, pseudothrombocytopenia can also occur in citrated blood.\textsuperscript{24}

As GPIIbIIIa antagonists can induce both real thrombocytopenia as well as pseudothrombocytopenia in more than 3% of patients,\textsuperscript{25,26} exclusion of pseudothrombocytopenia is crucial before any antiplatelet therapy is stopped or even prothrombotic treatments are initiated due to the high risk of acute in stent thrombosis.\textsuperscript{27}
Of note, also in case of real GPIIbIIIa-inhibitor induced thrombocytopenia major bleeding complications are rare and cessation of the GPIIbIIIa inhibitor usually sufficient.

Case 2: Sepsis

Scenario

A confused 64-year-old male patient with a history of multiple myeloma who had received a cycle of antineoplastic therapy (bortezomib, dexamethasone) the previous day, was admitted to the ICU with septic fever, shivering, and circulatory shock. A several day old blunt trauma of the right forearm was seen during physical examination. Laboratory assessment indicated massive systemic inflammation (C-reactive protein=247.0mg/L [normal value=<5.0mg/L], procalcitonin=223ng/mL [0-0.5ng/mL]), renal failure (creatinine=392µmol/L [49-97µmol/L]), and coagulopathy (international normalized ratio (INR)=1.7, activated partial thromboplastin time (aPTT)=34s [25-33s]). The platelet count was 48x10^9/L (Figure 1A).

Management

The low platelet count could have been associated with the multiple myeloma and/or the antineoplastic therapy. However, considering the clinical context, the most likely reason was sepsis with an unknown focus. Further workup excluded the most frequent causes of sepsis, i.e. pneumonia (chest x-ray), urinary tract infections (urine stick) or peritonitis (sonography, physical examination). Infection of the wound at the right forearm injury was then assumed as the source of sepsis in this immunocompromised patient. After taking blood cultures and starting broad-spectrum antibiotics, surgical debridement was performed (Figure 1B), for which three therapeutic platelet concentrates (each containing 2-4x10^{11} platelets/unit) were given prophylactically. The second prophylactic platelet transfusion was given five days later to allow surgical closure of the forearm wound.
Subsequently, the platelet count normalized as an indicator of successful sepsis treatment (Figure 1A).

Comment
This case illustrates how important it is to identify and to control the source of sepsis to allow normalization of the coagulation system including the platelet count. Sepsis accounts for ≈50% of all thrombocytopenias in the severely ill. The mechanisms leading to thrombocytopenia associated with sepsis are multifactorial and complex, and include decreased platelet production, increased platelet consumption as well as sequestration frequently by hemophagocytosis. Enhanced platelet consumption results from ongoing thrombin generation and increased adhesion of platelets to endothelial cells. In critically ill septic patients, thrombocytopenia is associated with a dysregulated host response, and it indicates poor prognosis in patients with septic shock.

Therapy of sepsis requires source control, antibiotic therapy, and supportive measures. Platelet transfusion is recommended in case of bleeding ≥WHO grade 2 (i.e. more than mild blood loss like epistaxis, hematuria, hematemesis), but invasive interventions like debridement of infected tissue may require prophylactic platelet transfusions.

Case 3: Trauma

Scenario
An 18-year-old female patient with multiple trauma after a fall from the fourth floor, including subarachnoidal hemorrhage, bilateral hemopneumothorax, and pelvic fracture, was admitted with hemorrhagic shock requiring prehospital resuscitation. Despite severe anemia (hemoglobin=6.0 g/dL), and coagulopathy (INR=1.3, aPTT=48 seconds), the platelet count was normal (299x10⁹/L) at admission. Computed tomography (CT) scan revealed retroperitoneal bleeding and ruptured pelvic vessels. Despite transfusion of two
platelet concentrates as part of the massive transfusion protocol, the platelet count rapidly declined during the first 7 hours after admission to 51x10^9/L (Figure 2).

**Management**

Traumatic bleeding from the pelvic arteries prompted embolization of the bleeding artery and subsequent retroperitoneal packing to control hemorrhage. In addition to massive transfusion (48 units RBCs, 22 units FFPs), fibrinogen was administered, as fibrinogen is the first coagulation factor that falls below critical values in the case of major bleeding\(^3\) (Figure 2). During the first four days, this patient was transfused with a total of 10 platelet concentrates (each 2-4x10^11 platelets/unit), mostly during (or shortly before) invasive procedures, with a targeted platelet count of >50x10^9/L. The platelet count increased spontaneously, after bleeding was stopped by interventional and surgical procedures (Figure 2).

