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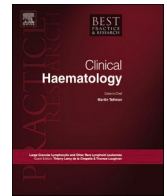
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## Vaccine-induced immune thrombotic thrombocytopenia

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## ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is primarily a complication of adenoviral vector-based covid-19 vaccination. In VITT, thrombocytopenia and thrombosis mediated by anti-platelet factor 4 (PF4) antibodies can be severe, often characterized by thrombosis at unusual sites such as the cerebral venous sinus and splanchnic circulation. Like in heparin-induced thrombocytopenia (HIT) and spontaneous HIT, VITT antibodies recognize PF4-polyanion complexes and activate PF4-treated platelets but additionally bind to un-complexed PF4, a critical finding that could be leveraged for more specific detection of VITT. Intravenous immunoglobulin and non-heparin-based anticoagulation remain the mainstay of treatment. Second dose/boosters of mRNA covid-19 vaccines appear safe in patients with adenoviral vector-associated VITT. Emerging data is consistent with the possibility that ultra-rare cases of VITT may be seen in the setting of mRNA and virus-like particle (VLP) technology-based vaccinations and until more data is available, it is prudent to consider VITT in the differential diagnosis of all post-vaccine thrombosis and thrombocytopenia reactions.

## 1. Introduction

In response to the COVID-19 pandemic, there has been an unprecedented effort to develop novel vaccines that minimize SARS-CoV-2 morbidity and mortality [1]. Following the initial roll-out of these vaccines in late 2020, reports of thrombocytopenia and thrombotic events after vaccination began to surface in early 2021. These reports were associated with the administration of adenoviral vector-based vaccines, ChAdOx1 nCov-19 (AstraZeneca) and Ad26.COV2.S (Janssen Johnson & Johnson). In response, several European member states paused the administration of ChAdOx1 nCov-19(2), and the Centers for Disease Control and Prevention (CDC) did the same for the Ad26.COV2.S vaccine in the United States [3]. After further evaluation by these agencies, the incidence of vaccine-induced immune thrombotic thrombocytopenia (VITT) was found to be rare, such that the adverse outcomes associated with COVID-19 disease significantly outweighed those related to VITT, and vaccine administration was resumed [3–7].

Given the rarity of VITT, the probability of identifying VITT as an adverse event following SARS-CoV-2 vaccination in clinical trials was exceedingly low. Only a single case of thrombosis and thrombocytopenia syndrome (TTS) consistent with VITT was noted in clinical trials evaluating Ad26.COV2.S vaccination [3], while none were seen in the ChAdOx1 nCov-19 trials. However, following the large-scale administration of vaccines in millions of individuals in response to COVID-19 worldwide, an increasing number of patients presenting with thrombocytopenia and thrombotic complications subsequent to SARS-CoV-2 vaccination were identified,

