Heparin Induced Thrombocytopenia with Thrombosis

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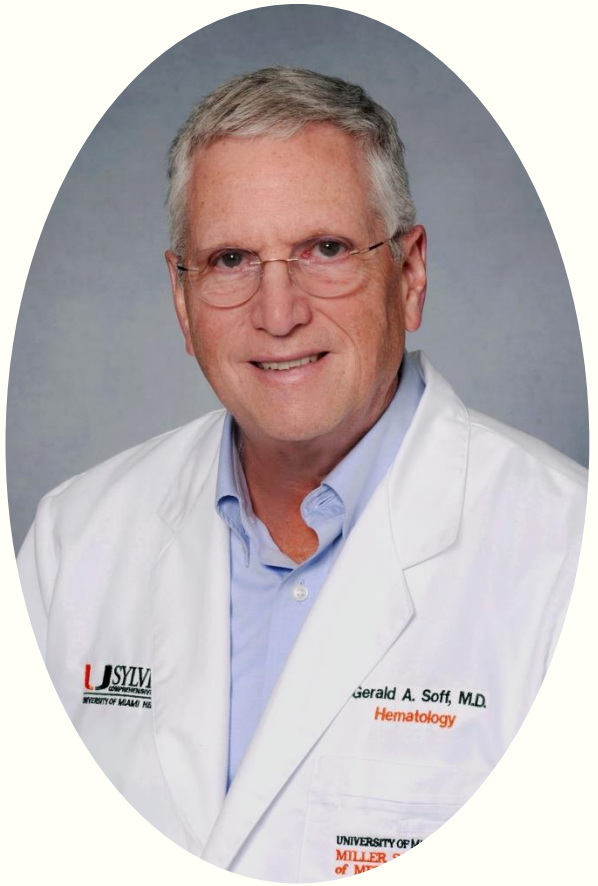
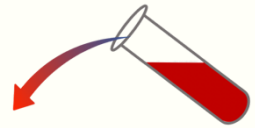


Disclosures

- Research Support (Past 2 years):
  - Amgen
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Data Safety Monitoring Committee
  - Alpine Immune Sciences
- Advisory Boards (Past 2 years)
  - Sanofi
  - Novartis

Learning Objectives

- Appreciate the mechanism of thrombocytopenia that develops in Heparin-Induced Thrombocytopenia & Thrombosis (HITT).
- Become familiar with the 4T score approach to suspect HITT.
- Recognize the clinical signs and manifestations of HITT.
- Become familiar with the treatment strategies for HITT.

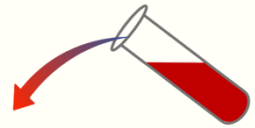


Topics to Cover

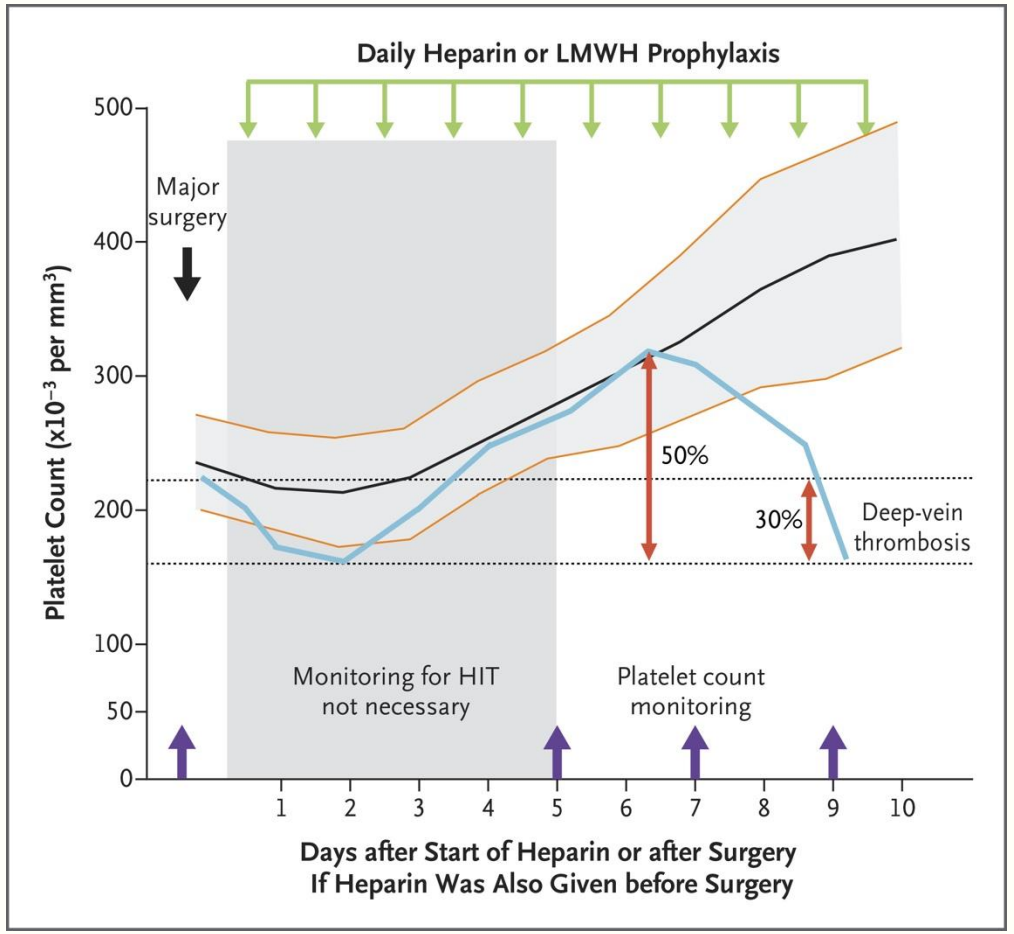
I. Introduction
II. Pathophysiology of HIT
III. Clinical Manifestations of HIT
IV. Diagnosis of HIT
V. Management and Treatment of HIT

I. Introduction to HIT

1) Common adverse reaction to Heparin
2) Immune-mediated reaction to Heparin:Platelet Factor 4 Complex.
3) Immune Thrombocytopenia, but increased risk of thrombosis, rather than bleeding.
4) Requires immediate recognition and management.



Timing of HIT and Rationale for Platelet Count Monitoring at Various Time Points.



Greinacher A. N Engl J Med 2015;373:252-261 DOI: 10.1056/NEJMcp1411910

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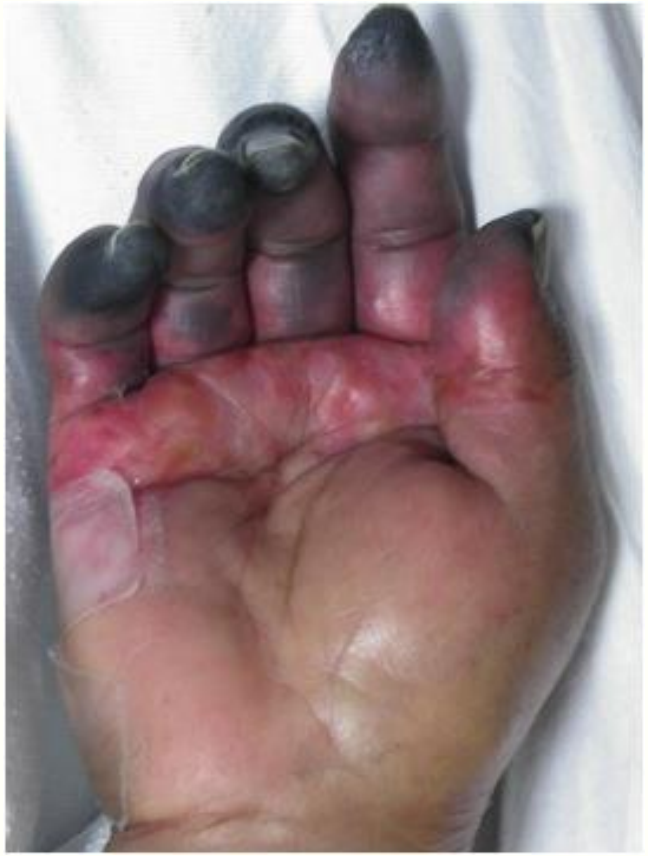

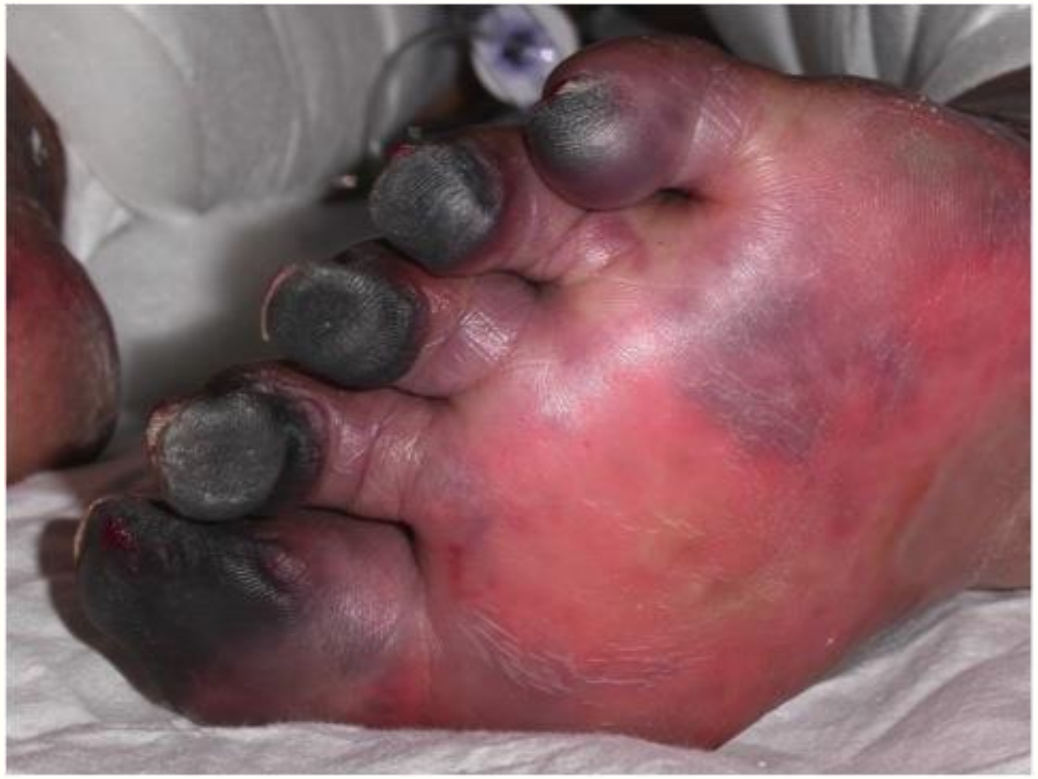

- Elective aortic valve replacement and mitral valve repair in 75 yr old woman.
- Cormack GM & Kaufman LJ. Journal of Medical Case Reports 2007, 1:13.

