Heparin-Induced Thrombocytopenia (HIT), Virus-induced Immune Thrombotic Thrombocytopenia (VITT), and VITT-like Disorders

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Objective:

To clinicians with the investigation and management of suspected and documented heparin-induced thrombocytopenia (HIT), virus-induced immune thrombotic thrombocytopenia (VITT), and VITT-like disorders.

Background:

Heparin-induced throbocytopenia

HIT is a transient, immune-mediated adverse drug reaction in patients recently exposed to heparin that causes thrombocytopenia and often results in venous and/or arterial thrombosis. HIT occurs in up to 5% of patients receiving unfractionated heparin (UFH) for longer than 4 days and in <1% who receive low molecular weight heparin (LMWH). HIT is characterised by immunoglobulin G (IgG) antibodies that recognize an antigen complex of platelet factor 4 (PF4) bound to heparin. These antibodies trigger a highly prothrombotic state by causing intravascular platelet aggregation, intense platelet, monocyte and endothelial cell activation, and excessive thrombin generation.

Virus-Induced Immune Thrombotic Thrombocytopenia (VITT) and Other Platelet Factor 4 (PF4) Thrombotic Syndromes:

Vaccine-induced immune thrombotic thrombocytopenia was initially identified during the COVID 2019 pandemic to describe a rare thrombosis syndrome, clinically resembling HIT, that developed as a result of adenovirus vector-based COVID-19 vaccines. These vaccines have since been discontinued in Canada. This syndrome was eventually understood to be caused by autoantibodies generated in response to adenovirus antigens or viral infection, which ultimately gave rise to the term virus-induced immune thrombotic thrombocytopenia. It is now known that both HIT and VITT are immune-mediated prothrombotic disorders that belong to a group of anti-platelet factor 4 (anti-PF4) disorders caused by platelet-activating anti-PF4 antibodies that can provoke thromboembolic complications. The family of anti-PF4 disorders is growing (e.g. autoimmune HIT and anti-PF4 monoclonal gammopathies of thrombotic significance), some of which occur without prior exposure to heparin or vaccine. Overall, this last group of disorders are extremely rare and described primarily in case reports.

Classic HIT, VITT, and VITT-like disorders are diagnosed and managed similarly, with some nuances that are highlighted below.

Clinical features:

HIT and VITT typically present with a fall in platelet count with or without venous and/or arterial thrombosis.

Specifically, HIT presnets as follows:

- Thrombocytopenia: A platelet count fall >30% beginning 5-10 days after UFH or LMWH exposure, in the absence of other causes of thrombocytopenia, should be considered to be HIT, unless proven otherwise. A more rapid onset of platelet count fall (often within 24 hours of heparin exposure) can occur when there is a history of heparin exposure within the preceding 3 months. Bleeding is very infrequent.
- Thrombosis: HIT is associated with a high risk (30-50%) of new venous or arterial thromboembolism. **Thrombosis may be the presenting clinical manifestation of HIT** or can occur during or shortly after the thrombocytopenia.
- Other clinical manifestations of HIT: Less frequent manifestations include heparin-induced skin lesions, adrenal hemorrhagic infarction (secondary to adrenal vein thrombosis), transient global amnesia, and acute systemic reactions (e.g. chills, dyspnea, cardiac or respiratory arrest following IV heparin bolus). Bilateral adrenal hemorrhage (due to adrenal vein thrombosis) is a rare complication that may cause hemodynamic collapse.

VITT typically presents similarly with thrombocytopenia (platelets <150×109/L or documented platelet count decrease by more than 50%), with or without thrombosis, and with onset of symptoms usually in the 30 days after vaccination or adenoviral infection. Notable features of VITT include elevated D-dimer (up to >8-fold the upper limit of normal) and some patients present with overt coagulopathy or disseminated intravascular coagulation (DIC). Cerebral vein sinus thrombosis (CVST) is a more common in VITT, and should be suspected in patients with severe persistent headache or neurological symptoms.

Diagnosis:

The diagnosis of HIT/VITT is based on the following criteria:

- For HIT, the patient is receiving or has had recent exposure to UFH or LMWH (within the past 100 days).
- For VITT, the patient has had recent exposure to vaccination with adenoviral vector or adenoviral infection (typically within 5-30 days).
- At least one clinical feature of the syndrome is present (significant fall in platelet count, new venous and/or arterial thrombosis).
- Laboratory evidence of heparin/PF4 antibodies for HIT or anti-PF4 antibodies for VITT.

Figure 1 and **Table 1** provide a rational approach to diagnosis.

Laboratory Assays:

Therapeutic decisions should not be delayed pending the results of laboratory testing if the clinical suspicion of HIT or VITT is intermediate or high. There are two main types of tests for detecting HIT and VITT:

- **immunologic assays** which detect antibodies to PF4/heparin complexes ("HIT antibodies"; e.g. enzyme-linked immunosorbent assay [ELISA], particle gel immunoassay, latex particle agglutination assay, chemiluminescence immunoassay)
- **functional assays** (e.g. serotonin release assay [SRA], heparin-induced platelet aggregation [HIPA], PF4-dependant functional assay [PIPA])

In most centres, only the immunologic assays are available on an urgent basis. Although both assay types are sensitive for HIT (≥90%), false positives are common with the immunologic assays.

