Heparin-Induced Thrombocytopenia (HIT)

A. What is HIT?

Heparin-induced thrombocytopenia, or HIT as it is commonly known, is a serious side effect that can happen when you are being treated with heparin. Heparin is a medication used to decrease clotting or "thin the blood." Unfortunately, heparin can occasionally lead to low blood platelet counts and to life-threatening blood clots.

B. The Basics

WHO GETS HIT?

Anybody who receives heparin can develop HIT. About 2-3% of patients treated with heparin develop HIT. It can also occur in less than 1% of patients treated with another type of heparin known as low-molecular-weight heparin (LMWH). In the US, tradenames for LMWHs include dalteparin (Fragmin®), enoxaparin (Lovenox®), and tinzaparin (Innohep®). HIT is more likely to occur when higher doses of these drugs are given. But HIT can also result from very low doses – for example, the amount typically used to flush (or clean out) intravenous lines.

WHAT IS HEPARIN?

Heparin is a medication that is injected into the skin or a vein to decrease clotting, or "thin the blood." There are two forms of heparin: unfractionated and LMWH. These medications are used to prevent clots from forming or expanding. For patients confined to hospital beds or who have undergone major surgery, heparin is often used to prevent clots from forming in the veins of the legs. It can also be used to treat heart attack, stroke, deep vein thrombosis (blood clots in the deep veins of the legs or arms), or pulmonary embolus (blood clots in the lung).

C. Causes & Complications

WHAT CAUSES HIT?

HIT is sometimes referred to as "heparin allergy." However, HIT is not a true allergy. Rather, it is caused by an overreaction by the immune system to heparin. Normally, our bodies make antibodies to protect us from infection. But for unknown reasons, the immune systems in some patients make antibodies in response to treatment with heparin.

When these antibodies form, they bind, or "attach" to platelets. These platelets then become activated and begin to form clots at the wrong time and/or wrong place. This can be harmful if the clots block blood flow to or from important parts of the body, such as the heart, brain, or a limb.

After antibodies bind to platelets, these platelets are removed from the bloodstream by the body. This can lead to a low platelet count. The medical term for a low platelet count is "thrombocytopenia."

Helpful Definitions:

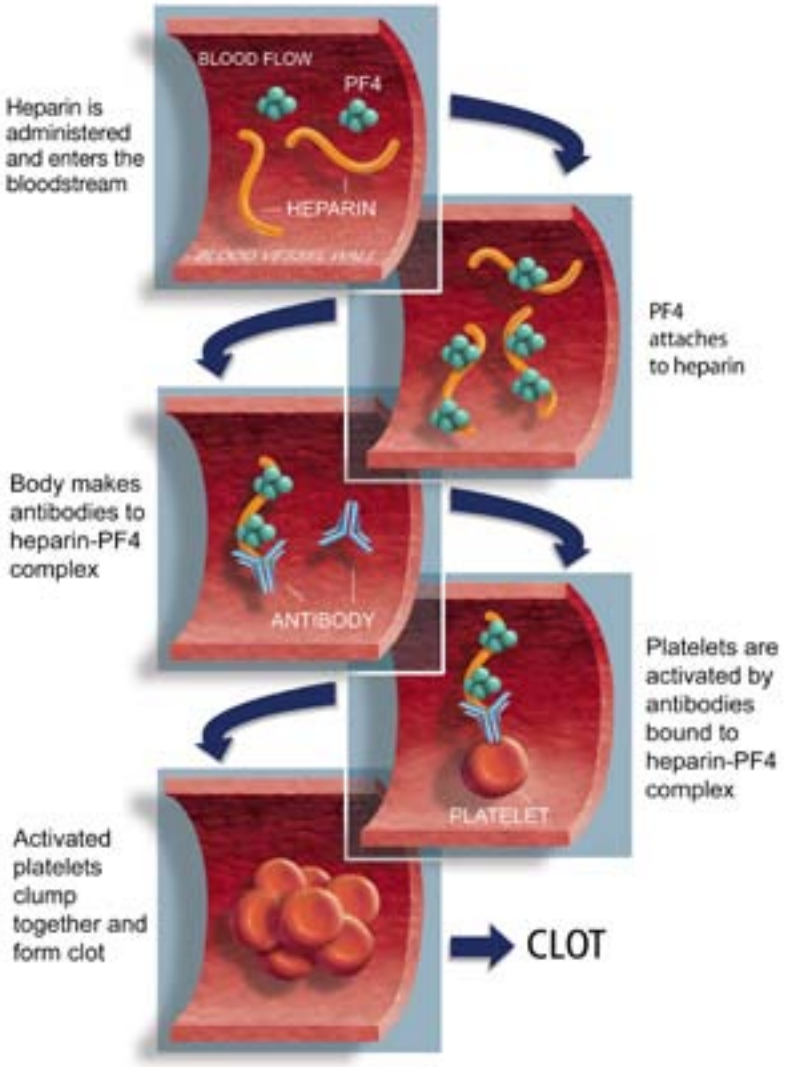
Heparin: a medication used to increase clotting or "thin the blood"

