The Strange Story of Heparin: When a Friend Turns Into a Foe

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Introduction

- Have you ever heard that a friend of yours can turn into a foe?
- We have an interesting story to tell about heparin, which is normally given to patients and is a friend because of heparin's action of preventing and reducing blood clots.
- In some cases, heparin can cause severe health problems, with a condition called Heparin Induced Thrombocytopenia (HIT).
- People undergoing cardiac surgery are at a high risk for HIT among the many populations exposed to heparin.
- Despite a few sporadic cases of spontaneous HIT, its prevalence is much less common.

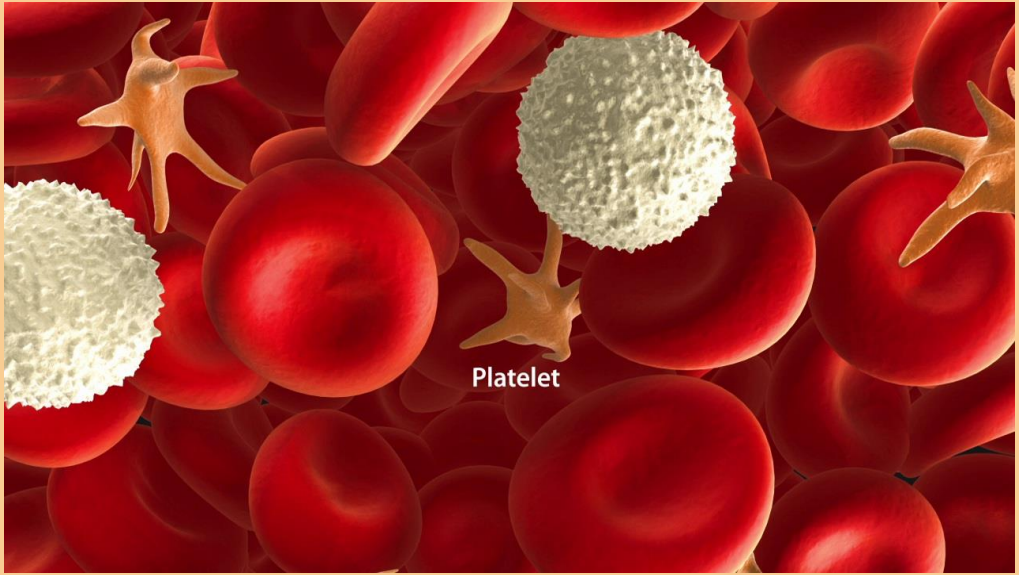
Causes of HIT

- HIT happens when patients are being treated with heparin.
- Heparin is used to treat or prevent blood clots.
- Heparin is an anticoagulant made in the liver, lungs, and other places in the human body. In certain cases instead of the heparin acting as an anticoagulant, it forms a blood clot instead.
- This happens because antibodies combine with the heparin and PF4 (Platelet Factor 4), a cytokine.
- A cytokine is a group of proteins that control growth and activity of immune cells and blood cells. Patients develop a hypercoagulable state, which is another way to say the patient has developed a blood clotting disorder.
- The patients have a higher chance of getting a blood clot.
- This complication of heparin is often confusing because in HIT, heparin does the opposite of what it is supposed to do: It forms rather than prevents new blood clots.

Causes of HIT, Contd.

- Under normal physiological conditions, PF4 is stored in alpha-granules of the platelets and is released upon platelet activation.
- PF4 is positively charged and can, therefore, bind to the negatively charged heparin (a heparin-like substance normally present on the endothelial cell surface), PF4 can also bind to exogenous heparin with a much higher affinity than heparin.
- PF4 binding to heparin may trigger the formation of Immunoglobulin G (IgG), IgA, or IgM antibodies specific to the heparin-PF4 complex.
- HIT can only occur if IgG, while attached to the heparin-PF4 complex, binds to the FC receptor on the platelet surface and leads to platelet activation.
- Activated platelets then release pro-thrombotic substances (such as thrombin) and PF4.
- As IgG activates more platelets, more PF4 is released forming more complexes with heparin, thus activating more platelets.
- This creates a severely hypercoagulable state and a continuous cycle that can only be broken when heparin is discontinued, and appropriate treatment is initiated.

Constituents of Blood



Platelets

When Does HIT Occur?

