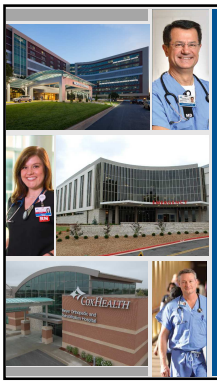

Evidence-Based Management of Heparin-Induced Thrombocytopenia and Transfusion

September 14, 2019

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Objectives

- Diagnose heparin-induced thrombocytopenia
- Use current guidelines to aid in decision to transfuse blood products

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Heparin-induced thrombocytopenia (HIT)

- Pathogenic IgG antibodies form to complexes of endogenous platelet factor 4 (PF4) and heparin
- Platelets are activated
- Thrombin is generated
- May cause hypercoagulation and life-threatening thrombosis

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Heparin family of drugs

- Most commonly used anticoagulants in hospitalized patients in the world
- Includes unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)
- Rapid onset
- Ease of monitoring
- Reversibility

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Incidence

- HIT occurs in ~ 1 in 5000 hospitalized patients
- The immune reaction to PF4-heparin complexes occurs in 8 to 50% of patients
- Thrombocytopenia and thrombosis only affect ~0.2 to 3% of patients exposed to heparin
- Antibody formation is more common in response to UFH than LMWH
- Anti-PF4-heparin antibodies are uncommon in healthy individuals (0.3% to 0.5%) and more common in context of surgical inflammation

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Risk factors

- Duration of heparin treatment (risk greatest with 7-10 days)
- Unfractionated heparin versus low-molecular-weight-heparin (UFH risk is 10-fold higher than LMWH)
- Dose
- Patient sex (females at greater risk)
- Major surgery and trauma is greater risk than minor surgery or general medical treatment

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Clinical diagnosis of HIT

- Thrombocytopenia and/or thrombosis in temporal association with heparin therapy
- Diagnosis of exclusion

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Clinical diagnosis of HIT: thrombocytopenia

- The cardinal manifestation of HIT is **thrombocytopenia**
- Unusual presentations of HIT can occur without thrombocytopenia
  - Heparin-induced skin necrosis
- Often HIT thrombocytopenia is moderate (50-70 x 10^9/L)
- Typically HIT thrombocytopenia has no associated bleeding complications
- HIT thrombocytopenia can occur either as
  - **Absolute** drop in platelet count (<150 x 10^9/L)
  - **Relative** decline of 30 to 50% from baseline platelet count

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Clinical diagnosis of HIT: thrombosis

- Severity of thrombocytopenia is a correlate of thrombotic risk
  - Marked thrombocytopenia (>90% decline from baseline platelet counts) have much greater risk of thrombosis
- Venous thromboses are most common, especially of lower limbs
- Bilateral adrenal hemorrhage, venous limb gangrene, skin necrosis should put HIT in differential
- Complications include pulmonary embolism and stroke; myocardial infarction is uncommon

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Clinical diagnosis of HIT: timing

- Thrombocytopenia and/or thrombosis develop **5 to 14** days after initial heparin therapy
- Rarely delayed-onset HIT may occur days to weeks after discontinuation of heparin
- Platelets rebound to normal range within 1 week of heparin discontinuation in ~65% of patients
- Risk of thrombosis remains for 4 to 6 weeks after diagnosis, despite platelet count rebound due to circulating antibodies

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4Ts clinical system

- Scoring system that calculates pre-test probability of HIT
- Do not test for or treat HIT in patients with low score (4T's of 0-3)
  - Non-heparin anticoagulants are expensive
  - Increases risk of bleeding
- Based on
  - **T**iming
  - Degree of **t**hrombocytopenia
  - Presence/absence of **t**hrombosis
  - Other possible causes of **t**hrombocytopenia

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4Ts clinical scoring system

- Recommended by American Society of Hematology (ASH)
- High negative predictive value for HIT with low score
- Intermediate or high 4Ts score indicates laboratory testing

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Score each category and sum the scores

Score	Thrombocytopenia (platelet count decrease/nadir)	Timing of onset: days after start of heparin	Thrombosis	Other cause of thrombocytopenia	Total Score
2	Decrease>50% Nadir ≥20 x 10^9/L	5-10 days, or ≤1 day (previous heparin exposure within 30 days)	New thrombosis, or skin necrosis at heparin injection sites, or acute systemic reaction after IV heparin	None apparent	6-8 (high)
1	Decrease 30-50% Nadir 10-19 x 109/L	>10 days or timeframe of onset unclear	Progressive or recurrent	Possible	4-5 (intermediate)
0	Decrease<30% Nadir <10x109/L	≤4 days, with no recent heparin exposure	None	Definite	0-3 (low)

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Re-exposure to heparin

- Patients with HIT who are re-exposed to heparin months or years after antibody disappearance seem to be at similar risk as other patients
- If patients have received heparin within the previous 90 days, anti-PF4-heparin antibodies may persist, and re-exposure to heparin can lead to rapid-onset HIT
  - sometimes anaphylactoid reaction within 30 minutes of heparin bolus