**Comment**

Trauma-induced coagulopathy together with hemodilution due to massive transfusion of RBCs and FFPs\(^3\) are common reasons for thrombocytopenia in the ICU.\(^1\) In the presented case, severe trauma, massive bleeding (more than a two-fold loss of the blood volume),\(^3\) and coagulopathy led to trauma-induced platelet loss and consumption. In addition, consumption of plasmatic coagulation factors, hyperfibrinolysis, and systemic inflammation\(^3\) as well as hemodilution due to infusion of fluids and transfusion of blood products, and shock-related metabolic acidosis enhance the bleeding risk.\(^3\)

In actively bleeding trauma patients, transfusion of platelet concentrates alone will usually not stop bleeding, but this situation of consumptive coagulopathy is nevertheless an absolute indication for platelet transfusion as a bridging therapy to maintain the target platelet count until the surgeon or the interventionalist mechanically stops the bleeding. Current
guidelines recommend platelet transfusions to maintain the platelet count >50x10⁹/L\(^3\) in trauma patients, and >100x10⁹/L in patients with ongoing bleeding and/or traumatic brain injury.\(^3\) In addition, tranexamic acid was given to correct hyperfibrinolysis.\(^3\),\(^3\),\(^4\) In the CRASH-2 trial\(^\text{41}\) application of 1g tranexamic acid as a bolus followed by infusion of another 1g over 8 hours reduced mortality in adult trauma patients compared to placebo (4.9% vs 5.7%; relative risk 0.85, 95% confidence interval 0.76-0.96; p=0.0077). Tranexamic acid should be given as early as possible in trauma patients.\(^4\)

**Case 4: Immune thrombocytopenia (ITP)**

**Scenario**

A 46-year-old male patient with a 10-year history of ITP suffered traumatic brain contusion from a bicycle accident. At ICU admission, the platelet count was 11x10⁹/L, and the neurosurgeons required 50x10⁹/L platelets in order to control bleeding. The outpatient file of this patient documented previous good platelet count responses to corticosteroids and intravenous immunoglobulin (Ig) G (IVIG).

**Management**

We transfused 4 therapeutic units of platelet concentrates targeting a platelet count of >35x10⁹/L at admission and gave 1g IVIG/kg body weight per day for two days, together with 100mg prednisone during the first week. Platelet-inhibiting agents, e.g. non-steroidal anti-inflammatory drugs, were avoided and no routine heparin thromboprophylaxis was given. Repeated CT scans over the next days showed the brain contusions at a constant size, and the patient remained in a stable clinical condition.

However, on day 5 he developed symptomatic pulmonary embolism. At that time the platelet count was 60x10⁹/L. UFH was given in escalating doses, first achieving an aPTT of 40 seconds, later of 50 seconds. The cardiopulmonary condition stabilized and the neurologic
Comment

Onset of ITP is extremely rare in adult ICU patients although the incidence of ITP (3-5/100,000 population) makes it possible that a patient with chronic ITP is admitted with life-threatening bleeding to the ICU. Because ITP is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets, immunosuppressive therapy is the first line treatment. Two gram IVIG per kg body weight (over two consecutive days), followed by 100 mg prednisone/d has been shown to result in the fastest increase of the platelet count in adult patients with (untreated) severe ITP. In contrast, platelet transfusions are usually not effective, but transfusion of large amounts of platelets can result in cessation of bleeding and even an increased platelet count, and are therefore recommended as first-line treatment (in addition to IVIG and corticosteroids) in ITP patients with life-threatening bleeding. However, in this situation, often more than 5 therapeutic units are required before bleeding is controlled.

