Heparin-Induced Thrombotic Thrombocytopenia (HITT)

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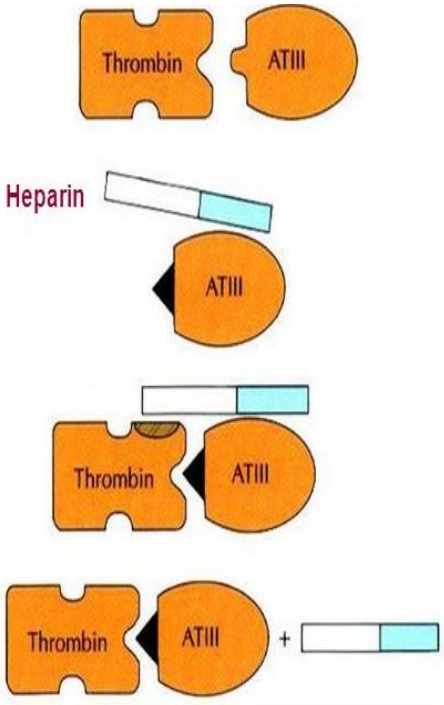
Introduction

- Heparin, an anticoagulant, is a common form of treatment for various thromboembolic conditions.
- These include DVT, VTE, PE, Heart Attack, Stroke, and various others.
- However, in a few cases, the administration can cause a condition known as Heparin Induced Thrombotic Thrombocytopenia. (HITT).
- Thrombocytopenia is a condition with reduced platelet count.

Mechanism of Action of Heparin



- The clotting cascade is a complex series of events involving the activation of clotting factors which eventually lead to the formation of a clot.
- Heparin exerts its action by reversibly binding to Antithrombin III – ATIII (a natural inhibitor of clotting factors), further enhancing the abilities of AT III.
- Through this, heparin accelerates the inhibition of thrombin and factor Xa, preventing further clotting from occurring.

Heparin in the Coagulation Cascade

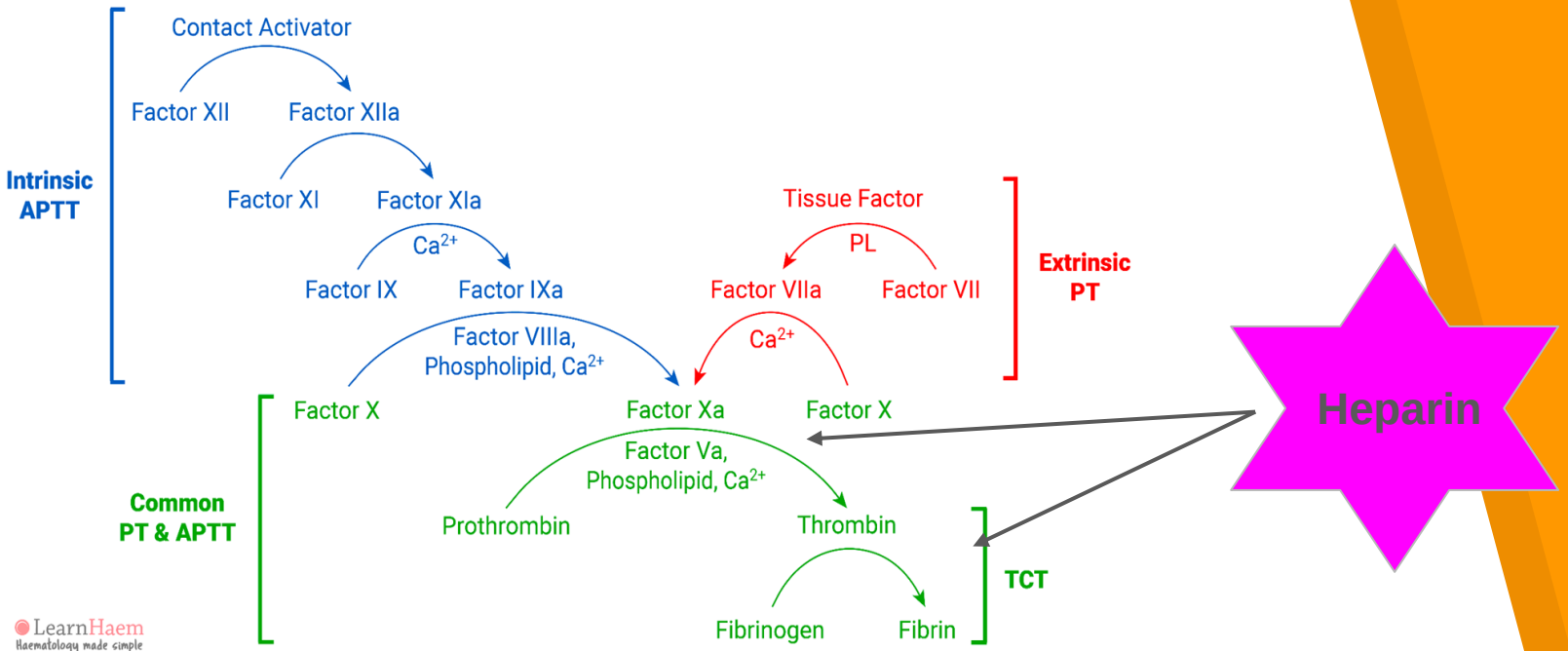


Figure 1: Coagulation cascade with its intrinsic, extrinsic, and common pathways.
(LearnHaem, 2020)