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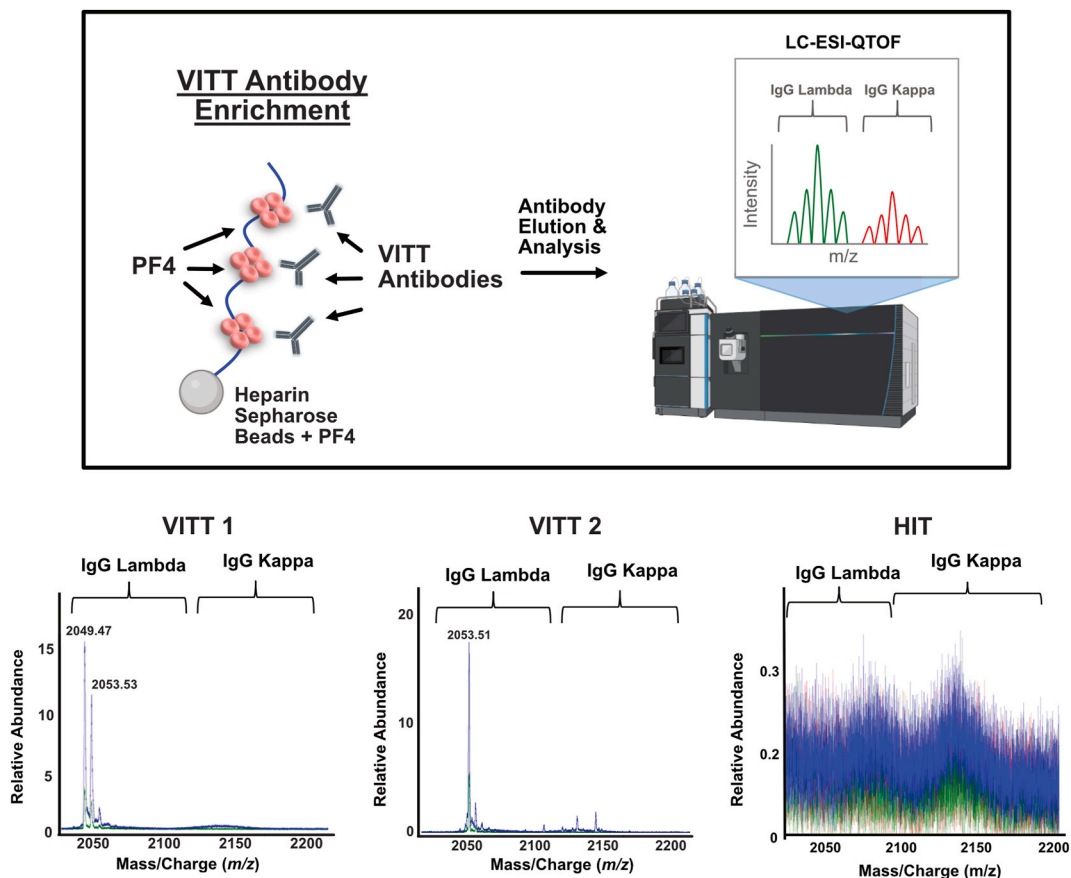
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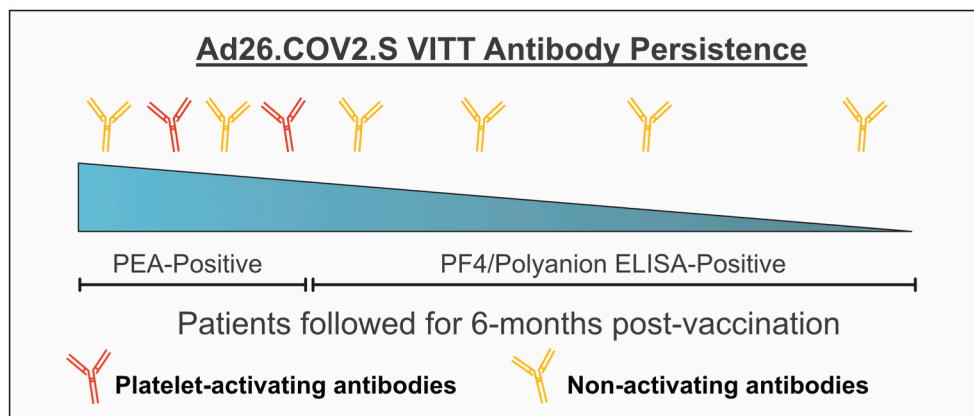
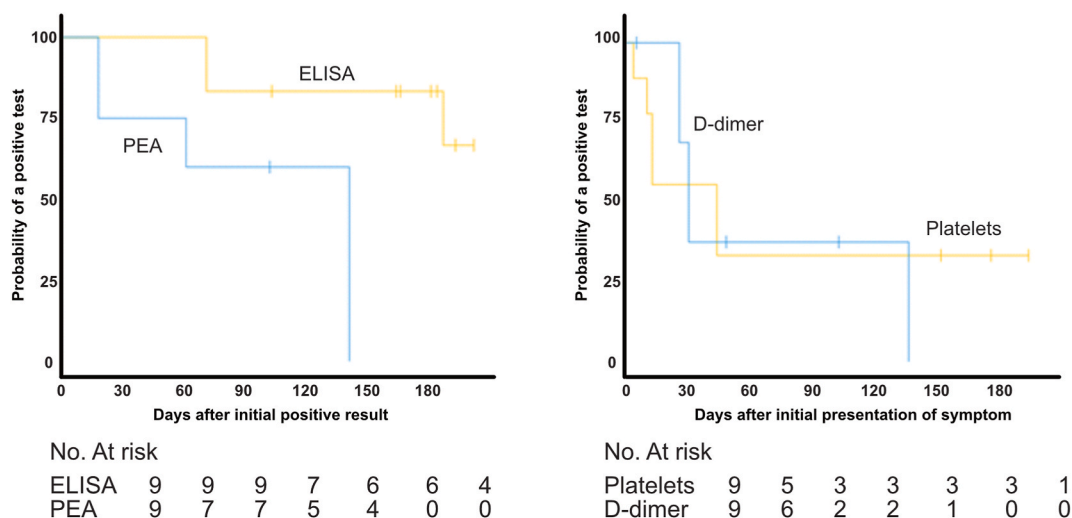
**Fig. 1.** VITT antibodies are mono/oligoclonal while HIT antibodies are polyclonal. VITT patient samples were enriched for anti-PF4 antibodies by affinity purification with PF4-heparin sepharose beads. Immunoglobulins were eluted, isolated using camelid nanobodies specific for lambda light chains (green), kappa light chains (red), or gamma heavy chains, and analyzed by liquid chromatography-electrospray ionization-quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF). Spectra displayed are the mass to charge ( $m/z$ ) distribution of all lambda containing light chains (green), all kappa containing light chains (red), and all kappa and lambda light chains associated with IgG heavy chains (blue). Representative VITT and HIT samples show a bi-clonal (VITT1), monoclonal (VITT2), and polyclonal (HIT) anti-PF4 antibody profile. Modified from Kanack et al. *Blood*. 2022 Jul 7; 140(1):73–77.

necessitating studies examining the etiology, pathophysiology, and treatment of VITT.