Severe thrombocytopenia, especially if associated with symptomatic bleeding, is a well-established contraindication for treatment with an anticoagulant, including pharmacological thrombosis prophylaxis. In the absence of prospective randomized trials, a widely used protocol in patients with malignancy-associated thrombocytopenia who have comorbidities, but who typically require therapeutic-dose anticoagulation (e.g., for treatment of symptomatic venous thromboembolism), is to reduce therapeutic-dose anticoagulation by half, if the platelet count falls below 50x10^9/L; and to use prophylactic dose anticoagulation if the platelet count falls below 30x10^9/L; and to stop all anticoagulants if the platelet count falls below 20x10^9/L. Patients with ITP have an increased risk for thrombosis as well as patients with intracranial hemorrhage undergoing neurosurgery. In these patients, thrombocytopenia per se does not necessarily protect against thrombosis in otherwise high-
risk situations. In the absence of acute bleeding, and especially when the platelet count has responded to treatment, increasing above \(20 \times 10^9/L\), critically ill ITP patients with additional risk factors for thrombosis, should receive pharmacologic thromboprophylaxis to reduce risk of acute thrombosis/pulmonary embolism, unless there is overt bleeding. Acute thrombosis mandates therapeutic-dose anticoagulation for the next three months, substantially increasing the risk for major bleeding in a patient with chronic ITP unless the platelet count can be stabilized at a higher level during this period (e.g., by thrombopoietin receptor agonists).53-55

**Case 5: Drug-induced thrombocytopenia**

*Scenario*

A 75-year-old female patient with stroke and right-sided hemiplegia, recurrent seizures, dysphagia and pneumonia required invasive ventilation. She received several drugs, including antibiotics, sedation, aspirin, UFH in prophylactic dose, diuretics, and anticonvulsants. At day 7, valproic acid was added to levetiracetam and lorazepam to control seizures. Ten days later the platelet count began to fall reaching values <\(50 \times 10^9/L\) (Figure 3).

*Management*

In the absence of any laboratory or clinical symptoms for sepsis, heparin-induced thrombocytopenia (HIT) was first suspected in our patient. When we applied the 4Ts score\(^56\) (Table 2) it revealed 4 points (platelet count decrease>50%=2 points; onset of platelet count fall >day 10=1 point; no thrombosis=0 point; thrombocytopenia in a patient on a ventilator as an assumed other reason for thrombocytopenia=1 point), consistent with a an intermediate risk for HIT, but the anti-platelet factor (PF) 4/heparin IgG enzyme immunoassay was negative, thus ruling out HIT.\(^57,58\)

On the other hand, valproic acid is known to cause both immune and non-immune mediated thrombocytopenia\(^59\) (Table 3). We stopped valproic acid while continuing all
other medications, and the platelet count recovered (Figure 3).

Comment

Drug-related thrombocytopenia is a relatively common cause of thrombocytopenia in ICU patients,17 whereby non-immune drug-induced thrombocytopenia (DTP), e.g. caused by toxic bone marrow suppression, is responsible for the vast majority of cases.60-65 With the exception of HIT, drug-induced immune thrombocytopenia (DITP) is much less frequent than DTP.17,60,64 In contrast to DTP, DITP typically presents with an abrupt platelet count fall evolving within one to two days, that begins usually 5 to 14 days after starting a new drug, and a nadir below 20x10^9/L, nearly always accompanied by mucocutaneous bleeding.59,65-69 Table 3 summarizes typical mechanisms and drugs of DTP and DITP.

More than 10% of patients treated with valproic acid develop DTP.59 Older age, female sex, higher valproic acid dosage, and lower baseline platelet counts are associated with an increased risk for DTP.59,66,67 However, valproic acid can also induce immune-mediated DITP. In both, DTP and DITP cessation of the drug is most important and usually sufficient.59,65-69 Recovery of the platelet count will occur thereafter and is often not very helpful for differentiation between DTP and DITP. In our patient the platelet count started to increase ≈48 hours after stopping valproic acid, but also in DITP platelet count recovery usually begins 5-7 half-times after cessation of the drug (half-time for valproic acid 5-7 hours = expected recovery after ≈50 hours). The relatively slow decline of the platelet count and especially the nadir above 20x10^9/L argued against DITP.

If a patient with DITP develops major bleeding symptoms, IVIG (1g/kg body weight on two consecutive days) is recommended.65 It augmented platelet count recovery in mouse models of DITP.70 However, corticosteroids are usually ineffective.65 In case of life-threatening bleeding transfusion of platelet concentrates might be considered.