HEPARIN INDUCED THROMBOTIC THROMBOCYTOPENIA INCIDENCES GRAPH

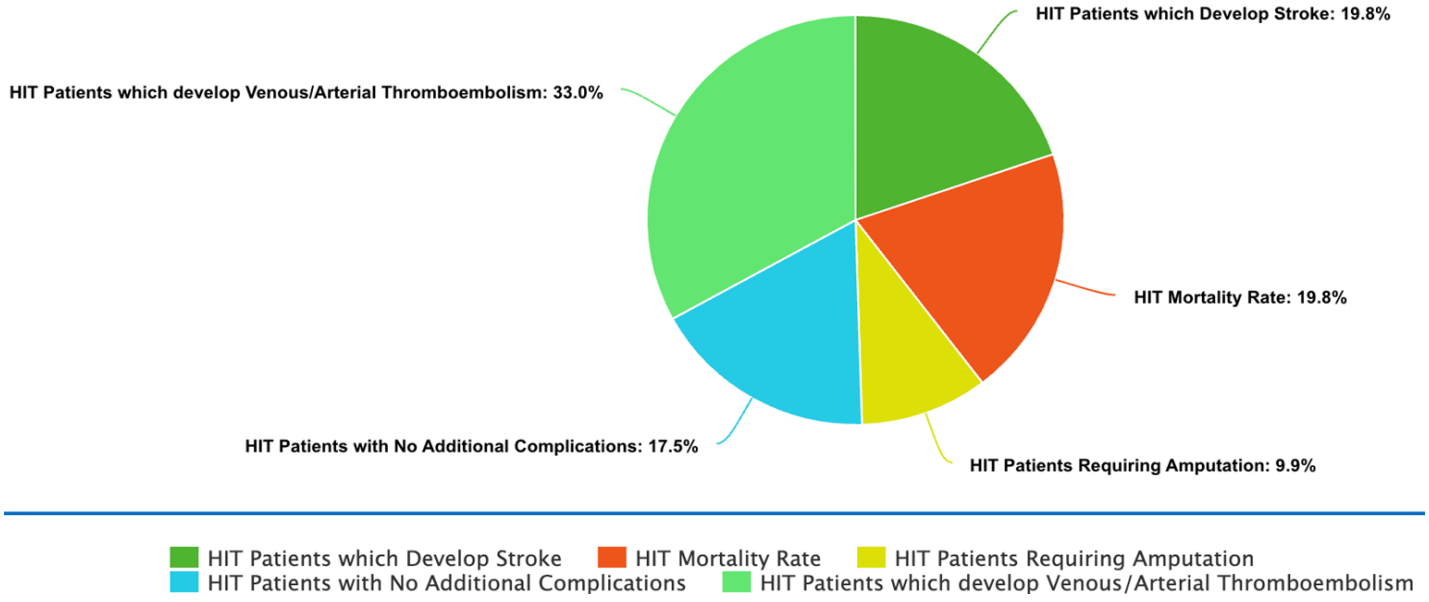


Figure 2: Showing the incidence of HITT
(Eke et al., 2023)

Incidence of HITT and Patient Population

- HITT incidence rates vary drastically depending on the treatment type of the patient
- For example, HITT incidence is highest in patients using unfractionated heparin.

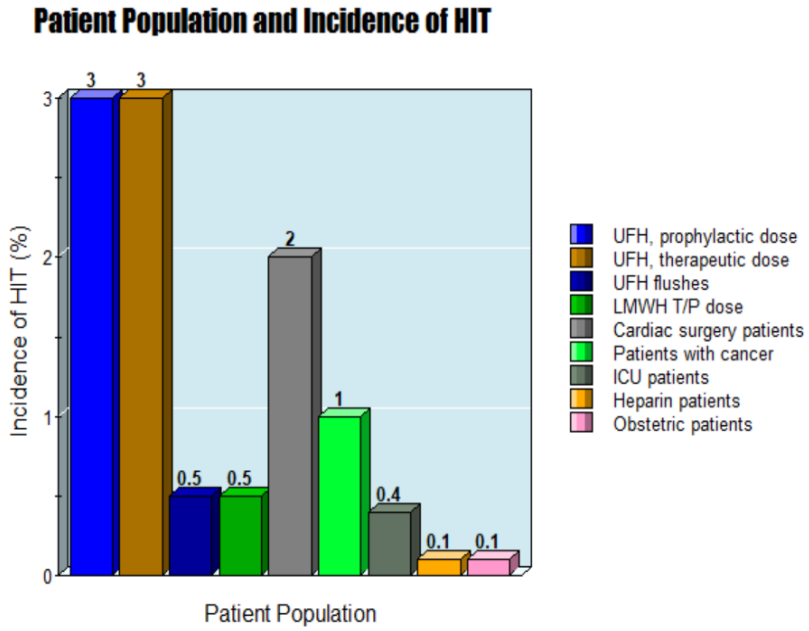


Figure 3: Incidence of HITT in various patient categories.
(Kyriakou et al., 2013)

Incidence of HITT and Patient Population

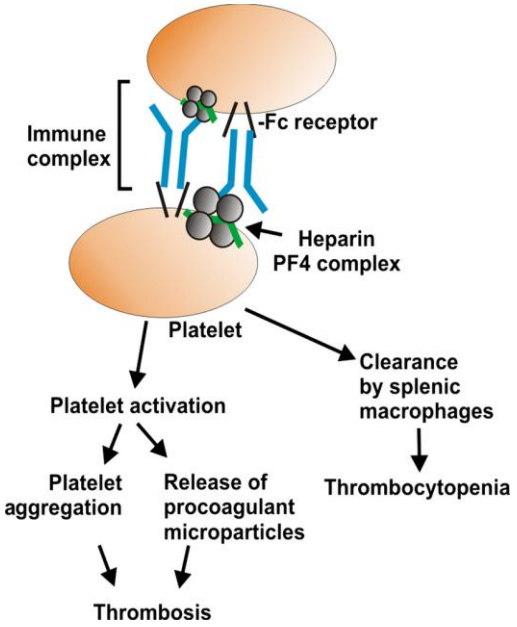
- Females are 1.7x more likely to have additional thrombotic complications of HITT

