Heparin Induced Thrombocytopenia

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Sample Case

- 64 yo woman with endocarditis
- Platelet count decreases from 161k on day 7 to 60k on day 9
- Been receiving low molecular weight heparin 40k daily since admission

HIT

- Does not induce bleeding
- Paradoxical PROTHROMBOTIC state
- 1 in 5000 patients
- 1 to 3% risk after cardiac surgery
- In 50 % of patients with HIT, thrombotic complications occur

HIT

KEY CLINICAL POINTS

EPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is characterized by a decrease in the platelet count of more than 50% from the highest platelet count value after the start of heparin, an onset 5 to 10 days after the start of heparin, hypercoagulability, and the presence of heparin-dependent, platelet-activating IgG antibodies.

Use of a scoring system that takes into account the timing and magnitude of the platelet count fall, new thrombosis, and the likelihood of other reasons for thrombocytopenia is helpful in assessing the pretest probability of HIT.

Delayed-onset HIT develops after the cessation of heparin, and spontaneous or autoimmune HIT develops in the absence of heparin exposure.

Platelet factor 4–heparin antibody tests should be ordered only if clinical features reasonably suggest HIT. These tests have a high negative predictive value but a low positive predictive value.

Treatment of acute HIT requires the cessation of heparin and the initiation of therapeutic-dose anticoagulation with an alternative agent (argatroban, danaparoid, fondaparinux, or bivalirudin).

Warfarin should be avoided in patients with acute HIT.

