

# Recent advances in classic heparin-induced thrombocytopenia (HIT), autoimmune HIT, spontaneous HIT, and vaccine-induced immune thrombotic thrombocytopenia

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## ABSTRACT

Anti-PF4 disorders are a group of platelet-consumptive disorders characterized by platelet-activating antibodies against platelet factor 4 (PF4), thrombocytopenia and an increased risk of thrombosis. PF4 is a chemokine released by platelet alpha granules upon activation, which can form immune complexes with negatively charged substances, such as heparin, cartilage components, nucleic acids, and viral and bacterial agents. Antibodies formed in response to PF4-polyanion complexes may display platelet-activating properties and cause pan-cellular activation, leading to the marked prothrombotic state of anti-PF4 disorders. In recent years, the landscape of anti-PF4 disorders has evolved to include classic heparin-induced thrombocytopenia (cHIT), autoimmune HIT (aHIT), spontaneous HIT (SpHIT), vaccine-induced immune thrombotic thrombocytopenia (VITT), and the newly recognized spontaneous VITT (SpVITT). These disorders have garnered increased attention due to their association with severe clinical outcomes. Recent discoveries have expanded the understanding of these conditions, highlighting the role of various triggers, such as upper respiratory tract infections and monoclonal gammopathy of undetermined significance, in their development. Compared to cHIT, the less common anti-PF4 disorders VITT, aHIT, SpHIT and SpVITT

generally appear more severe, with aggressive disease courses, more severe thrombocytopenia and a higher frequency of bleeding, thrombosis at unusual sites, involvement of the central nervous system and of multiple vascular beds. Clinical suspicion and knowledge of the less well-known triggers of anti-PF4 disorders are pivotal to ordering the appropriate laboratory tests and initiating the necessary treatments. Herein, we will review cHIT, aHIT, SpHIT and VITT, focusing on their clinical presentation and therapeutic management.

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## Introduction

Platelet-activating antibodies directed against platelet factor 4 (PF4), a chemokine released by platelet- $\alpha$  granules, are the mediators of anti-PF4 antibody disorders. This group of platelet consumptive disorders has included – until recently – classic heparin-induced thrombocytopenia (cHIT), two rare HIT variants [autoimmune HIT (aHIT) and spontaneous HIT (SpHIT)], and the newly recognized vaccine-induced immune thrombotic thrombocytopenia (VITT). The latest addition to this evolving field is a VITT-like disorder termed spontaneous VITT (SpVITT), occurring without recent heparin or vaccine exposure.<sup>1,2</sup> Each of these disorders is characterized by detectable platelet-activating anti-PF4 antibodies, thrombocytopenia, and an elevated risk of thrombosis. However, the mere presence of anti-PF4 antibodies, found in up to 6.6% of healthy blood donors<sup>3</sup> and 3.7% of healthy vaccinees with adenoviral vector vaccines (a notable fraction of the healthy population),<sup>4</sup> does not suffice for diagnosis. This is compounded by the fact that not all anti-PF4 antibodies display platelet-activating properties,<sup>5,6</sup> adding layers of complexity to the diagnosis and management of anti-PF4 disorders, which require a nuanced approach. Herein, we will review cHIT, aHIT, SpHIT, and VITT, focusing on their clinical presentation and therapeutic management. Insights concerning SpVITT will be given but should be considered preliminary and in need of further confirmation.

## Epidemiology

The epidemiological characteristics of cHIT, VITT, aHIT, and SpHIT are summarized in Table 1.<sup>7-10</sup>

### Classic heparin-induced thrombocytopenia

Classic HIT is an immune-mediated, prothrombotic adverse reaction to heparin. Due to the widespread use of heparin in hospital settings, it is not rare that the suspicion of cHIT is raised in everyday clinical practice. Nonetheless, cHIT is a rare cause of thrombocytopenia in hospitalized patients,<sup>11</sup> with an incidence ranging from 1 out of 5,000 inpatients to 3-5 out of 100 inpatients.<sup>7,12,13</sup> In fact, specific patient groups, including subjects receiving unfractionated heparin, undergoing major surgery (particularly orthopedic and cardiac surgery), and females, face a heightened risk of developing cHIT.<sup>7,14,15</sup>