- HITT is more common in surgical rather than medical patients (more common in cardiac and orthopaedic surgical patients than others)

Types of Heparin - UFH and LMWH

Unfractionated Heparin (UFH)	Low Molecular Weight Heparin (LMWH)
- Injected IV - Heterogenous mixture of molecular chains - Works very quickly - Requires regular checks on patients and more frequent dosing - Administered in hospitals - Reversible with protamine sulfate - Cost effective	- Derived from unfractionated heparin - Lower average weight resulting in more predictable pharmacokinetics - Less checks on patients required - Self-injectable - Only partially reversible with protamine sulfate - Expensive

Thrombocytopenia and Heparin



Platelets and their Significance

- Platelets (thrombocytes), are cell fragments that are a part of blood and are made in bone marrow
- When blood vessels are injured, platelets travel to the site of injury and group together, creating a platelet plug
- Platelets will change shape and become activated, then will release prothrombotic molecules such as ADP (adenosine diphosphate)
- This recruits more and more platelets to the site, forming a plug
- Activating platelets stimulates the coagulation cascade, which stimulates the formation of thrombin, causing even more platelet aggregation

Clinical Conditions or Causes of Thrombocytopenia

- Thrombocytopenia occurs when the blood in the body has a low platelet count
- Normal platelet count: 150,000 to 450,000 platelets per microliter of blood
- Patients with thrombocytopenia have a platelet count of under 140,000 platelets per microliter of blood
- Causes of thrombocytopenia include: enlarged spleen, anemia, cancer, or HIV

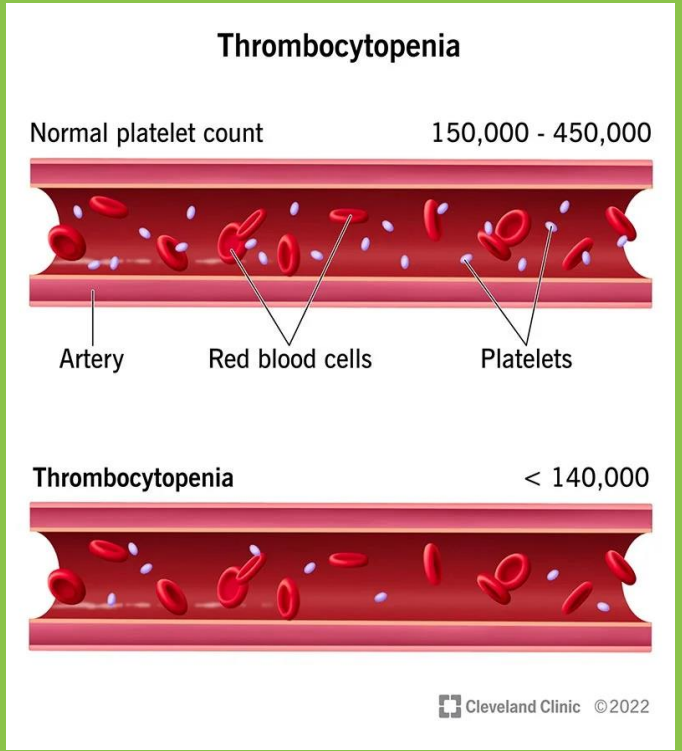


Figure 4 : Showing normal and low platelet counts in blood vessel
(Adapted from LearnHaem, 2020)

HITT

- Heparin-induced thrombotic thrombocytopenia is triggered by a reaction to the anticoagulant heparin.
- HITT causes the blood to clot excessively and platelet levels to drop.
- Patients on Heparin therapy have a decrease in platelet count by 50% or to less than 100,000 from 5 to 14 days of therapy.
- Heparin binds to platelet factor 4 (PF4) and forms the HPF4 complex. With HITT, the body will attack this complex, resulting in thrombocytopenia.