- Immune-mediated HIT usually occurs between 5 to 14 days after first beginning heparin therapy. In some exceptions, HITT develops infrequently either early (after a recent previous exposure to heparin) or late after heparin exposure.
- After heparin is administered to a patient, an immune complex can form between heparin and a specific blood factor (platelet factor 4, or “PF4”) that is released by platelets.
- The body views this “heparin-PF4” complex as a foreign substance. Therefore, an antibody is formed against the heparin-PF4 complex.
- The antibody binds to this complex and the platelets are destroyed.
- This disruption of platelets can lead to the formation of new blood clots in patients with immune-mediated HIT.
- The result can be a deep vein thrombosis (in the veins of the thigh or pelvis), pulmonary embolism, or even a heart attack or stroke.
- However, this does not seem to occur with the mild decrease in platelets associated with non-immune HIT.

Incidence of HIT

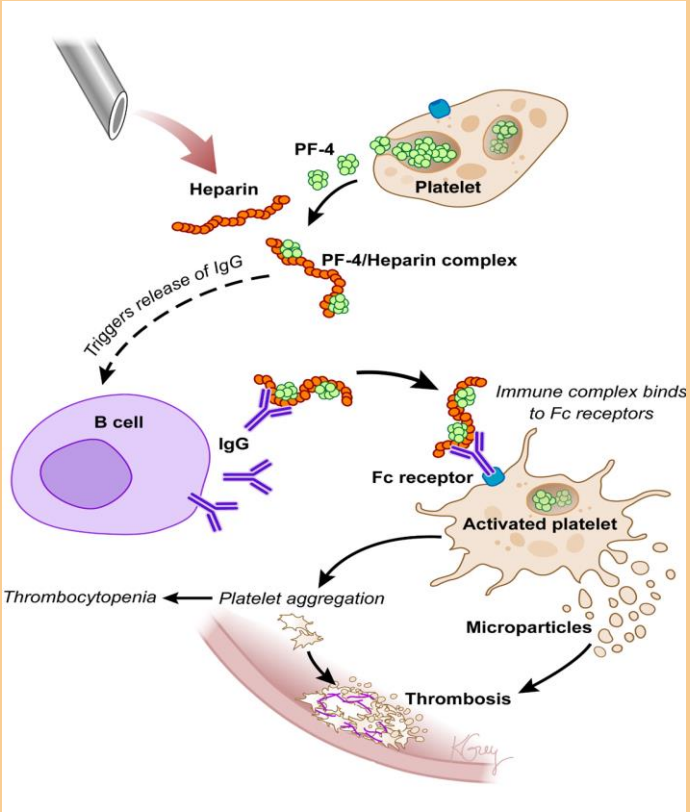
- HIT can occur in up to 5% of patients exposed to heparin products. HIT causes an extremely hypercoagulable state, where up to 50% of patients develop thromboembolic complications, associated with a mortality rate of up to 30%.
- HIT develops in 0.5% to 1% of individuals who receive unfractionated heparin for therapeutic or surgical purposes. In patients receiving low molecular weight heparin (LMWH), the incidence is significantly reduced (0.1%–0.5%).
- 5 % of 12 million = 600,000 every year
- Approximately 12 million inpatients in the United States alone are exposed to heparin each year.
- 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).
- One-third to one-half of cases of HIT are complicated by thrombosis, which may be venous or arterial and may be limb- or life-threatening.

Types of HIT

1. Nonimmune HIT, which occurs most frequently, is characterized by a mild decrease in the platelet count and is not harmful.
2. Immune-mediated HIT, occurs much less frequently but is dangerous. Immune-mediated HITT causes much lower platelet counts.