Platelet factor-4 (known as PF4): a small molecule within platelets that is important in the binding process

Antibody: a Y-shaped protein made by the body's immune system that binds to foreign substances (such as bacteria and viruses) and inactivate or marks them for removal by other parts of the immune system

Platelets: small cell-like particles in the bloodstream that help stop bleeding by forming clots

HERE'S HOW CLOTS CAN FORM IN HIT



WHAT PROBLEMS ARE CAUSED BY HIT?

HIT leads to a low platelet count, but it usually does not lead to bleeding. However, bleeding in the brain (hemorrhagic stroke) and blood loss through the intestinal tract can sometimes occur. Non-heparin blood-thinning medicines (see Table in "How is HIT Treated?") are often used to treat HIT and prevent blood clot(s) from forming or expanding. But these medicines themselves may also increase risk of bleeding.

HOW SERIOUS IS HIT?

If HIT is not recognized and treated rapidly, there's a 50% chance serious or life-threatening blood clots can form in both arteries and veins. Arteries are blood vessels that carry oxygen-rich blood away from the heart to the body. Veins return blood to the heart from the rest of the body.

Clots that form in the arteries that supply blood to the brain and heart can cause strokes and heart attacks. HIT may also cause arterial clot formation in the arms and legs, and a loss of blood supply to these areas. Clots that form in veins can lead to deep venous thrombosis (DVT), which occurs in the deep veins of the legs, arms, or the abdomen. Clots can also occur in the blood vessels in the lungs; this condition is called pulmonary embolism (PE). And clots can occur in blood vessels in the skin, leading to black and ulcerated skin lesions, called skin necrosis.

D. Diagnosis & Treatment

HOW DO I KNOW IF I'M AT RISK?

HIT is a serious medical condition and can even be fatal. You may feel well and have no worrisome symptoms even though HIT is developing. Therefore, your health care providers must periodically check your blood for platelet counts while you are being treated with heparin and for a period of time after receiving heparin. The exact schedule should be determined by your health care provider.

Your doctor may suspect you have HIT if:

- Your platelet count has fallen during treatment with heparin and if you have received heparin for at least 5 days
- You have been treated with heparin in the last 3 months
- You develop a new blood clot in spite of being on heparin

HIT usually leads to a fall in platelet count of at least 50% (from where it was prior to you receiving heparin). In rare cases, HIT may be present even though your platelet count has fallen very little, or not at all.

HOW IS HIT DIAGNOSED?

Your physician may use a scoring system called "4T score" to determine your likelihood of having HIT. The 4Ts refer to (1) Timing of the development of low platelets, (2) degree of Thrombocytopenia (i.e. degree of platelet decrease), (3) whether new Thrombosis (i.e. blood clot) has occurred during treatment with heparin, and (4) whether there is an alTernative reason for the low platelet count. If HIT is suspected, testing should be done immediately.

