Heparin Induced Thrombocytopenia

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Objectives

- Differentiate immune vs nonimmune HIT
- Contrast UFH vs LMWH
- Identify laboratory tests used to detect HIT
- Discuss alternative anticoagulant treatment options for patients with HIT

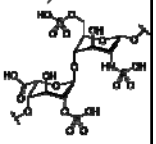
Heparin

- Therapeutic anticoagulant for treatment and prevention of thrombosis
- Extracted from porcine or beef intestinal mucosa.

Types of Heparin

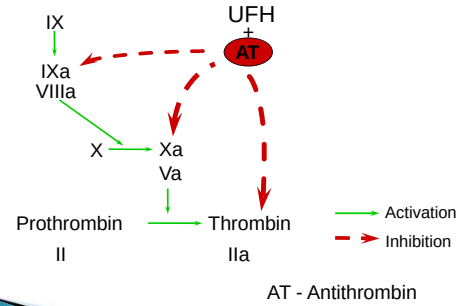
- Unfractionated Heparin (UH or UFH)
  - Isolated from liver in1916 by Jay McLean and William Howell (Johns Hopkins University)
  - Available for medical use since 1937
- Low Molecular Weight Heparin (LMWH)
  - Derived from UFH
  - Available for medical use since 1993
    - 1998 in US

Unfractionated Heparin (UFH)

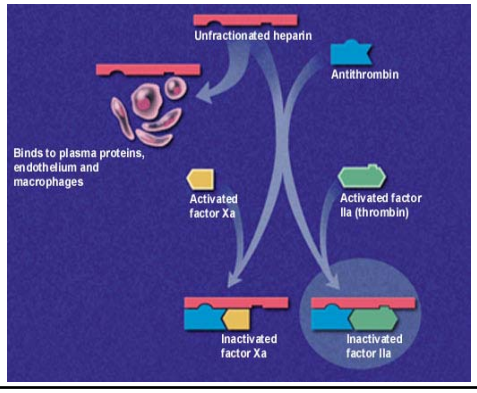


- Heterogeneous mixture of sulfated polysaccharide (glycosaminoglycan)
  - 4,000 – 35,000 Daltons
- Binds to Antithrombin (AT)
  - via unique pentasaccharide sequence
  - enhances ability of AT to inactivate Xa, IIa (thrombin), and other serine proteases
- Administered IV
  - CABG surgery, angioplasty, stent placement, orthopedic surgery
- Can also be administered SubQ
  - Treatment of VTE

Mechanism of Unfractionated Heparin



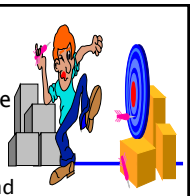
Unfractionated Heparin Mechanism



UFH

- Can be monitored by daily with APTT (1.5–2.5 times normal)
  - Inexpensive and readily available
- Can also monitor using anti-Xa assay and Activated Clotting Time (surgical arena)
- Can be neutralized easily by protamine sulfate
- Relatively inexpensive
- Can be used on dialysis patients
  - Not excreted by kidneys

Disadvantages of UH

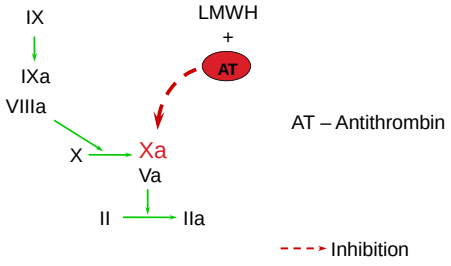


- Great variability in patient response
  - Inhibited by PF4
  - Short half-life
  - Can bind to other plasma proteins and endothelium
    - Adds to short plasma half-life problem
  - Difficult to monitor accurately with APTT
- Can be associated with
  - Osteoporosis with long-term use
  - Heparin Induced Thrombocytopenia (HIT)

Low Molecular Weight Heparin (LMWH)

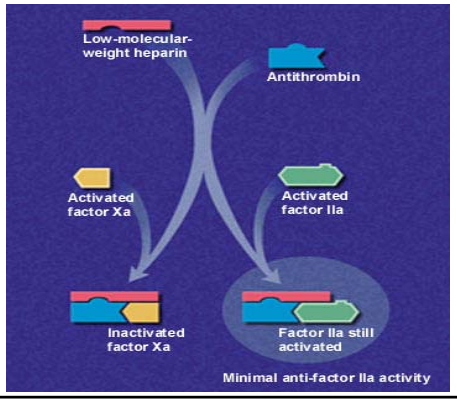
- Derived commercially by chemical or enzymatic fractionation of UFH
- Smaller molecule than UFH
  - Short chains of polysaccharides
  - <8000 Daltons
- Brands available in US
  - Lovenox® (Enoxaparin) – 1998 (Clexane®)
  - Fragmin® (Dalteparin) – 1999
  - Innohep® (Tinzaparin) – 2000