### Vaccine-induced immune thrombotic thrombocytopenia

VITT is an immune-mediated adverse reaction to adenoviral vector vaccines, which occurs in about 1 per 100,000 to 500,000 vaccinated individuals.<sup>8</sup> Unlike cHIT, VITT does not have a clearly defined population at risk, although younger vaccine recipients may bear a greater susceptibility.<sup>9</sup> Most cases of VITT have occurred after the first vaccine dose, with sparse occurrences following the second dose or first exposure to adenoviral vector vaccines for booster vaccination.<sup>16,17</sup>

### Autoimmune heparin-induced thrombocytopenia, spontaneous heparin-induced thrombocytopenia and spontaneous vaccine-induced immune thrombotic thrombocytopenia

The incidence rate of VITT aligns more closely with that of other rare HIT variants, such as aHIT and SpHIT.<sup>18</sup> Notably, autoimmune HIT is triggered by heparin or fondaparinux but persists, at least in part, through the action of heparin-independent anti-PF4 antibodies.<sup>19</sup> To date, five distinct aHIT disorders are recognized: delayed-onset HIT, persisting HIT, fondaparinux-

induced HIT, heparin “flush” HIT, and unusually severe HIT. Conversely, SpHIT occurs in the absence of previous heparin exposure, with literature documenting only a limited number of cases following orthopedic surgery (n=24) or within the context of an acute medical illness (n=15).<sup>18</sup> The global roll-out of COVID-19 vaccines has been pivotal in distinguishing VITT as a standalone disease entity. Notably, upper respiratory tract infections (URTIs) and other viral illnesses, including COVID-19, are among the precipitants of medical SpHIT. Recent studies suggest that current or previous adenovirus infections and URTIs might trigger conditions mediated wholly or in part by heparin-independent anti-PF4 antibodies.<sup>2,20-22</sup> This insight has led Schönborn *et al.* to reclassify certain cases of SpHIT as a distinct, VITT-like syndrome,<sup>2</sup> termed SpVITT by others,<sup>1</sup> owing to the inhibitory effect of heparin on antibody binding in laboratory tests. Recently, a proteomic analysis of antibodies from four patients with SpVITT after adenovirus infection has revealed that the anti-PF4 antibodies of patients with VITT and SpVITT are extremely similar.<sup>23</sup> Thus, the spectrum of HIT and VITT disorders appears to be supported by heparin-dependent and heparin-independent anti-PF4 antibodies, respectively.

Clinicians must be aware of the possible triggers of anti-PF4 mediated disorders, since clinical suspicion is pivotal to ordering the appropriate laboratory tests. Given the role of PF4 in innate immunity, a negative charge is shared by all known triggers. These include heparin, orthopedic surgery, particularly knee surgery leading to the release of negatively-charged cartilage substances, such as chondroitin sulfate and nucleic acids, as well as bacterial and viral pathogens, notably adenoviruses, present in adenoviral vector vaccines.<sup>18</sup> The production of platelet-activating anti-PF4 antibodies, whether by polyclonal B-cell clones (in cHIT) or by mono- or oligoclonal B-cell clones (in SpHIT, VITT and SpVITT),<sup>2,24</sup> has significant implications for the pathophysiology, clinical presentation and treatment of anti-PF4 disorders, which will be discussed below.

## Pathophysiology

### The role of platelet factor 4 in innate immunity

Platelet factor 4 (PF4) is a positively charged tetrameric protein belonging to the CXC chemokine family, stored in

**Table 1.** Epidemiology of anti-platelet factor 4 disorders.<sup>7-10</sup>

	Classic HIT	Autoimmune HIT	Spontaneous HIT	VITT
Frequency	1 out of 5000 up to 3-5 out of 100 inpatients <sup>7,12,13</sup>	NA	NA	1 out of 100,000/500,000 vaccinated individuals <sup>8</sup>
Trigger(s)	Heparin (unfractionated and low-molecular-weight)*	Heparin, fondaparinux	Infections, URTIs, orthopedic surgery (especially of the knee)	Adenoviral vector vaccines against SARS-CoV-2
Timing	5 to 10 days after exposure to heparin <sup>7</sup>	NA	NA	4 to 42 days after vaccination <sup>9</sup>
Populations at risk	Patients receiving UFH, surgical patients (especially orthopedic and cardiac surgery), females <sup>7</sup>	NA	NA	Patients under 50 years of age <sup>10</sup>

HIT, heparin-induced thrombocytopenia; VITT, vaccine-induced immune thrombotic thrombocytopenia; NA, not available; URTI, upper respiratory tract infections; UFH, unfractionated heparin.