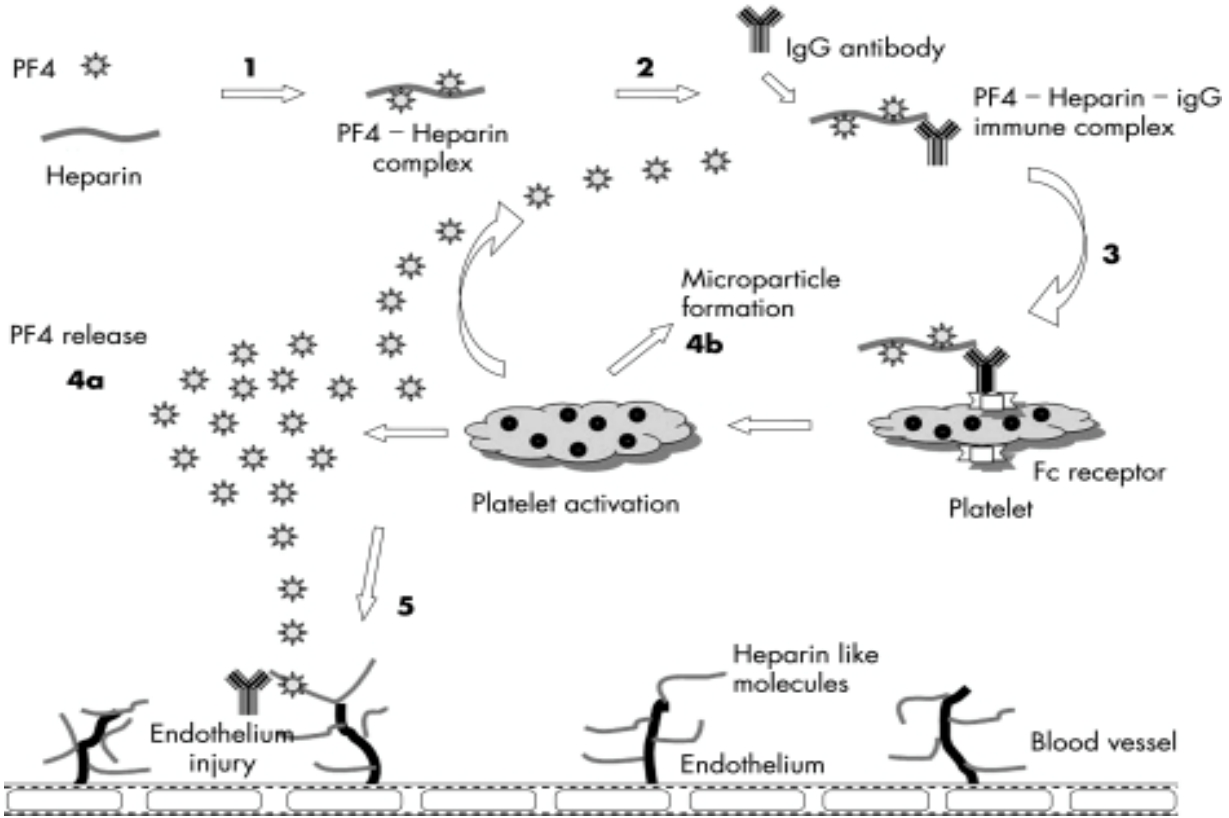
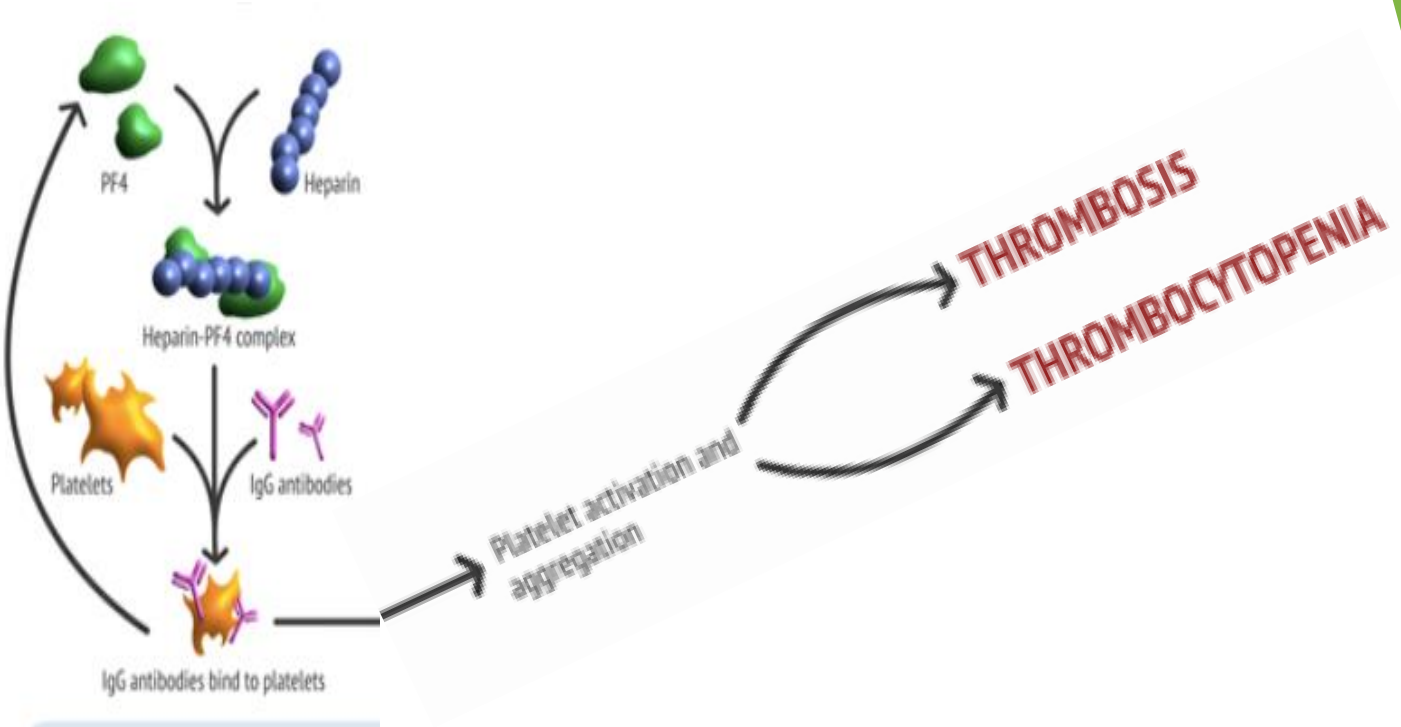


Figure 5: Onset of Heparin-induced thrombocytopenia

(Ahmed et al., 2007)


PF4
Heparin
Heparin-PF4 complex
Platelets
IgG antibodies
IgG antibodies bind to platelets
Platelet activation and aggregation
THROMBOSIS
THROMBOCYTOPENIA

Types of HITT

HITT Type I	HITT Type II
- Not considered a medical emergency - Occurs in up to 10% of patients on Heparin - Blood clots cannot be formed - Occurs about 48-72 hours after treatment - Platelet count will return to normal after about 4 days, and will require observation - More common than type II, and may not require treatment	- Considered a medical emergency - Occurs in about 1-3% of Heparin patients - Blood clots can be formed, leading to thrombosis and possible death - Occurs about 5-14 days after receiving Heparin - Treatment is required including halting heparin and using DTIs.