Laboratory tests for the detection of drug-dependent anti-platelet antibodies are helpful
to support the diagnosis DITP. However, these tests are performed only in specialized laboratories and are usually not available to guide acute management. In contrast to assays for detecting antibodies in HIT, the sensitivity of assays for all other DITPs is low and thus a negative test does not rule out the diagnosis. The clinical relevance of laboratory testing for DITP antibodies is twofold: first, it allows objective confirmation of an adverse drug effect (relevant for pharmacovigilance), and second it is important for the individual patient (future drug avoidance). We could not demonstrate valproic acid-dependent platelet-reactive antibodies in this patient, further supporting non-immune mechanisms.

**Case 6:**

*Scenario*

A 79-year-old female patient on aspirin and clopidogrel after implantation of coronary stents several weeks earlier developed in-stent thrombosis with myocardial infarction and cardiac arrest. After successful cardiopulmonary resuscitation and coronary angioplasty the patient was admitted to the ICU. Aspirin and clopidogrel were continued and therapeutic dose UFH was started. The patient was in cardiogenic shock with multiple organ failure, and the platelet count dropped from 326 to 28x10⁹/L by day 5 of ICU treatment (Figure 4).

*Comment*

Analyzing carefully the platelet count course is helpful for discerning among various explanations for thrombocytopenia. Typically, ICU patients present with a biphasic platelet count course: After an initial decrease to a platelet count nadir 2 to 4 days after ICU admission, platelets recover to higher-than-baseline values (so-called reactive thrombocytosis). Persistent or progressive thrombocytopenia therefore suggests ongoing consumption, bleeding, or severe organ damage. A slow decrease in platelet counts over several days is rather typical for infection, septicemia or bone marrow toxicity. Immune-
mediated causes should be considered, such as HIT or DITP, \(^72\) when the platelet count falls rapidly within 1-2 days during the second week of treatment, after an initial recovery.

**Management**

The initial platelet count fall was easily explained by the severe disease. However, when the platelets fell to \(<30 \times 10^9/L\) at day 5 we included HIT into the differential diagnoses of the low platelet count. The 4Ts score \(^56\) was 4 points (2 points for the Thrombocytopenia, 1 point for the timing, 0 points for Thromboses, and 1 point for other reasons), giving an intermediate pretest probability of HIT. As in patients with a 4Ts score of \(\geq 4\) the probability of HIT is \(>25\%\), \(^56\) we introduced alternative anticoagulation using danaparoid in prophylactic dose. Because the suspicion of HIT was vague and the risk of bleeding high, we first used prophylactic dose danaparoid to avoid further triggering HIT without increasing the bleeding risk. After the HIT antibody tests were highly suggestive for HIT (strongly positive anti-PF4/heparin IgG antibodies in the enzyme-immunoassay, and detection of heparin-dependent platelet-activating antibodies in the heparin-induced platelet activation assay; Figure 4) we escalated to therapeutic dose danaparoid. The positive HIT-antibody tests made the diagnosis of HIT possible (although HIT may not necessarily be present in the setting of early-onset and persisting thrombocytopenia even when HIT tests are positive). \(^73\) Indeed, the platelet count increased only moderately (Figure 4) over the next seven days, indicating that factors other than HIT were probably most responsible for thrombocytopenia.

**Comment**

Even in hindsight, it is unclear whether the strong platelet-activating anti-PF4/heparin antibodies were really the cause of the low platelet count, or simply an epiphenomenon, as these antibodies are detected incidentally in some patients without thrombocytopenia, especially after cardiac surgery this may be the case in \(>10\%\) of patients. \(^73,74\) However, the
further worsening of thrombocytopenia 5 days after starting heparin, at a time when platelet count recovery would otherwise have been expected, together with a strongly-positive functional assay, prompted us to change anticoagulation to a non-heparin anticoagulant, given the risk for new thrombosis (up to 5% per day) in acute HIT, to the absence of an effective anticoagulant.

