

# Management of Vascular Thrombosis in Patients with Thrombocytopenia

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## Abstract

Platelets play critical roles in hemostasis and thrombosis. While low platelet counts increase the risk of bleeding, antithrombotic drugs, including anticoagulants and antiplatelet agents, are used to treat thromboembolic events. Thus, the management of thrombosis in patients with low platelet counts is challenging with hardly any evidence available to guide treatment. Recognition of the underlying cause of thrombocytopenia is essential for assessing the bleeding risk and tailoring therapeutic options. A typical clinical scenario is the occurrence of venous thromboembolism (VTE) in cancer patients experiencing transient thrombocytopenia during myelosuppressive chemotherapy. In such patients, the severity of thrombocytopenia, thrombus burden, clinical symptoms, and the timing of VTE relative to thrombocytopenia must be considered. In clinical practice, distinct hematological disorders characterized by low platelet counts and a thrombogenic state require specific diagnostics and treatment. These include the antiphospholipid syndrome, heparin-induced thrombocytopenia (HIT) and (spontaneous) HIT syndromes, disseminated intravascular coagulation, and paroxysmal nocturnal hemoglobinuria.

## Keywords

- ▶ thrombosis
- ▶ bleeding
- ▶ thrombocytopenia
- ▶ anticoagulation
- ▶ platelet inhibition

## Zusammenfassung

Thrombozyten spielen in der Hämostase und Thrombose eine zentrale Rolle. Während niedrige Plättchenzahlen das Blutungsrisiko steigern, werden Antithrombotika wie Antikoagulantien oder Aggregationshemmer standardmäßig zur Therapie von Thromboembolien eingesetzt. Aus diesem Grund stellt die Thrombosebehandlung bei thrombozytopenen Patienten eine besondere Herausforderung dar. Für die Einschätzung des Blutungsrisikos und die gezielte Auswahl therapeutischer Maßnahmen ist die Kenntnis der Ursache einer Thrombozytopenie entscheidend. Ein typisches Szenario ist das Auftreten einer venösen Thromboembolie (VTE) bei Krebspatienten unter myelosuppressiver Chemotherapie. In dieser Situation müssen Ausmaß der Thrombozytopenie, Thrombuslast, klinische Symptome und zeitlicher Abstand zwischen VTE-Diagnose und Plättchenabfall berücksichtigt werden. Im klinischen Alltag erfordern bestimmte hämatologische Erkrankungen, die mit Thrombozytopenie und Thromboseneigung einhergehen, einer spezifischen Diagnostik und Therapie, z.B. Antiphospholipidsyndrom, heparininduzierte Thrombozytopenie (HIT), (spontane) HIT-Syndrome, disseminierte intravasale Gerinnung oder paroxysmale nächtliche Hämoglobinurie.

## Schlüsselwörter

- ▶ Thrombose
- ▶ Blutung
- ▶ Thrombozytopenie
- ▶ Antikoagulation
- ▶ Plättchenhemmung

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## Introduction

Platelets are critical cellular components in hemostasis and thrombosis with additional roles in immunity and inflammation.<sup>1</sup> During primary hemostasis, platelets adhere to the damaged vessel wall and form an initial wound-sealing plug upon activation and aggregation. During secondary hemostasis, activated platelets provide a catalytic surface for coagulation reactions to support thrombin generation and fibrin deposition. Thus, hemostasis is substantially impaired in patients with significant thrombocytopenia, resulting in an increased risk of spontaneous or trauma-/surgery-induced bleeding.

Platelet adhesion and aggregation are also critical events in arterial thrombus formation when rupture of an atherosclerotic plaque leads to the exposure of collagen and other thrombogenic material to the flowing blood. For this reason, pharmacological inhibition of platelet function is standard of care in patients with cardio- or cerebrovascular disease. In addition, platelets are involved in the pathophysiology of venous thromboembolism (VTE), a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE), although anticoagulants, and not antiplatelet agents, are generally used to prevent or treat VTE. Since both thrombocytopenia and antithrombotic drugs increase the risk of bleeding, the management of vascular thrombosis in patients with low platelet counts is particularly challenging in daily practice.<sup>2</sup>

Thrombocytopenia is defined as a platelet count below the lower limit of the normal reference range, that is, a platelet count of less than  $150 \times 10^9/L$ . Since platelet counts of  $100$ – $150 \times 10^9/L$  are not clinically relevant, thrombocytopenia is sometimes also considered as a platelet count of less than  $100 \times 10^9/L$ . For this article, the following severities of thrombocytopenia are defined, with categorization according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), version 5.0, provided in brackets:

- Mild thrombocytopenia—platelet count  $75$ – $150 \times 10^9/L$  (grade 1).
- Moderate thrombocytopenia—platelet count  $50$ – $75 \times 10^9/L$  (grade 2).
- Moderate-to-severe thrombocytopenia—platelet count  $25$ – $50 \times 10^9/L$  (grade 3).
- Severe thrombocytopenia—platelet count  $< 25 \times 10^9/L$  (grade 4).