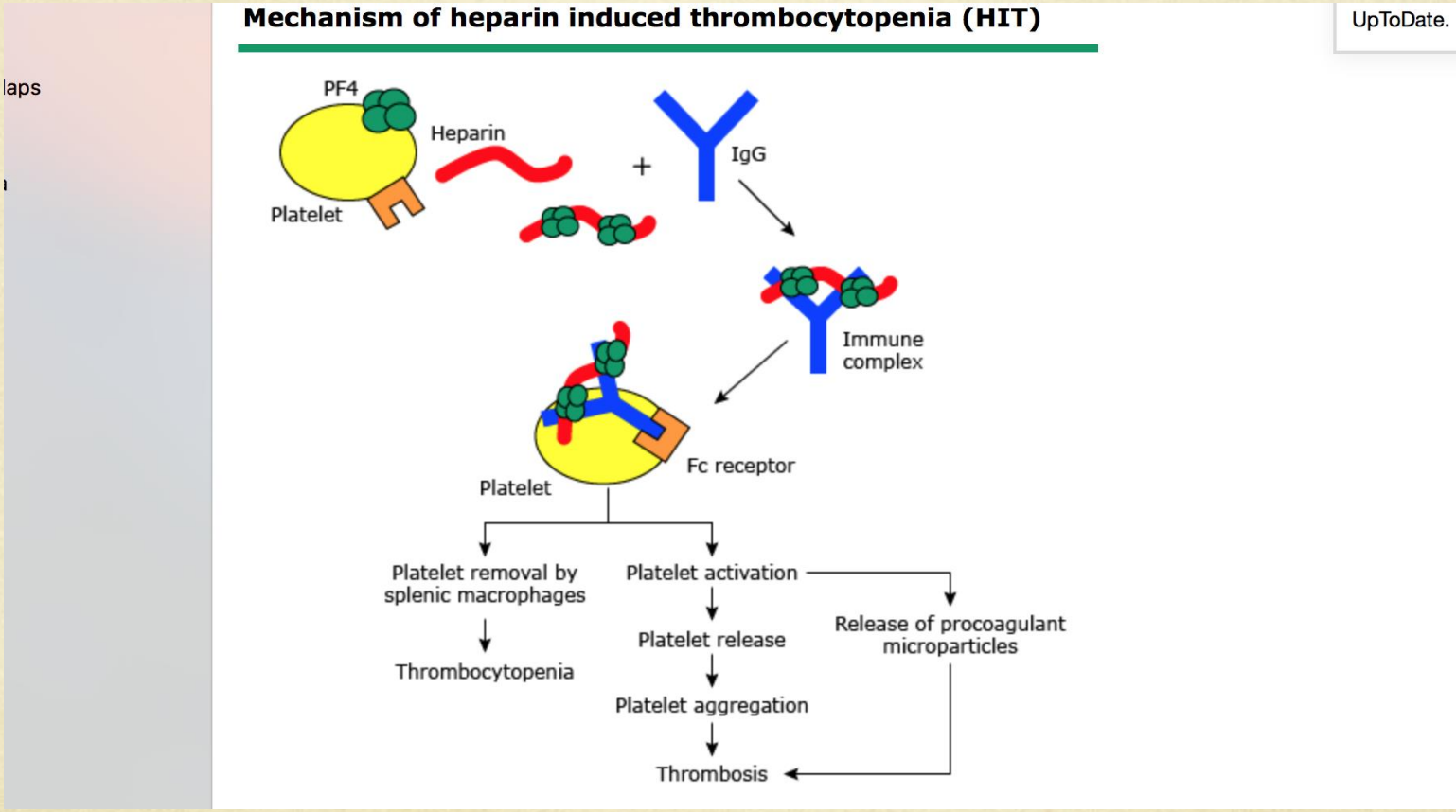
Onset of HIT

- 5-10 days after exposure
- Surgery can reset the clock
- Heparin exposure within 90 days
  - Abrupt onset HIT
  - Anaphalactic reaction within 30 min
- Catastrophic HIT

Pathogenesis

- IgG antibodies recogizes neoepitopes on positively charged chemokine PF4 within PF4-polyanion complexes
- PF4 binds heparin
  - Can bond other polyanions
  - Nucleic acids/polysaccharides on bacteria
- PF4-heparin complexes coat platelets
  - Induce IgG response

Pathogenesis



Risk of HIT

- 10x higher in unfractionated heparin
- Higher risk after major surgery
- Rare on obstetrics

Diagnosis of HIT

- More than 50% drop
- 5-10 days after exposure
- 4 T scoring system

Types of HIT

- Type 1
  - Within one to two days
  - Often returns to normal, with continued heparin
  - Non immune mediated platelet aggregation
  - Nadir typically 100k
- Type 2
  - Antibodies to PF4 complexed to heparin
  - Clinically significant

Type of HIT

Distinguishing characteristics of the two types of heparin-induced thrombocytopenia

	Type 1	Type 2
Frequency	10 to 20 percent	1 to 3 percent
Timing of onset	1 to 4 days	5 to 10 days after start of heparin
Nadir platelet count	100,000/microL	usually >20,000/microL; median nadir 60,000/microL
Antibody mediated	No	Yes
Thromboembolic sequelae	None	30 to 80 percent
Hemorrhagic sequelae	None	Rare
Management	Observe	Cessation of heparin, alternative nonheparin anticoagulation to prevent thrombosis

Adapted from: Brieger DB, Mak KH, Kottke-Marchant K, Topol EJ. Heparin-induced thrombocytopenia. J Am Coll Cardiol 1998; 31:1449.