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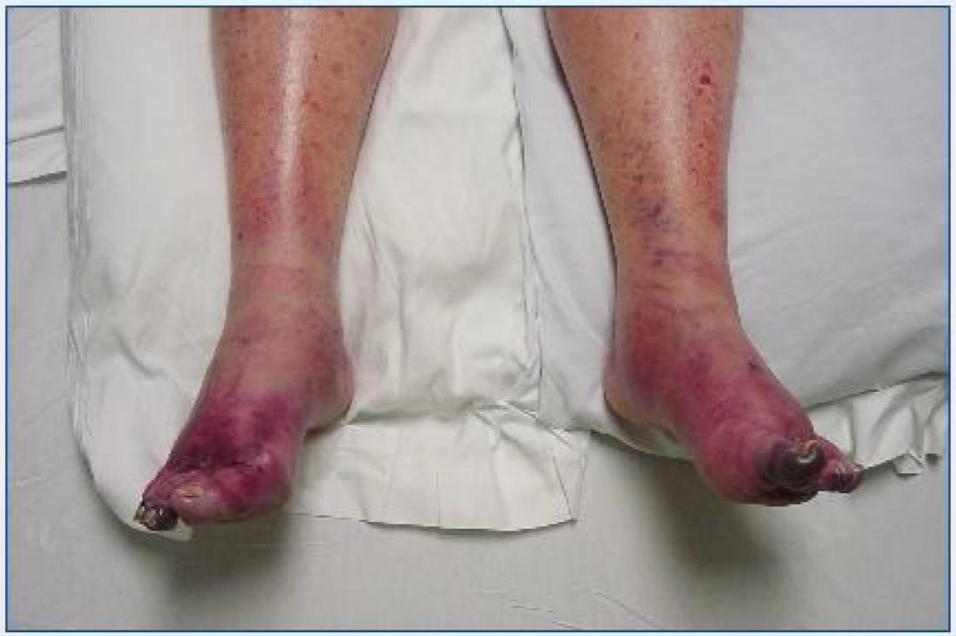
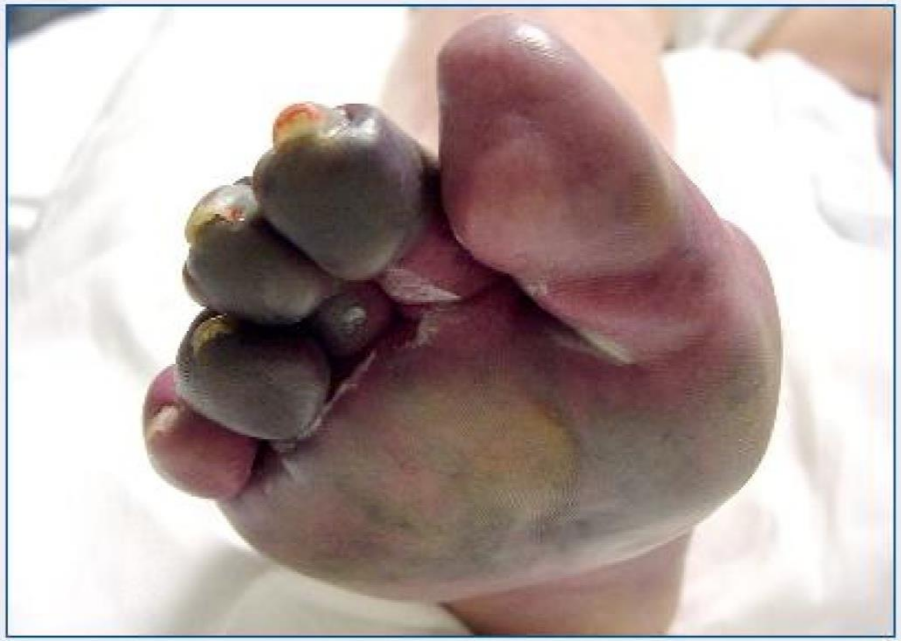
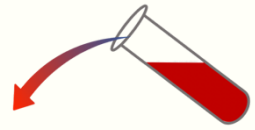




- Elective aortic valve replacement and mitral valve repair in 75 yr old woman.
- Cormack GM & Kaufman LJ. Journal of Medical Case Reports 2007, 1:13.

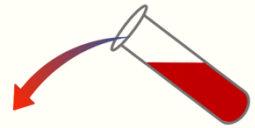
Heparin-Induced Thrombocytopenia

- "The incidence of HIT among these patients ranges from <0.1% to 7%, depending on the type of heparin (UFH vs LMWH), duration of heparin exposure, and patient population (eg, surgical vs medical)."
  - Cuker A, et al Blood Adv. 2018 Nov 27;2(22):3360-3392. doi: 10.1182/bloodadvances.2018024489. PMID: 30482768; PMCID: PMC6258919.
- Develops in about ~6-8% of patients receiving IV unfractionated heparin, ~0.8% with Low Molecular Weight Heparin.
- Typically develops 5 to 15 days after heparin starts.
- Unlike "Immune Thrombocytopenic Purpura" where the primary manifestation is a mucocutaneous pattern of bleeding from profound thrombocytopenia, HITT results in microvascular ischemic disease.
- Associated with activation of the platelets and a paradoxical thrombotic tendency.
- May be associated with loss of limb or life!
  - Salter BS, et al. J Am Coll Cardiol. 2016 May 31;67(21):2519-32. doi: 10.1016/j.jacc.2016.02.073. PMID: 27230048.
  - Linkins LA, et. Chest . 2012 Jan 23;141(2 Suppl):e495S–e530S. doi: 10.1378/chest.11-2303



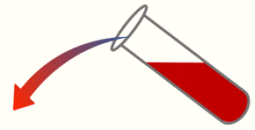
Any Route of Heparin Can Cause HITT

- IV heparin at therapeutic doses strongest risk, but
- Subcutaneous administration of prophylactic doses, central line flushes are also a risk. (Particularly, once HITT has started).