Regarding the underlying pathophysiology, three different mechanisms may lead to thrombocytopenia:

- Decreased platelet production (e.g., aplastic anemia, vitamin B<sub>12</sub>/folic acid deficiency, chemotherapy).
- Increased platelet consumption (e.g., disseminated intravascular coagulation [DIC], thrombotic microangiopathy [TMA], antibody-mediated platelet destruction/clearance).
- Altered platelet distribution (e.g., hemodilution during pregnancy, splenomegaly).

Recognizing the dominant mechanism of thrombocytopenia has significant implications for the management of

patients with vascular thrombosis and low platelet counts. First, in patients with thrombocytopenia due to decreased platelet production, low platelet counts are also likely associated with impaired platelet function, because maturation and proliferation of bone marrow megakaryocytes are significantly altered. In contrast, thrombocytopenia due to accelerated platelet clearance may be associated with increased proportions of hyperreactive immature platelets resulting from compensatory stimulation of healthy megakaryocytes. Thus, depending on the predominant pathomechanism, the overall bleeding risk may vary between patients with similarly low platelet counts. Determination of the immature platelet fraction (IPF), which represents the release of reticulated platelets from stimulated megakaryocytes, may help differentiate between impaired production and increased destruction/clearance of circulating platelets as the underlying cause of thrombocytopenia (→Fig. 1).<sup>3</sup> Second, knowledge of the expected duration of thrombocytopenia and the availability of symptomatic or causative treatment options to increase or correct platelet counts is of utmost importance for assessing the bleeding risk and for tailored prescription of antithrombotic agents.

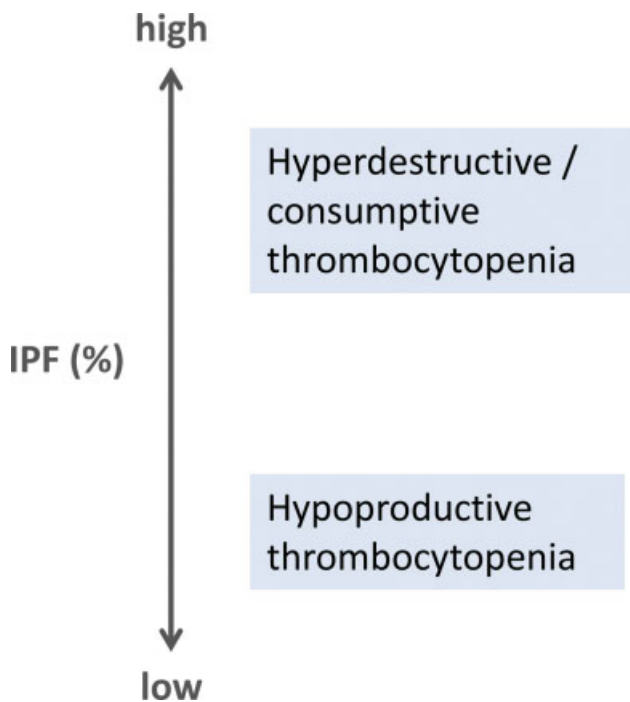
In the absence of robust clinical trial data, this article aims at summarizing the available empirical evidence on how to approach a patient with thrombocytopenia and vascular thrombosis, acknowledging that tools on how to assess the competing risks of bleeding and thrombosis in such a scenario have recently been reviewed.<sup>2</sup> In addition, specific hematological disorders characterized by both low platelet counts and a thrombogenic state are highlighted, because their knowledge and recognition have significant implications for diagnosis and treatment.

## Patients with Cancer and Thrombocytopenia

Patients with solid cancers or hematological malignancies have a significantly increased risk for both thromboembolic events and bleeding complications. Thrombocytopenia is a frequent finding in oncological patients and may be caused by the malignancy itself or its treatment with cytotoxic agents. Considering that the normal average lifespan of circulating platelets is 8–10 days, platelet counts typically start to decline on day 7 following initiation of myelosuppressive therapy, with a nadir reached at day 14 and a gradual return to baseline levels by days 28–35.<sup>4</sup> The frequency of thrombocytopenia associated with select cancer types and cytotoxic agents has recently been reviewed,<sup>5</sup> with grade 3/4 thrombocytopenia occurring, for example, in 8.6% of patients with biliary tract cancer treated with gemcitabine/cisplatin combination chemotherapy and 57% of patients with bladder cancer treated with the same regimen.