Overall, the incidence of VITT is rare in the setting of adenoviral vector-based vaccination, but individual rates for each vaccine appears to vary. For ChAdOx1 nCov-19, the rate of VITT after the first dose is estimated to be one case per 26,500 to 127,000 doses administered [7], while the incidence for Ad26.COVS2.S-associated VITT is estimated to be 3.83 cases per million vaccine doses administered [8]. One explanation for these differing rates is that the adenoviral vectors used to make each vaccine stimulate immune responses to varying extents. Whereas the Ad26.COVS2.S vaccine utilizes a human adenovirus-based vector; ChAdOx1 nCov-19 utilizes a chimpanzee adenovirus-based vector. Adenoviral vectors have also been used for other SARS-CoV-2 vaccines (e.g., Sputnik V, Ad5 and Ad26 nCov) and for vaccination against other diseases such as Ebola, without specific reports of VITT [9–11]. Younger and female patients may be more predisposed to this reaction [8]. However, in one large study of ChAdOx1 nCov-19-associated VITT, no female predominance was noted [12], and earlier reports may be due to the monitoring of healthcare workers with a majority of female participants.

## 2. Pathophysiology

On the surface, the pathophysiology of VITT is similar to that of heparin-induced thrombocytopenia (HIT). Both disorders occur due to anti-PF4 antibodies that engage platelet FcγRIIa receptors and mediate antibody-mediated platelet activation [13,14]. Multiple research groups rapidly identified anti-PF4 antibodies as the cause of platelet activation in VITT early during the emergence of this syndrome [15–17]. However, although HIT and VITT are similar in that anti-PF4 antibodies are implicated in their pathogenesis, essential distinctions exist that may differentiate these disorders. HIT antibodies develop after exposure to the anticoagulant heparin, whereas VITT antibodies develop after vaccination and without heparin exposure. There is also a significantly higher incidence of thrombi at unusual sites in VITT, typically in cerebral venous sinuses and the splanchnic circulation [17–20]. Lastly, whereas the



**Fig. 2. ELISA-positivity persists significantly longer than functional reactivity in VITT.** Kaplan Meier curves are displayed for nine Ad26.COVS-associated VITT patients with long-term follow-up. Indicated are the time to negative ELISA (OD < 0.4; yellow), time to negative PEA (<19%; blue), time to D-dimer normalization (cut-off varied by reference lab; blue), or normalization of platelet count ( $>150 \times 10^3/\mu\text{L}$ ; yellow). Non-activating antibodies (ELISA-positive/PEA-negative) persisted for longer periods than activating antibodies. Modified from Kanack et al. *Am J Hematol.* 2022 May; 97(5):519–526.

mortality rate associated with HIT is  $\sim 10\%$  [21], it appears to be higher in VITT at  $\sim 15\text{--}22\%$  [8,12].

Antibody specificities and repertoires also differentiate HIT and VITT pathologies. In VITT, patient antibodies primarily recognize the heparin-binding site on the surface of PF4, whereas HIT antibodies recognize the KKO-binding site on PF4, with roughly half the antibodies also recognizing portions of the heparin-binding site [22,23]. A recent mass spectrometric study demonstrates that HIT patients display polyclonal antibody repertoires towards PF4 in contrast to VITT, where anti-PF4 antibodies are mono- or oligoclonal (Fig. 1) [13]. Furthermore, VITT antibodies appear to have lambda light chains exclusively [13]. In another recent mass spectrometry-based study, Wang et al. demonstrated that 5/5 VITT patients had anti-PF4 immunoglobulins containing lambda light chains encoded by the IGLV3-21\*02 gene subfamily with identical light chain complementarity determining region lengths [24]. IgG heavy chains paired exclusively with lambda light chains likely highlight a common developmental pathway in VITT antibody production [13,24]. Lastly, antibodies in VITT appear to be more persistent relative to HIT, with anti-PF4 antibodies capable of stimulating platelet activation for several months after acute presentation and remaining detectable by enzyme-linked immunosorbent assay (ELISA) up to nine months or more [25–29] (Fig. 2). In contrast, HIT antibodies have reported half-lives of 50 and 85 days in functional and ELISA assays, respectively [30]. Taken together, the currently available data suggest that HIT and VITT antibodies share overlapping characteristics in some respects but are different in their immunological etiologies, diversity of antibody repertoires, antibody specificities, and duration of antibody persistence.