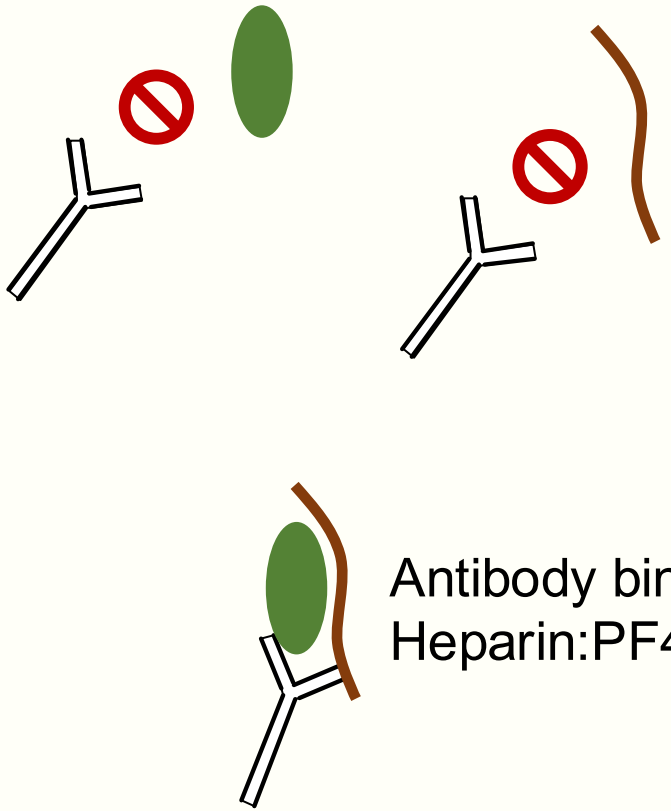


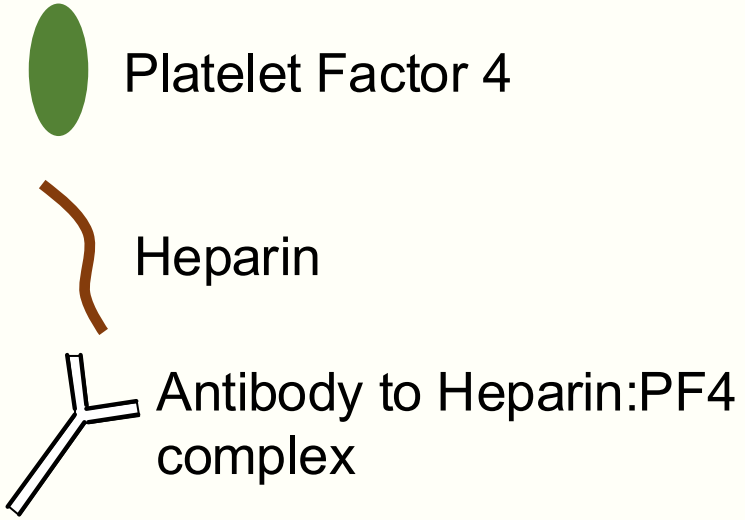
II. Pathophysiology of HITT

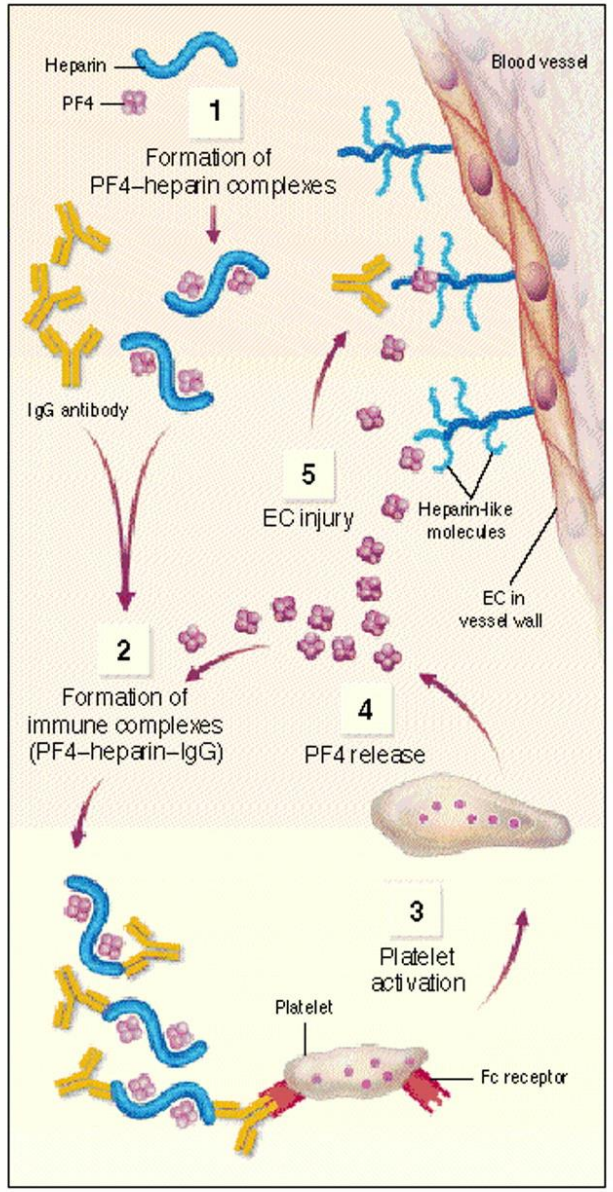
- Antibody formation to heparin: platelet factor 4 (PF4) complexes.
- Antibodies to heparin:PF4 complexes lead to platelet activation, rather than clearance.
- Associated with thrombosis rather than bleeding.
- Results in arterial/venous/microvascular thrombosis.
- Presence of IgG antibodies that recognize PF4/heparin complexes on platelet surfaces and vascular walls.
- Activated platelets release microparticles with prothrombotic activity.
- Platelet-derived PF4 binds Heparan Sulfate on endothelial cells, and antibodies then bind to the endothelial cells, inducing further hypercoagulable state.



Antibody:Heparin:PF4 Complex Associated With Arterial, Venous, and Microvascular Thrombosis.







Pathophysiology of Thrombocytopenia and Thrombosis in HITT

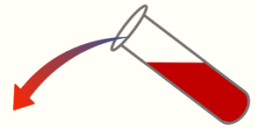
Aster R. N Engl J Med 1995;332:1374-1376

- Platelet activation and microangiopathic hemolytic anemia.
- Release of procoagulant microparticles.
- Release of PF4 which can bind to heparan (heparin-like proteoglycans) on endothelial cells, which forms heparan:PF4 complex and binds more antibodies, damaging endothelial cells.
- Two mechanisms for thrombotic microangiopathy, platelet activation and endothelial cell damage.

Types of HIT: Old Nomenclature

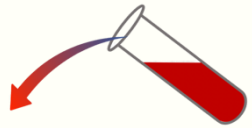
- Type 1 HIT: Non-immune, mild, transient thrombocytopenia.
  - Also "Heparin Associated Thrombocytopenia."
  - Common after surgery, such as cardiac surgery, where mild thrombocytopenia results from consumption, dilution, and multiple factors.
  - Absence of heparin-dependent antibodies.
  - Probably not a true entity.

- Type 2 HIT: Immune-mediated, leads to significant thrombocytopenia and thrombosis.



Differences Between HIT and Non-Immune HAT

	Non-Immune HAT	HITT-Type II
Onset	Within 4 days	Typically, 5 to 15 days (Sooner with heparin exposure in recent past)
Platelet Count	Typically, ~100,000/ul	Typically nadir ~ 50,000/ul
Complications	None	Thromboembolic Events
Incidence	5-30%	~6 %
Recovery	1-3 days	5-7 days
Cause	Platelet utilization, consumption	IgG antibody to heparin:PF4 complex



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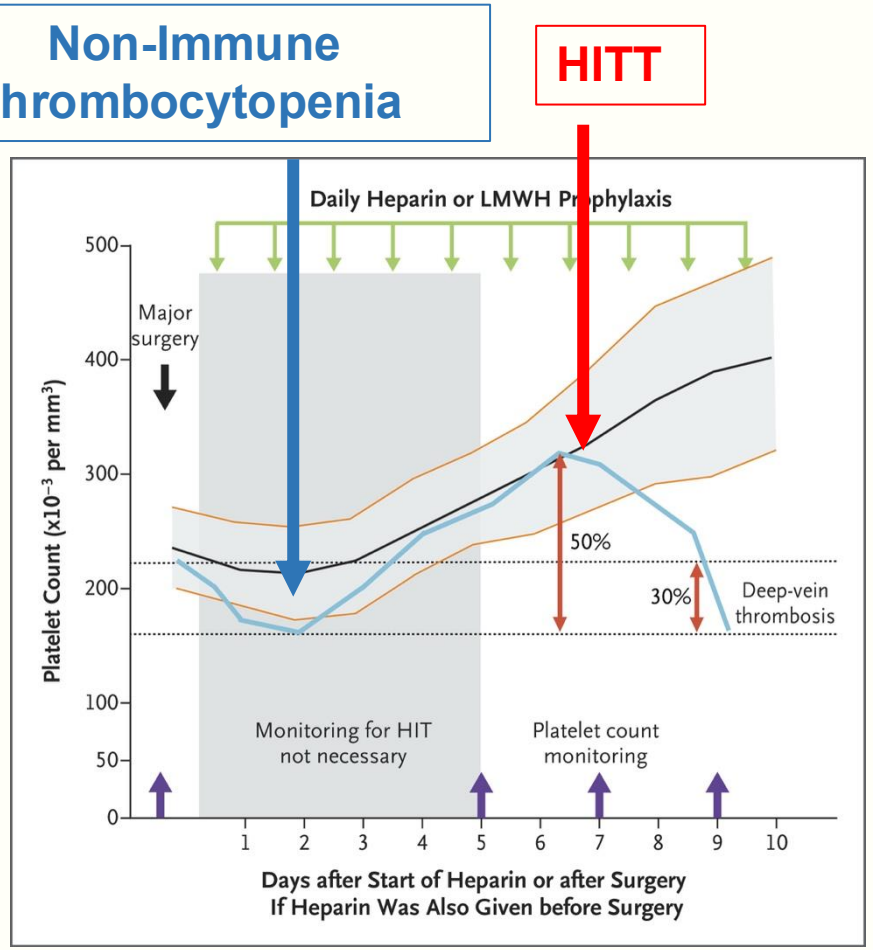

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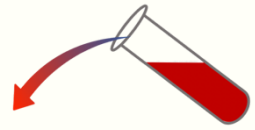
LMWH Is Associated With Significantly Lower Incidence of HIT & Thrombosis

	UFH (N-332)	Enoxaparin (n=333)	P Value
HIT	16 (4.8%)	2 (0.6%)	<0.001
Thrombosis	12 (3.6%)	1 (0.3%)	<0.001

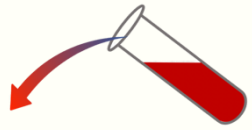
- Warkentin TE, et al. Arch. Int. Med. 2003, 163: 2518-2524.
- Warkentin TE, et al. NEJM 1995, 332: 1330-1335.



III. Clinical Manifestations

- Thrombocytopenia
- Arterial/Venous/Microvascular Thrombosis

- HIT has a markedly higher risk of thrombosis than any other “thrombophilia” (in untreated state), based on period of time.



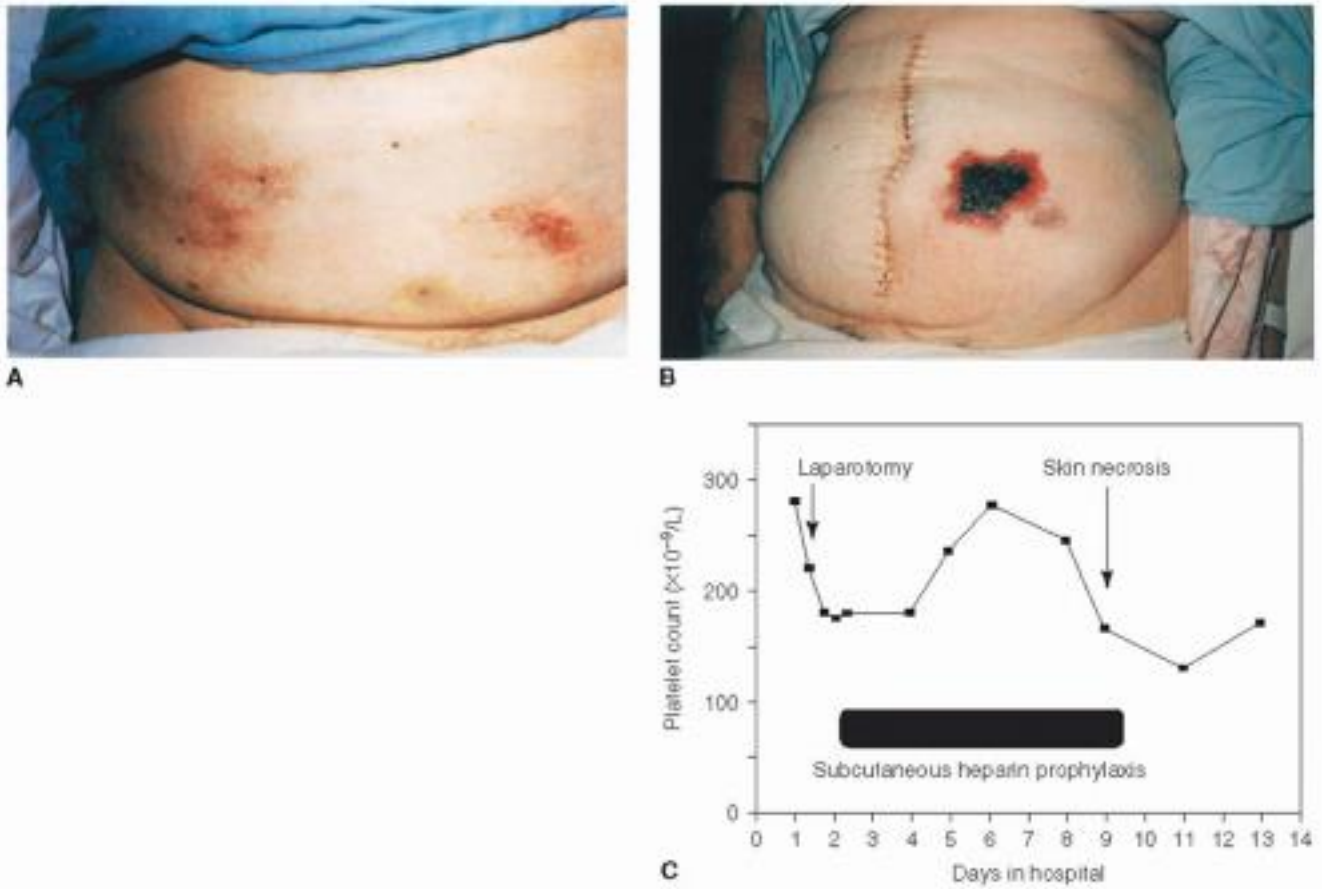
Thrombosis Rates in HITT

- In patients with isolated HIT who do not receive alternative anticoagulation, the risk of developing new thrombosis is 47.6% to 55.5% within 30 days.