\*The risk of developing HIT is 10-fold higher in recipients of unfractionated heparin compared to recipients of low-molecular-weight heparin.

platelet  $\alpha$ -granules ( $18 \pm 4 \mu\text{g}/10^9$  platelets). Normally, plasma PF4 levels are extremely low ( $1.8 \text{ ng/mL}$ ) but, upon platelet activation, they may exceed  $600 \text{ ng/mL}$ .<sup>25</sup> PF4 binds to negatively charged heparan sulfate on the endothelial cell surface,<sup>26,27</sup> leading to its rapid plasma clearance, which inhibits antithrombin activity and promotes coagulation.<sup>28</sup> PF4, however, has a higher affinity for exogenous heparin and other polyanions than for heparan sulfate. PF4-polyanion complexes, recognized as a danger signal, trigger immunoglobulin G (IgG) production.<sup>7</sup> Often, this results in the transient production of antibodies of the IgG class against PF4; however, anti-PF4 antibodies with platelet-activating properties may lead to the onset of anti-PF4 disorders. Notably, such disorders often follow proinflammatory states, such as major surgery and infections.<sup>29</sup>

### Types of anti-platelet factor 4 antibodies

Anti-PF4 antibodies can be classified into three categories (Table 2).<sup>18,25,30-32</sup> Type 1 antibodies are non-pathogenic and non-platelet-activating, despite recognizing PF4/heparin complexes. Type 2 antibodies are pathogenic, platelet-activating, and heparin-dependent antibodies, and are associated with cHIT. Type 3 antibodies are heparin-independent and highly pathogenic, as they recognize PF4 without heparin, and are implicated in the pathogenesis of VITT and SpHIT. Autoimmune HIT results from the simultaneous presence of type 2 antibodies – and potentially also type 1 antibodies – and heparin-independent type 3 antibodies, which play a crucial role in the mechanism of disease.<sup>30</sup>

### The pathogenesis of anti-platelet factor 4 disorders

Type 2 and 3 anti-PF4 antibodies trigger Fc $\gamma$  receptor-mediated pancellular activation of platelets, neutrophils, monocytes and the endothelium, substantially increasing the risk of thrombosis. In cHIT, antibodies target PF4-heparin complexes, activating neutrophils, with release of neutrophil extracellular traps, and induce a procoagulant state in the endothelium.<sup>33</sup> This creates a vicious cycle that can only be broken by discontinuing heparin and starting appropriate anticoagulation. In aHIT, type 3 anti-PF4 antibodies activate platelets independently of the presence of heparin, extending the duration of the condition beyond heparin exposure. Consequently, aHIT may last several weeks, but treatment with high-dose intravenous immunoglobulin (IVIG) can interrupt the state of anti-PF4 antibody-induced platelet activation, facilitating rapid platelet count recovery. The antigenic sites on the PF4 molecule that

interact with anti-PF4 antibodies with heparin-independent reactivity differ from those of antibodies with heparin-dependent reactivity.<sup>18</sup> VITT, like cHIT, is characterized by high levels of anti-PF4 antibodies, albeit in the absence of prior heparin exposure. VITT antibodies, moreover, show maximum reactivity with PF4 itself. The complexity of VITT arises from the presence of both PF4-dependent and PF4-independent antibodies, with one study showing a higher frequency of cerebral venous sinus thrombosis (CVST) in patients with PF4-independent antibodies.<sup>34</sup> PF4-independent VITT antibodies bind to two sites on the PF4 molecule, suggesting a different mechanism of action from PF4-dependent antibodies.<sup>34</sup> The precise cause of development of pathogenic anti-PF4 antibodies following adenoviral vector vaccination is uncertain, with potential factors including changes in PF4 antigenicity due to interactions with viral proteins or vaccine adjuvants.<sup>35</sup>

### Laboratory insights on anti-platelet factor 4 disorders

Recent advances in laboratory techniques, such as the development of a fluid-phase enzyme-linked immunoassay by the McMaster Platelet Immunology Laboratory, have enhanced the understanding of the binding patterns of anti-PF4 antibodies.<sup>1</sup> This novel assay can distinguish the reactivity of anti-PF4 antibodies against PF4 alone or PF4 complexed with heparin, revealing shared VITT-like patterns in patients with thrombotic involvement of the central nervous system (CNS). These findings suggest a potential underdiagnosis of disorders with VITT-like profiles in the past, highlighting the necessity for further research to clarify the mechanisms leading to CNS-specific thrombosis in these conditions.