Additionally, studies suggest that the intravenous administration of vaccine components may promote the formation of platelet-vaccine component complexes and increase their deposition in the splenic marginal zone [31,32]. Subsequently, this may drive B-cell development and the production of antibodies to PF4 and other platelet antigens (such as platelet surface integrins) [33]. Adenoviral vector-based vaccines have also been shown to bind to PF4 *in vitro* [34], which may increase adenoviral vector binding to

the platelet surface via PF4 interactions and could help to explain the relatively higher occurrence of VITT associated with adenoviral vector-based vaccination. Although the generation of a pro-inflammatory milieu may be beneficial for generating an antibody response after vaccination, the overstimulation of inflammatory pathways may increase the risk of autoantibody development. As adenoviral vector-based vaccines have been shown to generate greater inflammatory responses relative to mRNA-based vaccines, the probability of developing anti-PF4 antibodies may be more likely to occur after administration of adenoviral vector-based vaccines [35]. Although most research on VITT has focused on the platelet effects of anti-PF4 VITT antibodies, neutrophils and neutrophil extracellular traps (NETs) may also play critical roles in disease pathogenesis [32]. Lastly, the basis for the predilection of thrombosis in unusual sites (cerebral venous sinus and splanchnic vessels) is still unclear.

### 3. VITT presentation and clinical features

In two extensive VITT studies, the median time from vaccination to presentation of VITT was 14 days after ChAdOx1 nCoV-19 vaccination and nine days after Ad26.COV2.S vaccination [8,12]. Patients frequently presented with unremitting head or abdominal pain, abnormal breathing, tachycardia, chest pain, limb swelling, ischemia, or more severe cardiopulmonary complications [12, 36]. Classical cases present with both thrombosis and thrombocytopenia, although patients with isolated thrombosis [37,38] or isolated thrombocytopenia [17,39,40] have been noted. D-dimer levels are typically extremely elevated, and several patients demonstrate low fibrinogen values [8,12]. Depending on the location of suspected thromboses, appropriate diagnostic imaging should be performed for the conclusive detection of thromboses and complete blood counts to assess for thrombocytopenia. If available, D-dimer and fibrinogen levels should also be quantified as secondary indicators of ongoing thrombosis.

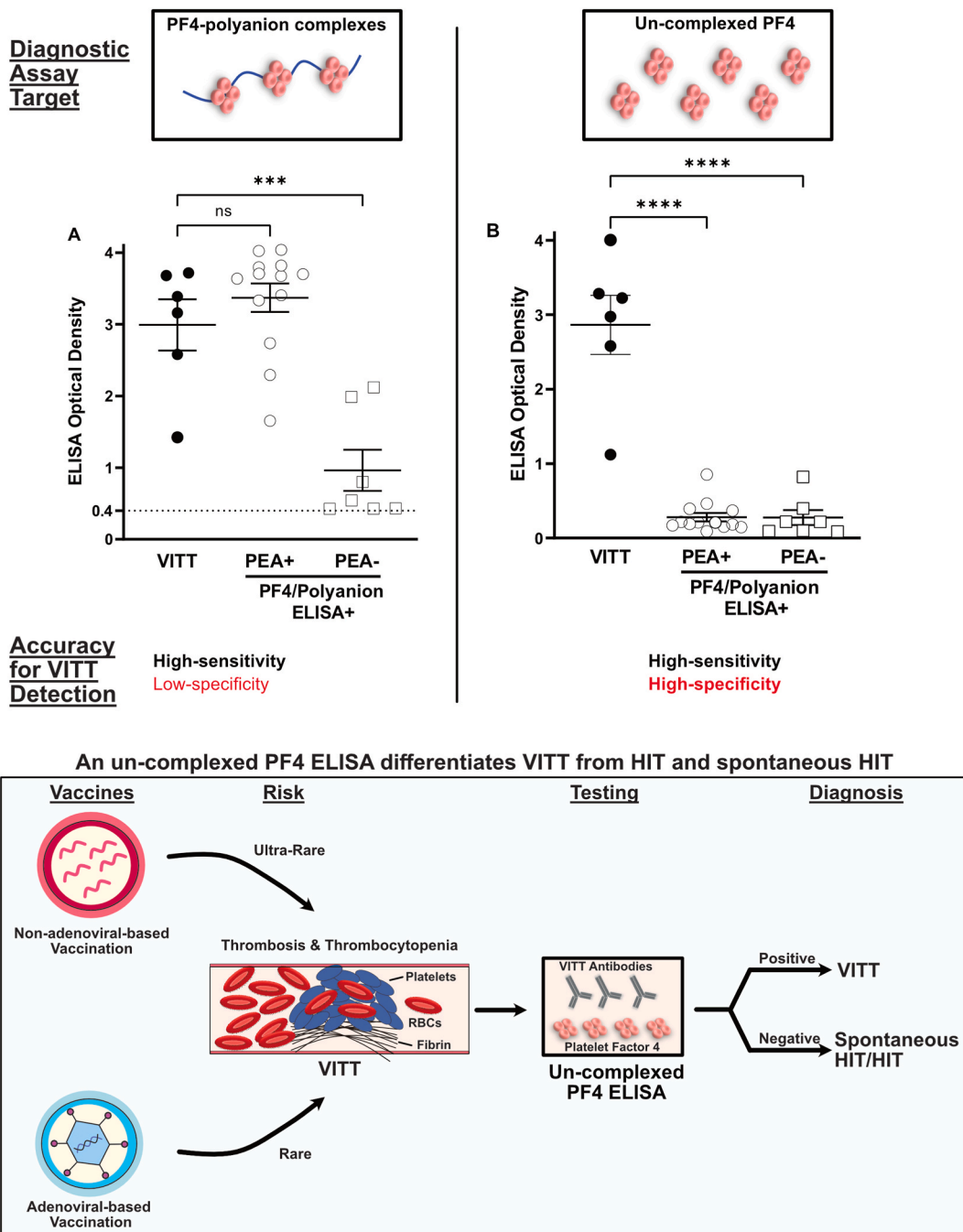
### 4. VITT case definition and diagnosis