Of note, *rapid* HIT immunoassays are not sensitive for VITT antibodies. An immunologic anti-PF4 assay should be used for suspected VITT and heparin-independent anti-PF4 disorders followed by a functional assay (e.g. PF4-enhanced SRA, or other PF4-dependent functional assay) if available.

4Ts Score for HIT:

Criteria for the 4Ts score, which is used to determine the likelihood that a patient has HIT, are outlined in **Table 1**. Given the high negative predictive value of the 4Ts score, laboratory testing for HIT is not always required for patients with low pre-test probability according to the 4Ts score, as long as all the elements of the score are known. Occasionally, there may be uncertainty about the score due to multiple missing platelet counts, unclear history of recent heparin exposure or concurrent potential causes of thrombocytopenia; in this case, testing for HIT should be done.

If the immunologic assay is positive and a functional assay is available (either locally or as a send-out test to a reference laboratory), then a functional assay should be ordered. This is because the majority of patients with a positive immunologic assay do not have HIT, and because of the long-term implications of a HIT diagnosis. A functional assay should also be ordered in patients with indeterminate results on an immunologic assay or in whom the clinical picture (4Ts score) and immunoassay are discordant. If a functional assay is not available, then a clinical decision to diagnose HIT is made based on the probability from the 4Ts score and the degree of positivity of the immunoassay. Consultation with a thrombosis specialist is advised in this situation.

Figure 1: Diagnostic approach to suspected HIT, VIT, and VITT-like disorders

[1] Adenoviral vector COVID-19 vaccinations were previously the main cause of VITT but are no longer used in Canada. Of note, VITT and VITT-like disorders are rare and if suspected, specialist consultation is recommended to assist with assessment and evaluation.

[2] Laboratory testing is not always required for low 4Ts score as long as all elements of the score are known (i.e. no missing counts/unknown exposure during recent admissions)

[3] Consider functional assay in patients with intermediate 4Ts score or ELISA OD <2.0 if available locally or as a send-out test to a reference laboratory

[4] Change to a non-heparin anticoagulant such as fondaparinux, rivaroxaban, argatroban, or others (see Table 2).

[5] e.g., serotonin-release assay (SRA) for HIT, or PF4-enhanced SRA for VITT

Table 1: 4 Ts clinical probability score

	2 points	1 point	0 points
Thrombocytopenia (platelet count)	>50% decrease to nadir ≥ 20 x 10^9/L	30-50% decrease, or nadir 10-19 x 10^9/L	< 30% decrease or nadir < 10 x 10^9/L
Timing of onset of platelet count fall or other sequelae of HIT. (Day 0 = first day of heparin exposure)	Days 5-10, or ≤ day 1 with history of heparin exposure within past 30 days	> Day 10 or timing unclear; or < day 1 with heparin exposure in past 31 – 100 days	< Day 4 (no recent heparin prior to current exposure)
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after IV UFH bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis	None
o**T**her cause(s) of thrombocytopenia	None evident	Possible	Definite

Total points	Clinical probability of HIT
6-8	High
4-5	Intermediate
0-3	Low

Management:

Patients with suspected or confirmed HIT, VITT, or anti-PF4 disorders are best managed by, or in consultation with, a specialist experienced in managing these presentations.

The points below pertain to the management of HIT. VITT and VITT-like disorders are managed similarly, with some nuances mentioned below.

- Stop all heparin exposure, including LMWH, prophylactic heparin, heparin locks or flushes, and remove heparin-coated catheters.
- Start anticoagulation with a non-heparin, HIT-safe anticoagulant such as fondaparinux, argatroban, a direct oral anticoagulant (DOAC), bivalirudin, or danaparoid (see **Table 2 for** dosing). If a new thrombotic event is present (HIT with thrombosis, or "HITT"), then the acute VTE treatment regimen for the DOAC is preferred, rather than the maintenance dosing regimen. For example, rivaroxaban should be initiated at 15 mg BID x 3 weeks followed by 20 mg daily.
- Consider imaging for thromboembolic complication. Patients with suspected venous or arterial thrombosis should have objective confirmation since this will affect the duration of HIT-safe

anticoagulant use. Even without a clinical suspicion of deep vein thrombosis (DVT), bilateral leg ultrasonography to screen for asymptomatic DVT are suggested, especially if the patient has additional risk factors for VTE. For patients with suspected VITT, headache or neurological symptoms should have appropriate imaging to rule out cerebral vein sinus thrombosis **(CVST). Imaging for CVST includes both parenchymal imaging and vascular imaging,** either with a CT head/CT venogram, or MR head/MR venogram and **this potential diagnosis should be investigated urgently with same-day neuroimaging.**

