Thrombocytopenia and Thrombosis in the Surgical Patient

General Surgery Half-Day
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St Joseph’s Hospital / McMaster University
Overview

- Case presentations
- Thrombocytopenia
  - Practical approach
- HIT
  - Diagnosis
  - Clinical presentation
  - Treatment
- Revisit case presentations
- Summary
Case #1

• 62 M presents with abdominal pain and distension
• Diagnosed with large bowel obstruction on X-ray
• Baseline bloodwork
  – Hb 85 (MCV 77), wbc 11.4, platelets 256
  – Creatinine 120, urea 11.3
  – INR 1.2, aPTT 28
• Admitted to hospital
  – IV normal saline, transfused 2 units rbc
  – DVT prophylaxis: Heparin 5000 units SC BID
• Endoscopy (done 2 days later): obstructing mass in right colon, pathology confirmed adenocarcinoma
• Booked for hemicolecotomy
Case #1

- Undergoes uncomplicated hemicolecctomy after 5 d in hospital
- Routine post-op care, including heparin prophylaxis
- Develops mild fever on POD 1, noted to have thrombocytopenia
  - Abdomen tender
  - CXR, cultures sent…abdominal US booked

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Case #2

- 50 F epigastric pain, fever; history of biliary colic
- Abdominal US distended gallbladder, stone in gallbladder neck
- Diagnosed with acute cholecystitis
- Baseline bloodwork
  - Hb 133, wbc 18.6, platelets 385
  - Creatinine 106, urea 10.3
- Admitted to hospital
  - IV normal saline
  - DVT prophylaxis: Heparin 5000 units SC BID
- Initially stabilized, then worsening symptoms by 5th hospital day, decision made for OR, undergoes laparoscopic cholecystectomy
Case #2

- Undergoes uncomplicated lap chole after 5 d in hospital
- Routine post-op care, including heparin prophylaxis
- Develops mild fever on POD 1, progressive thrombocytopenia
  - Abdomen tender
  - CXR, cultures sent...abdominal US booked

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Thrombocytopenia in the surgical patient
Thrombocytopenia – general aspects

• Defined as any platelet count below the range given as “normal” by the lab
  – Commonly 150,000 – 400,000/uL (150-400 x 10^9/L)

When do concerns arise?

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Thrombocytopenia - significance

• Bleeding
• Type of bleeding occurring with thrombocytopenia is usually mucosal (primary hemostasis)
  – GI bleeding, hematuria, epistaxis, gingival, petechiae, CNS bleeding
  – Not: hemarthrosis, soft tissue/muscle bleeds (think of coagulation factor defect (i.e. hemophilia) in these cases)
• Bleeding characteristics:
  – Oozing, continuous bleeding that is difficult to stop (compared to bleeding that stops, and re-starts)
A practical approach

Thrombocytopenia
(<150 x 10^9/L))

1. Check previous platelet counts
2. Ensure no platelet clumping

Blood smear (Repeat CBC)

Decreased production

Increased destruction

Dilutional Distribution
Platelet clumping

- May occur with anticoagulant used in blood collection tube (EDTA)
- ‘Pseudothrombocytopenia’
- Detected on blood smear, frequently reported by laboratory
Decreased production

- Platelets are made in the bone marrow (BM)
- Lifespan: 7-10 days
- Many of the causes of decreased platelet production are unlikely to affect platelets only
- Key test: CBC (look at Hb and wbc)
  - Involvement of >1 cell line = BM problem
- However, isolated thrombocytopenia does NOT rule out a BM problem...short life span often makes thrombocytopenia the first manifestation of disease
Thrombocytopenia
(< 150 x 10^9/L)

1. Check previous platelet counts
2. Ensure no platelet clumping

Blood smear
(Repeat CBC)

Decreased production

- Infiltration (heme - leukemia, MF; other cancers, storage diseases)
- Failure (aplastic anemia, MDS)
- Suppression (drug, EtOH, radiation, chemotherapy)
- Nutritional deficiencies (B12, folate, Fe)
- Infectious (HIV, EBV, CMV, parvo)

Increased destruction

Dilutional Distribution

CBC, vitamin B12, rbc folate; (viral testing)
Increased destruction

• More common etiology than decreased production in surgical patients
• Etiology frequently divided into ‘immune’ vs ‘non-immune’
• Key is to recognize potentially serious, and reversible causes of thrombocytopenia
  – Immune: HIT
  – Non-immune: DIC, TTP-HUS, drug-induced
• The serious disorders are frequently associated with coagulopathy or rbc fragmentation
• Key tests: INR, aPTT, DIC screen, blood smear
Thrombocytopenia and fragments