The Brighton Collaboration Case Definition [41] and level of certainty for thrombosis and thrombocytopenia syndrome (TTS) encompasses several criteria: (A) Evidence of thrombocytopenia after vaccination with no recent exposure to heparin; (B) Presence of thrombosis/thromboembolism confirmed by one or more established imaging methods or surgical procedure, pathologic exam, or severe persistent headache associated with significant elevation of d-dimer levels (8x upper limit of normal); (C) Clinical presentation suggestive of cerebral venous sinus thrombosis, deep vein thrombosis, pulmonary thromboembolism, intra-abdominal thrombosis, ischemic stroke, myocardial infarction and/or arterial thrombosis; (D) One or more imaging or lab findings supportive of the diagnosis of thrombosis/thromboembolism (e.g., Echocardiogram or Doppler ultrasound, computed tomography without contrast, MRI or D-dimer) and (E) One or more laboratory findings that are strongly supportive of the diagnosis of platelet-activating antibody-mediated thrombosis (D-dimer > four times ULN for age, positive anti-PF4 ELISA or functional tests performed with PF4-treated platelets). Levels of certainty range from one (high certainty) to five (low certainty) and are scored based on the presence/absence of the criteria detailed above. Notably, the Brighton collaborative uses the term “thrombosis and thrombocytopenia syndrome” (TTS) in their case definition instead of VITT to convey the point that “TTS” does not imply causality from the vaccine administered. While these criteria are very useful in ensuring that the ascertainment of TTS is uniform and is particularly helpful for reporting purposes, it should be noted that some VITT reactions may present with unusual features such as the absence of thrombocytopenia or thrombosis [17, 37–40]. Several other groups have put forth similar criteria for recognizing VITT, which are not discussed in this review.

HIT diagnostic ELISAs that employ PF4/polyanion complexes as antigenic targets appear sensitive for detecting VITT antibodies, with VITT patients typically demonstrating high optical densities (ODs) in this test [15,17]. However, rare cases (2.7%) have been found to be negative in PF4/polyanion ELISA [12]. There are challenges associated with relying on HIT ELISAs to diagnose VITT [1]: HIT ELISAs have a poor positive predictive value (~50%) for the presence of platelet-activating anti-PF4 antibodies based on their extensive use in HIT diagnostic testing [42], and many healthy individuals are positive in this assay [2]. For example, Cohen et al., in a study of ~2500 individuals, found that 2.0–2.3% of individuals who received the ChAdOx1 nCov-19 vaccine had positive results in HIT ELISA testing. Heparin-based functional assays such as the SRA and HIPA have poor sensitivity for VITT antibody detection and should be avoided [26,43,44]. Similarly, rapid diagnostic assays (e.g., lateral-flow immunoassays, latex immunoturbidimetric assays, particle gel immunoassay (PaGIA), and chemiluminescence immunoassay (CLIA)) have poor diagnostic sensitivity for VITT and should not be used [45–48].

Therefore, it is recommended that the presence of platelet-activating antibodies be confirmed using appropriate PF4-based functional platelet assays, which detect VITT antibodies with high sensitivity, such as the PEA([42,49,50]), PIPA([15]), or the PF4-SRA([43]), especially in patients who demonstrate non-classical VITT presentations, low/modest HIT ELISA ODs, or negative ODs with a clinical picture consistent with VITT. The reliance on PF4-platelet-based functional assays for diagnosing VITT requires testing in specialized reference laboratories due to assay requirements for freshly drawn donor platelets and complex assay endpoints such as flow cytometry, aggregometry, or the quantification of radiolabeled reagents. Notably, a recent technological breakthrough in platelet storage may help to decentralize VITT diagnostic testing by utilizing long-term cryopreserved platelets that are stable during cold chain transport to the testing hospital [51]. Of note, the assay's endpoint is the quantification of thrombospondin-1, an abundant alpha granule protein released by activated platelets, using ELISA, a technology many hospitals already routinely utilize [51].

