Heparin-Induced Thrombocytopenia

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Heparin-Induced Thrombocytopenia (HIT)

- Immune-mediated adverse drug reaction to heparin
- Thrombocytopenia with paradoxical prothrombotic state
- Life-threatening state requiring timely recognition for treatment initiation

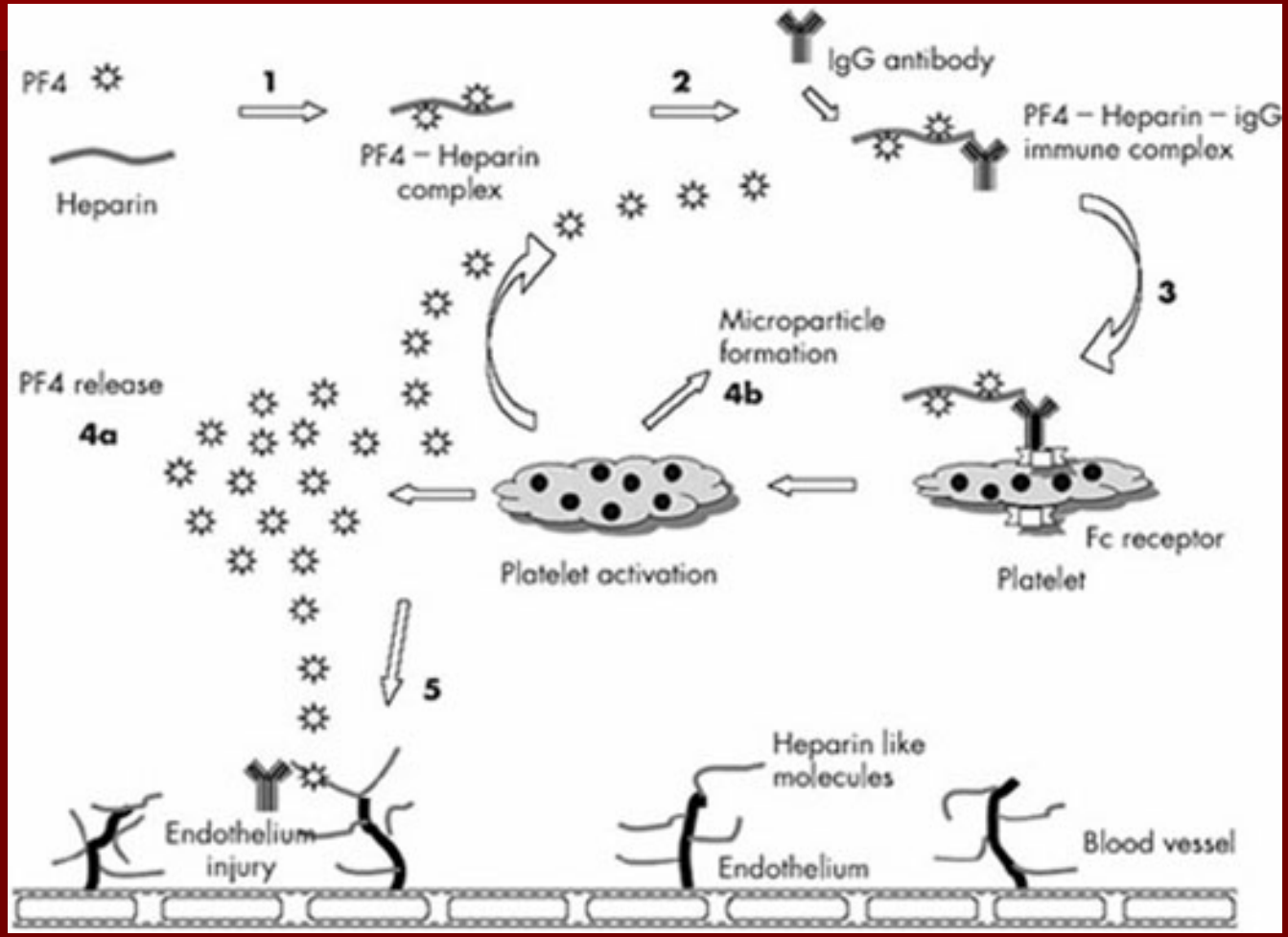
Pathophysiology

- Heparin activates platelets
  - Platelet activation releases platelet-factor 4 (PF4) from platelets
    - PF4 binds to heparin forming PF4-heparin complexes
      - IgG forms and binds to PF4-heparin complexes