Mechanism of LMWH



LMWH – Low Molecular Weight Heparin

LMWH Mechanism



LMWH

- Administered SubQ
- Preferentially enhances inhibition of Xa and to a lesser extent thrombin (IIa)
- Safer to use in settings when less anticoagulant effect is needed
  - VTE prevention
  - Treatment of DVT and PE
- Usually does not require monitoring

LMWH

- Fewer side effects
  - Reduced interference with platelet function and vascular permeability
  - Less non-specific binding to proteins and cell surfaces
- Easier to calculate dosage established by weight-based nomograms
- More predictable response
- Longer plasma half-life
- Resists inhibition by PF4
- Frequency of HIT is < 1%

Disadvantages of LMWH

- Higher doses, long term use or use during pregnancy may require some monitoring
- Must use chromogenic anti-Xa assay to measure/monitor
  - Much more expensive than APTT
  - Not available in all labs
- Mainly eliminated by kidneys
  - Problem for patients with end-stage renal disease

HIT

- Complication of heparin therapy (Usually UFH)
- Two types
  - Type 1
  - Type 2

Type 1

- **Non-immune**
- Presents within first 2 days after heparin exposure
- Thrombocytopenia usually mild
  - Platelet count will normalize with continued heparin therapy
- Results from direct effect of heparin on platelet activation

Type 2

- **Immune mediated**
- *Typical presentation*
  - 4 – 10 days after heparin exposure
- *Rapid onset presentation*
  - Fall in platelet count in first 24 hours
  - Not a new immune response
    - Patient already has circulating HIT antibodies associated with recent heparin exposure (past 100 days)

Type 2 (cont.)

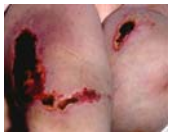
- *Spontaneous*
  - Typical clinical and lab picture without heparin exposure
    - PF4 binds to non-heparin platelet polysaccharides (e.g. chrondroitin sulfate)
    - Activate platelets even when no heparin is present
- *Delayed-onset HIT presentation*
  - Thrombocytopenia is delayed for up to 3 weeks post heparin
  - Antibodies activate platelets in absence of heparin
  - Thrombosis and thrombocytopenia without proximate heparin exposure
- *Persistant HIT* - low platelets for >30d post heparin

HIT Type 2

- Has life and limb threatening thrombotic complications
- Term HIT generally refers to Type 2

Signs of HIT

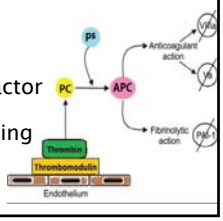
- Decrease in platelet count - moderate to severe
  - Fall in count >50% of baseline count even if count remains above 150,000/uL
- Necrotic skin lesions at heparin injection site



- Acute systemic reactions
  - Chills, fever, dyspnea, chest pain

Signs of HIT (cont.)

- Venous thrombosis -DVT/PE
- Venous limb gangrene
  - Especially DVT patients with HIT who are started on warfarin
    - Can lead to severe Protein C/Protein S depletion with likely loss of limb
    - Activated Protein C with cofactor Protein S are Vitamin K dependent **inhibitors** of clotting



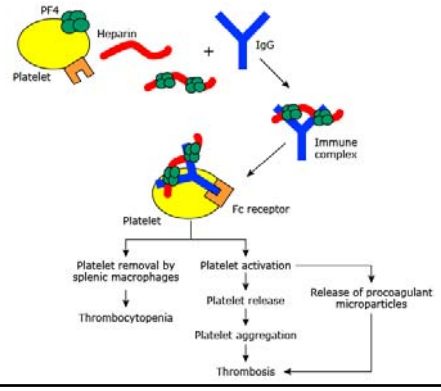
Consequenses of Type 2 HIT

- Venous thromboembolism
  - Deep Vein Thrombosis (DVT)
  - Pulmonary Embolism (PE)
- Arterial thrombosis - less common
  - Myocardial Infarction (MI)
- NOTE:
  - Disorder is sometimes referred to as HITT
    - Heparin Induced Thrombocytopenia Thrombosis