All commercially available HIT diagnostic assays suffer from a lack of specificity for VITT antibody detection. The specificity challenges of the HIT ELISA are noted above. Additionally, it is well known that PF4-treated platelets used in functional assays detect HIT and spontaneous HIT antibodies [42,52], making it impossible to differentiate these entities from VITT. Differentiating HIT from VITT is particularly challenging when heparin is administered to a patient presenting with non-classical VITT signs/symptoms, and suspicion for VITT arises after heparin therapy has been instituted. Furthermore, spontaneous HIT, like VITT, occurs in the absence of



**Fig. 3. An Un-complexed PF4 ELISA accurately and specifically differentiates HIT and spontaneous HIT from VITT antibodies.** Optical density values from six VITT patient samples, thirteen PEA-positive HIT patient samples (including two spontaneous HIT and three delayed-onset HIT), and seven HIT ELISA-positive/PEA-negative HIT-suspected patient samples tested in HIT ELISA against PF4/polyanion targets (top left panel), were compared to optical density values for the same samples in an ELISA with un-complexed PF4 as a target (top right panel). The un-complexed PF4 ELISA was specific for VITT, in contrast to PF4-polyanion (HIT) ELISA. Platelet-activating anti-PF4 antibodies elicited by adenoviral or non-adenoviral vector-based vaccines that cause VITT may be differentiated from HIT antibodies using the un-complexed PF4 ELISA. Modified from Kanack et al. *Am J Hematol.* 2022 May; 97(5):519–526 and Padmanabhan et al. *Am J Hematol.* 2022 Jun 1; 97(6):E223-E225.

proximate heparin exposure [8]. In an attempt to address the challenges of differentiating VITT, spontaneous HIT, and HIT antibodies, recent efforts have focused on evaluating the binding of VITT antibodies to PF4 un-complexed to any polyanions (“un-complexed” PF4 ELISA), based on the rationale that HIT and spontaneous HIT antibody binding requires neopeptides exposed upon PF4/polyanion complex formation, while VITT antibodies may not (Fig. 3) [26]. As expected, the HIT ELISA fails to differentiate VITT from HIT and



spontaneous HIT (Fig. 3). Strikingly, using the same patient samples, the uncomplexed PF4 ELISA clearly differentiates VITT from both HIT and spontaneous HIT (Fig. 3). While this promising data suggests that this novel and technically simple assay may be highly sensitive and specific for VITT diagnosis, it requires further validation. Additionally, the reactivity of VITT antibodies to un-complexed PF4 targets may correlate better with platelet recovery and D-dimer normalization compared to binding to PF4-polyanion targets, suggesting that the un-complexed PF4 ELISA may also help guide the duration of anticoagulation therapy.

## 5. VITT treatment

Intravenous immunoglobulin G (IVIg) is a key treatment modality for severe refractory HIT and spontaneous HIT [52–55]. Its primary mechanism of action is believed to be via binding of IVIg to the platelet FcγRIIa receptor, resulting in inhibition of HIT antibody-mediated platelet activation [53]. This prior data from the HIT/spontaneous HIT field has significantly helped guide the recommended treatment approach in VITT. In VITT, IVIg is administered along with non-heparin-based anticoagulants (i.e., direct thrombin inhibitors/direct oral anticoagulants), and in many cases, steroids [12,43]. The use of anticoagulants in the setting of extremely low platelet counts/bleeding patients can pose unique challenges and needs to be evaluated on a case-by-case basis. In patients refractory to these therapies, therapeutic plasma exchange has been used with some benefit, although no firm conclusions can be made regarding treatment efficacy [12,56]. Heparin is contraindicated in HIT but has been used to treat several patients with VITT prior to the identification of anti-PF4 antibodies as the pathogenic molecule in this syndrome. Although current data suggest that heparin anticoagulation in the context of VITT may not be associated with adverse effects [12,57], additional study needs to be directed toward this topic. Although epitope mapping studies of VITT antibodies suggest that heparin may compete with VITT antibodies for binding to the heparin-binding site on PF4([22]), more recent data suggest that some VITT antibodies may also bind PF4 at sites recognized by classical HIT antibodies (i.e., PF4 epitopes exposed after complexing to heparin) [58]. Thus, heparin should be avoided in HIT until further clarity is obtained. However, it may be reasonable to consider its use in resource-limited settings where non-heparin alternative anticoagulation and/or IVIg are unavailable.

Another critical question relates to how long a VITT patient should be anticoagulated given the extended persistence of anti-PF4 antibodies in diagnostic ELISA assays. Considering that the rate of recurrence of thrombocytopenia or thrombosis was found to be 12.6% in a study of ~150 VITT patients and that all recurrences were within 90 days of presentation [29], it may be appropriate for anticoagulation to be continued for at least three months after VITT is diagnosed.