Tests most commonly used in diagnosing HIT:

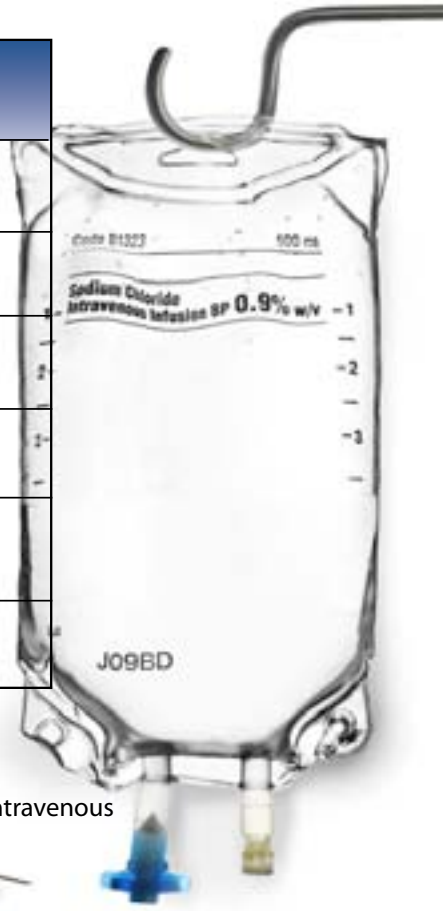
- PF4/heparin enzyme immunoassay (ELISA)
- Heparin-induced platelet aggregation assay
- Platelet serotonin release assay

Because tests results take time to get (up to several days in some cases), and because HIT requires rapid treatment, your health care providers may decide to treat you for HIT even if the testing has not been completed. In these instances, your health care providers may diagnose "possible" or "probable" HIT.

MEDICATIONS FOR HIT

Drugname(tradename)	Route of administration	Dosing frequency	Approved in U.S. for HIT?
Lepirudin (Refludan®)	IV	Continuous	Yes
Argatroban (Argatroban®)	IV	Continuous	Yes
Bivalirudin (Angiomax®)	IV	Continuous	Yes*
Desirudin (Iprivask®)	SC	Twice daily	No
Danaparoid (Orgaran®)†	IV SC	Continuous Twice daily	No
Fondaparinux (Arixtra®)	SC	Once daily	No

*Percutaneous coronary intervention only
† Not currently available in the US



IV = intravenous

SC = subcutaneous

OTHER AVAILABLE TREATMENTS

In addition to treatment with non-heparin blood thinners, your health care providers may also give you longer-term therapy with an oral blood thinner, such as warfarin (Coumadin®, Jantoven®). You can start on an oral blood thinner once your platelet count has increased to normal. Treatment with warfarin may be for a few weeks, a few months, or longer, depending mostly on whether or not you have developed a blood clot.

In some cases, serious or life-threatening clots may require surgery or treatment with special clot-dissolving drugs. Unfortunately, serious complications of clots still may develop, including loss of a limb, stroke, heart attack, or death.

Because bleeding is rare in patients with HIT and platelet counts usually return to the original level about 3-5 days after stopping heparin, platelet transfusions are typically not needed.

E. Steps You Can Take

WHAT DO I NEED TO KNOW NOW?

- If you have been diagnosed with HIT, you should inform all of your current and future health care providers that you have HIT.

- If you have been diagnosed with HIT, you should not receive heparin in any form unless advised to do so by your health care providers. This includes the LMWH drugs dalteparin (Fragmin®), enoxaparin (Lovenox®), and tinzaparin (Innohep®). In certain circumstances (such as during open-heart surgery), you may be able to receive time-limited exposure to heparin despite having had HIT. However, this is a decision that only you and your health care providers can make.

- Because blood clots due to HIT can form long after your platelet count has returned to normal, it is very important that you remain on a protective blood thinner (such as warfarin) until your health care providers tell you to stop taking it. This medication requires close lab monitoring and frequent dose adjustment, so regular follow-up with your health care provider is essential.