### Anti-platelet factor 4 antibody persistence

The immune response differs across different anti-PF4 disorders: cHIT is characterized by polyclonal antibodies, while VITT and SpHIT involve mono- or oligoclonal antibodies.<sup>24</sup> Mono- and oligoclonality suggest a restricted epitope specificity in VITT and SpHIT, and might explain the longer persistence of anti-PF4 antibodies in these conditions.<sup>31,36-39</sup> In fact, although most anti-PF4 antibodies are transient, persistent cases are noted, especially in a minority of VITT cases and in cases of SpHIT and, mostly, SpVITT linked to monoclonal gammopathy of undetermined significance.<sup>40-43</sup> Recurrences in some patients underscore the need for ongoing research into the durability and clinical implications of these antibodies.<sup>2</sup>

**Table 2.** Pathophysiology of anti-platelet factor 4 disorders.<sup>18,24,30-32</sup>

	Classic HIT	Autoimmune HIT	Spontaneous HIT	VITT
Anti-PF4 antibody type	Type 2 (heparin-dependent) <sup>18,30</sup>	Type 2 (heparin-dependent) and Type 3 (heparin-independent) <sup>18,30</sup>	Type 3 (heparin-independent) <sup>18,30</sup>	Type 3 (heparin-independent) <sup>18,30</sup>
Anti-PF4 antibodies clonality	Polyclonal	NA	Oligo- or monoclonal <sup>24</sup>	Oligo- or monoclonal <sup>24</sup>
Antibody persistence	Up to 50 days (PAAs) and 85 days (EIAs) <sup>31</sup>	NA	NA	Up to 196 days (PAAs) <sup>32</sup>

HIT, heparin-induced thrombocytopenia; VITT, vaccine-induced immune thrombotic thrombocytopenia; PF4, platelet factor 4; NA, not applicable; PAA, platelet activation assay; EIA, enzyme-linked immunosorbent assay.

## Clinical features

From a clinical point of view, all anti-PF4 disorders are characterized by the copresence of thrombocytopenia and an increased risk of thrombosis. The main clinical features of anti-PF4 disorders are shown in Table 3 and reviewed below.<sup>1,13,16,17,44-47</sup>

## Thrombocytopenia and other laboratory findings

### Classic heparin-induced thrombocytopenia

In inpatients, thrombocytopenia, often detected through routine complete blood count (CBC) monitoring, is the first objective clinical finding that can arise clinical suspicion for an anti-PF4 disorder. The hallmark of cHIT is a significant drop in the platelet count, typically greater than 30% from baseline, occurring 5 to 10 days after exposure to heparin.<sup>7</sup> Distinctly, the platelet count nadir is generally between  $40 \times 10^9/L$  and  $80 \times 10^9/L$  in cHIT.<sup>7,18</sup> This pattern may not only differentiate cHIT from other causes of thrombocytopenia in inpatients, such as drug-induced thrombocytopenia, but also underscores the intricate balance between heparin use and its adverse effects.

### Autoimmune heparin-induced thrombocytopenia and spontaneous heparin-induced thrombocytopenia

The platelet count trends of aHIT and SpHIT are less well documented due to their rarity. A distinguishing feature of aHIT is the loss of the temporal relationship with heparin exposure, attributed, at least in part, to the involvement of heparin-independent anti-PF4 antibodies. The platelet count can drop below  $20 \times 10^9/L$  in severe aHIT – a form of aHIT that can lead to disseminated intravascular coagulation (DIC) and microvascular thrombosis.<sup>18</sup> SpHIT also presents with severe thrombocytopenia, with reported nadirs below  $20 \times 10^9/L$  in a subset of cases,<sup>18</sup> further complicating the clinical picture and the differential diagnosis.