HIT is immune-mediated and usually occurs 5 to 14 days after starting heparin in case of HIT. However, in contrast to other DITP: a) platelets fall below 20x10⁹/L in only ~10 to 15% of cases, b) thromboses rather than bleeding are the typical clinical complications, c) treatment requires substituting heparin with an alternative (non-heparin) anticoagulant, and d) antibodies usually disappear 50 to 80 days after the acute episode of HIT. This makes re-exposure to heparin possible under special circumstances, for example, during cardiovascular surgery, when antibodies are no longer detectable. HIT can occur within hours in preimmunized patients who receive heparin when platelet-activating anti-PF4/heparin antibodies are still present in the circulation, so-called rapid-onset HIT. Although this had been possible in our patient due to pretreatment with heparin during the first episode of ACS a few weeks before, rapid-onset HIT appeared unlikely as the platelet count started to decrease after day 2 only.

**Platelet transfusions in ICU patients**

A major issue in thrombocytopenic ICU patients is whether and when platelet transfusions should be given:

*Therapeutic platelet transfusions* are generally indicated in patients with bleeding ≥WHO grade 2 (i.e. more than mild blood loss like epistaxis, hematuria, hematemesis). In many ICU patients, thrombocytopenia is associated with acquired mild to moderate platelet function defects, which are caused or aggravated e.g. by medications (antibiotics, analgesics); platelet activation on extracorporeal circuits; or cleavage of platelet receptors by released
enzymes in case of sepsis.\textsuperscript{28} Therefore, in thrombocytopenic patients bleeding symptoms are much more relevant than the platelet count for deciding whether platelets should be transfused. In patients with immune-mediated thrombocytopenia, e.g. ITP and DITP, however, platelet transfusions should be restricted to patients with serious or life-threatening bleeding.\textsuperscript{47,65} The same accounts for patients with acute HIT or thrombotic thrombocytopenic purpura (TTP).\textsuperscript{84,85}

Due to the lack of prospective randomized trials major uncertainty exists in regard to prophylactic platelet transfusions in ICU patients with thrombocytopenia (with or without DIC) and/or platelet function defects without active bleeding \textgtr \ WHO grade 2. As in patients with hypoproliferative thrombocytopenia due to chemotherapy, ICU patients with spontaneous bleeding of the oropharyngeal mucous membranes (so-called "wet purpura") indicate an increased risk for life-threatening bleeding into the central nervous system or retinal bleeding, and should prompt platelet transfusions in case of non-immune mediated thrombocytopenia. In patients with immune-mediated thrombocytopenia, e.g. ITP and DITP, however, other measures like high dose IVIG are more appropriate. As no data exist demonstrating that ICU patients benefit from prophylactic platelet transfusion in regard to bleeding or mortality,\textsuperscript{86} the authors consider it reasonable to restrict platelet transfusions to ICU patients with symptomatic bleeding irrespective of the platelet count. However, a recent expert recommendation suggests to prophylactically transfuse platelets in patients with severe sepsis at a threshold of $\leq 10 \times 10^9$/L, and if the patient has a significant risk of bleeding even at a threshold of $\leq 20 \times 10^9$/L.\textsuperscript{32}

Another issue is platelet transfusion \textit{before invasive procedures} for which only observational studies exist. Table 3 summarizes the established recommendations for prophylactic platelet transfusions before invasive procedures and the strength of the recommendation.\textsuperscript{33}

A further dilemma in critically ill patients is evaluation on whether a platelet
transfusion was successful. Often one cannot observe the expected platelet count increase of
≈15x10^9/L in an ICU patient after transfusion of a single therapeutic platelet unit, because
ongoing consumption of platelets due to the underlying disease or concomitant treatment, e.g.
during application of antimycotic drugs. Transfusion of two fresh ABO blood group identical
platelet concentrates (therapeutic units) usually overcomes nonimmune causes of platelet
transfusion refractoriness. If the platelet count still does not increase, presence of platelet-
reactive antibodies, especially anti-human leukocyte antigen (HLA) class I antibodies, should
be excluded, especially in multiparous women. If high-titer anti-HLA class I antibodies are
detectable, HLA compatible platelet concentrates often result in an appropriate platelet count
increase. Rarely, anti-human platelet antigen (HPA) alloantibodies are implicated in patients
who test positive for anti-HLA antibodies but remain refractory to HLA-matched platelet
concentrates.