- Retrospective case series show that when heparin is simply discontinued without initiating alternative anticoagulation, new thrombotic events occur in 38% to 55.5% of patients.
  - Linkins LA, et. Chest . 2012 Jan 23;141(2 Suppl):e495S–e530S. doi: 10.1378/chest.11-2303

- ”Left untreated, HIT is associated with an initial 5% to 10% daily risk of thromboembolism, amputation, and death”.
  - Cuker A et al Blood Advances. . 2018 Nov 27;2(22):3360-3392. doi: 10.1182/bloodadvances.2018024489. PMID: 30482768; PMCID: PMC6258919.

Two types of skin lesions are described: painful, red plaques and frank skin necrosis



https://oncohemakey.com/heparin-induced-thrombocytopenia-4/#F5-108

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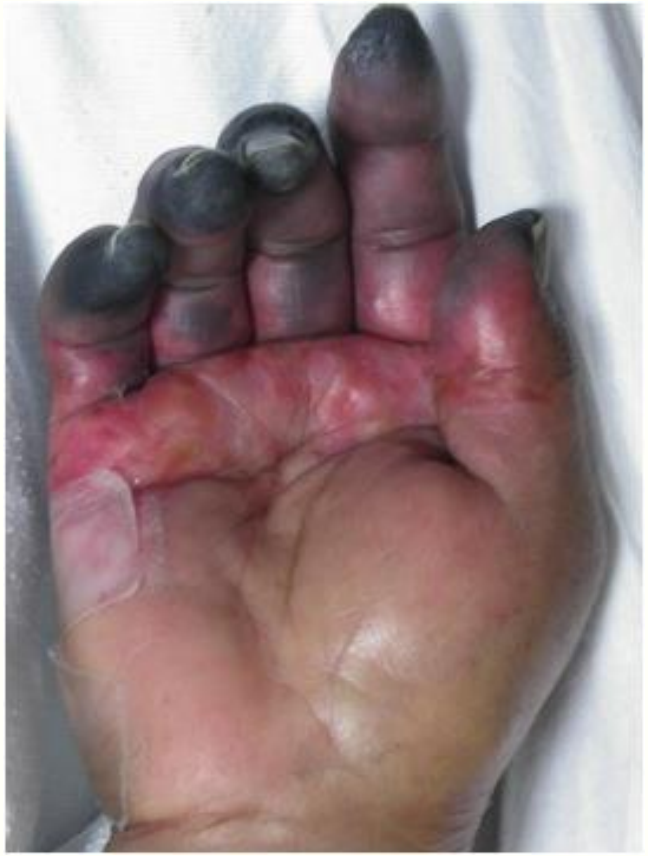
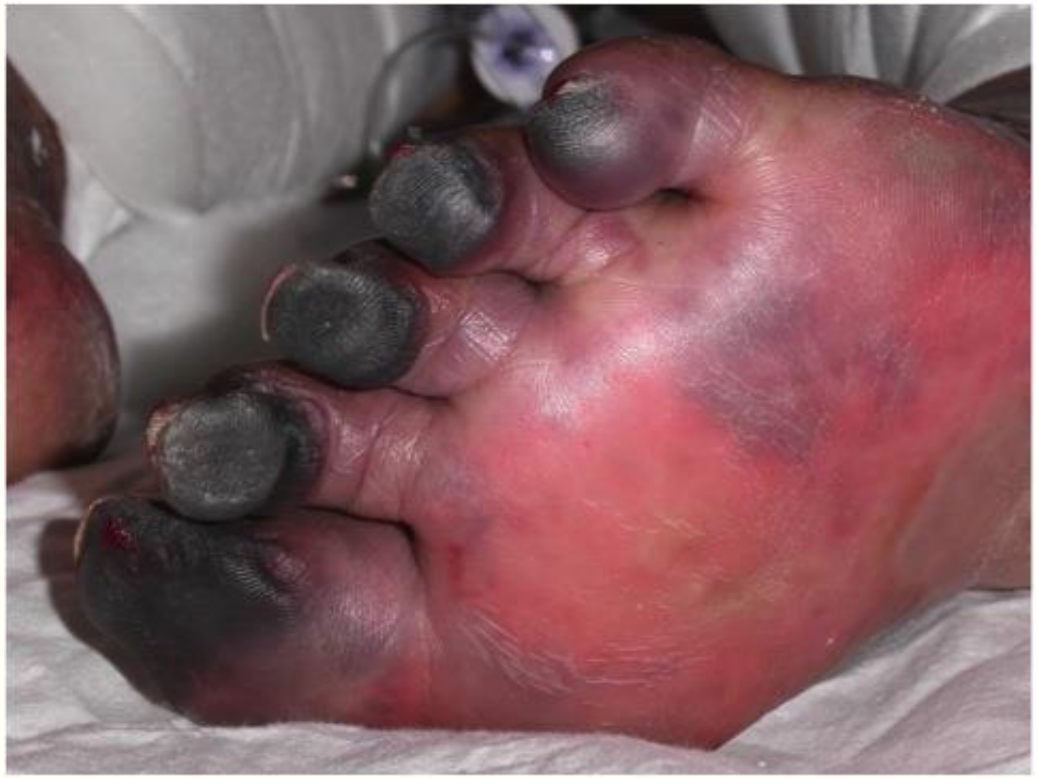
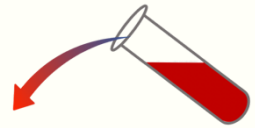




- Elective aortic valve replacement and mitral valve repair in 75 yr old woman.
- Cormack GM & Kaufman LJ. Journal of Medical Case Reports 2007, 1:13.

HIT Patients Presenting with Thrombosis

- Deep venous thrombosis (50%)
- Pulmonary embolism (25%)
- Skin lesions at injection site (10% to 20%)
- Acute limb ischemia (5% to 10%)
- Warfarin-associated venous limb gangrene (5% to 10%)
- Acute thrombotic stroke or myocardial infarction (3% to 5%)
- Acute systemic reactions following IV bolus (~25%)
  - Warkentin. *Thromb Haemost*. 1999;82:439-447.
  - Warkentin. *J Crit Illness*. 2005;20(1):6-13.



Thrombosis Rate in Patients With HIT Ranges From 50% to 89% in Untreated Patients.

Type of Thrombosis	Approximate Proportion	Specific Manifestations
Venous thrombosis	~75-80% of thrombotic events	Deep vein thrombosis (DVT), pulmonary embolism (PE)
Arterial thrombosis	~20-25% of thrombotic events	Limb artery thrombosis, stroke, myocardial infarction
Special populations	Variable	After cardiac surgery: arterial and venous occur with similar frequency

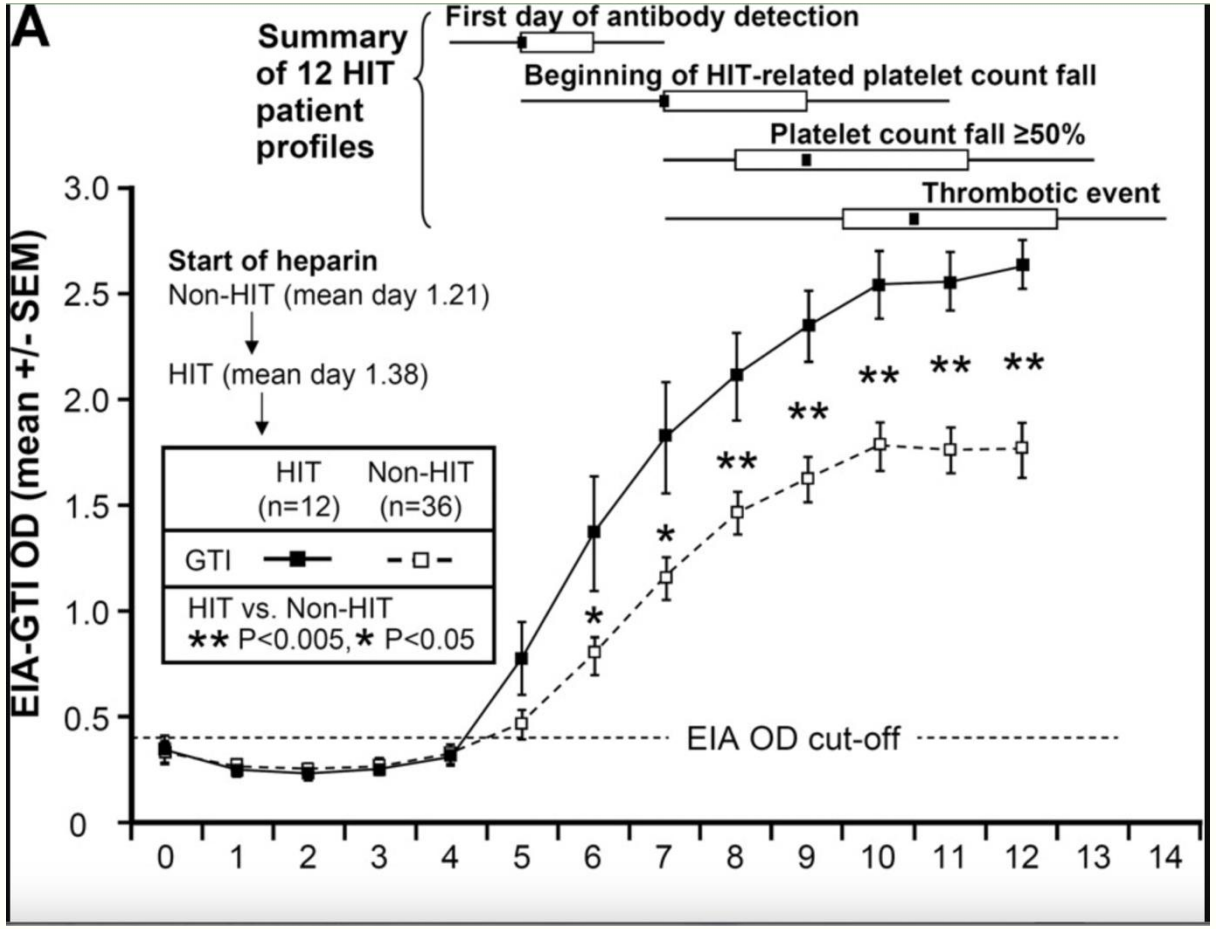
- Salter BS, et al. J Am Coll Cardiol. 2016 May 31;67(21):2519-32. doi: 10.1016/j.jacc.2016.02.073. PMID: 27230048
- Linkins LA, et. Chest . 2012 Jan 23;141(2 Suppl):e495S–e530S. doi: 10.1378/chest.11-2303
- Warkentin TE. J Thromb Haemost. 2018 Nov;16(11):2128-2132. doi: 10.1111/jth.14264. Epub 2018 Sep 8. PMID: 30099843.

