Heparin-Induced Thrombocytopenia and Thrombosis: Preventing your Thrombolysis Practice from Taking a HITT

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Abstract

Keywords

- ▶ HITT
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- ▶ interventional radiology
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- workup

Heparin-induced thrombocytopenia and thrombosis (HITT) is an under-recognized cause of deep venous thrombosis treatment failure and of complications during catheter-directed thrombolysis. After a review of HITT pathophysiology, diagnosis, and management, three different cases are presented in this article. Each case highlights subtleties and challenges of HITT diagnosis and management. An example of a practical approach to the diagnosis of HITT is presented.

Heparin-induced thrombocytopenia and thrombosis (HITT), previously known as HIT type II,¹ is a potential cause of lytic therapy failure. If not diagnosed in a timely fashion, HITT may lead to complications including limb amputations and death.² Heparin-exposed patients have a 0.2 to 5%³ chance of developing HITT. Given that interventional radiologists (IR) often provide second-line therapy to patients who have already failed anticoagulation, the incidence of patient with HITT within an IR practice may be even higher. Thirty percent of hospital patients are exposed to heparin in the United States;⁴ 600,000 people per year will develop heparin-induced thrombocytopenia, of which a subset will have HITT.⁵

HITT is caused by the development of antibodies against heparin/platelet factor 4 (PF4) complexes.⁶ Once bound to these complexes, the antibodies induce platelet activation and subsequent thrombosis as well as platelet consumption via the Fc-gamma receptor IIa.⁶

Diagnosing HITT requires a high degree of suspicion as well as a systematic diagnostic approach. The most commonly used clinical assessment for HITT is the 4T score,⁷ although there are other assessments used variably clinically.⁸ ▶ **Table 1** lists the components of the 4T score. A score of ≤ 3 is highly specific to exclude HITT, while higher scores are highly sensitive for HITT

but require further laboratory confirmation.⁹ A PF4/heparin optical density (OD) assay should be performed, which has high sensitivity (at OD above 0.4) but lacks specificity.⁹ Higher OD threshold values increase specificity at the expense of sensitivity.^{10–12} For patients with a high clinical probability of HITT (4T ≥ 6), a strongly positive PF4 (OD ≥ 1) is sufficient to diagnose HITT.¹⁰ For all other cases, a functional assay is required to confirm the diagnosis. The serotonin release assay (SRA) is the most widely accepted laboratory evaluation used for HITT confirmation:¹² sensitivity is 88 to 100%, with a specificity of 89 to 100%.¹³

Management of HITT requires prompt cessation of all heparin exposure and alternative anticoagulation to manage HITT-associated thrombotic complications. Importantly, warfarin is contraindicated for the treatment of HITT until the platelet count normalizes, as the early prothrombotic effects of warfarin significantly increase HITT-associated thrombotic complications.² Currently approved options for treatment include either factor Xa or direct thrombin inhibitors.¹⁴ ▶ **Fig. 1** outlines the authors' HITT assessment and management algorithm for catheter-directed thrombolysis (CDT) or deep venous thrombosis (DVT) treatment failure in heparin-exposed patients.

Table 1 Components of 4T scoring system as reported by Lo et al⁷

Constituent	4T score
	0–3 HITT unlikely; 4–5 intermediate probability; 6–8 HITT highly likely
Thrombocytopenia	2 points: Fall in platelets > 50% of previous value and nadir ≥ 20
	1 point: Fall in platelets 30–50% or nadir 10–19
	0 point: Fall in platelets < 30% or nadir < 10
Timing	2 points: Clear onset between 5 and 10 d after heparin initiation or ≤ 1 d with prior heparin exposure ≤ 30 d
	1 point: Consistent with 5–10 d but unclear; onset > 10 d; fall ≤ 1 d with prior heparin exposure within 30–100 d
	0 point: Drop <5 d without prior heparin exposure
Thrombosis	2 points: New proven thrombosis, skin necrosis, or systemic reaction
	1 point: Progressive or recurrent thrombosis, silent thrombosis, or red skin lesions
	0 point: No new symptoms
Other potential cause for thrombocytopenia	2 points: No other cause
	1 point: Possible alternative cause
	0 point: Definite alternative cause

Abbreviation: HITT, heparin-induced thrombocytopenia and thrombosis.

Fig. 1 HITT assessment and management algorithm for DVT or CDT treatment failure with heparin exposure. CDT, catheter-directed thrombolysis; DVT, deep venous thrombosis; HITT, heparin-induced thrombocytopenia and thrombosis.

The three cases presented below occurred among 81 venous thrombolysis cases performed at the authors' institution over a 2-year period. Each case demonstrates unique challenges in the diagnosis and management of HITT.