- In HITT, the antibodies created against HPF4 can trigger a cascade of reactions against other cell types.
- These can activate endothelial cells lining against blood vessels and white blood cells known as leukocytes.
- This activation process can create a procoagulant environment which increases the risk of thrombosis.
- This overall involvement of different cell types differentiates HITT from other thrombotic conditions.

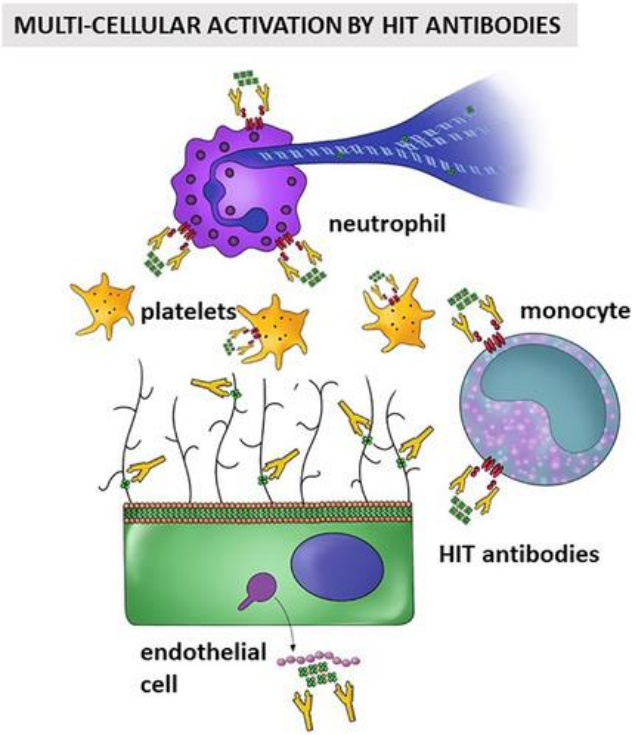


Figure 6: Showing multi-cellular activation by HIT antibodies.

(Arepally and Padmanabhan, 2020)

Cellular Contributions to HIT Thrombosis

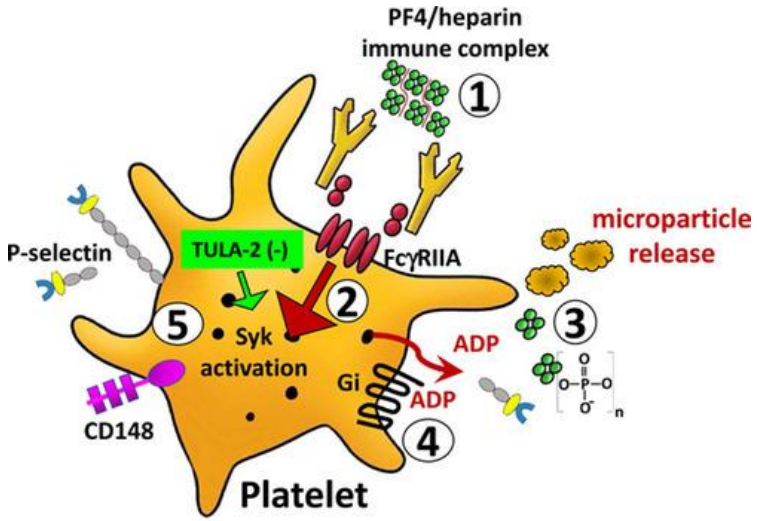


Figure 7: Cellular contributions to HIT pathology

(Arepally and Padmanabhan, 2020)

The hypercoagulable state in the blood is caused by the activation of the PF4 antibodies.

- This activates the Fcγ receptor, FcγRIIA, which binds to the protein Immunoglobulin G.
- This causes the ITAM motifs to phosphorylate (attach a phosphate group) and release ADP.
- These bind to G-coupled receptors, which generates coated platelets, which are covered in procoagulant proteins.

HITT - Hypercoagulable States

Example of an extreme complication of HITT:

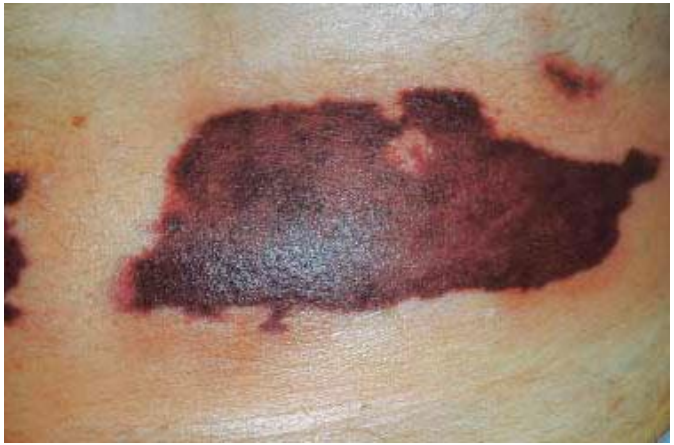


Figure 8: HITT Cutaneous Manifestation of Hypercoagulable State
(Liu, 2021)
Image Adapted from Published Description of Patient of Dr. Lucy Liu

HITT - Hypercoagulable State

- In extreme cases, hypercoagulable states can result in skin necrosis (death of the skin) due to a compromised blood supply.
- In certain cutaneous manifestations of hypercoagulable states, they appear to people as bruises.
- It is important that physicians administering heparin in patients monitor for any cutaneous abnormalities after each dosage.