**Summary:**

Thrombocytopenia is common in the ICU. It is a sensitive marker for the severity of the
disease and associated with increased mortality. Identifying the underlying cause is
essential for successful treatment. Platelet transfusions can be helpful in situations of
platelet loss and/or consumption, but might be deleterious in patients with increased
intravascular platelet activation. A detailed history and careful physical examination are keys
to achieving the right diagnosis, supported by a few laboratory tests and interpreting these
data within the clinical context.
Authorship and conflict of interest

Both authors contributed equally to the manuscript. S.S. and A.G. are members of the current ASH guideline committee on heparin-induced thrombocytopenia. A.G. is: - member of the ISTH scientific subcommittees on platelet immunology and cochair of the subcommittee on perioperative management. - Member of the working group „Guidelines for treatment with blood components of the German Medical Association“ – der Bundesärztekammer Member of regular working group „Guidelines for production of blood and blood components and the treatment with blood products“ (Hemotherapy) der Bundesärztekammer
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Figure legends:

Figure 1: This figure illustrates thrombocytopenia in a septic intensive care unit (ICU) patient. Although recent cytostatic therapy could have been the reason of the low platelet count at ICU admission (48x10^9/L), sepsis from an infected lower arm wound was responsible for the low platelet count. Causative therapy of sepsis, and thereby of the thrombocytopenia, consisted of antibiotic therapy and surgical source control. Transfusion of fresh frozen plasma (FFP), prothrombin complex (PCC)\(^\#\), and 4 therapeutic platelet concentrates (each containing 2-4x10^{11} platelets/unit) were given to allow the surgical treatment. After the source of sepsis could have been controlled, the platelet count returned to normal without any further measures (A). INR = international normalized ratio; aPTT = activated partial thromboplastin time; sec = seconds. \(^\#\) Four factor PCCs are used in some European centers to improve hemostasis, especially if the patient does not tolerate transfusion of large fluid volumes. This differs from current medical practice in North America.

Figure 1B shows the operative site during debridement of the infected right forearm injury at an earlier (above) and a later (bottom) time point of surgery.

Figure 2: This figure illustrates thrombocytopenia in an intensive care unit patient with multiple trauma. Transfusion of platelet concentrates (each containing 2-4x10^{11} platelets/unit) was part of the massive transfusion protocol. The platelet count returned only to normal after the source of bleeding could have been controlled with using surgical and interventional measures. (CT = computed tomography; INR = international normalized ratio; aPTT = activated partial thromboplastin time; sec = seconds)
Figure 3: Stopping the valproate medication was sufficient to treat thrombocytopenia in a case of valproate-induced non-immune drug-induced thrombocytopenia.

Figure 4: Heparin-induced-thrombocytopenia (HIT) was assumed to be the cause of thrombocytopenia beyond day 5 of intensive care unit treatment because high-titer anti-platelet factor 4 immunoglobulin G (IgG) antibodies were detectable by enzyme-immunoassay (EIA) as well as the heparin-induced activation assay (HIPA) was strongly positive at day 6 of heparin treatment. However, the moderate increase of the platelet count after switching to non-heparins indicated that HIT was probably not the only cause for the thrombocytopenia. (EIA = enzyme-immunoassay; IgG = immunoglobulin G; OD = optical density; HIPA = heparin-induced platelet activation assay)
Table 1: Major mechanisms of thrombocytopenia and typical clinical scenarios in the intensive care unit (ICU)

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<td>Platelet aggregates in EDTA-anticoagulated blood; therapy with glycoprotein IIbIIIa-receptor antagonists</td>
<td>Thrombocytopenia is unexpected and bleeding symptoms are absent. Preceding therapy with glycoprotein IIbIIIa-receptor antagonists. Repeat platelet count in citrated blood and control for aggregates in the blood smear. Note: glycoprotein IIbIIIa antagonists often induce pseudothrombocytopenia also in citrated blood</td>
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<td><strong>Platelet consumption:</strong></td>
<td></td>
</tr>
<tr>
<td>Blood loss</td>
<td>Bleeding, anemia, prolonged clotting times as signs of coagulation factor loss and/or consumption</td>
</tr>
<tr>
<td>Massive blunt trauma</td>
<td>History, physical and radiological examination</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Shock, infection, obstetrical complications, or other typical underlying causes, prolonged clotting times, increased fibrin split products, nucleated red cells in the differential</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Fever, further sepsis criteria, and positive blood cultures</td>
</tr>
<tr>
<td>Extracorporeal circuit</td>
<td>Organ failure requiring extracorporeal circuit; consider areas of high shear stress in the circuit</td>
</tr>
</tbody>
</table>
**Platelet sequestration:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis/Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>History, typical comorbidity (e.g. liver cirrhosis or osteomyelofibrosis), sonography or other diagnostic radiology</td>
</tr>
</tbody>
</table>