Case 1: Treatment Failure Referral Due to Undiagnosed HITT

A 16-year-old girl was referred for treatment for worsening symptoms of left leg DVT, despite 3 weeks of therapeutic

Fig. 2 Drop in platelet count with heparin exposure and subsequent rebound with nonheparin therapy for Case 1. CDT, catheter-directed thrombolysis.

anticoagulation that consisted of enoxaparin bridged to warfarin. Computed tomographic (CT) imaging demonstrated occlusive thrombus extending from the left femoral vein to the common iliac vein. Admission laboratories included a platelet count of 339,000/ μ L, international normalized ratio (INR) of 1.2, and activated partial thromboplastin time (aPTT) of 37 seconds. She was started on a heparin drip on admission (day zero), then underwent catheter-directed therapy (CDT), and had a stent placed for an underlying May-Thurner lesion. She was continued on enoxaparin as a bridge to therapeutic warfarin. On day 4, the patient's leg pain and swelling increased; imaging revealed rethrombosis. Her platelet count was 227,000/ μ L and aPTT was 42.4 seconds. The patient was treated with CDT again with complete resolution. On day 8, her DVT again recurred. At this time, her platelet count had fallen to 181,000/ μ L (to eventually reach a nadir of 74,000) with aPTT of 91 seconds. Her platelet count and recurrent treatment failure raised the suspicion for HIT. Laboratory evaluation revealed a 4T score of 6, a PF4 OD of 1.42, but a negative SRA. Despite the negative SRA, given the strength of the clinical syndrome, the patient was switched to argatroban (GlaxoSmithKline, Triangle Park, NC). All heparin products and warfarin were discontinued. Under this regimen, the patient remained recurrence free. **►Fig. 2** demonstrates the trend in her platelet counts superimposed with anticoagulant therapy and clinical events. The equivocal HIT laboratory results are remarkable, but it is important to remember that the sensitivity of the SRA is 88 to 100%, which is high but not foolproof. As such, the clinical course of this patient made a compelling case for HIT.

Case 1 take-home points: It is important to remember that the sensitivity of the SRA is less than 100%. In a case like this, a high 4T score and PF4 OD, and very suggestive clinical

syndrome, as reflected in the authors' management algorithm, SRA confirmation is unnecessary (**►Fig. 1**).

Case 2: Positive PF4/Heparin IGG without HIT

An 18-year-old man with previous history of right lower extremity (RLE) DVT 12 months prior (treated with warfarin for 6 months) presented with a 2-week history of left lower extremity (LLE) swelling and erythema. He reported no recent travel or trauma, and had a maternal uncle with clotting history. He was started on rivaroxaban (Xarelto, Janssen Pharmaceuticals, Raritan, NJ), and had no known exposure to heparin in the prior 100 days. Physical exam showed a diffusely swollen LLE with erythema extending from the ankle to the upper thigh, as well as mild tenderness to palpation. Doppler ultrasound revealed an acute occlusive thrombus extending from the tibial and popliteal veins, involving the deep and superficial femoral veins, and extending into the common iliac vein. There was also a nonocclusive thrombus within the inferior vena cava (IVC; **►Fig. 3**). On the RLE, residual chronic DVT was noted in the right femoral, popliteal, and tibial veins. Admission laboratories included a platelet count of 129,000/ μ L, INR of 1.5, and aPTT of 39 seconds.

Upon admission (day zero), the patient was started on an intravenous heparin infusion. On day 1, he underwent mechanical thrombectomy, balloon angioplasty, and placement of a suprarenal IVC filter, followed by 48 hours of CDT of the LLE DVT. Completion venogram on day 3 demonstrated decreased clot burden with improved flow. The patient was continued on a heparin drip until day 5, when he was discharged home on rivaroxaban. Laboratory testing at

Fig. 3 CT coronal reconstruction of Case 2 presentation, demonstrating inferior vena cava thrombosis.

that time revealed negative anticardiolipin immunoglobulin G (IgG)/immunoglobulin M (IgM) and β -2-glycoprotein 1 IgG/IgM, and a platelet count of 85,000/ μ L. The patient was diagnosed as heterozygous for factor V Leiden with otherwise negative hypercoagulability workup.

On day 14, the patient returned for evaluation of recurrent left leg pain. Ultrasound demonstrated recurrent acute clot in the left popliteal, femoral, and iliac veins, as well as the IVC. The patient was continued on rivaroxaban, and repeat CDT was

initiated on day 18 with mechanical thrombolysis followed by CDT for 48 hours. Day 20 completion venogram demonstrated reestablishment of inline venous flow to the IVC.

Treatment failure and heparin exposure warranted HIT evaluation. **►Fig. 4** demonstrates this patient's platelet trend superimposed with anticoagulant therapy and clinical events. His 4T score was 4 (intermediate risk) (1 point for thrombocytopenia, 1 point for platelet fall within less than 5 days with remote [>100 days] heparin exposure, 1 point for recurrent thrombosis, 1 point for possible alternative cause). His OD result was 0.509 (weakly positive) corresponding to a $<5\%$ chance of HIT. SRA was negative, essentially excluding the diagnosis of HIT. Although a false-negative SRA is possible as noted in Case 1 above, the patient's intermediate 4T combined with weakly positive PF4 OD was considered consistent with a negative HIT evaluation. Most notably, his thrombocytopenia did not appreciably recover following transition to nonheparin therapy (**►Fig. 4**, platelet trend beyond day 19). Additionally, the patient suffered further recurrent thrombosis, which further demonstrates a non-HIT cause of thrombosis and thrombocytopenia.