Untreated HIT has a mortality rate of up to 30% with a 5-10% daily risk of thromboembolism, amputation and death.

Diagnosis of HITT:

- Clinical Diagnosis
- Patient History
- Laboratory Diagnosis

Physical Examination in patients with HITT

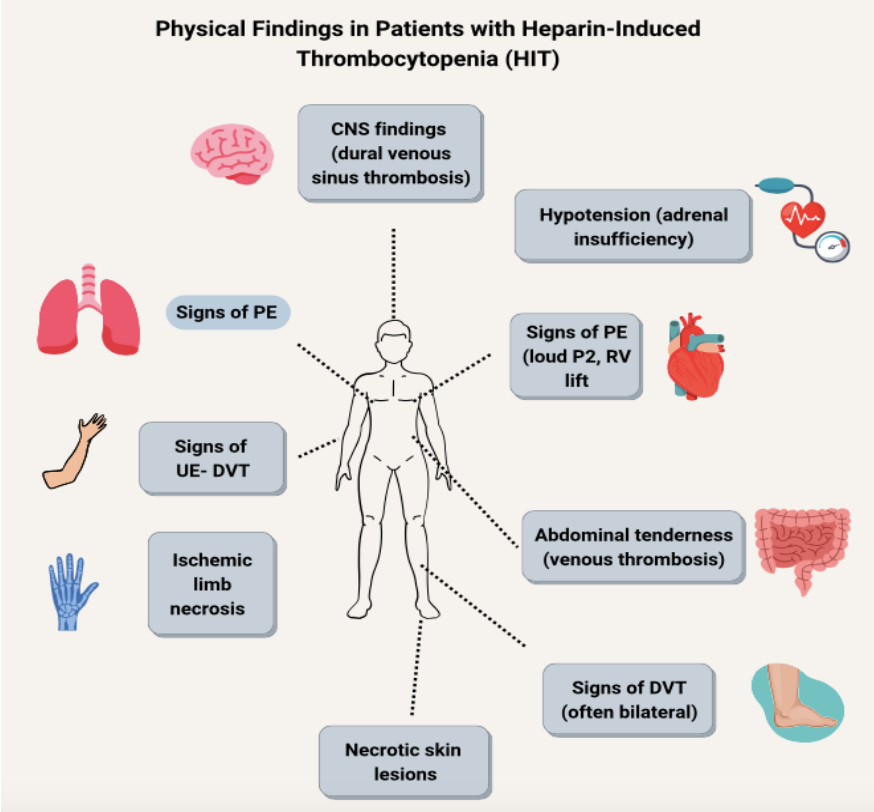


Figure 9: Showing physical examination in patients with HITT (bloodproject.com)

HITT Diagnosis - 4T Score

Thrombocytopenia	**T**iming of platelet count fall	**T**hrombosis or other sequelae	Other causes of **T**hrombocytopenia
How much has the platelet count fallen? (%)	When did platelet count fall after exposure to heparin?	Does the patient have thrombosis or skin necrosis?	Could there be other causes of thrombocytopenia?

Table 1: 4T Score for Decision Making (Cuker et al., 2012)

4Ts category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20	Platelet count 30%-50% or platelet nadir 10-19	Platelet count fall < 30% or platelet nadir < 10
Timing of platelet count fall	Clear onset days 5-10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (eg, missing platelet counts); onset after day 10; or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

6-8 points = High risk of HITT

4-5 points = Intermediate risk of HITT

0-3 points = low risk

How is HITT diagnosed in a Laboratory?

The two main laboratory procedures involved in the diagnosis of Heparin Induced Thrombotic Thrombocytopenia:

- ELISAs (Enzyme Linked Immunosorbent Assays)
- Chemiluminescence Assays

ELISAs

The Enzyme Linked Immunosorbent Assay (ELISA) is a test which is uses the properties of enzymes to display immune reactions in order to indicate if HITT is present or not.

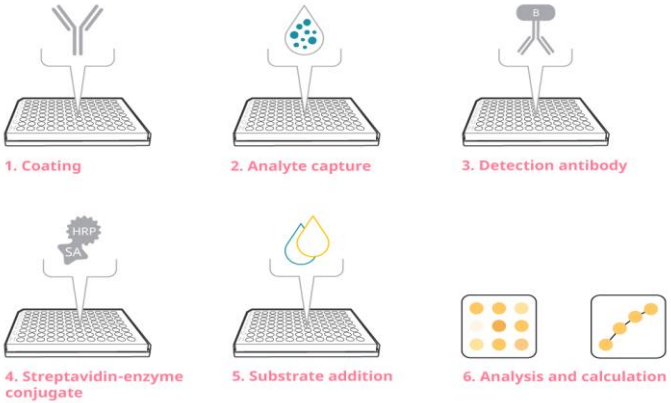


Figure 10: Showing ELISA technique
(Cleveland Clinic, 2023)