## 6. VITT after non-adenoviral vector-based vaccines

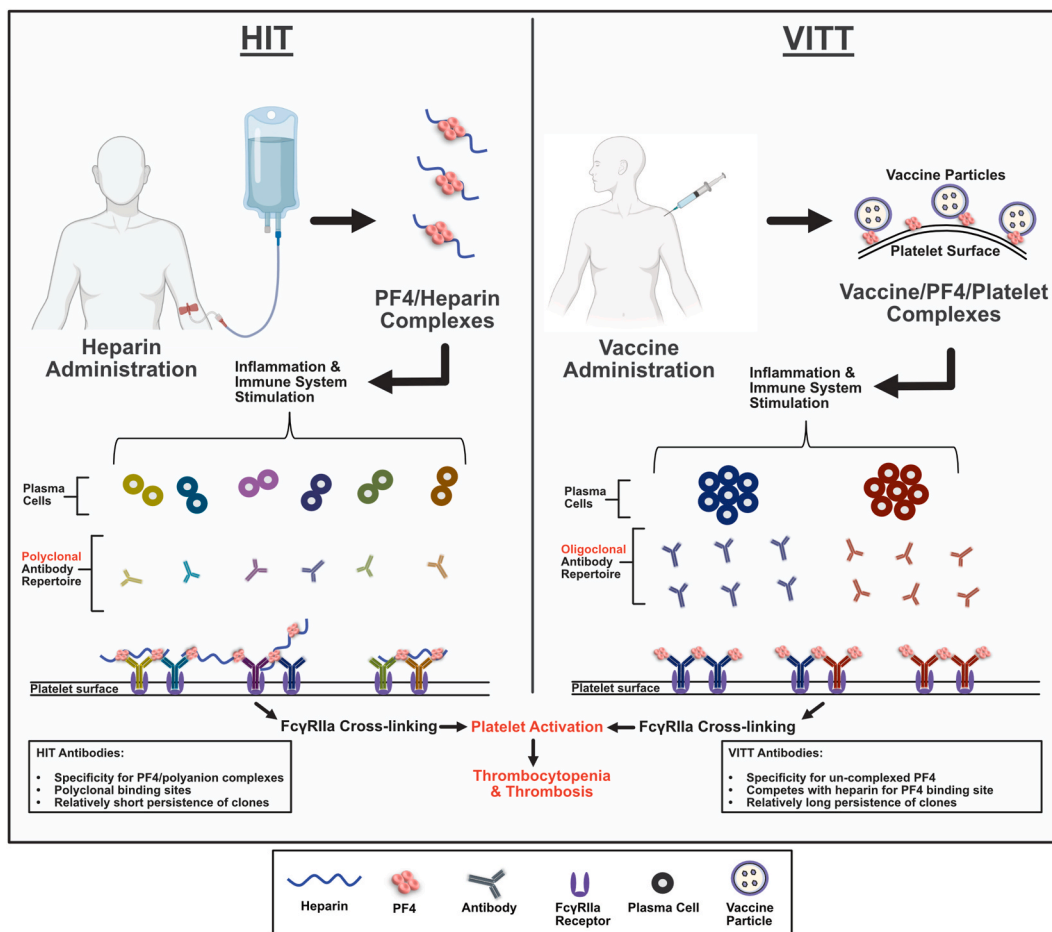
Rare cases of VITT have been reported after administration of mRNA-1273 (Moderna) or BNT162b2 (Pfizer) mRNA-based vaccines [8] [36,59–62]. The incidence of mRNA vaccine-associated VITT is extremely infrequent, with an estimated incidence rate of less than one case per 100 million vaccine doses [8]. Whether these TTS reactions seen in the setting of mRNA vaccines represent spontaneous HIT or VITT is controversial. However, given the recent development of the more specific un-complexed PF4 ELISA for VITT, we tested a suspected VITT patient vaccinated with an mRNA-based vaccine in this ELISA. Results demonstrated very strong reactivity to un-complexed PF4 ELISA targets, consistent with VITT([62]).

Inactivated SARS-CoV-2 vaccines (e.g., Sinopharm BBIBP-CorV) have been administered widely, primarily in the developing world [63], with two reports of TTS in this setting presented in the medical literature [64,65]. Limited testing of these samples (e.g., no testing in the un-complexed PF4 ELISA) precludes any firm conclusions related to VITT risk in this setting.

Notably, recombinant human papillomavirus 9-valent vaccine (Gardasil) prepared from purified virus-like particles (VLPs) has also been reported as the likely cause of a single case of TTS([66]). The patient had not received SARS-CoV-2 vaccination, had no history of thrombosis or heparin exposure, and had been HPV vaccinated ten days before hospitalization. Consistent with VITT, the patient presented with thrombocytopenia and thrombosis, had elevated D-dimer levels, strong positivity in HIT ELISA, and tested positive for platelet-activating anti-PF4 antibodies in the PEA(66). This sample was tested in the un-complexed PF4 ELISA, yielding strong positivity in that assay, also consistent with VITT([67]). This case is especially noteworthy as it should raise clinician awareness of the possibility of VITT even after non-covid-19 vaccines.