## Management of Venous Thromboembolism

When approaching a thrombocytopenic patient with cancer-associated VTE, thrombus burden, clinical symptoms, and the timing of thrombocytopenia relative to the occurrence of VTE should be considered in addition to absolute platelet



**Fig. 1** Assessing the immature platelet fraction (IPF), e.g., by flow cytometry, may help distinguish between different causes of thrombocytopenia. In healthy controls, IPF ranges of 1–18% (mean values, 7–8%) have been reported.<sup>17</sup>

counts (→Table 1).<sup>5–8</sup> In patients with a platelet count of  $\geq 50 \times 10^9/L$ , therapeutic-dose anticoagulation with low-molecular-weight heparin (LMWH) or a direct oral anticoagulant (DOAC) is generally considered acceptable. In patients with a platelet count of less than  $50 \times 10^9/L$  and acute VTE, that is VTE occurring within the previous 4 weeks, a transfusion strategy may be considered to allow for therapeutic-dose anticoagulation as long as platelet counts are increased to more than  $40\text{--}50 \times 10^9/L$ . This strategy appears particularly justified in patients with a large thrombus burden (e.g., extensive proximal DVT or massive PE) and/or significant clinical symptoms (e.g., dyspnea without exertion, tachycardia, hypotension, massive leg edema). In case a transfusion

strategy is not available or inefficacious, parenteral anticoagulation with LMWH at intermediate, half-therapeutic dosages may be an option in patients with acute VTE and a platelet count of  $25\text{--}50 \times 10^9/L$ . This also applies to patients with chronic VTE, that is, VTE occurring more than 4 weeks ago, who have already received adequate anticoagulation prior to thrombocytopenia to sufficiently resorb or consolidate intravascular thrombus manifestations, and in whom prophylactic anticoagulation with LMWH at dosages approved for situations with a high risk of VTE may also be acceptable. In patients with acute or chronic VTE and a platelet count of less than  $25 \times 10^9/L$  (grade 4), withholding anticoagulation or prophylactic dosages of LMWH are generally recommended. Insertion of a retrievable inferior vena cava (IVC) filter, accompanied by LMWH thromboprophylaxis when acceptable, may be an option only in highly symptomatic patients with a large thrombus burden. Due to significant risks associated with the procedure, the decision to place IVC filters should be based on careful discussion by a multidisciplinary team considering patient values and preferences.

Treatment of hematological malignancies is associated with extensive periods of thrombocytopenia due to aggressive cytotoxic regimens and/or bone marrow failure inherent to the blood cancer. In a retrospective analysis of 82 patients with hematological disorders experiencing VTE during grade 3/4 thrombocytopenia, mostly patients with acute myeloid leukemia and central venous catheter (CVC)-related thrombosis, 82% ( $n=67$ ) had been treated with anticoagulants and 88% ( $n=59$ ) had been managed with transfusion support to achieve a platelet count of  $\geq 50 \times 10^9/L$ .<sup>9</sup> VTE progression/recurrence was documented in seven patients (8.5%) and any bleeding event, predominantly grade 2 according to the World Health Organization (WHO) criteria, in 31 patients (37.8%). Eleven patients (13.4%) suffered from transfusion reactions, and 30 patients (36.6%) had to be treated with diuretics or dialysis for volume overload. Of note, most bleeding events occurred when the platelet count was  $\geq 50 \times 10^9/L$ . Taken together, these findings show that patients with blood cancer-associated VTE and thrombocytopenia represent a

**Table 1** Recommendations for the management of VTE in cancer patients with thrombocytopenia

Platelet count	Risk of VTE progression/recurrence	
	High <sup>a</sup>	Low
$\geq 50 \times 10^9/L$	Full-dose, therapeutic anticoagulation (LMWH or DOAC)	
$25\text{--}50 \times 10^9/L$	Full-dose, therapeutic anticoagulation (LMWH or DOAC) with platelet transfusion support (target platelet count, $> 40\text{--}50 \times 10^9/L$ ) <sup>b</sup>	Reduced-dose, e.g., half-therapeutic or prophylactic anticoagulation (LMWH)
$< 25 \times 10^9/L$	No anticoagulation or prophylactic LMWH <sup>c</sup>	

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Source: Adapted from various studies.<sup>5–8</sup>

<sup>a</sup>Risk of VTE progression/recurrence is considered high in patients with acute VTE ( $< 4$  weeks), particularly in those with large thrombus burden and/or significant clinical symptoms.

<sup>b</sup>If a transfusion strategy is not feasible, anticoagulation with LMWH at reduced (e.g., half-therapeutic) dosages should be used.

<sup>c</sup>On rare occasions (e.g., in highly symptomatic patients with large thrombus burden), insertion of a retrievable inferior vena cava filter may be considered.

particularly vulnerable population with significant risks for recurrent thrombosis and transfusion-related adverse outcomes. In such patients, platelet count–adjusted LMWH dosing (in acute VTE) or temporarily withholding anticoagulation (in chronic VTE) are reasonable options.<sup>10,11</sup>

A retrospective management study supports an individualized, risk-adapted approach to cancer patients with acute VTE and thrombocytopenia. While subtherapeutic LMWH dosages were generally preferred in patients with platelet counts of less than  $100 \times 10^9/L$  or the presence of cerebral metastasis, patients with PE or symptomatic VTE were more likely to receive therapeutic-dose anticoagulation.<sup>12</sup>