## Vaccine-induced immune thrombotic thrombocytopenia

The temporal profile of platelet count decrease in VITT is challenging to delineate because affected individuals are often young, otherwise healthy outpatients. The presentation of VITT is frequently dominated by symptoms of thrombosis rather than isolated thrombocytopenia, with some individuals exhibiting *pre-VITT*, a syndrome characterized by new-onset headache without overt thrombosis.<sup>48</sup> A drop in the platelet count below  $150 \times 10^9/L$  during the disease course aligns with the diagnosis of VITT as per the American Society of Hematology (ASH) criteria.<sup>10</sup> We found that a notable proportion of VITT patients experienced a platelet count nadir below  $50 \times 10^9/L$ .<sup>44</sup> Another relevant laboratory finding of VITT is a marked elevation in the D-dimer levels; of note, levels of more than four times the upper limit of normal are considered among the ASH diagnostic criteria for VITT.<sup>10</sup> DIC is estimated to be present in approximately 50% of patients with VITT and – interestingly – is also relatively frequent in reports of aHIT.<sup>18,19</sup> Markedly elevated D-dimers have been reported in all of the 8 patients who had D-dimers measured in the 9 SpVITT cases series described by Schönborn *et al.*<sup>2</sup>

## Thrombosis

Thrombosis is the most feared complication of anti-PF4 disorders, as it is potentially life-threatening, although it is not an essential diagnostic criterion.

### Classic heparin-induced thrombocytopenia

In cHIT, thrombosis occurs in approximately 50% of patients,<sup>7</sup> with two independent studies highlighting an overall venous to arterial thrombosis ratio of 4 to 1.<sup>45,46</sup> However, in cHIT, the risk and type of thrombosis vary significantly by patient group and treatment context. For instance, among a French cohort of 144 patients with confirmed cHIT, those who had undergone cardiac surgery exhibited a higher frequency of

**Table 3.** Clinical presentation of anti-platelet factor 4 mediated disorders.<sup>1,7,18,19,44-47</sup>

	Classic HIT	Autoimmune HIT	Spontaneous HIT	VITT
Platelet count nadir	Typically $40-80 \times 10^9/L$ <sup>18</sup>	Can be below $20 \times 10^9/L$ <sup>18</sup>	Can be below $20 \times 10^9/L$ <sup>18</sup>	Typically below $50 \times 10^9/L$ <sup>44</sup>
Thrombosis frequency	50% <sup>7</sup>	Very high (~90%) <sup>19</sup>	Very high (>87%) <sup>18,1</sup>	Very high (>95%) <sup>18</sup>
Venous to arterial thrombosis ratio	4 to 1 <sup>45,46</sup>	NA	NA	4 to 1 <sup>44</sup>
Commonest thrombosis sites	PE, DVT, limb artery thrombosis, AMI, stroke <sup>45</sup>	Frequent microvascular and CNS involvement <sup>18</sup>	Frequent CNS involvement <sup>18</sup>	CVST, PE, SVT, cerebrovascular events <sup>44</sup>
Multivessel involvement	Possible	Frequent <sup>18</sup>	Frequent <sup>18</sup>	Frequent <sup>44</sup>
Bleeding frequency	5.7% <sup>47</sup>	NA	High frequency of adrenal bleeding/necrosis in orthopedic SpHIT <sup>18</sup>	36% <sup>44</sup>
ICH frequency	0.9% <sup>47</sup>	NA	NA	26% <sup>44</sup>
Mortality	6.3-15.9% <sup>46</sup>	NA	NA	24% <sup>44</sup>

HIT, heparin-induced thrombocytopenia; VITT, vaccine-induced immune thrombotic thrombocytopenia; NA, not available; PE, pulmonary embolism; DVT, deep vein thrombosis; AMI, acute myocardial stroke; CNS, central nervous system; CVST, cerebral venous sinus thrombosis; SVT, splanchnic vein thrombosis; SpHIT, spontaneous heparin-induced thrombocytopenia.

arterial thrombosis when compared to patients from other surgical settings (13.2% vs. 2.4%).<sup>46</sup> In a case series of 127 cHIT patients, the most common thrombotic event was pulmonary embolism (PE) (25.2% of patients).<sup>45</sup> Other notable thrombosis sites include deep vein thrombosis (DVT), limb artery thrombosis, acute myocardial infarction, and stroke. The frequent – and potentially catastrophic – involvement of the lower limbs in cHIT underscores its potential as a limb-threatening condition, with a markedly increased risk of amputation (adjusted odds ratio of 5).<sup>11</sup>

### **Vaccine-induced immune thrombotic thrombocytopenia, autoimmune heparin-induced thrombocytopenia, spontaneous heparin-induced thrombocytopenia and spontaneous heparin-induced thrombocytopenia**