**Decreased platelet production:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis/Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intoxication (alcohol and other drugs)</td>
<td>History of abuse or medication, toxicology screening</td>
</tr>
<tr>
<td>Viral infection (HIV, HCV, EBV, CMV)</td>
<td>Diagnostic workup of viral infections</td>
</tr>
<tr>
<td>Bone marrow infiltration (leukemia, tumors)</td>
<td>Bone marrow examination, nucleated red cells in the differential blood film, tear drop cells</td>
</tr>
<tr>
<td>Radiation</td>
<td>History</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>History</td>
</tr>
</tbody>
</table>

**Platelet destruction:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis/Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenia</td>
<td>Anti-platelet antibodies, normal or increased megakaryocytes in bone marrow, platelet count response to IVIG or steroids, comorbidities typical for secondary ITP (e.g. SLE, hepatitis C, CLL)</td>
</tr>
<tr>
<td>Drug-induced immune thrombocytopenia</td>
<td>Medication history (new drug started during the last 7-14 days), platelet counts &lt;2x10^9/L, increase of platelet counts after cessation of suspected/detected medication, confirmation: detection of drug dependent antibodies</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>50% decrease in platelet count (typical nadir 20-80x10^9/L) between day 5 and 14 of heparin treatment, w/o thromboembolic events with ongoing heparin therapy, heparin-dependent, platelet activating anti-</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Thrombotic microangiopathies (TTP, HUS, HELLP-syndrome)</td>
<td>Hemolysis with negative direct coombs test, fragmented red cells in blood smear, typical platelet count nadir 10-30x10⁹/L, thrombotic events with neurological (TTP) or renal (HUS) symptoms, pregnancy (HELPP-syndrome), elevated lactate dehydrogenase</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>Transfusion history, history of pregnancy, platelet count nadir &lt;10x10⁹/L, bleeding symptoms, high titer anti-HPA-1a antibodies</td>
</tr>
<tr>
<td>Passive alloimmune thrombocytopenia</td>
<td>Abrupt, transient fall in the platelet count after transfusion of plasma containing blood products (which passively transmit the platelet alloantibody), typically from a multiparous donor.</td>
</tr>
</tbody>
</table>

EDTA = ethylenediaminetetraacetic acid; HIV = human immune deficiency virus; HCV = hepatitis C virus; CMV = cytomegaly virus; EBV = Epstein-Barr virus; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulins; SLE = systemic lupus erythematoses; CLL = chronic lymphatic leukemia; TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic uremic syndrome; HELLP = hypertension, elevated liver enzymes, proteinuria
Table 2: The 4Ts score for estimating the pretest probability of heparin-induced thrombocytopenia

<table>
<thead>
<tr>
<th>Points</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia (acute)</strong></td>
<td>&gt;50% platelet count fall to nadir ≥20x10⁹/L</td>
<td>30-50% platelet count fall to nadir 10-19x10⁹/L</td>
<td>&lt;30% platelet count fall to nadir ≤10 x10⁹/L</td>
</tr>
<tr>
<td><strong>Timing of fall in platelet count or other sequelae</strong></td>
<td>Onset d 5-10 or &lt;1d (if heparin exposure within 30d)</td>
<td>&gt;d10, or timing unclear, or &lt;d1 with recent heparin 31-100 d</td>
<td>Platelet count fall &lt;d 4 (without recent heparin exposure)</td>
</tr>
<tr>
<td><strong>Thrombosis or other sequelae</strong></td>
<td>New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction</td>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed</td>
<td>None</td>
</tr>
<tr>
<td><strong>OTher cause for thrombocytopenia</strong></td>
<td>No other cause for platelet count fall is evident</td>
<td>Possible other cause is evident</td>
<td>Definite other cause is present</td>
</tr>
</tbody>
</table>

Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low
Table 3: Mechanisms of drug-induced thrombocytopenias (data from\textsuperscript{61-63,65,88})