- Presence of rbc fragments indicates micro (or macro) angiopathic process

DDx
- **TTP/HUS**
- **DIC** (think of causes of DIC)
- Preeclampsia/eclampsia, PIH
- Vasculitis/CTDs
Medications and thrombocytopenia

- Common medications that cause thrombocytopenia
  - Heparin
  - Antibiotics (penicillins, sulfonamides, trimethoprim)
  - Sedatives/anticonvulsants (diazepam, valproic acid, dilantin, tegretol)
  - Quinine, quinidine, methyldopa
- Don’t forget anti-platelet agents which will affect the platelet function
  - ASA, NSAIDs
Thrombocytopenia (< 150 x 10^9/L)

1. Check previous platelet counts
2. Ensure no platelet clumping

Blood smear (Repeat CBC)

Decreased production

- CBC, vitamin B12, rbc folate; (viral testing)

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Increased destruction

Blood smear, INR, aPTT, DIC screen

- Non-immune
  - DIC
  - Sepsis
  - Drug-induced
  - TTP-HUS
  - Mech heart valves
  - Vasculitis
  - Pregnancy

- Immune
  - HIT
  - ITP
  - Alloimmune

Dilutional Distribution

Non-immune

- DIC
- Sepsis
- Drug-induced
- TTP-HUS
- Mech heart valves
- Vasculitis
- Pregnancy

- Immune
- HIT
- ITP
- Alloimmune
Dilutional thrombocytopenia

• Another common cause in surgical patients
• Frequently seen post-operatively
• Usually mild-moderate thrombocytopenia that resolves spontaneously
• No associated coagulopathy, may see dilutional anemia (low hematocrit)
Thrombocytopenia (<150 x 10^9/L)

1. Check previous platelet counts
2. Ensure no platelet clumping

Blood smear (Repeat CBC)

Decreased production
- CBC, vitamin B12, rbc folate; (viral testing)
- Infiltration (heme-leukemia, MF; other cancers, storage diseases)
- Failure (aplastic anemia, MDS)
- Suppression (drug, EtOH, radiation, chemotherapy)
- Nutritional deficiencies (B12, folate, Fe)
- Infectious (HIV, EBV, CMV, parvo)

Increased destruction
- Blood smear, INR, aPTT, DIC screen
- Non-immune
  - DIC
  - Sepsis
  - Drug-induced
  - TTP-HUS
  - Mech heart valves
  - Vasculitis
  - Pregnancy
- Massive transfusion or resuscitation
  - Splenomegaly, hypersplenism

Dilutional Distribution
- (Abdominal US)
  - Non-immune
  - Immune
    - HIT
    - ITP
    - Alloimmune

- Immune
  - HIT
  - ITP
  - Alloimmune
Heparin-induced thrombocytopenia

When should this diagnosis be considered?
How is the diagnosis made?
What is the appropriate treatment?
Heparin-induced thrombocytopenia

- Clinical-pathological (laboratory) diagnosis
  Therefore, diagnosis is based on:
  1) Presence of the ‘HIT antibody’
     - Platelet-activating IgG Ab recognizing heparin-PF4 complex
  2) Clinical presentation – thrombocytopenia
     - No alternate explanation for thrombocytopenia
- Condition characterized by both activation of platelets and activation of coagulation (results in procoagulant state)
- Many patients with HIT develop thrombosis (OR 20-40)
Pathophysiology of heparin induced thrombocytopenia

Schematic representation of the mechanism of heparin-induced thrombocytopenia. In susceptible subjects, heparin bound to platelet factor 4 (PF4) induces an antibody response. An IgG antibody directed against the heparin-PF4 complex binds platelets through the Fc receptor, leading to platelet activation and microparticle formation. Platelet-rich thrombi form at sites of preexisting pathology or sites of endothelial cell (EC) injury. (Reproduced with permission from Brieger, DB, Mak, KH, Kottke-Marchant, K, Topol, EJ. J Am Coll Cardiol 1998; 31:1449.)
HIT assays

2 methods of diagnosing HIT Ab:

1) Platelet activating assays
   • Platelet serotonin release assay (gold standard)
   • Higher specificity

2) Antigen assays
   • Enzyme immunoassays used to detect binding of patient Ab to PF4/polyanion bound to microtitre plate
   • More sensitive than SRA

• Both tests are positive in patients with HIT
• In Hamilton, all HIT assays done twice a week at MUMC
  – Currently done Tues and Thurs, turnaround time of ~24 h
HIT antibody facts

• HIT Ab are transient
  – Usually not detectable 100 days (3 mo) following an episode of HIT

• Repeated heparin exposure in patients with HIT does not usually cause recurrence of HIT Ab
  – BUT not recommended to re-expose patients to heparin if alternate anticoagulant is available

