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Turkish Society of Hematology

Heparin Induced Thrombocytopenia

Elif G UMIT



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Plan of the lecture

- Terminology of HIT
- Incidence and Risk Factors
- Diagnosis
- Management



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Terminology

Type I HIT

- Mild-transient decline in platelet counts
- Within the 2 days of heparin exposure and returns to normal with continued heparin administration
- Regarded as non-immune platelet aggregation

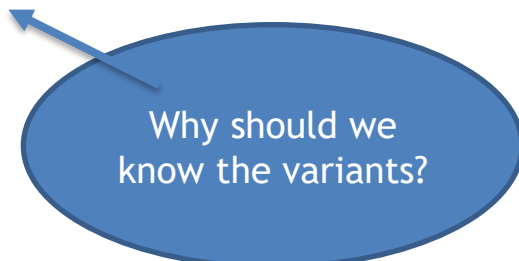
Type II HIT

- The condition we all refer to, when use the name HIT
- Also called as HITT (Heparin induced thrombocytopenia and thrombosis)



Terminology-Variants

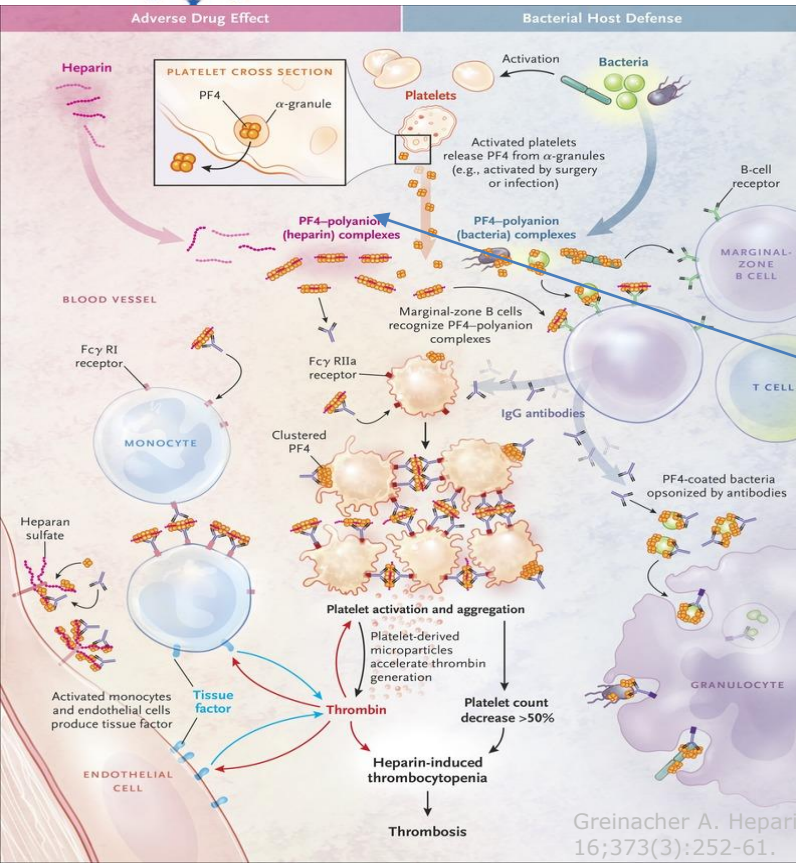
- Delayed Onset HIT: thrombocytopenia occurring ≥ 5 days after heparin was stopped.
- Refractory (Persistent) HIT
- Spontaneous HIT: In the absence of heparin exposure
 - Vaccine induced thrombocytopenia and thrombosis



Why should we know the variants?