### Management of Arterial Thrombosis

Expert guidance is available for the management of antiplatelet therapy in acute coronary syndrome (ACS) patients with thrombocytopenia.<sup>13</sup> General measures to reduce the bleeding risk include avoidance of nonsteroidal anti-inflammatory drugs, utilization of proton pump inhibitors (PPIs) unless contraindicated, preference of a radial approach for percutaneous coronary intervention (PCI), preference of second-generation drug-eluting over bare-metal stents, restriction of dual-antiplatelet therapy (DAPT) to 1 month after PCI, avoidance of glycoprotein (GP) IIb/IIIa inhibitors and of triple therapy in patients with an indication for oral anticoagulation (OAC), and use of lower doses (i.e., 75–100 mg per day) instead of higher doses of acetylsalicylic acid (ASA). In patients with a platelet count of less than  $50 \times 10^9/L$  or active bleeding, stopping all antiplatelet agents and avoidance of PCI are suggested. In patients with a platelet count of  $\geq 50 \times 10^9/L$  and no active bleeding who undergo PCI, DAPT for 1 month followed by clopidogrel monotherapy together with PPI appears reasonable. In case PCI is not an option, clopidogrel monotherapy and PPI are suggested.

More aggressive antiplatelet therapy may be warranted in ACS patients with cancer-associated thrombocytopenia due to the inherent hypercoagulable state of malignancy.<sup>14,15</sup> In such patients, ASA monotherapy is an option when the platelet count is more than  $10 \times 10^9/L$ , and DAPT with ASA and clopidogrel may be considered when the platelet count is  $30\text{--}50 \times 10^9/L$ . Ticagrelor, prasugrel, and GPII/IIIa inhibitors are suggested only when the platelet count is more than  $50 \times 10^9/L$ . Duration of DAPT should be decided on after careful risk–benefit analysis and multidisciplinary discussion. A similar approach appears reasonable in thrombocytopenic cancer patients with atherothrombotic stroke who have an indication for DAPT.

## Specific Hematological Disorders

### Immune Thrombocytopenia

Immune thrombocytopenia, or idiopathic thrombocytopenic purpura (ITP), is caused by autoantibody formation against platelet GPs with increased platelet destruction and phagocytic clearance by reticuloendothelial cells, mainly located in the spleen.<sup>16</sup> Although acute pediatric ITP is typically self-limiting and preceded by viral infections or vaccinations, adult ITP may evolve into a chronic disorder requiring

treatment in case of significant thrombocytopenia and/or bleeding symptoms. Diagnosis of ITP is primarily based on the exclusion of other causes of thrombocytopenia and may involve bone marrow biopsy or aspiration cytology. The role of detecting platelet GP-specific antibodies is unclear.<sup>17</sup> Although relative thrombopoietin deficiency contributes to impaired megakaryocytopoiesis, patients with ITP have increased IPFs and may thus present with a comparably mild bleeding phenotype despite profound thrombocytopenia. Although platelet activation is not a characteristic feature of ITP, the disorder is associated with an increased incidence of venous and arterial thrombosis.<sup>18</sup> While classical (e.g., advanced age, obesity, hormonal contraceptives, pregnancy/puerperium, cancer, recent surgery, history of VTE) and treatment-related risk factors (e.g., corticosteroids, high-dose intravenous immunoglobulins [IVIg], splenectomy) contribute to the etiopathogenesis of VTE in ITP, thrombocytopenia does not protect against thrombosis.<sup>19</sup> Likewise, anticoagulation seems to be feasible in most patients with ITP and VTE despite persistently low platelet counts, which is consistent with a bleeding protective effect of increased IPFs.<sup>19</sup>

Expert guidance on how to approach ITP patients with VTE or arterial thrombosis has recently been published.<sup>20</sup> Similar to patients with cancer-associated VTE, full-dose anticoagulation with LMWH or DOACs is considered acceptable in patients with a platelet count of greater than  $50 \times 10^9/L$ . In patients with a platelet count of  $25\text{--}50 \times 10^9/L$ , reduced-dose anticoagulation with LMWH is the preferred strategy, with unfractionated heparin (UFH) being an option in patients with unstable thrombocytopenia and/or a perceived high risk of bleeding due to its shorter half-life and the more predictable reversibility of its anticoagulant effect by protamine administration. DOACs may be an option on a case-by-case basis. In patients with a platelet count of less than  $25 \times 10^9/L$ , specific ITP treatment should be considered to elevate the platelet count to more than  $50 \times 10^9/L$ . In refractory cases, the management of VTE must be highly individualized and based on a particularly thorough risk assessment. In patients with ITP and arterial thrombosis such as ACS, DAPT, preferably with ASA and clopidogrel, may be used when the platelet count is greater than  $50 \times 10^9/L$ , while single-antiplatelet therapy is recommended when the platelet count is  $25\text{--}50 \times 10^9/L$ . Similar to patients with VTE, specific ITP treatment should be considered when the platelet count is less than  $25 \times 10^9/L$ . In patients with refractory ITP and a platelet count of greater than  $10 \times 10^9/L$ , the authors of this article consider monotherapy with ASA an option, when the risk of bleeding is considered to be low. Individual patients with platelet counts of  $25\text{--}50 \times 10^9/L$  may also be candidates for DAPT (e.g., patients < 60 years of age without relevant comorbidities such as renal impairment, uncontrolled hypertension, or gastrointestinal ulcerations).

### Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by arterial, venous, and/or microvascular thrombosis in the presence of persistently elevated

antiphospholipid antibodies (aPLs).<sup>21</sup> In routine diagnostics, aPLs include IgG/IgM antibodies to cardiolipin or  $\beta_2$ -glycoprotein-I ( $\beta_2$ -GPI) and the lupus anticoagulant (LA). Additionally or alternatively to vascular thrombosis, APS may be associated with obstetrical complications such as recurrent early miscarriages, late fetal loss, or preterm delivery due to preeclampsia or intrauterine growth restriction. Although not part of the main diagnostic criteria for definite APS,<sup>22</sup> thrombocytopenia is a frequent finding in APS patients with a prevalence of 20–40%.<sup>23</sup> Low platelet counts may be caused by accelerated autoantibody-mediated platelet destruction/clearance as observed in ITP or, possibly, by increased consumption due to the hypercoagulable state. Consistent with the latter pathomechanism, APS-associated thrombocytopenia may improve or completely resolve following initiation of efficacious antithrombotic therapy.<sup>24,25</sup>

Anticoagulation with a vitamin K antagonist (VKA) is the treatment of choice in APS patients with arterial thrombosis and patients with VTE who have a high-risk (i.e., triple- or LA-positive) aPL profile. Low-dose ASA may be considered in APS patients with arterial thrombosis and a low-risk aPL profile or a high risk of bleeding, such as in those with significant thrombocytopenia.<sup>26</sup> According to a consensus statement of different German medical societies, standard-dosed DOACs are an option in patients with VTE and isolated cardiolipin and/or  $\beta_2$ -GPI antibodies.<sup>27</sup> Addition of low-dose ASA to VKA therapy may be considered upfront in high-risk APS patients with arterial thrombosis or as an adjunct to OAC in patients with recurrent arterial events.<sup>26</sup>

Catastrophic APS (CAPS or Asherson's syndrome) is characterized by multiorgan failure due to widespread microvascular thrombosis.<sup>28</sup> Diagnostic criteria for definite CAPS include at least three new thrombotic organ manifestations within 1 week and evidence of microvascular thrombosis on organ biopsy. Patients with CAPS may present with profound thrombocytopenia due to DIC and/or TMA. Since the disorder is associated with significant morbidity and mortality, an aggressive multimodal treatment strategy is warranted, including therapeutic anticoagulation with heparin, corticosteroids, cyclophosphamide, plasma exchange therapy, and

high-dose IVIGs.<sup>29</sup> Investigational drugs are rituximab, which targets autoantibody-producing B cells, and eculizumab, which prevents cleavage activation of complement component 5 (C5).

### Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin therapy mediated by platelet-activating IgG antibodies against the platelet factor 4 (PF4)/heparin complex.<sup>30,31</sup> The risk of HIT is higher in surgical than in medical patients and after UFH compared with LMWH exposure. Activation of platelets, monocytes, granulocytes, and endothelial cells by IgG-PF4/heparin immune complexes through an Fc-dependent mechanism triggers a vicious cascade of thrombo-inflammatory events, which results in massive intravascular thrombin generation with an exceedingly high risk for venous, arterial, or microvascular thrombosis. In classical HIT, platelet-activating IgG antibodies against PF4/heparin complexes are detectable as soon as 4–5 days after initiation of heparin, with thrombocytopenia and/or thromboembolic events typically occurring after 5–14 days. The clinicopathological diagnosis of HIT involves a multistep process: First, in patients with suspected HIT, pretest clinical probability should be assessed using the 4Ts score (–Table 2). Second, in patients with a 4Ts score greater than 3 or uncertainty regarding the validity of information required to calculate the score, a screening test for PF4/heparin or PF4/polyanion antibodies should be ordered. Third, a positive HIT screening test should be followed by a functional platelet activation test to confirm HIT, for example, heparin-induced platelet activation (HIPA) test or serotonin release assay (SRA). Pathophysiologically relevant antibodies show a characteristic reaction pattern, with no platelet activation in the absence (0 IU/mL) or presence of excess heparin (50–100 IU/mL) and maximal platelet activation at therapeutic heparin concentrations (0.2–1.0 IU/mL).

In patients with either a high pretest clinical probability for HIT (i.e., 4Ts score  $\geq 6$ ), a strongly reactive (i.e., optical density  $> 1.0$  units) quantitative PF4/heparin (polyanion) enzyme immunoassay (EIA) or a positive qualitative PF4/heparin particle gel immunoassay, or confirmed HIT,

**Table 2** 4Ts score to assess the pretest clinical probability of HIT

Points	Thrombocytopenia	Onset of thrombocytopenia	Thrombosis or other symptoms	Other causes of thrombocytopenia
2	Platelet count decrease $> 50\%$ and nadir $\geq 20 \times 10^9/L$	Days 5–10, or day 1 if heparin exposure within previous 30 d	New thrombosis or skin necrosis or acute systemic reaction	None
1	Platelet count decrease 30–50% or nadir $10\text{--}19 \times 10^9/L$	$>$ Day 10, or day 1 if heparin exposure within previous 30–100 d	Progressive or recurrent thrombosis or non-necrotizing skin lesions	Possible
0	Platelet count decrease $< 30\%$ or nadir $< 10 \times 10^9/L$	$\leq$ Day 4 with no recent heparin exposure	None	Definite

Abbreviation: HIT, heparin-induced thrombocytopenia.