- You should wear a medical alert bracelet or necklace, or carry a wallet card, indicating "Heparin allergy — HIT." You can ask your physician how to obtain one, or your drug store or the Internet (www.medicalert.org) can help.

WHERE ELSE CAN I GO FOR MORE INFORMATION?

On the internet:

- Clot Connect (www.clotconnect.org) has information material for patients and health care professionals on blood clotting disorders, blood clots, and "blood thinners."
- A website maintained by the commercial supplier of argatroban provides a webpage indicating frequently asked questions about HIT: www.argatroban.com/hit_faqs.htm
- You can find informative articles on the Internet by searching for "heparin-induced thrombocytopenia" using your web search function. Be sure to consult with your health care provider about any information you find.

F. References

Note: The following articles were published in peer-reviewed medical journals and may include medical terminology that may not be familiar to most patients.

- Martel N. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106(8): 2710-2715.
- Warkentin TE. Treatment and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133:340S-380S.
- Arepally GM. Clinical Practice: Heparin-induced thrombocytopenia. N Engl J Med. 2006;355(8):809-817.
- Lo GK. Evaluation of pretest clinical score (4 Ts) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006;4:759-765.
- Cuker A. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost. 2010;8:2642-2650.
- HIT Pocket Guide for the Health Care Professional: http://lnx.mednemo.it/wp-content/uploads/2010/01/hemat.pdf

FOR YOUR PHYSICIAN

The health care provider who diagnoses you with HIT should fill out this "Patient History: HIT" document. You can then provide this document to other health care providers who are currently or will be taking care of you.

PATIENT HISTORY: HIT

(Heparin-Induced Thrombocytopenia)

Patient name: _____
Provider name: _____
Institution/Contact #: _____

Diagnosis (mark one):

☐ 4T score: ….. (enter value: 0-8; see table on next page)
☐ definite HIT
☐ possible/probable HIT

Date of diagnosis:_____

Clot present?_____
Clot treatment?_____

Platelet count prior to heparin (if known):
Platelet _____ Date _____
Platelet count nadir (lowest value):
Platelet _____ Date _____
Platelet count recovery (first day >150 x 10^9)
Platelet _____ Date _____

Confirmatory lab test (mark all that apply):

☐ heparin-PF4 ELISA
☐ heparin-induced platelet aggregation assay
☐ platelet serotonin release assay

Date of above testing: _____

Heparin exposure history:

☐ Unfractionated heparin
☐ LMWH:_____

Date of first heparin dose: _____ Dose: _____
Date of last heparin dose: _____ Dose: _____

Treatment
Alternative anticoagulant used: _____
Dates: _____ Dose: _____
Oral anticoagulant: _____
Dates: _____ Dose: _____
Goal INR: _____ Next INR check: _____

AID FOR YOUR PHYSICIAN TO CALCULATE AND UNDERSTAND YOUR 4T SCORE:

The 4T (thrombocytopenia, timing, thrombosis, and other causes) pretest probability of heparin-induced thrombocytopenia

Score:	2	1	0
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥20 x 109	Platelet count fall 30% - 50% or platelet nadir 10-19 x 109/L	Platelet count fall <30% or platelet nadir < 10 x 109/L
Timing* of fall in platelet count or thrombosis or other sequalae	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall but not clear or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent heparin exposure
Thrombosis or other clinical sequalae	New thrombosis; skin necrosis; anaphylactoid reaction after IV heparin bolus	Progressive recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis/not confirmed	None
Other cause for thrombocytopenia	No other explanation	Possible other cause evident	Definite other cause present

High probability: 6 to 8 point; intermediate probability 4 to 5; low probability 0 to 3

*Timing refers to first day of exposure to heparin

ABBREVIATIONS:

- HIT: Heparin-induced thrombocytopenia
- LMWH: low-molecular-weight heparin
- PF4: platelet factor 4

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