Pathophysiology

- PF4-heparin-IgG immune complexes
  - Monocytes and macrophages attack immune complexes and eliminate them
    - Thrombocytopenia occurs
  - By activating platelets, thrombin is released through feedback mechanism
    - Prothrombotic state results

Pathophysiology



HIT

- Causes
  - UFH
    - IV > SC
  - LMWH
    - UFH > LMWH
- Thrombocytopenia
  - Absolute
    - Platelet decrease to < 150,000 mm^3
  - Relative
    - Platelet decrease of 50% or more after heparin started
  - Nadir rarely < 20,000 mm^3

HIT

- Type I
  - Transient, mild thrombocytopenia due to the effect of heparin on platelets, causing platelet aggregation
  - Early onset (<4 days after heparin start)
  - Non-immune mediated
  - Low thrombosis risk

HIT

- Type II
  - Severe, immune-mediated adverse drug reaction
  - Typical onset **(5-10 days after heparin start)**
  - Classic "HIT" with life-threatening thrombotic considerations
  - Requires immediate treatment if suspicion is intermediate or high

HIT

- Outcomes
  - Thromboembolic complications
    - Deep vein thrombosis (DVT)
    - Pulmonary embolism (PE)
    - Myocardial infarction (MI)
    - Stroke
  - Limb amputation
  - Death

HIT vs HITTS

- HIT
  - HIT diagnosed before thrombosis occurs
- HITTS
  - Heparin-Induced Thrombocytopenia with Thrombosis
  - HIT diagnosed with an existing thrombus
  - Venous or arterial thrombus
- Treatment is the *same*

Risk

- Heparin exposure > 4 to 5 days
  - UFH > LMWH
  - Bovine > porcine sources
- Patients
  - Post-op surgery > general medicine
    - Orthopedic surgery > cardiac and vascular surgery
  - Female > male

Is it HIT?

- *Clinical judgment is key*
- Consider differential diagnoses
  - Other drug causes, illnesses, infection, procedures/surgeries
- Level of HIT suspicion
  - Low, Intermediate, High
- Laboratory Tests

Laboratory Tests

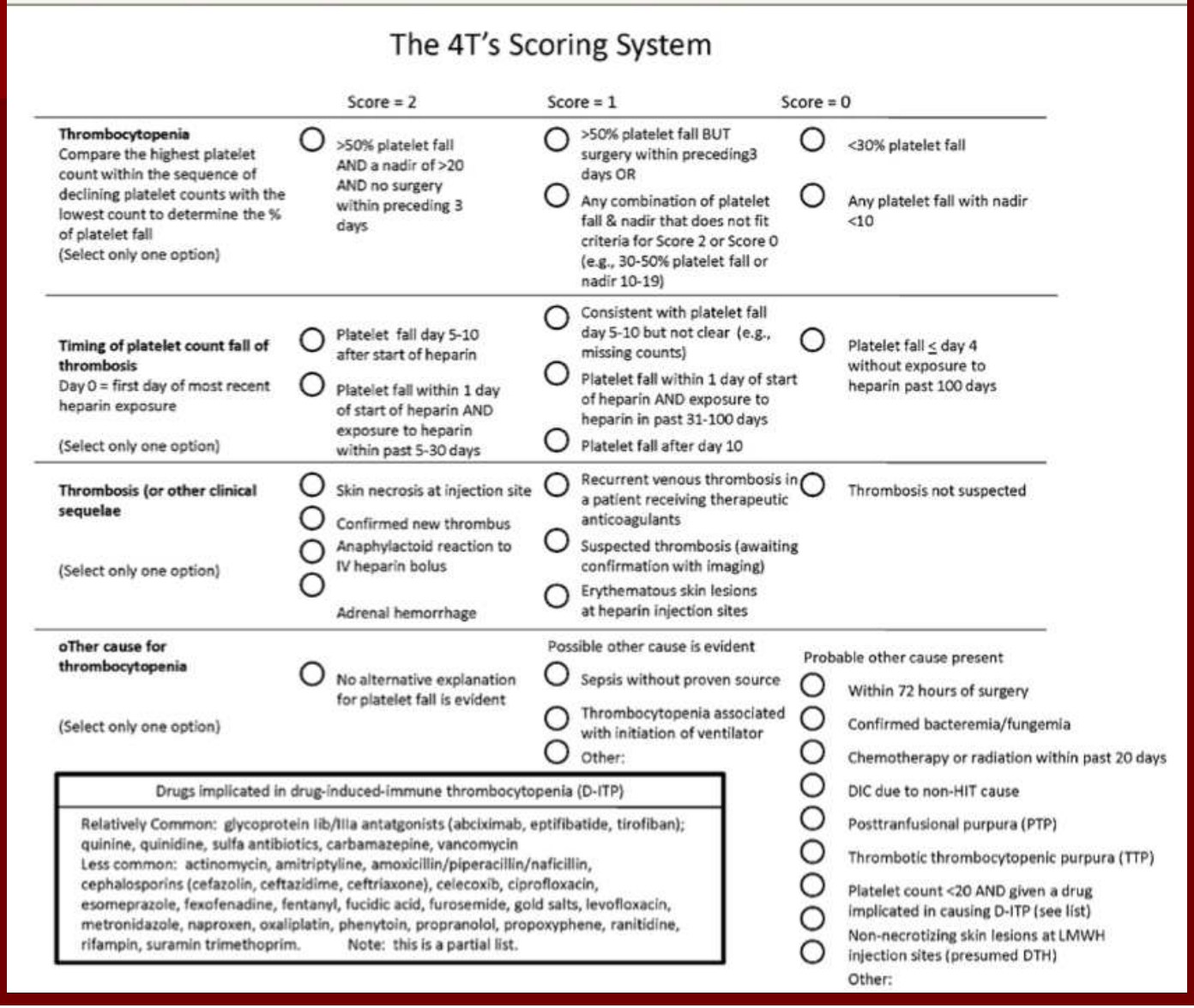
- Serologic/Antigenic Assays
  - ELISA assay
  - Detects antibodies against PF4-heparin complex
  - Highly sensitive, less specific
    - High false positive rate
- Functional Assays
  - Serotonin Release Assay (SRA)
  - Highly sensitive and specific for HIT (>95%)
  - Provides confirmation of + ELISA result