Thrombosis is remarkably prevalent in VITT, where more than 95% of patients are believed to experience this complication.<sup>18</sup> This high prevalence is likely attributed to the identification method of VITT, primarily through symptomatic thrombotic events rather than through routine CBC monitoring. In VITT, thrombosis predominantly manifests in unique and severe forms, with CVST, PE, splanchnic vein thrombosis (SVT), and arterial cerebrovascular events being among the most common thrombotic events.<sup>40,44,49-51</sup> Interestingly, CVST, which is rare in cHIT,<sup>52</sup> emerges as a more frequent concern in VITT and other anti-PF4 disorders like aHIT, SpHIT, and SpVITT. Cerebrovascular events and CVST occurred, respectively, in around 30% and 40% of patients with either acute or chronic medical SpHIT.<sup>18</sup> Seven out of the 9 SpVITT patients from the Greifswald cohort displayed CNS involvement (n=4 CVST; n=3 arterial stroke).<sup>2</sup>

In aHIT, similarly to VITT, thrombosis is highly prevalent, reaching a frequency of 90%.<sup>2,19</sup> This, once again, could reflect the way cases are identified, especially in the context of delayed-onset HIT, which occurs or worsens after heparin discontinuation. Likewise, multivessel involvement is frequent in VITT, aHIT, and SpHIT.<sup>18,44</sup>

Recent insights into anti-PF4 disorders suggest that distinct pathomechanisms correlate with clinical presentations, and particularly with thrombosis patterns. The laboratory characteristics of VITT antibodies, such as their persistence, their clonality, and their patterns of heparin inhibition of antibody binding (seen with fluid-phase EIAs and a novel anti-PF4 chemiluminescence assay) and of PF4-independence (seen with the PF4-Serotonin Release Assay), appear to be intricately linked to the involvement of the CNS.<sup>1,2,34</sup> A systematic review from our group confirmed that VITT exhibits a distinct clinical profile, predominantly characterized by a high frequency of venous thrombosis at unusual sites, alongside the involvement of the CNS and multiple vascular beds.<sup>44</sup> Notably, CVST and arterial CNS thrombosis occur more frequently in VITT, and typically in isolation compared to other thrombotic manifestations.<sup>44</sup> This pattern underscores the unique pathophysiological mechanism driving VITT, distinct from other anti-PF4 mediated disorders. The neurotropism of VITT critically influences its clinical severity and associated mortality rates. In the same systematic review, we showed that the overall mortality of VITT patients is 24% [95% confidence interval (CI) 19-29]

and increases to 31% (95% CI 24-38) in patients with CVST. The mortality rate reaches 77% (95% CI 58-90) in instances where CVST is complicated by intracranial hemorrhage (ICH).<sup>44</sup> These findings emphasize the paramount importance of recognizing and promptly managing VITT to mitigate its potentially fatal outcomes. The question remains whether CNS involvement serves as a more specific marker of VITT and VITT-like conditions, potentially indicative of a broader category of anti-PF4 disorders mediated by heparin-independent and PF4-independent antibodies.

## **Bleeding**

### *Classic heparin-induced thrombocytopenia*

Despite the presence of thrombocytopenia, significant bleeding in cHIT is relatively uncommon. A study based on hospital discharge data revealed that bleeding complications occur in 5.7% of inpatients diagnosed with cHIT.<sup>47</sup> In this study, gastrointestinal and genitourinary bleeds were the most frequently reported bleeding events, occurring in 2.7% and 2.2% of patients, respectively, while CNS bleeding remained notably rare at 0.9%. The rarity of bleeding can be attributed both to the generally moderate decrease in platelet counts, characteristic of cHIT, and to the locations of thrombosis. Altogether, these data underscore the predominantly prothrombotic nature of cHIT.