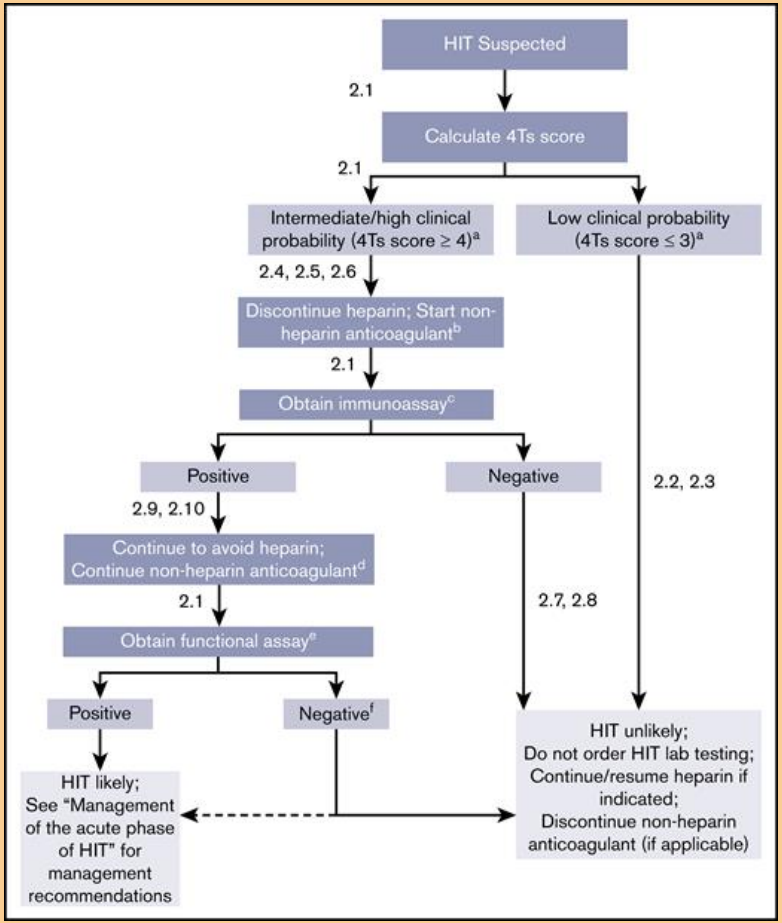
- HIT is an adverse drug reaction, mediated in most cases by immunoglobulin G antibodies that target complexes of platelet factor 4 (PF4) and heparin.
- Unfractionated heparin (UFH) and LMWH are the most widely used anticoagulants in the world among hospitalized patients.

What is the pathology of HIT?



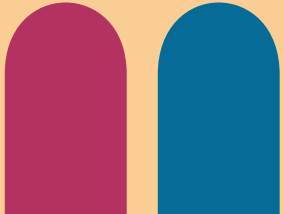
How is HIT Diagnosed?

- HIT can often be diagnosed by measuring the platelet count and PF4 antibody level in the blood. Symptoms of new blood clot formation may suggest HIT.
- Symptoms of deep vein thrombosis include pain or tenderness, sudden swelling, discoloration, visibly large veins, and skin that is warm to the touch.
- Dislodgement of clot from the deep leg veins and passage into the lungs (pulmonary embolism) may present as shortness of breath, a change in heart rate, sharp chest pain, dizziness, or feelings of anxiety and excessive sweating.
- Elevation of the 4T score (the sum of the values for each of the 4 categories). Scores of 1-3, 4-5, and 6-8 are considered to correspond to a low, intermediate, and high probability of HIT, respectively.
- Severe indicators of HIT are skin changes that present as bruising or blackening around the heparin injection site as well as the fingers, toes, and nipples that may progress to gangrene.
- The extremities are especially susceptible to the small clots that form because of HIT. If you have any of these signs or symptoms, call your doctor.