Note: Total scores of 0–3, 4–5, and 6–8 indicate a low, intermediate, and high pretest clinical probability for HIT, respectively.

Source: Adapted from Erkan et al.<sup>28</sup>

heparin should be replaced by therapeutic dosages of an appropriate alternative anticoagulant, such as danaparoid, argatroban, or fondaparinux.<sup>32</sup> Despite profound thrombocytopenia and recent surgery, patients with confirmed HIT typically lack severe bleeding symptoms, and prophylactic platelet transfusion is thus not indicated. In HIT patients with overt thrombosis, anticoagulation should be continued for 3–6 months, depending on the severity of the thromboembolic event, the presence of residual vein thrombosis or persisting clinical symptoms, and tolerance of anticoagulant therapy. Provided that platelet counts have stabilized above the lower limit of the normal reference range, both VKA and DOACs are valid options for oral maintenance therapy following initial parenteral treatment with non-heparin anticoagulants. Increasing evidence also exists for the (off-label) use of DOACs in acute HIT.<sup>33</sup> The optimal duration of anticoagulation in patients without overt thrombosis is not clear.<sup>34</sup> While some experts deem cessation of anticoagulation acceptable upon platelet count recovery, others prefer treatment for up to 3 months, considering that HIT-associated vascular thrombosis might have been clinically obscure. In most patients with HIT, platelet-activating PF4/heparin IgG antibodies are no longer detectable 3 months after heparin discontinuation.

Regarding timing of thrombocytopenia relative to heparin initiation, classical HIT can become manifest as typical-onset HIT (i.e., drop in platelet counts after 5–14 days) or rapid-onset HIT (i.e., drop in platelet counts within 1–2 days), when heparin exposure within the previous 3 months has resulted in preformed, not yet cleared PF4/heparin IgG antibodies. In either case, the time course of antibody formation is consistent with a secondary rather than a primary immune response, with anti-PF4/heparin IgG occurring as early as 4–5 days after heparin initiation. A potential explanation is that naturally occurring polyanions such as bacterial lipopolysaccharide, RNA/DNA, or polyphosphate can also interact with cationic PF4 and mimic HIT antigens, suggesting that classical HIT represents a misdirected, evolutionarily ancient (antimicrobial) immune response.<sup>35</sup> Likewise, non-heparin polyanionic drugs like hypersulfated chondroitin sulfate or pentosan polysulfate can trigger “HIT” with characteristic PF4/heparin (polyanion)-dependent reaction patterns in screening and functional HIT assays, but without proximate heparin exposure.

#### **Autoimmune HIT and (Spontaneous) HIT Syndromes**

In some patients with proximate heparin exposure, PF4/heparin antibodies may develop to autoantibodies that persist despite cessation of heparin and that are responsible for autoimmune HIT (aHIT) entities like delayed-onset HIT, persisting (refractory) HIT, heparin “flush” HIT, or fondaparinux-associated HIT.<sup>35</sup> Although antibody formation is initially triggered by heparin or other exogenous polyanions, the primary antigen in aHIT is PF4 in the (relative) absence of heparin. In functional assays (HIPA, SRA), aHIT antibodies thus strongly activate platelets without addition of heparin, albeit endogenously released polyanions may play a role.<sup>35</sup>

Over the past decade, HIT-like disorders without proximate heparin exposure have been described. These include spontaneous HIT syndrome observed in surgical patients following major orthopedic procedures, such as knee arthroplasty, or in medical patients following viral or bacterial infections, and, recently, vaccine-induced immune thrombotic thrombocytopenia (VITT) following active immunization against SARS-CoV-2 with viral vector-based vaccines.<sup>35–38</sup> In these disorders, which are characterized by atypically located thromboses such as cerebral venous thrombosis and a DIC-like coagulopathy, the primary antigen is PF4, although pathophysiologically relevant IgG antibodies are also detected by some, but not all, PF4/heparin (polyanion) EIAs.<sup>39</sup> While serum from a subgroup of patients with spontaneous HIT syndrome or VITT shows platelet activation with buffer, addition of PF4 is typically required to induce a platelet response.<sup>36</sup> Although platelet activation is not further enhanced or even inhibited by heparin, patients with spontaneous HIT syndrome or VITT should be preferentially treated with non-heparin anticoagulants. High-dose IVIGs are an option in particularly severe or refractory cases.<sup>40,41</sup> Similar to isolated HIT, SARS-CoV-2-vaccinated individuals with thrombocytopenia due to PF4-dependent platelet-activating antibodies may present without clinically overt thrombosis. In such patients, the term “vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)” may more adequately describe the hypercoagulable state. Still, specific and swift treatment with non-heparin anticoagulants and possibly IVIGs is warranted to prevent catastrophic vascular thrombosis.<sup>42,43</sup> Choice of anticoagulants and duration of anticoagulant therapy in patients with spontaneous HIT syndrome and VITT/VIPIT are likely similar to those in classical HIT.