Coating the Microplate

Blocking Excessive Active Sites

Incubation and Binding

Washing any Unbound Materials

Adding Secondary Antibodies

Adding the Substrate/Enzyme Catalysis

Analysis of Results

Chemiluminescence Assays

Chemiluminescence Assays work in a 6 step series. The first 4 steps are the same as those of ELISAs but involve a divergence in process during the 5th and 6th steps. These steps include:

1) Coating the Microplate
2) Blocking Excessive Active Sites
3) Incubation and Binding
4) Washing any Unbound Materials

} Same as ELISA

5) Chemiluminescent Conjugation
6) Luminometric Light Measurement
7) Quantification of Antibodies

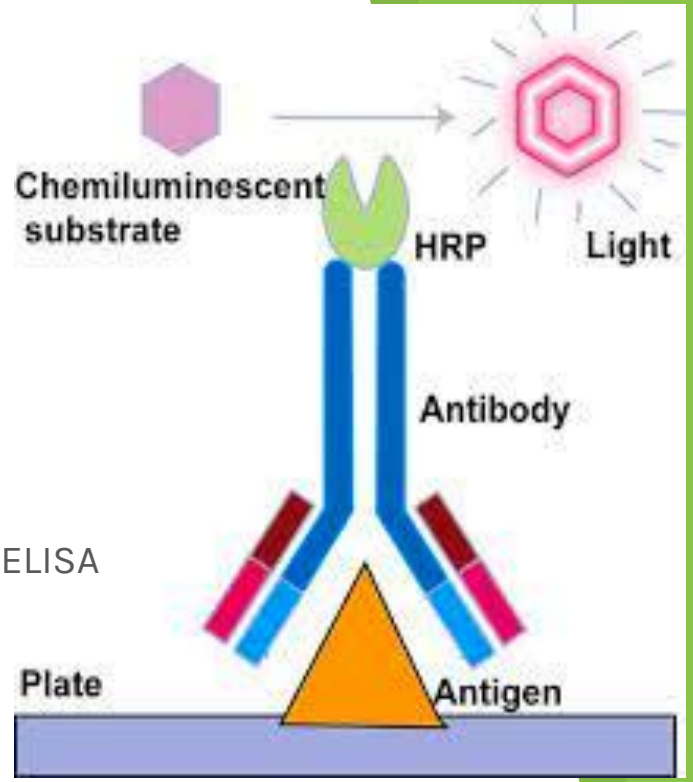


Figure 11: Showing principle of Chemiluminescence assay
(Tapeshwar Yadav, 2018)

Comparison of ELISA vs Chemiluminescence Assays

Advantages to ELISAs:

- Cost Efficient
- Long-Standing Usage

Disadvantages to ELISAs:

- Lower in sensitivity compared to newer technologies
- Limited in detection when compared with other tests
- Requires skilled technicians to perform the test
- Time consuming, requiring 3-4 hours

Advantages to Chemiluminescence Assays:

- Higher Sensitivities than ELISAs
- Shorter Incubation Periods, allowing Faster Results
- Carried Out by an automated analyzer

Disadvantages to Chemiluminescence Assays:

- Expensive to perform
- Require different equipment that is not found in all laboratories (ie. Luminometers)

Management of HITT

- **STOP HEPARIN**

- As, on average, it takes about 50-80 days for HITT antibodies to disappear, it is important that an alternative anticoagulant is used.
- Patients are typically placed on a **direct thrombin inhibitor (DTI)**, which is another form of anticoagulant.
  - Ex: Argatroban, bivalirudin

Treatments

- Direct thrombin inhibitors are a form of anticoagulant that bind directly to thrombin and have an anti-platelet effect, which makes the blood less sticky.
- **Unlike heparin, DTIs do not bind to other plasma proteins.**
- Some DTIs are derived from hirudin, which is originally from the saliva of leeches. An example of this is lepirudin or desirudin.
- Bivalirudin is another type of DTI that is synthetically engineered from 20 amino acids. Unlike hirudins, bivalirudin is reversible.
- Argatroban is a type of DTI that selectively inhibits the active site of thrombin.

Mechanism of Action - Bivalirudin and Argatroban

- Bivalirudin directly inhibits thrombin (an enzyme responsible for converting fibrinogen to fibrin, which helps clots form) by binding to the active and anion-binding exosites on thrombin.
- Unlike in heparin, bivalirudin does not bind to platelet factor 4, and cannot cause HITT.
- Argatroban also binds directly to thrombin. However, unlike bivalirudin, it only binds to the active site of thrombin.