Frequency of Clinical Sequelae in Untreated HITT

Sequelae	Incidence
Thrombosis	30%–50%
Amputation	20%
Death	30%

- Note: Bleeding is not sequelae!
- Levine et al. *Ann Emer Med*. 2004;44:511-515.

Development of HITT After Heparin Exposure

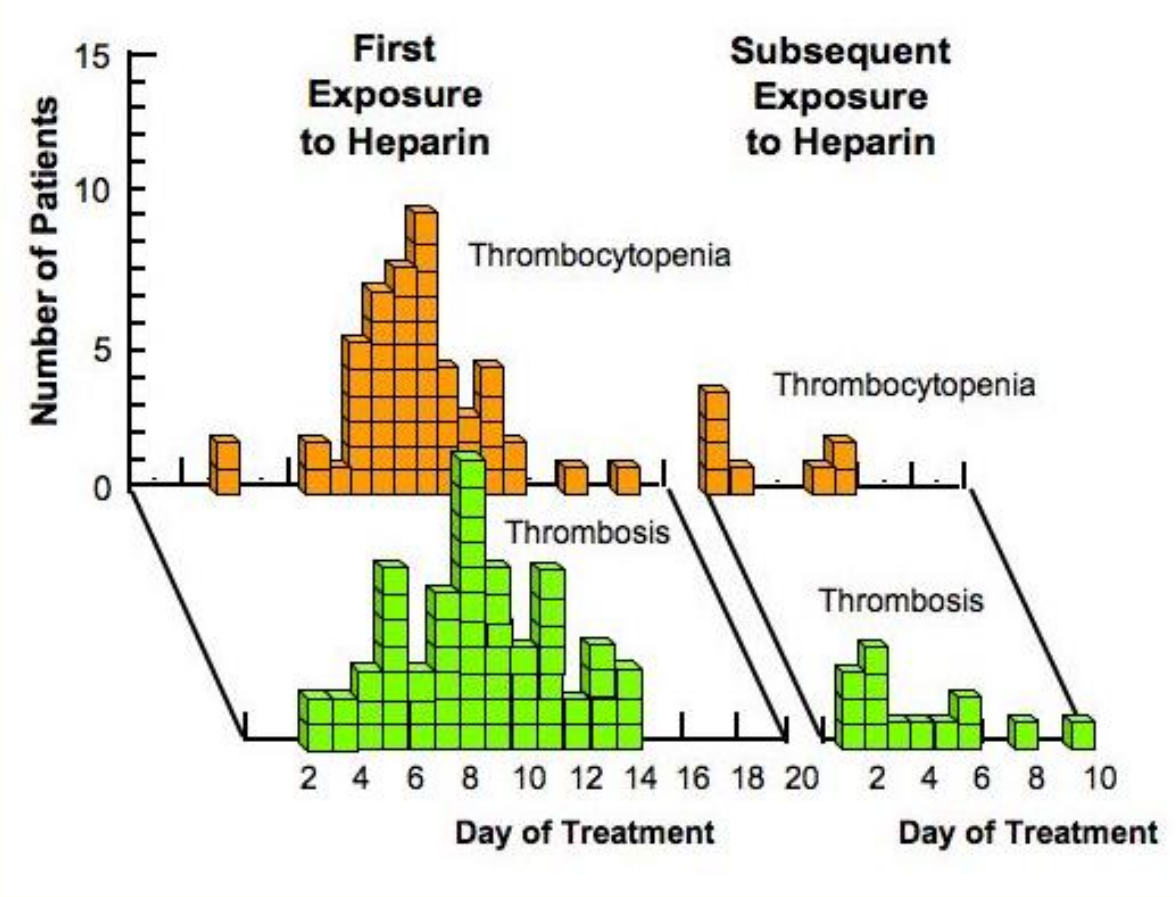


➢ **In Patients who developed HITT.**

Event	Day (Median)
Anti-PF4/heparin antibodies became detectable.	4
Onset of platelet count fall	7
Platelet count decline criteria indicating HIT (50% platelet count fall)	9
Onset of a thrombotic event	10.5

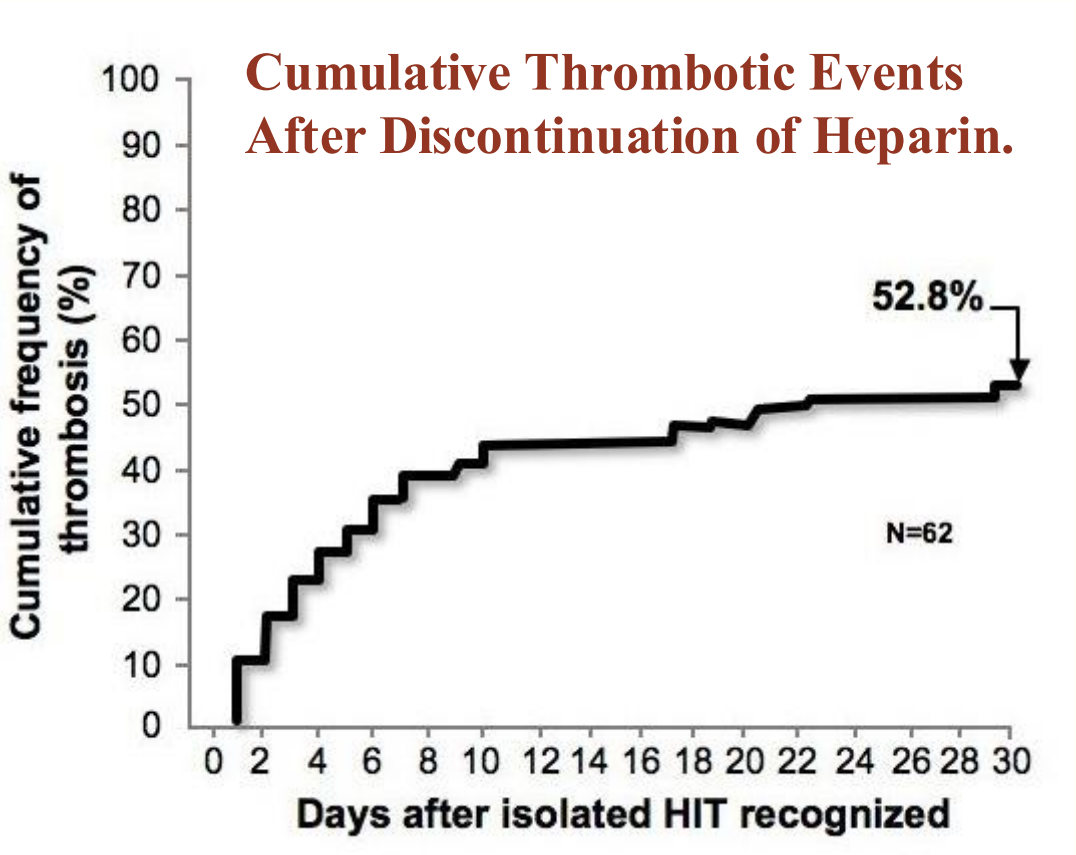
➢ Warkentin et al, Blood 2009; 113 (20): 4963–4969. doi: https://doi.org/10.1182/blood-2008-10-186064

Onset of Thrombocytopenia: Influence of Prior Exposure



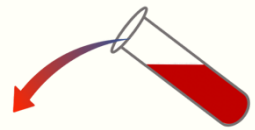
Adapted from King DJ, Kelton JG. *Ann Intern Med*. 1984;100:536–540.

Thrombotic Risk Does Not End with Cessation of Heparin.



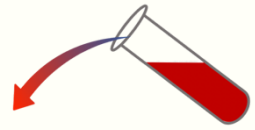
- The hypercoagulable state persists (~10 days) after discontinuation of heparin.
- Therefore, simply stopping heparin is not appropriate!
- One must use an alternative anticoagulant!
  - 14-year experience of HITT (n=127 patients).
  - Prior to era of Direct Thrombin Inhibitors and specific therapy for HITT.
  - Warkentin and Kelton. Am J Med. 1996;101:502-507.