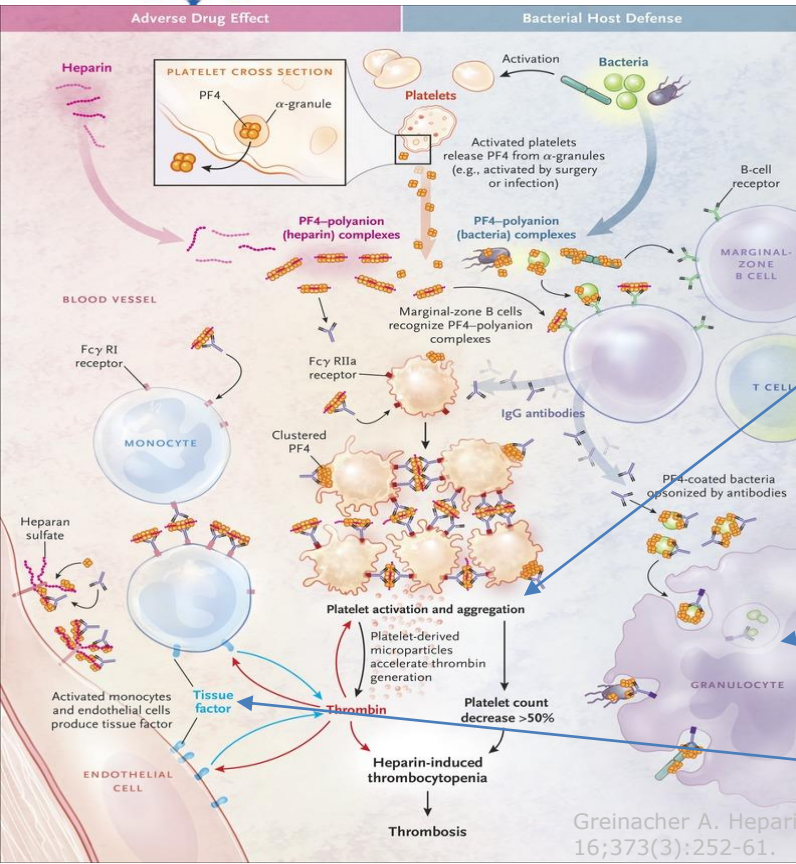


Patophysiology



Heparin forming polyanion complex with PF4

Mechanism of thrombosis



Platelet activation and aggregation


NETosis

Tissue factor from endothelial activation



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Incidence and Risk Factors

- Surgery
- Unfractionated heparin
- Dose of heparin (therapeutic/prophylaxis)
- Female sex 
- Age



When to suspect?

- New onset of thrombocytopenia
 - A decrease in platelet count by 50%
 - Venous/arterial thrombosis 50%
 - Necrotic skin lesions of injection (esp fatty areas)
 - Acute systemic reactions after heparin injection
- } 85-90%



Probability Score «4Ts»

- Thrombocytopenia

- Fall >50% and nadir $\geq 20 \times 10^9/l$ **2 points**
- Fall 30-50% or nadir $10-19 \times 10^9/l$ **1 points**
- Fall <30% or nadir $<10 \times 10^9/l$ **0 points**

- Timing of platelet decline

- Clear onset between days 5-10 or fall ≤ 1 day if there is a history of exposure within 30 days **2 points**
- Fall at days 5-10, after day 10 or fall ≤ 1 day if there is a history of exposure within 30-100 days **1 point**
- Fall <4 days **0 points**

- Thrombosis



- Confirmed thrombosis **2 points**
- Progressive or recurrent or suspected **1 point**

- Other causes

- None apparent **2 points**
- Possible **1 point**



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Interpretation of «4Ts»

- 0-3 points: Low probability
- 4-5 points: Intermediate probability
- 6-8 points: High probability