#### **Immune Thrombotic Thrombocytopenic Purpura**

Immune thrombotic thrombocytopenic purpura (iTTP) is a TMA caused by a severe autoantibody-mediated deficiency in the von Willebrand factor (VWF)-cleaving metalloproteinase, ADAMTS13.<sup>44</sup> Formation of platelet- and VWF-rich microthrombi leads to microangiopathic hemolytic anemia with the detection of red blood cell (RBC) fragments on peripheral blood smears and organ impairment (e.g., neurological deficits, heart failure, renal insufficiency). Treatment of iTTP includes immediate plasma exchange therapy, corticosteroids, and caplacizumab, a nanobody targeting the GPIIb-binding site on the VWF A1 domain.<sup>45</sup> Rituximab should be considered in refractory/relapsing iTTP or upfront in cases with vital organ damage. Although the pathophysiology of iTTP involves microvascular thrombosis induced by supranormal VWF multimers, routine use of antiplatelet agents such as ASA or P2Y<sub>12</sub> ADP receptor antagonists during the acute phase is not recommended.<sup>46</sup> Low-dose ASA may be considered, however, following recovery of platelet counts to greater than  $50 \times 10^9/L$ . In iTTP patients with macrovascular thrombosis and an indication for therapeutic-dose anticoagulation or antiplatelet therapy, the increased risk of bleeding during treatment with caplacizumab, which impairs VWF-dependent primary hemostasis, must be considered.

### Disseminated Intravascular Coagulation

DIC is characterized by systemic activation of the hemostatic system resulting in diffuse thrombin generation, fibrin deposition, and platelet sequestration.<sup>47,48</sup> Formation of hyaline thrombi in small- and medium-size vessels may lead to organ dysfunction, while activation of the fibrinolytic system together with platelet and clotting factor consumption may result in a severe bleeding tendency. DIC is caused by an underlying disease and can be grouped in four categories according to prevailing pathophysiological mechanisms and clinical symptoms.<sup>48</sup>

#### Type 1—Bleeding Type (or Hyperfibrinolysis Predominance Type)

This type of DIC is commonly seen in patients with acute promyelocytic leukemia or vascular causes such as aortic aneurysms. Inadequate (reactive) activation of the fibrinolytic system leads to increased plasmin generation with a diffuse bleeding tendency.

#### Type 2—Organ Failure Type (or Hypercoagulation Predominance Type or Hypofibrinolysis Type)

This type of DIC is typically observed in patients with bacterial sepsis. The pathophysiology is multifactorial, involving increased expression and/or secretion of tissue factor, plasminogen activator inhibitor-1 (PAI-1), DNA, histones, leukocyte proteases (e.g., elastase, cathepsin G), and neutrophil extracellular traps (NETs). PAI-1-mediated impairment of fibrinolysis promotes the formation of microthrombi and organ dysfunction.

#### Type 3—Massive Bleeding Type (or Consumptive Type)

This type of DIC is caused by massive concomitant activation of procoagulant and fibrinolytic pathways leading to consumptive coagulopathy and an acute, life-threatening bleeding tendency. Characteristic causes are major traumatic, surgical, or peripartum hemorrhages with extensive tissue damage.

#### Type 4—Nonsymptomatic Type (or Pre-DIC)

This type of DIC is typically observed in patients with solid malignancies. A comparably weak and more chronic activation of coagulation and fibrinolysis is associated with no or little symptoms.

Various scoring systems are available to diagnose DIC, one of which is the ISTH/SSC score for overt DIC.<sup>47</sup> This score is based on platelet count (0–2 points), prothrombin time (0–2 points), plasma fibrinogen (0–1 point), and plasma fibrin generation markers such as soluble fibrin monomer (SFM) or fibrin degradation products (FDPs, e.g., D-dimer [0–3 points]). A sum score of  $\geq 5$  is compatible with overt DIC.