Graphic 50170 Version 2.0

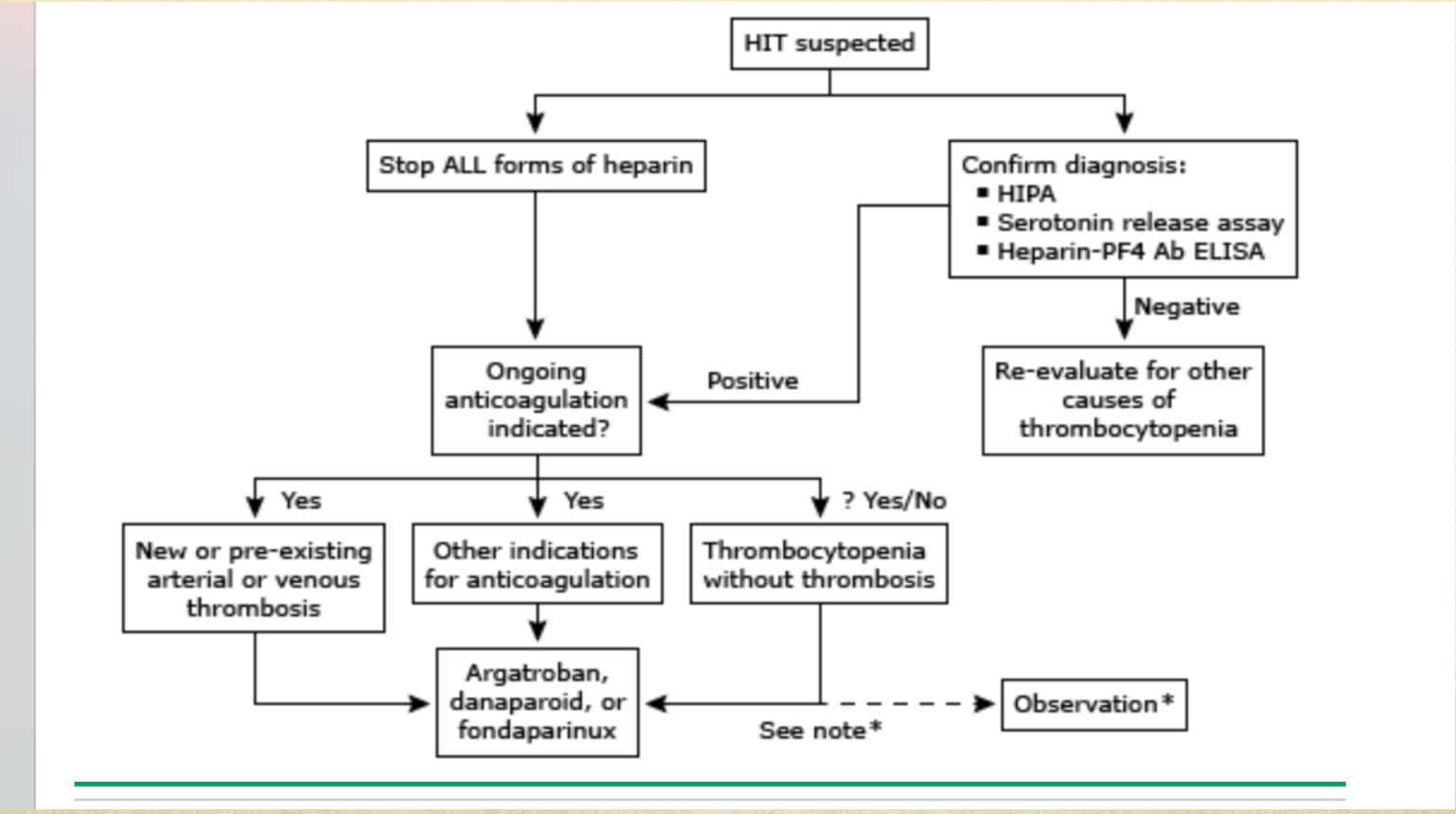
4 T score

Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.*

Variable	Score		
	2	1	0
Acute thrombocytopenia	Platelet count decrease of >50% and nadir ≥20,000/mm^3	Platelet count decrease of 30–50% or nadir 10,000–19,000/mm^3	Platelet count decrease of <30% or nadir ≤10,000/mm^3
Timing of onset	Day 5–10, or day 1 if recent heparin exposure	>Day 10 or unclear exposure	≤Day 4 with no recent heparin exposure
Thrombosis	New thrombosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other cause of thrombocytopenia	None	Possible	Definite
Total score	6–8, indicating high score	4 or 5, indicating intermediate score	0–3, indicating low score

* Adapted from Lo et al.[31] A low 4T score (0 to 3 points) has a high negative predictive value. The day that heparin was started is considered as day 0. The onset of heparin-induced thrombocytopenia (HIT) is defined as the day that the platelet count begins to decrease. Patients in whom the score is difficult to apply, owing to missing platelet count values or coexisting conditions causing thrombocytopenia, and those with an intermediate or high score require further evaluation

HIT


HIT suspected
Stop ALL forms of heparin
Confirm diagnosis:
HIPA
Serotonin release assay
Heparin-PF4 Ab ELISA
Negative
Positive
Ongoing anticoagulation indicated?
Re-evaluate for other causes of thrombocytopenia
Yes
Yes
? Yes/No
New or pre-existing arterial or venous thrombosis
Other indications for anticoagulation
Thrombocytopenia without thrombosis
Argatroban, danaparoid, or fondaparinux
See note*
Observation*