IV. Diagnosis: Clinical Suspicion

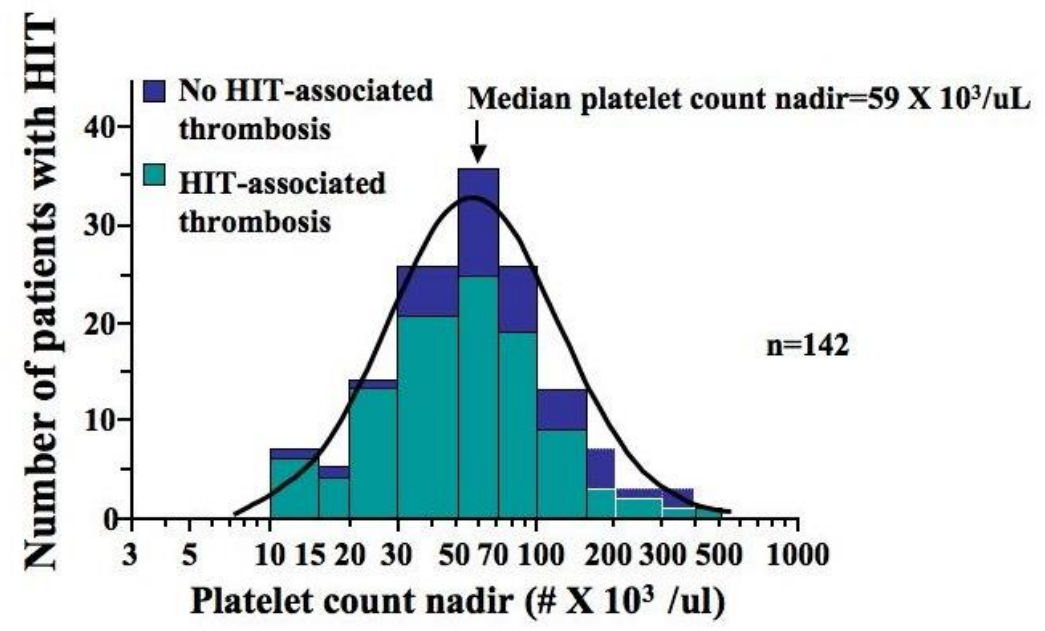


HIT:Diagnostic Overview

- Strongly consider HIT when:
  - Platelet count falls within 5-15 days of start of heparin:
    - 30% - 50% from baseline and/or
    - <150,000/ul
  - New thrombotic or thromboembolic event occurs while on heparin.
- Absolute platelet count is not sole criterion for diagnosis: platelet nadir can remain in normal range in patients with HIT.



Distribution of Platelet Counts in HITT at Nadir



- Severe thrombocytopenia is rare.
- Thrombocytopenia is less severe than ITP
- Thrombotic event risk does not correlate with severity of thrombocytopenia.
  - Warkentin. *Semin Hematol.* 1998;35(suppl 5):9-16.

4T Scoring System for Pretest Probability

Points	2	1	0
Thrombocytopenia	>50% fall in PLT or PLT nadir of 20K-100K	30-50% fall in PLT or PLT nadir 10K-19K	<30% fall in PLT or PLT nadir of <10K
Timing	5-10 d post heparin [<1 day if previous heparin within 100 days]	Unclear or PLT fall after 10 days	PLT fall <5 days and without recent heparin
Thrombosis	New thrombosis, skin necrosis	Progressive or recurrent thrombosis, some skin lesions e.g., erythema	None
Other causes of Thrombocytopenia	None	Possible	Other causes clearly identified

Score ≤3: < 5% chance of HIT
Score 4-5: Intermediate risk
Score ≥ 6: Very high risk of HIT

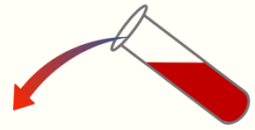
A low probability score (≤ 3) was associated with a high NPV for HIT (0.998; 95% CI, 0.970-1.000)

Cuker, A. et al. Blood 2012, 120(20): 4160–4167.
Lo GK, et al. Journal of Thrombosis and Haemostasis. 2006;4(4):759-65.

HIT Testing: Screening ELISA

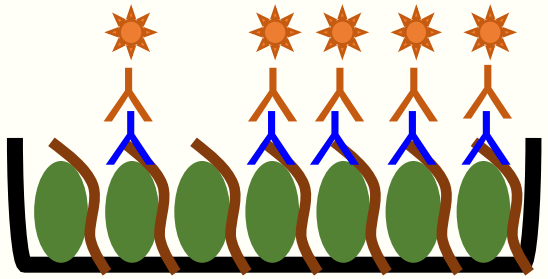
- Antibodies to heparin-PF4 complexes
  - Polyspecific Assay: Combined IgG, IgA, IgM titers.
  - Monospecific Assay, IgG only titer (OD) are more specific.
    - McFarland et al, Am J Hematol. 2012 Aug; 87(8): 776–781.
- High Negative Predictive Value*.
  - If the result is below the pre-specified cutoff, (Typically, <0.4 OD units) can be confident that HIT is not present.
  - If result if ≥ 0.4, this does not indicate that HIT is present, but rather it still needs to be considered.

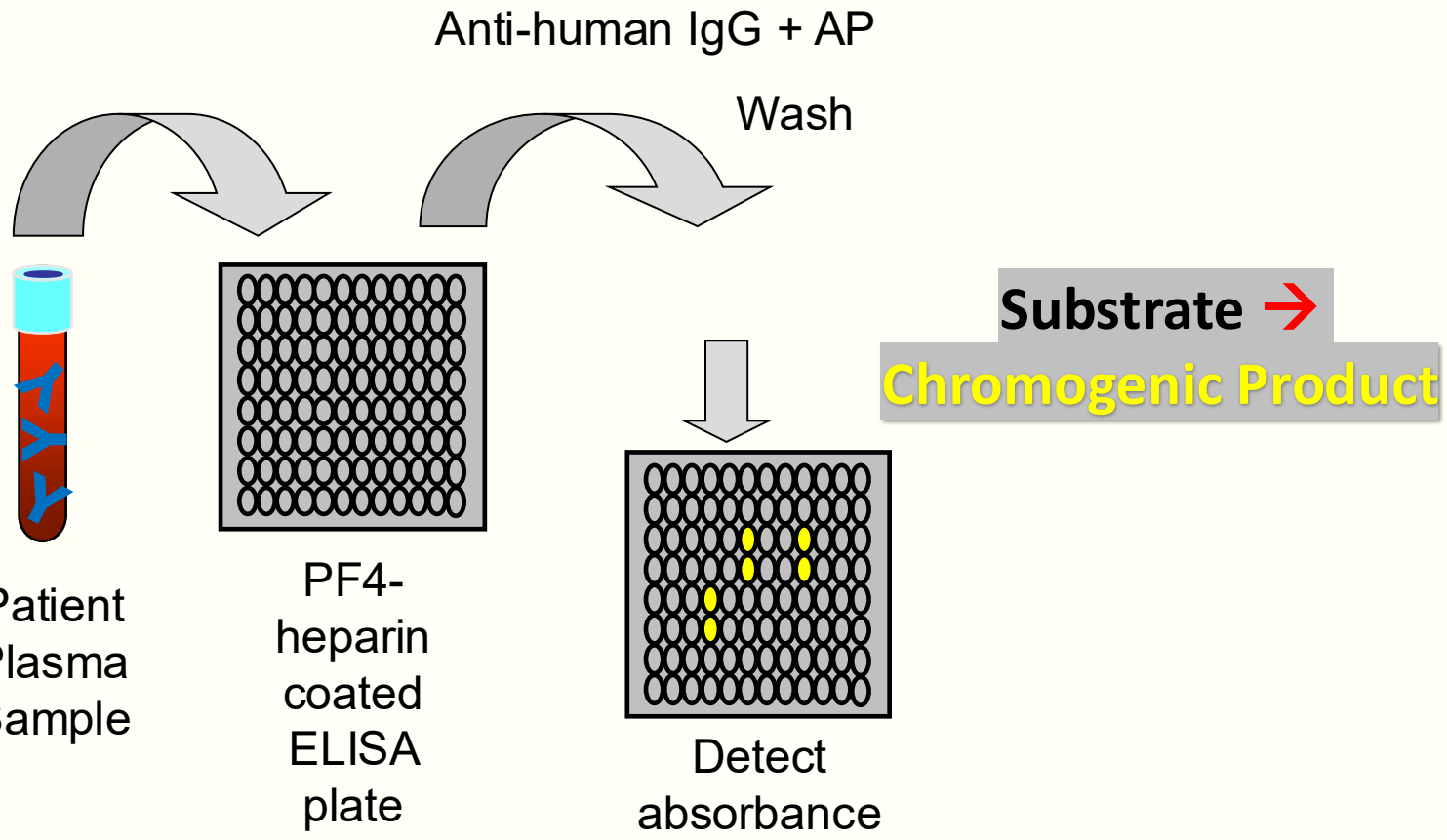
**A negative predictive value (NPV) is the probability that if the test is negative, the subject does not have the disease.*



ELISA-Based Assay: Antibody Capture

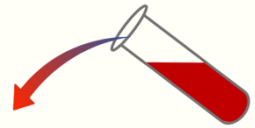
- Anti-human IgG + AP
- Patient Antibody
- Heparin:PF4 complex





HIT/T ELISA Results

- Negative ELISA screen– HIT unlikely
- Positive ELISA screen- consistent with HIT/T in the appropriate clinical setting. Does not mean that HIT/T is confirmed!
- Need confirmatory test (Serotonin Release Assay).



Interpretation of HIT Titers In View of Serotonin Assay Confirmatory Results

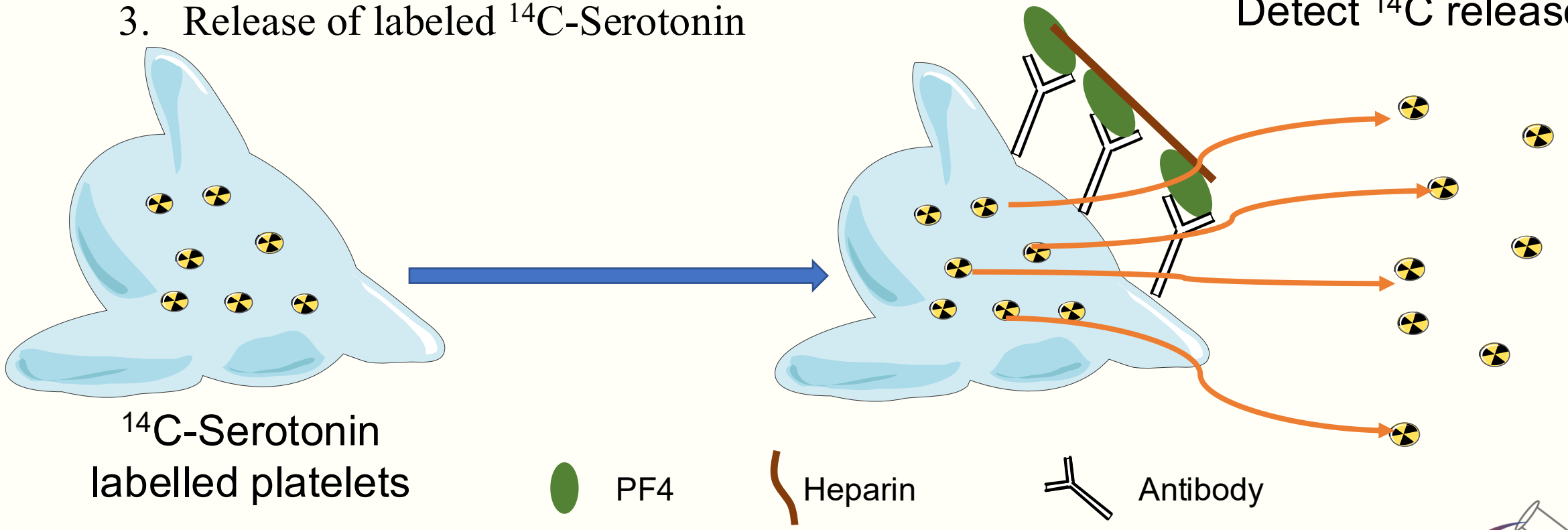
HIT Titer (OD)	Probability of Serotonin Assay POSITIVITY
< 0.4	~0 - <1%
0.4 - < 1.00	< 5%
1.00 - 1.50	~ 25%
1.50 - < 2.00	~ 50%
≥ 2.00	>90%

Warkentin et al. Thromb Haemost 2008;6:1304-12.