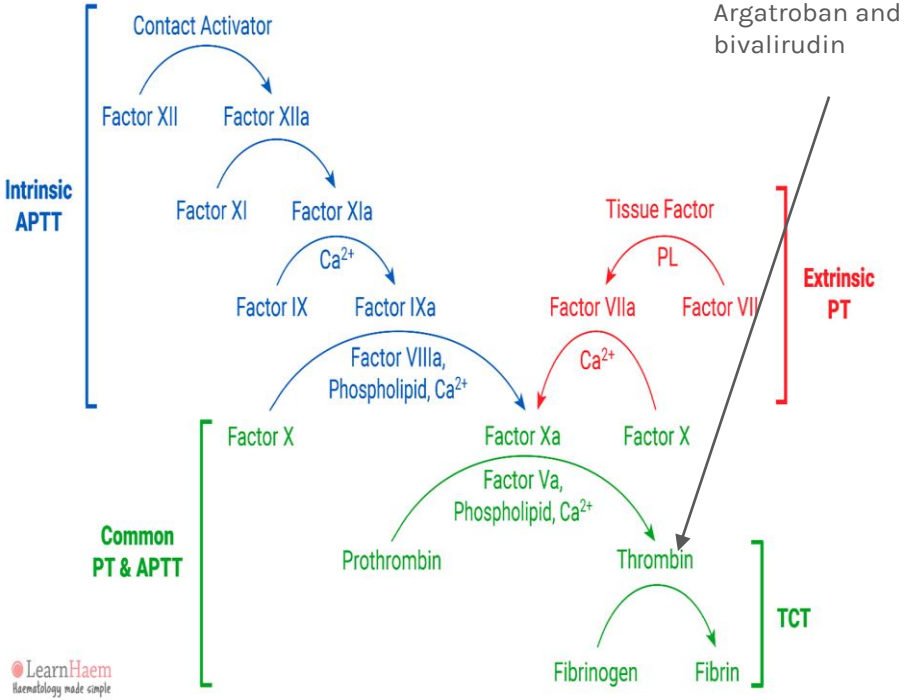


Figure 12: Coagulation cascade (LearnHaem, 2020)

Conclusions

After heparin exposure, a condition called HITT can occur. Because of this, platelet counts in the blood may drop, which can lead to many serious complications like stroke, deep venous thrombosis, pulmonary embolism, or even death.
If HITT is diagnosed, it is very important that patients are placed on alternate anticoagulants such as direct thrombin inhibitors.

HITT is a clinical emergency and requires immediate management and treatment.

Acknowledgments

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References

Ahmed, I., Majeed, A. and Powell, R. (2007). Heparin induced thrombocytopenia: diagnosis and management update. *Postgraduate Medical Journal*, [online] 83(983), pp.575–582. doi:https://doi.org/10.1136/pgmj.2007.059188.

Arepally, G.M. and Padmanabhan, A. (2020). Heparin-Induced Thrombocytopenia. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 41(1). doi:https://doi.org/10.1161/atvbaha.120.315445.

Cleveland Clinic (2023). *ELISA Technique*. [online] Cleveland Clinic. Available at: https://my.clevelandclinic.org/health/articles/24990-elisa.

Cleveland Clinic (n.d.). *What Are Direct Thrombin Inhibitors?* [online] Cleveland Clinic. Available at: https://my.clevelandclinic.org/health/treatments/25036-direct-thrombin-inhibitors.

Dowd, F. (2007). *Argatroban - an overview | ScienceDirect Topics*. [online] www.sciencedirect.com. Available at: https://www.sciencedirect.com/topics/medicine-and-dentistry/argatroban [Accessed 2 Jan. 2024].

References Ctd.

Drugbank (2018). *Heparin*. [online] go.drugbank.com. Available at: https://go.drugbank.com/drugs/DB01109.

Eke, S., May, S., Talavera, F., Nagalla, S. and Schick, P. (2023). Heparin-Induced Thrombocytopenia: Practice Essentials, Pathophysiology, Etiology. *eMedicine*. [online] Available at: https://emedicine.medscape.com/article/1357846-overview?form=fpf#a6.

Evans, E. (2022). *Coagulation Cascade | Intrinsic + Extrinsic | Geeky Medics*. [online] Geeky Medics. Available at: https://geekymedics.com/the-coagulation-cascade/.

ICU Advantage (2022). *The Clotting Cascade EXPLAINED!* [online] www.youtube.com. Available at: https://www.youtube.com/watch?v=dl6uMKJRJmQ.

Lee, C.J. and Ansell, J.E. (2011). Direct thrombin inhibitors. *British Journal of Clinical Pharmacology*, [online] 72(4), pp.581–592. doi:https://doi.org/10.1111/j.1365-2125.2011.03916.x.

McCarty, D. and Robinson, A. (2015). Factor Xa inhibitors: a novel therapeutic class for the treatment of nonvalvular atrial fibrillation. *Therapeutic Advances in Cardiovascular Disease*, 10(1), pp.37–49. doi:https://doi.org/10.1177/1753944715605011.

References Ctd.

Palta, S., Saroa, R. and Palta, A. (2014). Overview of the coagulation system. *Indian Journal of Anaesthesia*, [online] 58(5), p.515. doi:https://doi.org/10.4103/0019-5049.144643.

Páramo, J.A., Lozano, M.L., González-Porras, J.R. and Mateo, J. (2022). Current status of diagnosis and treatment of heparin-induced thrombocytopenia (HIT). *Medicina Clínica (English Edition)*, [online] 158(2), pp.82–89. doi:https://doi.org/10.1016/j.medcle.2021.05.010.

Practical Haemostasis (2018). *HIT 4T score*. [online] Practical-haemostasis.com. Available at: https://practical-haemostasis.com/Clinical%20Prediction%20Scores/Formulae%20code%20and%20formulae/Formulae/HIT/4T_HIT_score_2.html [Accessed 2 Jan. 2024].

step1.medbullets.com. (n.d.). *Heparin-Induced Thrombocytopenia (HIT) - Hematology - Medbullets Step 1*. [online] Available at: https://step1.medbullets.com/hematology/107098/heparin-induced-thrombocytopenia-hit [Accessed 12 Jan. 2024].

Tapeshwar Yadav (2018). *Chemiluminescence Immunoassay (CLIA) Technique*. [online] Slideshare. Available at: https://www.slideshare.net/TapeshwarYadav1/chemiluminescence-immunoassay-clia-technique