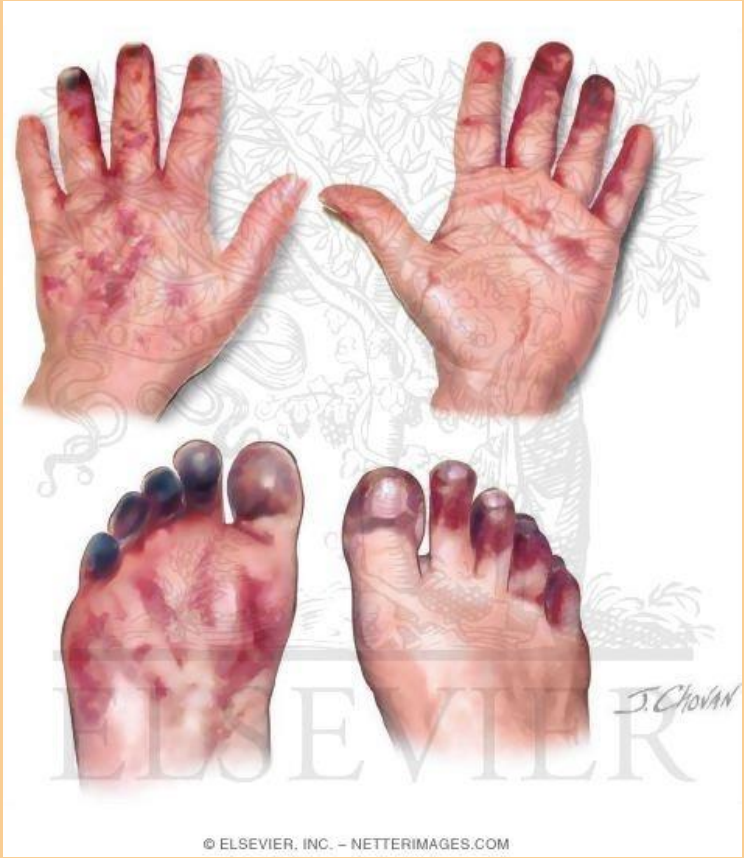

HIT Suspected
2.1
Calculate 4Ts score
2.1
Intermediate/high clinical probability (4Ts score ≥ 4)[a]
Low clinical probability (4Ts score ≤ 3)[a]
2.4, 2.5, 2.6
Discontinue heparin; Start non-heparin anticoagulant[b]
2.1
Obtain immunoassay[c]
Positive
Negative
2.2, 2.3
2.9, 2.10
Continue to avoid heparin; Continue non-heparin anticoagulant[d]
2.1
2.7, 2.8
Obtain functional assay[e]
Positive
Negative[f]
HIT likely; See "Management of the acute phase of HIT" for management recommendations
HIT unlikely; Do not order HIT lab testing; Continue/resume heparin if indicated; Discontinue non-heparin anticoagulant (if applicable)

Symptoms of HIT

- Sudden onset of discomfort, redness, and swelling in an arm or leg are among some of the symptoms.
- There may be chest pain, shortness of breath, tachycardia, hypertension, fever, and chills. Others can experience a skin rash with red patches.
- Usually, a sore or rash appears where a heparin shot was given.
- Enlargement, extension, or the creation of a new blood clot are the most typical symptoms of HIT.
- This could develop as clots in the veins or arteries.
- Deep vein thrombosis, or venous thrombosis, can affect the arm or leg, while pulmonary embolism affects the lungs.



Symptoms: Continued



Complications of HIT

- HIT is significantly linked to thromboembolic complications, including deep vein thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and amputation.
- These complications might be venous, arterial, or both.
- In addition, 10–20% of patients have skin lesions at the injection site, and up to 25% of individuals with circulating HIT antibodies develop acute systemic reactions, which are characterized by fever, chills, hypertension, tachycardia, chest discomfort, dyspnea, and gangrene.

Management of HIT

- The first step is to discontinue heparin on suspicion of HIT.
- The next step is to treat HIT using an alternative type of anticoagulant.
- Even though the platelet count is low, it is important to avoid platelet transfusions, which can “add fuel to the fire.”
- In patients with HITT non heparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a vitamin K antagonist (VKA).

Medications

- Direct thrombin inhibitors (DTI) are a class of anticoagulant medications that do not cause HIT. These drugs are administered by continuous intravenous infusion. Three DTIs have been approved by the Food and Drug Administration: argatroban, and bivalirudin. Fondaparinux can also be used.
- After several days, blood will be tested to make sure that the platelet count has returned to normal. At that point, the oral blood thinner warfarin may be prescribed in addition to the fondaparinux or DTI.
- Early identification of HIT and avoidance of inappropriate heparin therapy can help promote a safe and effective anticoagulation strategy.

Prevention of HIT

- For patients receiving heparin in whom clinicians consider the risk of HIT to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first).

The HIT Alert Card

Heparin Induced Thrombocytopenia Alert

Patient Name:_____

Date of Birth:_____

I was diagnosed with Heparin-Induced Thrombocytopenia (HIT) on (date)_____

at _____Hospital/Office, while under the care of

_____ MD.

I am currently taking Warfarin (Coumadin).

_____

I am currently on NO blood thinners (anticoagulation).

My history of heparin-induced thrombocytopenia should be taken into consideration if I require anti-coagulation. An alternative medication other than heparin and low molecular weight heparin may be required.

Conclusions

1. Today, we have reviewed a very rare but serious condition called HIT.
2. HIT appears in patients who have been given heparin.
3. HIT is an immune reaction by the body.
4. HIT can result in some serious complications including gangrene.
5. Management of HIT involves stopping heparin immediately, and administration of medications.
6. This is a strange case where our friend heparin, in some cases, can turn into a foe.

Acknowledgements

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References

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