HIT/T Testing: Serotonin Release Assay

Uses fresh platelets, "loaded with ^{14}C-Serotonin" in dense granules.

1. Exposure to Antibody:Heparin:PF 4 Complex.
2. Activation of platelets
3. Release of labeled ^{14}C-Serotonin

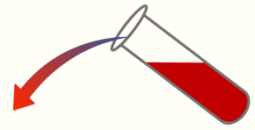


Laboratory Testing for HIT

Test	Advantages	Disadvantages
Enzyme Linked ImmunoSorbent Assay (ELISA)	High sensitivity Commercially available	Low specificity
Serotonin Release Assay (SRA)	Sensitivity >85%	Technically demanding Reference lab only Radioisotopes Very slow turn-around
Heparin-Induced Platelet Aggregation (HIPA) *	Specific	Variable sensitivity (30% –80%) Technically demanding Reference lab only

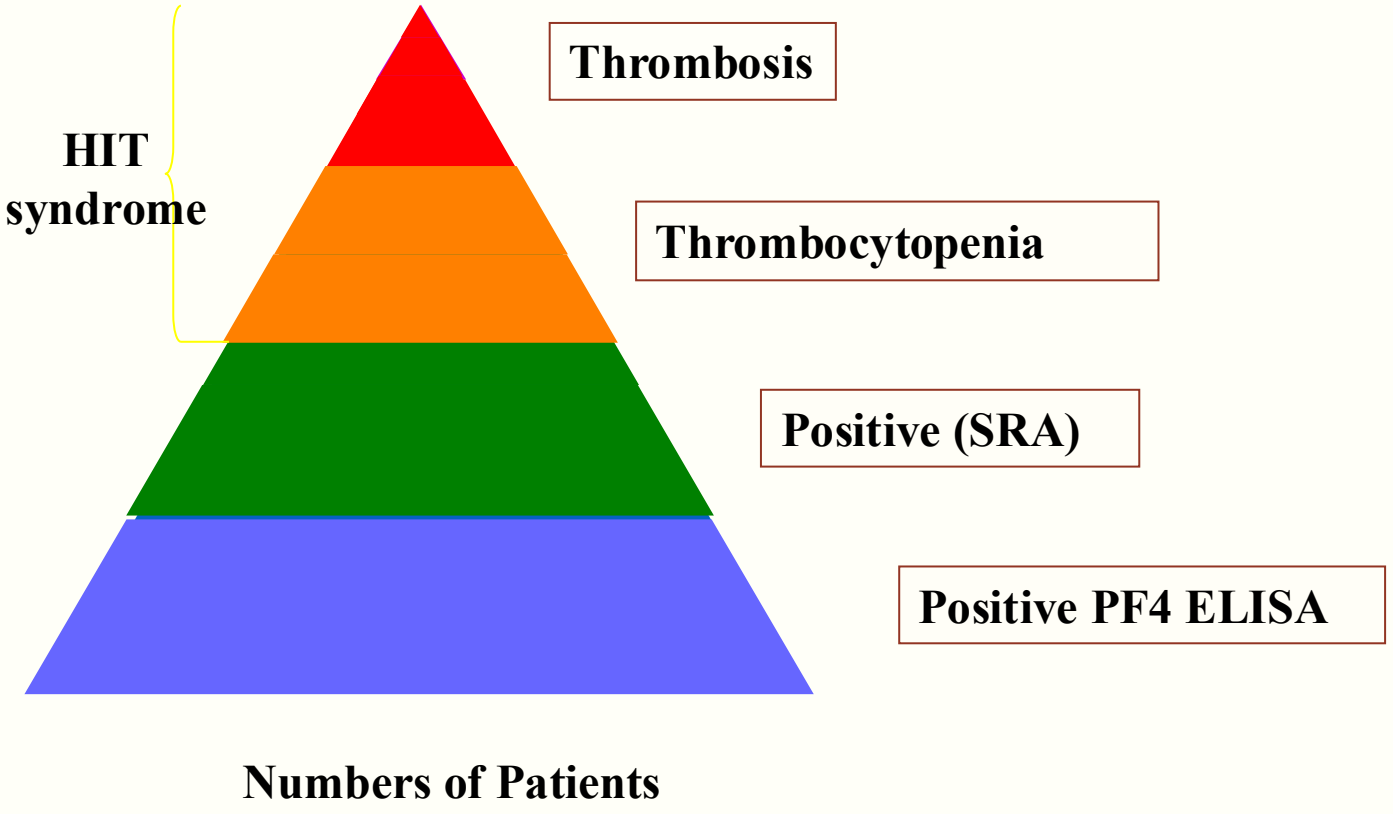
* "Serotonin release assay (SRA) is the "gold standard" confirmatory test for heparin-induced thrombocytopenia (HIT), but the heparin-induced platelet aggregation (HIPA) is another confirmatory test, more commonly used in Europe and more convenient for hospital-based laboratories that want to avoid radioactive material".

Mohammad B et al, American Journal of Clinical Pathology, Volume 161, Issue 2, February 2024, Pages 122–129, https://doi.org/10.1093/ajcp/aqad117

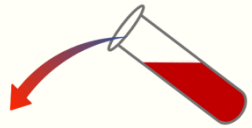


"Iceberg Model" of HIT/HITT
Adapted from Warkentin TE. Br J Haematol 2003,121:535

- HIT and associated thrombosis occurs in the subset of patients with platelet-activating anti-PF4/H antibodies.

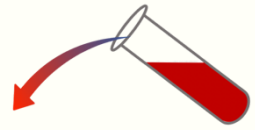


V. Management of HITT



HIT: Treatment Paradigms

- Thrombocytopenia results in a clotting disorder, not bleeding.
- Platelet transfusion can increase thrombosis risk.
- Simply stopping heparin will not prevent thrombosis.
- Warfarin contraindicated as acute monotherapy.

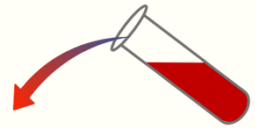


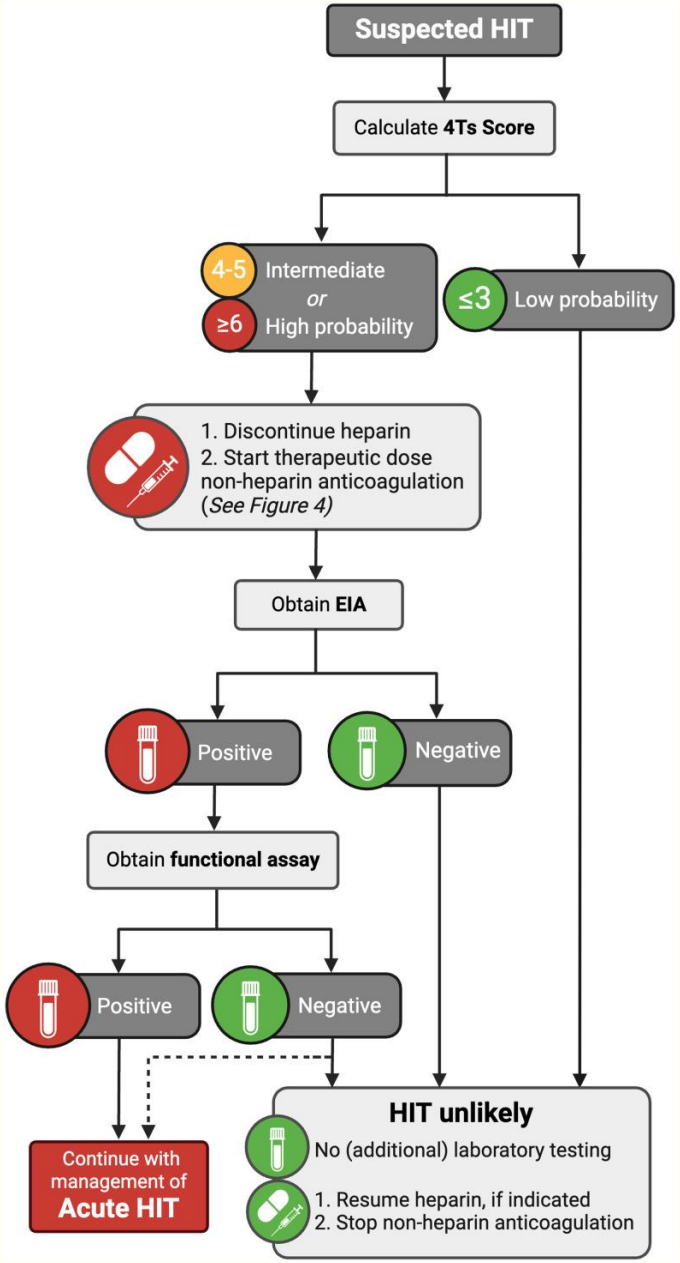
Management of Suspected HITT

- If one has enough suspicion to send the HITT assay:
  - Stop all Heparin! (IV, subcutaneous, central line flushes)
  - Including Low Molecular Weight Heparin.

- One must start an appropriate alternative anticoagulant.
  - Risk of new, potentially catastrophic thrombotic event necessitates alternative anticoagulant, even if initial heparin use was only for prophylaxis.
  - Simply stopping heparin or LMWH is not adequate!
  - Do not wait for laboratory test results.
  - Do not delay treatment: Laboratory assays are only confirmatory.