Delayed Onset HIT

- Thrombosis after heparin has been withdrawn
- > than 5-10 days after exposure
- High morbidity, can present with thrombosis on readmission
  - If treated with heparin, higher complication rate

HIT

- Subclinical HIT
  - Refers to patient has recovered from HIT
  - Still present antibodies

HIT

- Spontaneous HIT
  - Has been described without heparin exposure
  - Associated with venous and arterial thrombosis
  - Typical previous infectious (gram neg bacteria) or inflammatory event
  - Pos immunoassay
  - Significant inflammatory response causing activation of PF4 without need for heparin, causing platelet activation
  - Non heparin polyanions causing activation of PF4 directed antibodies

Complications

Complications

- Venous more common than arterial events
- Complications of thrombosis
  - Skin necrosis
  - Gangrene
  - Organ ischemia

Testing after surgery

Patient population, frequency of HIT-IgG antibodies, and clinical HIT

Patient population	Days of treatment	Frequency heparin-induced antibodies		Frequency of clinical HIT, percent
		Activation assay, percent	Antigen assay, percent	
Cardiac, UFH	5.1 ± 2.2 (SD)	20.0	50.0	1.0
Orthopedic, UFH	9.2 ± 2.2	9.3	14.1	4.9
Orthopedic, LMWH	9.5 ± 3.0	3.2	7.5	0.9

Lab Testing for HIT

- ELIZA testing: Anti PF4 heparin enzyme immunoassay
  - Low positive predictive value
  - Can lead to overdiagnosis/treatment
  - Antibodies typically present before drop in platelets

Lab testing for HIT

- Functional Assays
  - Increase specificity
  - Longer time to get results
- Serotonin Release Assay
  - Negative value essentially rules out HIT
- Use of T score and ELIZA to help determine need of treatment

Bleeding

- Typically low complications of bleeding
- No need for prophylactic transfusions
- Rarely < 20k
- Platelets can be transfused if needed/bleeding

Differential Diagnosis

- Disseminated Intravascular Coagulation
- Thrombotic microangiopathic process
- ITP
- Thrombocytopenia from medications

Treatment of HIT

- Prompt cessation of heparin products
- Alternative anticoagulation at a therapeutic dose
  - Prophylactic dosing not sufficent

Timing of alternative anticoagulation

- Plt count > 150 x 2 days
- Then consider Vit K antagonists
- Risk of gangrene/limb loss
  - Decreasing protein C

Treatment of alternative anticoagulation

- Overlap of second anticoagulant needed
  - At least 5 days!

Treatment

- Argatroban
  - FDA approved HIT
- Danaparoid
  - FDA approved HIT
- Fondoparinux
  - Not FDA approved
- Bivalrudin
  - FDA approved more in HIT patients undergoing PCI

Argatroban

- Used in critically ill patients
- Requires IV administration
- Affects INR
  - Makes bridging difficult
  - Recall need baseline INR, may need to keep on argatroban until INR > 4
  - Need to bridge x 5 days

Danaparoid

- IV or subcutaneous administration
- Can be monitored using Xa levels

Fondaparinaux

- Nice alternative in outpt setting
- Not approved
  - Retrospective Data

Direct thrombin inhibitors

- No studies
- Theoretically could be considered but need more data
- Some case reports
  - Possibly consider if no other options.....

Length of anticoagulation

- If no thrombosis
  - Unclear need for length of anticoagulation
  - At least one month (my preference is 3 months)
- If thrombosis
  - 3months is the minimum
  - ? Need to repeat HIT antibodies

Rechallenge

- Avoid if at all possible….
- CPB after HIT
  - Repeat functional assays
    - Consider rechallenge if negative
  - Bivalrudin or Argatroban if urgent or positive assay

Patience....


"Your insurance has run out. We're discharging you from the 'Observation Care' floor to the 'Who Cares?' room in the basement."
CARTOONSTOCK .com
Search ID: cwln567

Case

- Decrease in platelet count after LMWH
- T score 5 (decrease in platelet count 2, timing 2, thrombosis 0, and likelihood of other reasons 1)
- Testing and then treatment

THANK YOU !!!!