- Avoid platelet transfusions unless the patient is bleeding or requires a procedure associated with a high risk of bleeding.
- Early use of warfarin should be avoided in acute HIT since it may worsen the prothrombotic state. If warfarin has already been started when HIT is diagnosed, it should be stopped and vitamin K administered to reverse the warfarin effect. Warfarin alone is insufficient to protect against thrombosis secondary to HIT as long as HIT is considered active (i.e. platelets less than 150×10^9/L).
- Warfarin or a DOAC are appropriate for longer-term anticoagulation, if indicated, after thrombocytopenia has resolved. If transitioning to warfarin from a HIT-safe anticoagulant:
    - Do not initiate warfarin until platelet count is $\geq 150 \times 10^9$/L.
    - Overlap warfarin with therapeutic doses of the HIT-safe anticoagulant for ≥5 days and until the international normalized ratio (INR) is therapeutic. Caution should be used when transitioning to warfarin from argatroban because it also increases the INR.
- Duration of anticoagulation for HIT with thrombosis: at least 3 months (similar to other types of provoked VTE).
- Duration of anticoagulation for HIT without thrombosis: at least 4 weeks and until platelet recovery to patient baseline level.
- Heparin or LMWH should not be given to a patient with previous HIT without consultation with a specialist.
- Given the rarity of VITT and other anti-PF4 disorders such as autoimmune HIT, specialist consultation for consideration of IVIG or B-cell directed therapy is strongly encouraged.

NOTE: All suspected adverse events following immunization (AEFI), including thrombosis, and both presumptive and confirmed vaccine-induced events, should be reported to the local Public Health Unit.

Table 2: Non-heparin anticoagulants for the treatment of acute HIT*

Anticoagulant	Pharmacology	Initial Dosing			Monitoring
Argatroban	Mechanism: Direct thrombin inhibitor Clearance: Hepatic Half-life: 40-50 min Prolongs aPTT, PT/INR	Bolus: None Continuous Infusion: 0.5 – 1.5 ug/kg/min IV Reduce dose to 0.5 mcg/kg/min or avoid in patients with: • hepatic insufficiency • heart failure • multiple organ failure • severe anasarca • post-cardiac surgery			aPTT 2h after initiation or dosage change, then at least daily once therapeutic Target: 1.5-2.5 x patient baseline (or mean laboratory) aPTT, not to exceed 100 sec
Bivalirudin (not approved for treatment of HIT)	Mechanism: Direct thrombin inhibitor Clearance: Plasma proteases and renal Half-life: 25 min Prolongs aPTT, PT/INR	Bolus: None Continuous Infusion: 0.1-0.2 mg/kg/h IV Reduce dose in renal failure:	**Creatinine Clearance (mL/min)**	**Initial Infusion Rate (mg/kg/h IV)**	aPTT Target: 1.5-2.5 x patient baseline (or mean laboratory) aPTT
			> 60	0.10	
			30-60	0.08-0.10	
			< 30 or renal replacement therapy	0.03-0.05	
Fondaparinux (not approved for treatment of HIT and rare cases of fondaparinux-induced HIT have been reported)	Mechanism: Factor Xa-inhibitor Clearance: Renal Half-life: 17-20 hours No effect on aPTT, PT/INR	Bolus: None SC Injection:	**Weight (kg)**	**Dosage**	Not routinely required
			< 50	5 mg SC daily	
			50-100	7.5 mg SC daily	
			> 100	10 mg SC daily	
Danaparoid	Mechanism: Factor Xa-inhibitor Clearance: Renal Half-life: 25 hours No effect on aPTT, PT/INR Clinical cross-reactivity with HIT antibodies in 3%	Bolus:	**Weight (kg)**	**IV Bolus (units)**	Anti-Xa levels Target: 0.5-0.8 anti-Xa U/mL (using danaparoid standards)
			< 60	1,500	
			60-75	2,250	
			75-90	3,000	
			> 90	3,750	
		Continuous Infusion: 400 units/h IV x 4h, then 300 units/h IV x 4h, then 200 units/h IV			
Rivaroxaban** (not approved for treatment of HIT)	Mechanism: Factor Xa-inhibitor Clearance: Renal Half-life: 9 hours No effect on aPTT, Transient effect on PT/INR	HIT with thrombosis: 15 mg bid x 3 weeks (longer if platelets not recovered) then 20 mg daily HIT: 15 mg bid until platelet recovery then 20 mg daily			

*This table does not address special populations and circumstances such as children, pregnancy, percutaneous coronary interventions, cardiac surgery,
vascular surgery, and renal replacement therapy
**Apixaban and dabigatran have also been used to treat patients with HIT; however, there is less data than for rivaroxaban

Special considerations for HIT:

Pediatrics:

The incidence of HIT is less than in adults, but the approach to investigation and management is similar. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with HIT. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

Pregnancy:

HIT is infrequent in pregnancy. The approach to investigation is as outlined above. Danaparoid does not cross the placenta and has been used to treat HIT in pregnancy. The use of fondaparinux (with the cautions noted above) is an option where danaparoid is not available; however, this drug has been reported to cross the placenta in small amounts and experience with fondaparinux in pregnancy is very limited (especially during the first trimester). Argatroban use has been described in pregnant patients with HIT. DOACs should not be prescribed during pregnancy or breast-feeding.

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