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Delayed-onset HIT

- HIT may develop/worsen after heparin discontinuation
- Thrombosis up to three weeks after heparin exposure

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Autoimmune HIT

- Very rare
- No exposure to heparin
- Most often after major surgery, especially knee replacement

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Laboratory diagnosis of HIT

- Laboratory evidence of anti-PF4/heparin antibodies is mandatory
- Two types of assay detect HIT antibodies
  - Platelet activation aka functional assays
    - Lower sensitivity, higher specificity, high positive predictive value
    - Serotonin-release assay (SRA) is the gold standard test for HIT diagnosis due to its high sensitivity and specificity
  - Immunoassays
    - Higher sensitivity, lower specificity
    - Specificity may be improved through detection of igG antibodies and numerical quantification of optical density (OD) and/or titers

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Why not lab test those with low 4Ts score?

- Negative predictive value of low 4Ts score is very good
- Immunoassay has high false positive rate
- Functional assay (including serotonin-release assay) require reagents only available at send-out reference labs, so they take too long to inform initial clinical decision-making
- Cessation of heparin could lead to thrombosis
- Alternative anticoagulants may be expensive and have additional risk of major hemorrhage

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Best laboratory testing approach

- Do NOT monitor platelet count in low-risk patients to screen for HIT (per American Society of Hematology guidelines)
- DO monitor platelet count in patients receiving heparin with intermediate or high risk, beginning before heparin initiation
- Reflex testing
  - Enzyme-linked immunosorbent assay (ELISA) to detect heparin-PF4 IgG antibodies
    - If ELISA positive then test with serotonin-release assay to confirm

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Monitoring platelet count

- Check platelet count every 2-3 days in intermediate risk patients
- Check platelet count days 4 until day 14 or when heparin is stopped
- In high risk patients, check platelet count every other day
- Low risk: minor surgery, obstetrics
- High risk: major surgery or trauma

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Management

- Never treat empiricially
- Cessation of heparin
- Initiate nonheparin anticoagulant (argatroban, danaparoid, fondaparinux, bivalirudin, direct oral anticoagulants)
- Avoid vitamin K antagonist (warfarin) until platelet count recovers
- Delays in treatments are associated with risk of thrombosis, amputation, or death

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Platelet transfusion and HIT

- If patients are at average bleeding risk, do not transfuse platelets
- If patient is actively bleeding or at high risk of bleeding, platelet transfusion may be an option

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Plateletpheresis units

- Equivalent to 6-8 whole blood derived platelet units
- Expect a ~30,000 bump upon transfusion

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AABB platelet transfusion guidelines

- Recommendation 1: transfuse hospitalized adult patients prophylactically with one apheresis unit at platelet count <10,000 cells/µL
- Recommendation 2: prophylactic platelet transfusion for patients having central venous catheter placement with platelet count <20,000 cells/µL

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AABB platelet guidelines

- Recommendation 3: prophylactic platelet tranfusion for patients having lumbar puncture with platelet count <50,000 cells/µL
- Recommendation 4: prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with platelet count <50,000 cells/µL
- Recommendation 5: AGAINST routine prophylactic platelet transfusion for non-thrombocytopenic cardiac surgery or cardiopulmonary bypass patients with perioperative; only transfuse these patients with perioperative bleeding or with thrombocytopenia

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Basic red cell transfusion guidelines

- Transfusion trigger of 7g/dL in non-bleeding standard patient
- Transfusion trigger of 8g/dL in non-bleeding post-op or heart disease patient
- Signs and symptoms of anemia and/or major bleeding "trump the numbers"
- Why give two when one will do?
  - One unit of RBC is the standard dose

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Choosing Wisely®: American Society of Hematology

- Don't transfuse more than the minimum RBC units necessary to relieve symptoms of anemia
- **Smallest effective dose of RBCs is recommended**; Clinicians are urged to avoid the routine 2 units of RBCs if 1 unit is sufficient

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Choosing Wisely ® AABB

- **Don't transfuse more units of blood than absolutely necessary. Single unit** red cell transfusions should be the standard for non-bleeding, hospitalized patients.
- Don't transfuse RBC for iron deficiency without hemodynamic instability

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Choosing Wisely ®

- **American Society of Anesthesiology:** Don't administer (PRBCs) in a young healthy patient without ongoing blood loss and **hgb ≥ 6 g/dL** unless symptomatic or hemodynamically unstable
- **Critical Care Societies :** Don't transfuse RBC in hemodynamically stable, non-bleeding ICU patients with a **hgb > 7 g/dL**

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Dose-dependent complications

- Dose-dependent complications of transfusion in include
- Mortality
- Pneumonia
- Sepsis
- Increased length of hospital stay

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Thank you!

- Questions?
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