Is it HIT?

- "4 T's" Scoring System
  - Helps to identify need for laboratory HIT testing
  - Assigns a point value to the likelihood of HIT
  - Correlates with ELISA laboratory test results
    - Thrombocytopenia
    - Timing
    - Thrombosis
    - Other causes of thrombocytopenia

4 T's

Figure 2. The 4-T's scoring system. DIC = disseminated intravascular coagulation, DTH = delayed-type hypersensitivity; IV = intravenous, LMWH = low-molecular-weight heparin. Reprinted with permission from reference 5.



The 4T's Scoring System

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall (Select only one option)	○ >50% platelet fall AND a nadir of >20 AND no surgery within preceding 3 days	○ >50% platelet fall BUT surgery within preceding3 days OR ○ Any combination of platelet fall & nadir that does not fit criteria for Score 2 or Score 0 (e.g., 30-50% platelet fall or nadir 10-19)	○ <30% platelet fall ○ Any platelet fall with nadir <10
Timing of platelet count fall of thrombosis Day 0 = first day of most recent heparin exposure (Select only one option)	○ Platelet fall day 5-10 after start of heparin ○ Platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	○ Consistent with platelet fall day 5-10 but not clear (e.g., missing counts) ○ Platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days ○ Platelet fall after day 10	○ Platelet fall ≤ day 4 without exposure to heparin past 100 days
Thrombosis (or other clinical sequelae (Select only one option)	○ Skin necrosis at injection site ○ Confirmed new thrombus ○ Anaphylactoid reaction to IV heparin bolus ○ Adrenal hemorrhage	○ Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants ○ Suspected thrombosis (awaiting confirmation with imaging) ○ Erythematous skin lesions at heparin injection sites	○ Thrombosis not suspected
oTher cause for thrombocytopenia (Select only one option)	○ No alternative explanation for platelet fall is evident	Possible other cause is evident ○ Sepsis without proven source ○ Thrombocytopenia associated with initiation of ventilator ○ Other:	Probable other cause present ○ Within 72 hours of surgery ○ Confirmed bacteremia/fungemia ○ Chemotherapy or radiation within past 20 days ○ DIC due to non-HIT cause ○ Posttranfusional purpura (PTP) ○ Thrombotic thrombocytopenic purpura (TTP) ○ Platelet count <20 AND given a drug implicated in causing D-ITP (see list) ○ Non-necrotizing skin lesions at LMWH injection sites (presumed DTH) Other:

Drugs implicated in drug-induced-immune thrombocytopenia (D-ITP)

Relatively Common: glycoprotein IIb/IIIa antatgonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin
Less common: actinomycin, amitriptyline, amoxicillin/piperacillin/naficillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin trimethoprim. Note: this is a partial list.