Case 2 take-home points: There are numerous causes of hypercoagulability aside from HIT. Furthermore, only a fraction of patients with positive PF4/heparin IgG actually have HIT.

Case 3: Rethrombosis Due to HIT with Relative Thrombocytopenia

A 26-year-old woman presented with right hip pain and burning sensation after starting a new running regimen the previous week. She had no significant past medical history other than a complicated perinatal course, but her mother

Fig. 4 Platelet count trend for Case 2 showing persistent thrombocytopenia. CDT, catheter-directed thrombolysis.

Fig. 5 Platelet count trend for Case 3. CDT, catheter-directed thrombolysis.

had a history of DVT following hip arthroplasty. The patient was taking oral contraceptive pills but denied recent travel or trauma.

Examination showed RLE swelling without erythema and a positive Homan's sign. Ultrasound demonstrated a long segment occlusive DVT extending from the right popliteal vein to the external iliac vein, then to the bilateral common iliac veins with extension into the proximal IVC. Her platelet count was 185,000/ μ L, aPTT of 36.4 seconds, and INR of 1.2. Initial hypercoagulability workup was normal.

On day zero, an intravenous heparin infusion was initiated. She underwent CDT for 24 hours. Completion venography demonstrated restoration of flow in the right popliteal, femoral, and iliac veins. She was continued on a heparin infusion, which was discontinued on day 3 in favor of enoxaparin. On day 4, she was discharged on enoxaparin as a bridge to warfarin therapy. At discharge, her platelet count was 232,000/ μ L, having reached to a nadir of 142,000/ μ L on day 2.

On the day after discharge (day 5), the patient re-presented to the emergency department with recurrent RLE symptoms. Ultrasound showed a recurrent right-sided DVT with extension from the external iliac vein through the calf vessels, as well as new occlusive DVT in the LLE extending from the iliac vein through the superficial femoral vein. Her platelet count was 350,000/ μ L, and INR was 3.0. The patient's hypercoagulability workup was still normal.

Suspicion for HIT was warranted with a 4T score of 4, and despite the lack of sustained thrombocytopenia, her platelet count dropped by $> 30\%$ with a brief reexposure to heparin during her repeat CDT. The patient was treated successfully for her recurrent DVT with mechanical thrombectomy. PF4/heparin assay OD was 2.016 (strongly positive), suggesting a high likelihood of HIT; this was later confirmed by a positive SRA. **Fig. 5** demonstrates her platelet trend superimposed with anticoagulant therapy and clinical events. The patient was discharged on rivaroxaban and remains symptom free.

Table 2 Summary of case characteristics of three patients

Case	Presentation	Platelets (initial/nadir)	4T	PF4/IgG	SRA	Diagnosis
1	Treatment failure	212 (74)	6	+, OD 1.416	Negative	HITT
2	Treatment failure	129 (65)	4	+, OD 0.509	Negative	Hypercoagulability due to factor V Leiden
3	Treatment failure with new thrombosis	185 (142)	4	+, OD 2.016	Positive	HITT

Abbreviations: HITT, heparin-induced thrombocytopenia and thrombosis; OD, optical density; SRA, serotonin release assay.

Case 3 take-home points: HIT should be considered even in the absence of absolute thrombocytopenia. In these cases, SRA can be helpful even with a strongly positive PF4 OD to help guide clinical decision making.

Discussion

Each of the above cases highlights a unique aspect of HIT evaluation and management (see **Table 2**).

Platelet counts should be monitored in all patients undergoing treatment with heparin, and if suspicion for HIT is sufficiently high (such as with a 4T score ≥ 6), heparin products should be immediately discontinued and replaced with an alternative anticoagulant. Warfarin should also be avoided until thrombocytopenia resolves. It is also of note that cases of HIT may be atypical, such as platelet loss without sustained absolute thrombocytopenia. Early involvement of hematologists in cases such as this is recommended. For patients with intermediate or low probability of HIT, it is reasonable to continue heparin products while awaiting laboratory results.

Diagnosis of HIT should be confirmed with PF4/heparin antibody assay, as well as with SRA evaluation in cases with intermediate 4T scores (4–5) and/or weakly positive PF4 OD (<1). The SRA can be confirmative, but can also occasionally be falsely negative. Laboratory diagnosis is nuanced, as evidenced by PF4/heparin antibody assay positivity at much higher rates than the clinical incidence of HIT. According to one study, the incidence of the formation of antiheparin/PF4 antibodies is 17% in patients treated with unfractionated heparin, and 8% in patients treated with low-molecular-weight heparin¹⁵—comparing this with HIT incidence of 0.2 to 5% indicates a high risk for false positives with the PF4 antibody. For example, in the study group alluded to above, of the patients with a positive HIT PF4 antibody test, 57% had HIT. Overall, the incidence of HIT was 5% in our CDT population. As illustrated by these cases, correctly diagnosing HIT in CDT patients can be challenging, but the benefits to the patient are substantial.

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