### *Vaccine-induced immune thrombotic thrombocytopenia*

In stark contrast, VITT presents with a significantly higher frequency of bleeding compared to cHIT. In one of the largest described VITT patient cohorts, bleeding complications occurred in 21% of patients.<sup>51</sup> Our systematic review further highlighted that bleeding occurs in over one-third of patients (131/366, 36.0%),<sup>44</sup> a figure that notably exceeds the bleeding incidence in cHIT. This increased bleeding frequency, however, should not be misconstrued as indicative of an inherent bleeding propensity specific to VITT. Instead, it appears to largely result from the anatomical location of the venous thrombotic events characteristic of this condition. ICH and adrenal gland hemorrhage emerge as the predominant bleeding events in VITT, accounting for 68% and 9% of all bleeds, respectively.<sup>44</sup> These bleeding events are primarily driven by increased venous pressure secondary to thrombosis, with ICH being associated with CVST in the majority of cases.<sup>44</sup> Notably, adrenal hemorrhage, a significant bleeding event in VITT, also finds parallels in aHIT<sup>19</sup> and in post-orthopedic SpHIT,<sup>18</sup> suggesting a complex relationship between the pathophysiology of anti-PF4 disorders and bleeding outcomes. In conclusion, the juxtaposition of the bleeding tendencies of cHIT and VITT reveals novel critical differences between the two. While cHIT displays a low bleeding propensity, attributable to its less severe thrombocytopenia, VITT showcases a higher bleeding risk, stemming from the critical locations of thrombotic blockages.

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## **Treatment**

The management of anti-PF4 disorders is summarized in Table 4.<sup>10,11,32,53-56</sup>

### Classic heparin-induced thrombocytopenia

The cornerstone of the treatment of cHIT is the immediate cessation of heparin and the initiation of full-dose anticoagulation with an alternative agent.<sup>32</sup> This is the only strategy that fully addresses the prothrombotic nature of this condition, as discontinuing heparin alone fails to significantly mitigate the risk of thrombosis. Historical data highlight that, without alternative anticoagulation, the thrombosis risk remains high, with a reported 30-day thrombosis risk of approximately 50%.<sup>45</sup> The use of vitamin K antagonists (VKAs) is contraindicated in the acute phase of cHIT due to the risk of limb-threatening venous limb gangrene resulting from protein C depletion in the setting of uncontrolled HIT-associated hypercoagulability.<sup>7</sup> If a VKA is ongoing at the time of cHIT diagnosis, it should be reversed and discontinued.<sup>53</sup> Recommended non-heparin anticoagulants include: argatroban (intravenous), danaparoid (intravenous, subcutaneous), bivalirudin (intravenous), fondaparinux (subcutaneous), and, with caution, direct oral anticoagulants (DOACs, oral), as there is limited experience with the use of the latter.<sup>32,53</sup> The choice of the alternative anticoagulation regimen should take into consideration the clinical stability of the patient, the existence of concomitant renal or liver dysfunction, and local availability and experience issues.<sup>11</sup> Typically, the vast majority of anti-PF4 disorders are transient, and thus do not require long-term antithrombotic treatment. However, the optimal duration of anticoagulation in the setting of confirmed cHIT is presently unclear. In the case of cHIT with thrombosis, a minimum of 3 months of anticoagulation is advisable. For cHIT without thrombosis, anticoagulation should last until normalization of the platelet count but not exceed three months.<sup>32,53</sup> It is currently unknown if there is a minimum duration of anticoagulation in this context. Given the low bleeding risk, prophylactic platelet transfusions are generally not necessary and could increase the risk of arterial thrombosis.<sup>47</sup> In patients with known previous cHIT, re-exposure to heparin should be avoided, if possible.<sup>53</sup> In cases

in which re-exposure to heparin is the best clinical option (*i.e.*, cardiac surgery), it should be noted that there have been descriptions of safe short-term re-exposure to heparin in patients with no platelet-activating anti-PF4 antibodies.<sup>57</sup>

### Autoimmune and spontaneous heparin-induced thrombocytopenia

Optimal management strategies for aHIT and SpHIT are less well-defined due to their rarity. Since aHIT is triggered by heparin and is maintained, at least in part, by heparin-dependent antibodies, heparin should not be administered, and alternative agents should be used for full-dose anticoagulation, bearing in mind that cross-reactivity with fondaparinux is possible in this clinical context.<sup>54</sup> Venous limb gangrene is a well-described complication of aHIT, with some reported cases occurring with no ongoing warfarin therapy;<sup>58,59</sup> thus, VKAs should be avoided also in this setting.<sup>19</sup> Given the presence of heparin-independent antibodies that contribute to widespread cellular activation, the administration of IVIG at a dosage of 1 g/kg for two consecutive days has proven effective. This treatment strategy directly targets and mitigates the specific pathomechanism responsible for anti-PF4 antibody-driven pancellular activation, offering a critical intervention for managing this complex condition.<sup>54</sup> Before starting IVIG treatment, it is important to collect diagnostic samples, since IVIG can alter test results.<sup>60</sup> The duration of anticoagulation is guided by the normalization of the platelet count.<sup>54</sup>