Patients with DIC type 2 or 4 are at significant risk of VTE, and prophylactic anticoagulation with LMWH or UFH should thus be considered in the absence of acute bleeding symptoms, while therapeutic anticoagulation is indicated in patients with overt thrombosis.<sup>48</sup> Dose adjustment may be required dependent on platelet count and perceived bleeding

risk. Post hoc subgroup and meta-analyses suggest that antithrombin (AT) substitution reduces all-cause mortality in patients with septic DIC by 35–40%, with more pronounced effects in patients not receiving prophylactic anticoagulation.<sup>49,50</sup> However, currently available evidence is not sufficient to promote routine use of AT concentrates in this clinical scenario. According to the personal opinions of the authors, substitution of AT may be considered on an individual basis in patients with sepsis-associated DIC, signs of micro- or macrovascular thrombosis, and significantly reduced AT plasma levels (i.e.,  $< 30\text{--}50\%$ ), particularly in those not deemed eligible for adequate anticoagulation. Still, the increased bleeding risk associated with AT supplementation must be considered.<sup>49</sup> Other drugs introduced to restore the anticoagulant capacity in severe sepsis have either been withdrawn from the market due to lack of efficacy (recombinant human activated protein C, drotrecogin alfa [activated]) or have not been approved outside Japan (recombinant human soluble thrombomodulin, ART-123). Nevertheless, a retrospective analysis of the PROWESS study suggested that drotrecogin alfa (activated) has a favorable risk–benefit profile in patients with sepsis and overt DIC,<sup>51</sup> supporting the concept that restoration of natural anticoagulants may prove beneficial in patients with a high risk of multiorgan failure due to widespread microvascular thrombosis.

Sepsis-induced coagulopathy (SIC) is an entity located upstream of DIC in the continuum of acquired coagulation abnormalities observed in patients with sepsis and thrombocytopenia.<sup>52</sup> While diagnosis of SIC is also based on platelet count and prothrombin time, the variables plasma fibrinogen and SFM/FDPs are replaced by the SOFA score indicating organ damage. Compared with patients with overt DIC, patients with SIC have less pronounced derangement of the hemostatic system and a lower risk of bleeding, warranting more aggressive antithrombotic strategies to prevent or treat thrombosis despite thrombocytopenia.

### Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired pluripotent hematopoietic stem cell disorder with an incidence of 0.1–0.2 per 100,000 person-years.<sup>53</sup> The etio-pathogenesis of PNH involves a two-step process. The first step is an acquired somatic mutation in the phosphatidylinositol glycan class A gene (*PIGA*), which leads to loss of glycosylphosphatidylinositol (GPI)-anchored membrane proteins, such as complement regulatory factors CD55 and CD59. The second step is a cellular immune reaction against healthy hematopoietic stem cells, which do not carry the *PIGA* mutation and are thus not deficient in GPI-anchored membrane proteins. T- and natural killer cell-mediated cytotoxicity results in normal bone marrow failure and expansion of the PNH clone. Complement-induced damage of CD55- and CD59-deficient erythrocytes causes hemolytic anemia, hemoglobinuria, and nitric oxide (NO) depletion. In PNH, the coagulation and complement cascades cooperate with intravascular RBC lysis in the generation of a highly thrombogenic state with significant risks for venous, arterial, and microvascular thrombosis.<sup>54</sup> Thromboembolic events,

renal failure, and pulmonary hypertension have negative impacts on patient survival. Dysphagia, abdominal pain, erectile dysfunction, and fatigue contribute to morbidity. Diagnosis is based on flow cytometric detection of the PNH clone, which can be achieved by analysis of RBC CD55/CD59 expression or leukocyte binding of fluorescent aerolysin (FLAER), an inactive variant of the bacterially derived aerolysin with high specificity and affinity for the GPI anchor.<sup>55</sup>

In PNH, venous thromboembolic events (80–85%) are more frequent than arterial thromboembolic events (15–20%).<sup>53,54</sup> Thrombosis occurs at unusual sites (e.g., hepatic/visceral veins, intracranial vessels, cutaneous microcirculation), precedes PNH diagnosis in 5–10% of patients, and is associated with the PNH clone size.<sup>56</sup> Complement inhibition with C5 monoclonal antibodies, eculizumab or ravulizumab, is standard of care in all symptomatic PNH patients with a hemolytic phenotype, significantly reducing the risk of thrombotic events.<sup>57</sup> Additional OAC with a VKA or DOAC is indicated in patients with a history of thrombosis and should be considered as primary thromboprophylaxis in asymptomatic patients not receiving anti-C5 therapy (e.g., in those with a large PNH clone size and/or additional risk factors for thrombosis).

In clinical practice, PNH testing is warranted in patients with venous or arterial thromboembolism meeting at least one of the following criteria:

- Signs of hemolysis (elevated lactate dehydrogenase, bilirubin, and reticulocytes; low haptoglobin).
- Thrombosis at unusual sites.
- Cytopenia (including low platelet counts).
- Recurrence of thrombosis despite appropriate anticoagulation.

## Conclusion

The management of vascular thrombosis in thrombocytopenic patients remains largely empirical until additional data from prospective observational cohort studies such as MATTER (NCT03195010) become available. In patients with a platelet count of less than  $50 \times 10^9/L$ , management options include no change, temporarily withholding antithrombotic therapy, reducing the dose, changing the regimen, and increasing the platelet transfusion threshold.<sup>58</sup> In any case, careful evaluation of the risks and benefits by a multidisciplinary team with particular consideration of patient values and preferences is indicated. Hematology and thrombosis/hemostasis consults should be aware of distinct disorders associated with thrombocytopenia and a hypercoagulable state that require specific diagnostic tests and treatment strategies.

### Conflicts of Interest

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