- Avoid platelet transfusions.
- Monitor platelet counts and and possible thrombotic complications.



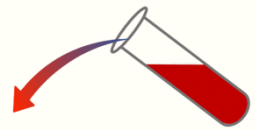


- May J & Cuker A. ; Hematology Am Soc Hematol Educ Program 2024; 2024 (1): 388–395. doi: https://doi.org/10.1182/hematology.2024000566

Treatment of HITT

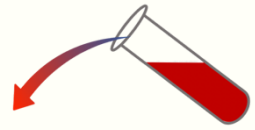
	Dosing	Titration/Monitoring	Cautions
Fondaparinux	Standard therapeutic	None	Long half-life
Apixaban	Standard therapeutic	None	
Rivaroxaban	Standard therapeutic	None	
Argatroban	Bolus: None Continuous infusion/Initial rate: Normal organ function → 2 mcg/kg/min Liver dysfunction, Heart failure, anasarca, post-cardiac surgery → 0.5–1.2 mcg/kg/min	Adjust to APTT 1.5–3.0 times baseline	Hepatic Clearance
Bivalirudin	Bolus: None Continuous infusion: Normal organ function → 0.15 mg/kg/h Renal or liver dysfunction → dose reduction may be appropriate.		Renal Clearance

- Argatroban and Bivalirudin require transition to an alternative anticoagulation, once platelet count has recovered.
- Apixaban and Rivaroxaban can be used for acute and longer-term anticoagulation.
- Fondaparinux can be used in outpatient setting.



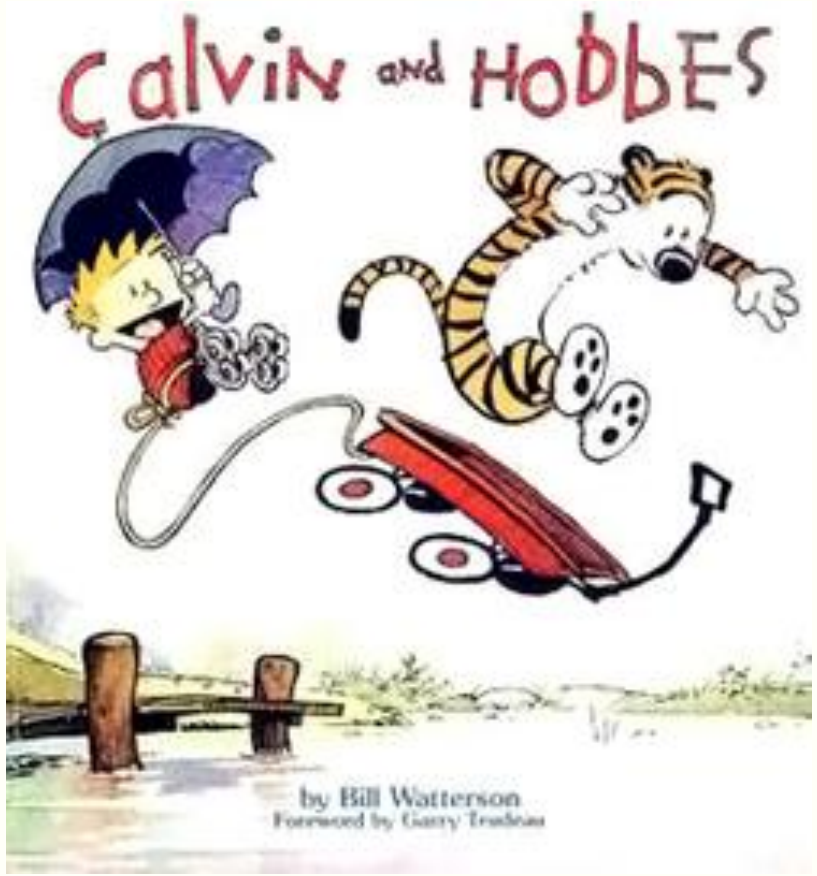
DO NOT USE LMWH once HITT suspected or confirmed.

- Low Molecular Weight Heparins: Even though LWMH have lower incidence of initiation HITT, often the antibodies cross-react.
- Fondaparinux (Arixtra®): A pentasaccharide (ultra-low molecular weight heparin) does not cross-react with the antibody and can be used as once daily injection. Not FDA approved for HITT, but useful for DVT prophylaxis in patient with history of HITT.



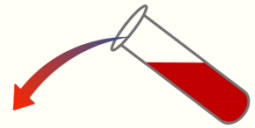
Rechallenge with Heparin ?

Are you crazy?



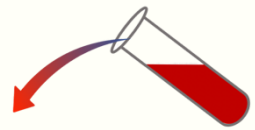
Re-Challenge with Heparin ?

- Not necessarily crazy!
- BRIEF re-exposure, (i.e. for cardiac catheterization)
  - If the episode of HITT was at least 100 days prior,
  - AND the heparin-associated antiplatelet antibody is not detectable,
  - AND exposure will be for brief period, may cautiously re-administer heparin.
- BUT, no prolonged exposure for prophylaxis or treatment of thrombosis.



How To Prevent HITT?

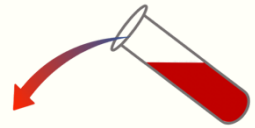
- Check if prior/recent heparin exposure.
- Limit heparin duration, whenever possible, to <5 days.
- Avoid heparin flushes
- Monitor CBC/platelet count daily while inpatient on heparin.
- Use LMWH or other anticoagulant, if possible.



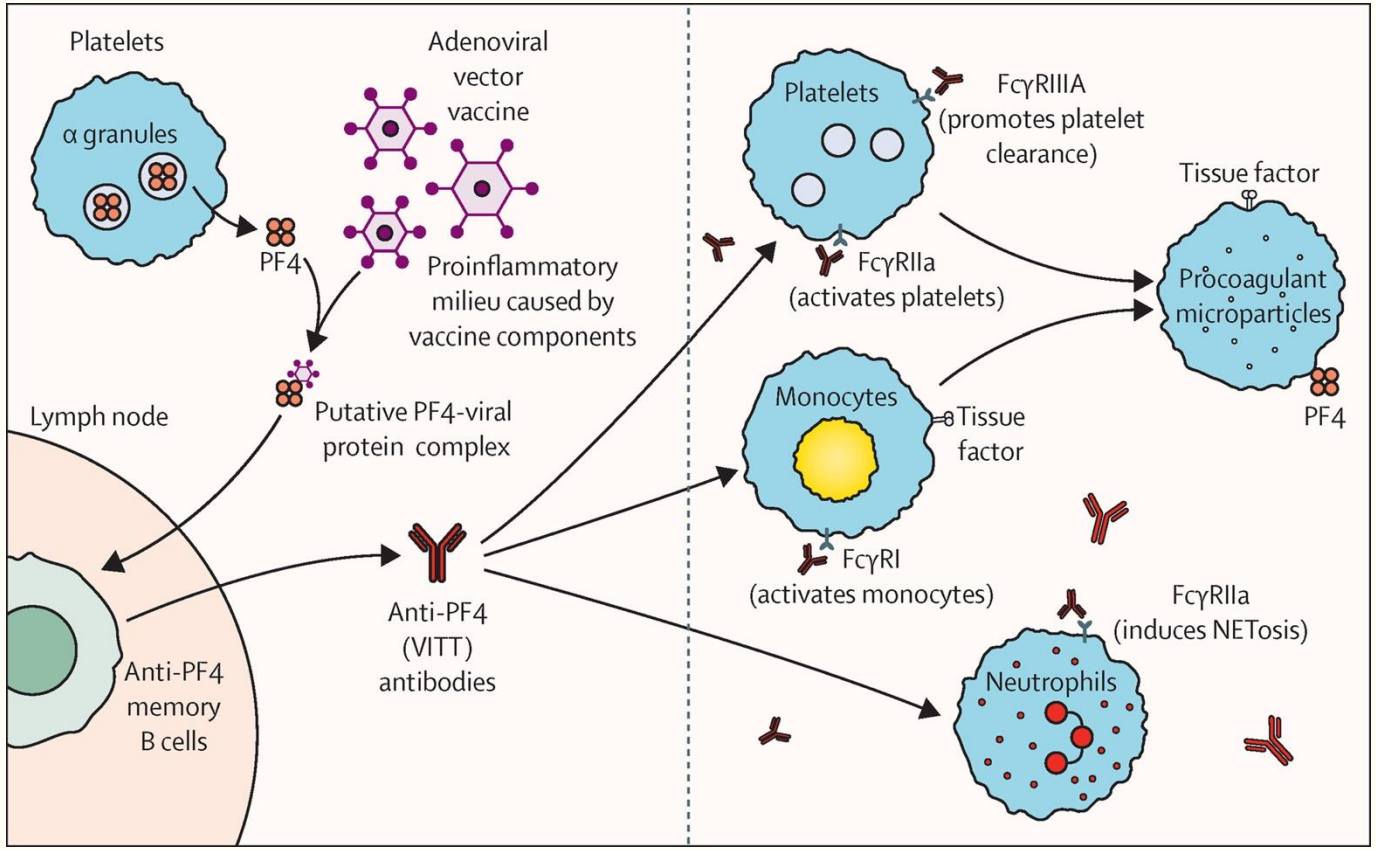
VITT: Vaccine Induced Immune Thrombotic Thrombocytopenia

VITT: Vaccine Induced Immune Thrombotic Thrombocytopenia

- Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is a rare and severe adverse effect of vaccination, characterized by thrombocytopenia and major venous or arterial thrombosis.
- VITT occurs after COVID-19 vaccination with two adenovirus viral vector vaccines.
- Mechanism is poorly understood.
  - Autoimmune response,
  - IgG antibodies against platelet factor 4 (PF4),
  - Platelet activation activate platelets through FcγRIIa receptors, and
  - Stimulation of the coagulation system.
- Heparin-dependent and VITT antibodies can only be differentiated by their binding patterns to distinct PF4 epitopes.
- USA estimated the overall incidence of VITT at 3.8 cases per million doses of the Johnson & Johnson vaccines.
  - Magalhaes JV, et al. Cochrane Database Syst Rev. 2024 Feb 29;2024(2):CD015369. doi: 10.1002/14651858.CD015369. PMCID: PMC10903294.



Proposed Pathophysiology of Vaccine-Induced Immune Thrombotic Thrombocytopenia



Klok, FA, et al. The Lancet Haematology, Volume 9, Issue 1, 2022, e73 - e80.