### Vaccine-induced immune thrombotic thrombocytopenia

The treatment of VITT draws from experience with the management of aHIT and SpHIT. The cornerstone of treatment is full-dose anticoagulation and IVIG.<sup>10,55,56</sup> The safety of heparin use in VITT remains uncertain with consideration of the heparin-independent nature of VITT antibodies.<sup>18</sup> The ASH, the British Expert

**Table 4.** Management of anti-platelet factor 4 disorders.<sup>10,11,32,53-56</sup>

	Classic HIT	Autoimmune HIT	Spontaneous HIT	VITT
Cornerstone of management	Stop heparin Full-dose anticoagulation with alternative agents* <sup>32</sup>	No heparin Full-dose anticoagulation with alternative agents** IVIG (1 g/kg for two days) <sup>54</sup>	No heparin	Full-dose anticoagulation with alternative agents* IVIG (1 g/kg over or for two days) <sup>10,55,56</sup>
Adjunctive treatments (may be considered)	VKA reversal (if required) <sup>65</sup> Platelet transfusions <sup>32</sup>	VKA reversal (if required) <sup>54</sup>		VKA reversal (if required) Corticosteroids <sup>55</sup> PEX <sup>55</sup> Rituximab <sup>55</sup> Eculizumab <sup>3</sup> Platelet transfusions <sup>10,55</sup>
Experience with DOACs	Greatest with rivaroxaban and apixaban <sup>11</sup>	Scarce <sup>54</sup>	NA	Scarce
Duration of anticoagulation	HIT without thrombosis: at least until platelet count normalization <sup>32,56</sup> HIT with thrombosis: at least 3 months <sup>32</sup>	Until stable normalization of the platelet count <sup>54</sup>	NA	Not defined

HIT, heparin-induced thrombocytopenia; VITT, vaccine-induced immune thrombotic thrombocytopenia; IVIG, intravenous immune globulin; VKA, vitamin K antagonist; DOACs, direct oral anticoagulants; PEX, plasma exchange; NA, not available. \*Argatroban (IV), danaparoid (SQ, IV), bivalirudin (IV), fondaparinux (SQ), DOACs (oral). The safety of heparin use in VITT remains uncertain with consideration of the heparin-independent nature of VITT antibodies; \*\*same agents that are used for classic HIT, although the possibility of cross-reactivity with fondaparinux should be considered.

Hematology Panel, and Thrombosis Canada, in light of the existing evidence, all recommend the use of alternative anticoagulants.<sup>10,55,56</sup> Due to the limited number of described cases and the recent recognition of VITT, the experience with the use of DOACs is scarce in this context, as in aHIT and SpHIT. Additional treatments for VITT may include corticosteroids,<sup>55</sup> plasma-exchange,<sup>55</sup> rituximab,<sup>55</sup> and eculizumab.<sup>10</sup> Platelet transfusions may be reserved for specific needs.<sup>10,55</sup> The optimal duration of anticoagulation for VITT is under investigation, with ongoing studies, like those from the Greifswald VITT cohort, providing remarkable insights. In most treated cases of VITT, patients do not experience additional thrombotic complications.<sup>37</sup>

## Future prospects

The accelerated introduction of SARS-CoV-2 vaccines has not only been a critical step in contrasting the COVID-19 pandemic but also a moment of significant learning for researchers, particularly in the field of hemostasis, thrombosis, and anti-PF4 disorders. It has brought to light VITT and similar VITT-like anti-PF4 disorders, highlighting a spectrum of conditions that, while rare, present severe and potentially fatal outcomes. These conditions demand prompt recognition, thorough laboratory investigation, and immediate intervention to alter their potentially dire courses. Educational initiatives targeted at clinicians are vital to bridge knowledge gaps regarding the evolving landscape of these disorders. Moreover, there is a pressing need for basic and translational research to answer currently open questions, such as the reasons for the different immune responses observed in cHIT, SpHIT, VITT, and SpVITT; understanding the underlying mechanisms that predispose certain individuals to these disorders; and investigating the intriguing phenomenon of neutropenism observed in SpHIT, VITT, and SpVITT. Furthermore, it is crucial to determine the most effective treatment protocols, evaluate the risk-benefit ratio of heparin in non-cHIT conditions, the identification of cases that may benefit from additional therapies and the optimal duration of anticoagulation.

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