Treatment

- Discontinue ALL forms of heparin
  - Pharmacist's role
  - IV, SC, flushes, coated catheters
- AVOID
  - LMWH
  - Coumadin alone
  - Platelet transfusions

Treatment

- Direct Thrombin Inhibitor (DTI) Therapy
  - Argatroban infusion
    - FDA approved for HIT treatment
  - Bivalirudin infusion
    - FDA approved for HIT treatment in patients undergoing PCI or cardiac surgery
  - Lepirudin
    - No longer available due to manufacturer financial reasons

Argatroban

- Continuous intravenous infusion
- Monitored by aPTT
  - Baseline, 2 hours after initiation and each rate change
  - Target range 1.5 – 3 times control
- Half-life 39-51 minutes
- Hepatic elimination
- Falsely elevates INR

Argatroban Dosing

Patient Characteristic	Initial Infusion Rate
HIT	≤2 mcg/kg/min
HIT plus Hepatic Impairment	0.5 – 1.2 mcg/kg/min
HIT plus Critically Ill	0.5 – 1.2 mcg/kg/min

Bivalirudin

- Continuous intravenous infusion
- aPTT monitoring
  - Target range 1.5 to 2.5 times control
- Half-life 10-24 minutes
- 80% enzymatic elimination
  - 20% renal elimination

- HIT Treatment Protocol at Memorial

Treatment

- Goals of Therapy
  - Prevent and/or treat thrombosis associated with HIT
    - With alternative anticoagulation
  - Allow platelets to restore to baseline value or >150,000 mm^3

Treatment

- Length of Therapy
  - When platelets > 150,000 mm^3 or return to baseline, initiate warfarin for long-term treatment
    - DTI + warfarin for 5 days minimum
    - Discontinue DTI when INR therapeutic for at least 48 hours *and* at least 5 days have passed
    - No thrombotic event: warfarinx 4 weeks minimum
    - Thrombotic event: warfarin X 3 months minimum
    - Initial warfarin doses no > 5 mg

Future Treatment Options

- Oral DTI
  - Pradaxa
- Arixtra (fondaparinux)
- Oral Anti-Xa Inhibitors
  - Xarelto
  - Eliquis

Memorial Pharmacy

- Daily Reports
  - Platelet decrease > 50% in 7 days
  - Current HIT panel report
- Patient's Profile
  - Heparin allergy entered
  - ADR entered
- Pharmacist ensures no heparin products on MAR

Case Study

- A 60 yo male with coronary artery disease who recently underwent CABG surgery presents to the ED with dyspnea.
- Platelet count is 86,000 mm^3. Platelet count was 225,000 mm^3 at discharge 9 days earlier.
- Chest x-ray is unremarkable; chest CT shows a pulmonary embolism.
- HIT is suspected.

Test Your Knowledge

- HIT is a disorder of _____.
  - A) only bleeding
  - B) only clotting
  - C) disseminated intravascular coagulation
  - D) bleeding and clotting

Test Your Knowledge

- The typical onset for the classic HIT presentation is:
  - A) 4-6 days after first heparin dose
  - B) 8-12 days after last heparin dose
  - C) 5-10 days after first heparin dose
  - D) 4-6 days after last heparin dose

Test Your Knowledge

- What is the most appropriate initial HIT treatment strategy in this patient (high suspicion of HIT)?
  - A) Wait for positive HIT panel results, then initiate a DTI continuous infusion
  - B) Discontinue all forms of heparin
  - C) Discontinue all forms of heparin and immediately initiate a DTI continuous infusion
  - D) Discontinue all forms of heparin and immediately initiate warfarin therapy

Conclusions

- HIT is a severe, life and limb-threatening condition
- Must be recognized early and treated adequately
- Laboratory tests confirm clinical suspicion
- Direct Thrombin Inhibitors are the mainstays of HIT treatment

Questions?

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