• Not all HIT Ab result in platelet activation
  – We are only interested in clinically significant Ab (i.e. Ab causing thrombocytopenia); hence monitoring with platelet count is more useful than serial HIT Ab testing

• The ‘iceberg model’ of HIT

Warkentin et al. NEJM 2001;344
Clinical presentation

1. Thrombocytopenia (95%)
Definition: Fall in platelet count $\geq 50\%$ of the (postoperative) peak

1. Timing
   - Typical onset (70%): 5-10 days after starting heparin*
   - Rapid onset (25-30%): < 24 h after starting heparin
     • Pre-formed Ab due to recent (<100 d) heparin exposure
   - Delayed onset (rare): days following heparin D/C

2. Severity: Mild-moderate (nadir $\sim 50-60 \times 10^9$/L)
   - 10% of patients will have plts < 20
   - 90% will have plts < 150

* 1st day of heparin = day 0, seen in 70% of pts with HIT
Clinical presentation

2. Thrombosis (35-75%)
   - One of the few clinical conditions predisposing to both arterial and venous thrombosis
     • VTE: DVT > PE > limb gangrene, adrenal necrosis, cerebral sinus thrombosis
     • ATE: peripheral arterial > stroke > MI
   - DVT is the most common complication
     • Clinical factors influence whether pts get ATE or VTE
       • Orthopedic surgery patients: VTE > ATE
       • Cardiac surgery patients: ATE > VTE
       • Medical patients: VTE = ATE
     • Severity of thrombocytopenia predicts risk of thrombosis
Other clinical manifestations

• **Skin lesions** at heparin injection sites
  – Erythematous plaques or skin necrosis
  – Begins >6 days after starting SC heparin
  – Usually no associated thrombocytopenia

• **Acute systemic reactions** to IV heparin bolus
  – Cardiorespiratory signs and symptoms with rapid platelet fall occurring 5-30 min after IV bolus
    • Fever, chills, hypertension, tachycardia, SOB, chest pain, flushing
Is HIT common?

Depends on:

- **Type** of heparin preparation
  - 8-fold increased risk with UFH compared to LMWH
  - Heparin chains need to be 12-14 saccharide units to form the HIT Ag with PF4

- **Duration** of heparin treatment
  - Reflects time needed to initiate Ab formation (humoral immune response)

- Patient population
<table>
<thead>
<tr>
<th>Patient population</th>
<th>Days of treatment</th>
<th>Activation Assay (percent)</th>
<th>Antigen Assay (percent)</th>
<th>Frequency of clinical HIT (percent)</th>
</tr>
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<tbody>
<tr>
<td>Cardiac, UFH</td>
<td>$5.1 \pm 2.2$ (SD)</td>
<td>20.0</td>
<td>50.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Orthopedic, UFH</td>
<td>9.2 ± 2.2</td>
<td>9.3</td>
<td>14.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Orthopedic, LMWH</td>
<td>9.5 ± 3.0</td>
<td>3.2</td>
<td>7.5</td>
<td>0.9</td>
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UFH = Unfractionated heparin; LMWH = Low molecular weight heparin

Management of HIT

1. D/C all heparin
2. Send off HIT assay
3. Start alternate, non-heparin anticoagulant
   - Low molecular weight heparin is not an acceptable alternative although risk of HIT is less

Options:
- Heparinoid
  - Danaparoid
- Direct thrombin inhibitors
  - Argatroban, Hirudin, Lepirudin
- Synthetic pentasaccharide
  - Fondaparinux
## Alternate anticoagulants for HIT

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Half-life</th>
<th>Monitoring</th>
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<tr>
<td>Danaparoid (Orgaran)</td>
<td>SC: therapeutic: 1500 U BID, prophylactic: 750 U BID IV: loading 2250 anti-Xa U, then 400 aXU for 4 h, 300 aXU for 4 h, then maintenance (150-200 aXU/h)</td>
<td>25 h</td>
<td>Anti-Xa levels (danaparoid) Avoid in renal failure</td>
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<tr>
<td>Argatroban</td>
<td>IV: start 2 ug/kg/min then adjust by aPTT (target 60-85)</td>
<td>40-50 min</td>
<td>aPTT Avoid in liver failure</td>
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<td>Lepirudin</td>
<td>IV: load 0.4 mg/kg then 0.15 mg/kg/h</td>
<td>80 min</td>
<td>aPTT Avoid in renal failure</td>
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HIT management

HIT assay

- **Negative**
  - Replace alternate anticoagulant with heparin

- **Positive**
  - **No thrombosis**
    - Continue with alternate anticoagulant until platelets improved and stabilized
  - **With thrombosis**
    - Continue with alternate AC until platelets > 100 and start warfarin
      - Overlap anticoagulants
      - Stop alternate AC when INR > 2.0 x 2 days
HIT management