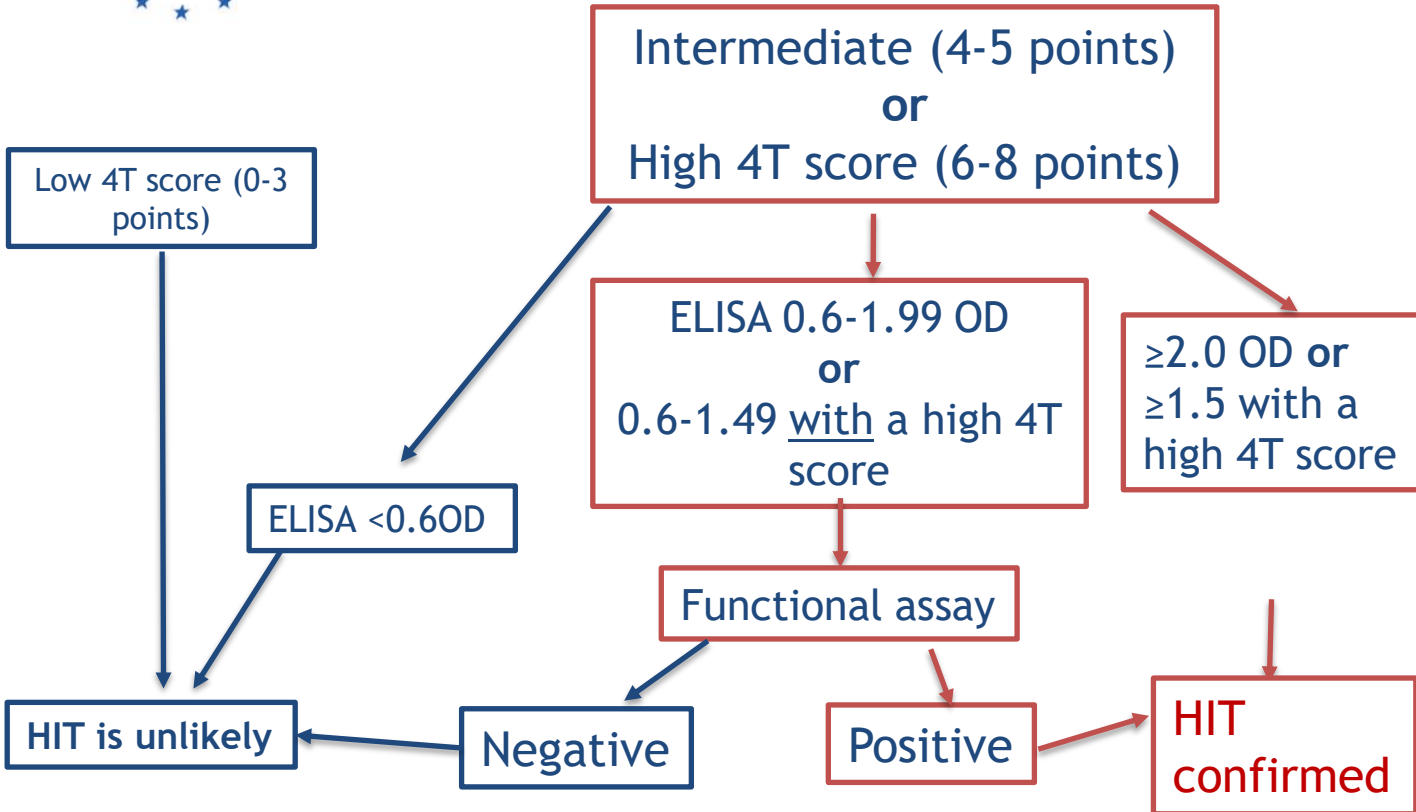
Diagnostic Tests

- HIT antibody testing
 - Aggregation
 - Immunoassays (aka PF4-heparin ELISA): expressed in optical density (OD)
 - Functional assays: the ability of PF4 heparin antibodies to bind and activate platelets
 - Serotonin release assay
 - Heparin induced platelet activation (HIPA)



Other assays

- PF4 dependent P-selectin expression assay (PEA)
- Functional flow cytometric assay: heparin dependent platelet activation with an anti- p – selectin (CD41a and CD62)





Management

Two major goals

- To terminate and control platelet activation
 - To eliminate heparin exposure
- To anticoagulate with a non-heparin anticoagulant at a therapeutic level
 - Risk of thrombosis is high even there is no thrombotic event



- Stop heparin if there is a suspected HIT
 - Use 4Ts to rationalize the decision
- If warfarin is used, hold or reverse until you're sure that the patient is adequately anticoagulated at a therapeutic level
- Start full dose anticoagulation with a non heparin anticoagulant



Why do we need to anticoagulate?

- Cessation of heparin alone is not sufficient.
 - In patients with HIT but without thrombosis, the subsequent 30 day thrombosis risk is 53% and 45%*

* Warkentin TE A 14 year study of heparin induced thrombocytopenia Am J Med 1996

* Wallis DE et al. Failure of early heparin cessation as treatment of HIT Am J Med 1999



Choice and dose of anticoagulation

- Not warfarin for initial anticoagulation
- Argatroban: direct thrombin inhibitor. Monitored with aPTT
 - Starting dose 1-2 mcg/kg/min
 - Dose adjustment not required in renal insufficiency.
 - If bilirubin is >1.5 mg/dL start with a lower dose



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- Bivaluridin: direct thrombin inhibitor. Monitored with aPTT.
 - Starting dose *.15 mg/kg/hour
 - Lower dose in renal or hepatic insufficiency



- Danaparoid: a heparinoid, monitored with antiXa activity
- Fondaparinux: a heparin version which does not interact with PF4.
 - Starting dose 5-10 mg/day (usually 7.5 for an average adult)



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DOACs

- Rivaroxaban
- Apixaban
- Edoxaban

- Dabigatran

Tran PN, Tran MH. Emerging Role of Direct Oral Anticoagulants in the Management of Heparin-Induced Thrombocytopenia. Clin Appl Thromb Hemost. 2018 Mar;24(2):201-209.

Barlow A, Barlow B, Reinaker T, Harris J. Potential Role of Direct Oral Anticoagulants in the Management of Heparin-induced Thrombocytopenia. Pharmacotherapy. 2019 Aug;39(8):837-853



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Duration of anticoagulation

- At least 4 weeks if there is no thrombotic event
- 3 months if there is a thrombotic event

*ASH 2018 guideline states, the duration may be shorter in nonthrombotic patients



Additional Management

- IVIG:
 - In persistent/refractory cases
 - 1g/kg once daily for 2 days
 - or
 - 0.4/kg/day for 4-5 days



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Prevention

- Life long heparin avoidance!



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