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most frequent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow depression</td>
<td>Toxic bone marrow depression</td>
<td>Chemotherapeutics, linezolide, non-steroidal anti-inflammatory drugs, azathioprine; valproic acid</td>
</tr>
<tr>
<td><strong>Immune mediated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic drug-dependent antibodies</td>
<td>Drug, platelet glycoproteins, and antibodies form a three-molecular complex, which results in increased platelet destruction by the reticuloendothelial system. Onset typically 7 to 20 days after start of a new drug, or immediately in case of reexposure. Platelet nadir &lt; 20x10^9/L.</td>
<td>Quinine, quinidine, antibiotics (sulfamethoxazole trimethoprim, vancomycin, rifampicin cephalosporins), antiepileptics (valproate, carbamazepine, phenytoin), diuretics (furosemide, thiazides), ranitidine, non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen),</td>
</tr>
<tr>
<td>Hapten-induced antibodies</td>
<td>Drug acts as a hapten that binds to large molecules (e.g. proteins) on the platelet surface and stimulates antibody production. Onset typically 7 to 20 days after start of an antibiotic. Platelet nadir variable, often &gt;20x10^9/L.</td>
<td>Penicillin, cephalosporins,</td>
</tr>
<tr>
<td>Drug-specific antibodies</td>
<td>F(ab) fragments of a monoclonal antibody bind to glycoprotein IIbIIIa on platelets and become targets of naturally occurring antibodies provoking increased platelet destruction. Onset within hours after start of the drug. Platelet nadir often &lt;20x10^9/L; exclude pseudothrombocytopenia.</td>
<td>Abciximab</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Production of platelet-specific autoantibodies is induced and maintained by a drug (exact mechanism unknown).</td>
<td>Procainamide, levodopa, gold</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
</tbody>
</table>

**Prothrombotic**

<table>
<thead>
<tr>
<th>Heparin-induced thrombocytopenia</th>
<th>IgG antibodies against PF4/polyanion complexes activate platelets via the platelet Fc-receptor, inducing thrombin generation</th>
<th>Heparin, low molecular weight heparin, potentially also other polyanionic drugs (e.g. aptamers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic microangiopathy</td>
<td>Auto-antibodies against ADAMTS13 are produced in presence of the drug causing ADAMTS13 deficiency. Onset 5 to 20 days after start of a new drug; platelet count nadir 10 to 30x10^9/L.</td>
<td>Quinine, cyclosporine, tacrolimus, gemcitabine</td>
</tr>
</tbody>
</table>
Table 4: Recommended triggers for platelet transfusion in critically ill patients\textsuperscript{33,89,90}

<table>
<thead>
<tr>
<th>Transfusion indication</th>
<th>Threshold platelet count (x10^9/L)</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic transfusion of adult patients</td>
<td>10</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Before central vein catheter placement</td>
<td>20</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Before elective diagnostic lumbar puncture</td>
<td>50</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Urgent diagnostic lumbar puncture</td>
<td>20</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Before major elective surgery (excluding neurosurgery)</td>
<td>50</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Prophylactic transfusion of nonthrombocytopenic patients before cardiopulmonary bypass surgery</td>
<td>No transfusion (only in case of bleeding)</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Patients with intracranial hemorrhage and antiplatelet drugs</td>
<td>No platelet transfusion</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Figure 1a
Platelet count (x10^9/L)

Day of Intensive Care Unit Treatment

- CT scan
- Angiography
- Laparotomy
- Laparotomy

- Packed red cells = 48 units
- Fresh frozen plasma = 22 units
- Fibrinogen = 10 grams
- Platelet concentrates
- Tranexamic acid

INR
aPTT (sec)

Figure 2
Figure 4

- Coronary angioplasty
- Unfractionated heparin in therapeutic dose*
- Non-heparin therapeutic-dose anticoagulation
- Re-exposure after recent heparin therapy
- EIA IgG positive (OD 1.263)
- HIPA positive (4 of 4 donors)
- Intermittent renal replacement therapy

Platelet count (x10^9/L) vs. Day of Intensive Care Unit Treatment
How I evaluate and treat thrombocytopenia in the intensive care unit patient

Andreas Greinacher and Sixten Selleng