Warfarin
- Only start when platelets recovered >100
- Start at expected daily dose (no loading dose)
- Overlap with non-heparin anticoagulant, and only discontinue non-heparin anticoagulant when INR > 2.0
- Avoid warfarin-associated venous gangrene

Avoid platelet transfusions as management
- BUT use if patient is bleeding and platelets are low
Prevention of HIT

Can HIT be prevented?
• Use of anticoagulants that do not produce HIT Ab

Detection of thrombocytopenia
• Patients receiving heparin should have platelet counts monitored on alternate days from days 4-14
• Recent exposure to heparin should have platelet count starting on day 1
• Early detection and starting a non-heparin AC associated with decreased risk of serious consequences
Summary of the diagnostic approach
Thrombocytopenia – clinical approach

1. Check previous platelet counts
2. Rule out platelet clumping, spurious result
3. Check patient’s co-morbidities
   - Underlying malignancy
   - Connective tissue disease
4. Check patient’s medications
   - D/C medications that may be causing thrombocytopenia
   - Consider D/C anti-platelet agents
   - Check for heparin exposure (current and recent < 100 days)
5. Think about other possible causes for thrombocytopenia
   - Send off bloodwork (blood smear, coags, cultures)
   - HIT assay if appropriate
Does thrombocytopenia need Rx?

6. Assess whether something needs to be done
Questions to ask:
• Is the patient bleeding?
  – Site of bleeding: surgical site vs other
• Is the platelet count dropping rapidly (and is moving into the serious range)?

• Bleeding and thrombocytopenic patients need platelet transfusions and definitive management
Back to the case scenarios
Case #1 – colon cancer

- 62 M with right colon adenocarcinoma post hemi-colectomy
- Fever on POD 1 with tender abdomen

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- What investigations would you like next?
Case #1 – colon cancer

- Previous platelet counts normal (acquired) and lab confirmed
- Current medications
  - Heparin 5000 u BID
  - Amp/Gent/Flagyl

Is HIT a possibility?
- Timing possible, although plts dropping earlier
- Severity uncharacteristic

Are there more likely diagnoses?

What would you do next?
- Consider d/c or changing antibiotics
- Hold heparin
- (Non-heparin anticoagulant)
- TED stockings

Send off investigations:
- Blood smear
- INR, aPTT
- DIC screen
- Blood/urine cultures
Case #1 – colon cancer

Results
• Blood smear – occ fragment
• D-dimer elevated
• Fibrinogen low
• INR 1.6
• aPTT 42
• Blood cultures: E coli

Diagnosis: Disseminated intravascular coagulation (DIC)
Triggers: Sepsis, cancer-associated

Management
• Treat underlying cause
• Antibiotics
• Monitor bleeding symptoms and transfuse if needed
• Monitor for thrombotic symptoms
• Non-pharmacologic DVT prophylaxis (TEDs)
Case #2 - cholecystitis

- 50 F acute cholecystitis post laparoscopic cholecystectomy
- Fever on POD 1 with tender abdomen

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- What investigations would you like next?
Case #2 – cholecystitis

• Previous platelet counts normal (acquired) and lab confirmed
• Current medications
  – Heparin 5000 u BID
  – Amp/Cipro/Flagyl

Is HIT a possibility?
• Timing is right (day 8)
• Severity characteristic

Are there more likely diagnoses?

What would you do next?
• D/C heparin
• Start non-heparin anticoagulant
• TED stockings
• Consider d/c or changing antibiotics

Send off investigations:
• HIT assay
• Blood smear
• INR, aPTT
• DIC screen
• Blood/urine cultures
Case #2 – cholecystitis

Results

- Blood smear
- D-dimer elevated
- Fibrinogen normal/low
- INR 1.0
- aPTT 28
- Blood cultures: negative
- HIT assay: positive

Diagnosis: HIT

Management

- Continue non-heparin AC
- Danaparoid 750 U SC BID
- Monitor platelet counts
- Monitor for bleeding symptoms and transfuse if needed
- Monitor for thrombotic symptoms (DVT, could consider screening US)
- Non-pharmacologic DVT prophylaxis (TEDs)
Summary

• Thrombocytopenia and heparin use are common in hospitalized patients
• Have a systematic approach to thrombocytopenia and assess for other potential causes
  – Most common cause in surgical patients: dilutional, increased destruction (DIC, sepsis, drug-induced including HIT)
• HIT characterized by drop in platelets after 5-10 days of heparin exposure, mild-moderate thrombocytopenia and associated with thrombosis in 50%
• If HIT truly suspected (clinically compatible, no alternate diagnoses), send HIT assay, D/C heparin and start alternate anticoagulant
• Many HIT Ab are subclinical, so interpret findings in light of available clinical information