## 7. Second dose administration of adenoviral vector-based vaccines and vaccine boosters

The incidence of VITT after a second dose of adenoviral vector-based vaccine appears to be low, with single cases each of definitive, probable, and possible VITT identified after administration of a second dose of ChAdOx1 nCov-19(68). In a second study, one patient with confirmed VITT and one with possible VITT received ChAdOx1 nCov-19 without adverse effects [69]. This data suggests an incidence rate of VITT after second vaccination well below 1 per 1,000,000 doses administered [68,70]. No recurrence of VITT after administration of an mRNA vaccine used as a booster has been reported [69,71]. While published data on booster administration in Ad26.COVS2.S-associated VITT patients are limited; a recent case report suggests the safety of mRNA-based vaccines in this setting [72]. These limited studies suggest that VITT patients can receive a second dose of SARS-CoV-2 vaccine, with a low probability of VITT recurrence, and that mRNA-based vaccines should receive preference for the follow-up vaccination of VITT patients.



**Fig. 4.** A proposed pathophysiological model for the development of VITT. HIT patients develop platelet-activating anti-PF4 antibodies that recognize PF4/heparin complexes after exposure to heparin. In HIT, production of anti-PF4/heparin antibodies is polyclonal, and antibody persistence is relatively short. VITT patients develop platelet-activating anti-PF4 antibodies after vaccination. Plasma cells produce a persistent oligoclonal antibody response whereby epitopes overlapping with the heparin-binding site on PF4 are recognized.

## 8. Summary

VITT, like HIT, is an anti-PF4 antibody-mediated disorder that causes platelet activation and thrombosis. However, these two disorders can be differentiated based on their differing immunological etiologies, antibody repertoires, antibody specificities, and duration of antibody production, in addition to clinical presentation, although overlapping areas exist. A model highlighting this is presented in Fig. 4. It appears likely that some vaccines or vaccine components bind PF4 (possibly on the platelet surface), triggering immune responses that generate anti-PF4 antibodies that cause VITT. Of vaccine types, adenoviral vector-based vaccines are most likely to be causative of this process, particularly after first dose administration. However, we believe that VITT should remain on the differential diagnosis of TTS reaction even after non-adenoviral vector and non-covid-19 vaccines due to emerging data of ultra-rare cases in non-adenoviral vaccine settings. ELISAs and PF4-dependent functional tests have high diagnostic sensitivity for VITT but are not specific. A novel un-complexed PF4 ELISA holds promise as a technically simple assay that is both sensitive and specific for VITT, but one that needs to be evaluated in more extensive studies. Patients with VITT may be considered for a heterologous booster with mRNA-based vaccines based on reports of safety of this approach. IVIg, in conjunction with alternative anticoagulants, are key treatment modalities in VITT, and therapeutic plasma exchange may be helpful in refractory patients. Due to the expectation of large-scale ongoing SARS-CoV-2 vaccination resulting from the emergence of new variants [73], it will be important to continue investigating the immunological underpinnings of VITT.



## Practice points

- *Early detection of VITT incorporating clinical, imaging, and laboratory criteria is critical for timely treatment*
- *Rapid HIT tests and heparin-based functional tests such as the SRA/HIPA are insensitive for detecting VITT antibodies and should not be used*
- *HIT ELISAs and PF4-dependent functional assays are highly sensitive for VITT but also detect HIT and spontaneous HIT. The uncomplexed PF4 ELISA holds promise as a more specific VITT test.*
- *Intravenous immunoglobulin and non-heparin anticoagulants are key treatment interventions in VITT patients.*
- *mRNA-based covid-19 vaccines appear to be safe for use as 2nd/booster doses in patients with adenoviral vector vaccine-associated VITT*
- *Current data suggests that ultra-rare cases of VITT may occur in the setting of non-adenoviral/non-covid-19 vaccines. VITT should be on the differential diagnosis of TTS after all vaccine types until more conclusive information is obtained.*

## Research agenda

- *The immunological basis of VITT should be investigated, and attention given to the cloning/characterization of B/plasma cells producing anti-PF4 antibodies*
- *Studies should examine whether some VITT antibodies demonstrate heterogeneity in PF4 epitope recognition, a key question before firm guidance on the use of heparin can be provided*
- *Novel ways to inhibit VITT antibody-mediated platelet activation should be explored to expand the range of therapeutics available to treat this syndrome*
- *The mechanism of VITT should inform research in the area of vaccine development platforms to eliminate/minimize the risk of this adverse reaction*

## Declaration of competing interest

AP reports pending patents/patents (Mayo Clinic/Retham Technologies/Versiti Inc), equity ownership in and serving as an officer of Retham Technologies, and serving on the advisory board of Veralox Therapeutics. AJK reports no conflicts.

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