Pathophysiology of HIT

- Platelet Factor 4(PF4)
  - Released from plt α-granules during activation
  - Binds to heparin and forms complex
    - Can neutralize heparin-like molecules on endothelial cells
- IgG antibodies form to PF4-Heparin complexes
  - Seen in 90% of patients with clinical HIT diagnosis
  - Antibodies bind to PF4-Heparin complex on platelet surface and activate platelets
  - Can also be found in patients exposed to heparin but without clinical manifestations of HIT
- Much more likely to occur with UFH than LMWH

Heparin Induced Thrombocytopenia Mechanism



Epidemiology

- About 12 million people in US have some heparin exposure yearly (1/3 of all hospitalized patients)
- Frequency of HIT
  - 1- 5% in patients on IV UFH*
  - <0.1% in patients receiving subQ UFH
- Overall risk
  - ~0.2% of hospitalized heparin-exposed patients

*More common in surgical patients receiving prolonged post op thromboprophylaxis
(e.g. for 10- 14 days post orthopedic or CABG/valve replacement surgery)

Mortality/Morbidity in HIT Patients

- Thrombotic complications in ~30%
- Overall mortality ~20%
  - Recent improvements in early diagnosis – better prognosis
- ~10% require amputations or suffer other major morbidity

Race/Sex/Age

- Nonwhites
  - 2 – 3 times more likely to progress to HIT-associated thrombotic outcome
- Men
  - Less risk than women
  - Difference in risk is most striking in UFH treated women vs men
    - No relationship between sex and risk for HIT in patients treated with LMWH
      - Better to use LMWH for surgical thromboprophylaxis in women ?
- Age
  - Retrospective study of 408 patients with HIT
    - 66% were >60

Summary of increased risk for HIT

- UFH vs LMWH
- IV vs SubQ heparin
- Longer duration of heparin use
- Surgical (esp cardiac, ortho) vs medical patient
- Female
- Over 60

Diagnosing HIT

- 4T's score
  - Thrombocytopenia
  - Timing of thrombocytopenia relative to heparin exposure
  - Thrombosis or other sequelae of HIT
  - Likelihood of oTher causes of thrombocytopenia

4 T's Score

Feature	2 points	1 point	0 points
Thrombocytopenia	>50% drop **AND** nadir >20,000	30%-50% drop **OR** nadir 10-19,000	>30% drop **OR** nadir <10,000
Timing of platelet count fall	5-10 days **OR** fall ≤1 day if heparin exposure in past 30 days	5 -10 days fall but not clear; **OR** ≤1 day fall if heparin exposure 30-100 days ago	Platelet count fall in <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis **OR** skin necrosis; acute systemic reaction after IV UHF bolus	Progressive **OR** recurrent thrombosis; erythematous skin lesions	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

Warkentin et al Br J Haematol 2003

Total scores and HIT probability

- 0 – 3; Low probability
  - Negative predictive value – 0.998
  - Might exclude HIT without further lab testing and heparin can be continued
- 4 – 5; Intermediate probability
  - ~10-14% chance of HIT
- 6 – 8; High probability
  - ~64% chance of HIT

Overdiagnosis of HIT?

- Thrombocytopenia is common in hospitalized patients, esp. in ICU
- Retrospective study of surgical intensive care unit patients
  - 8.6% of patients with low-probability 4T scores (0-3) were positive for HIT with lab testing
  - 57% of patients with high-probability 4T scores (6-8) were HIT negative
- Conclusion
  - Testing or treatment for HIT should **NOT** depend on 4T score alone

HIT Expert Probability score (HEP)

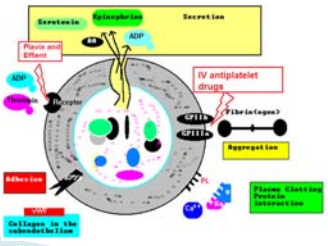
- More detailed
- Improved diagnostic utility of 4T score
- Shown to be100% sensitive and 60% specific for HIT
- Better correlation with serologic HIT testing
- Not yet multicenter validated

Complicating Conditions

- Septicemia
- DIC
- ITP
- TTP
- HUS
- Liver disease with hypersplenism
- Transfusion reactions

Medications known to cause decreased plts

- GP IIb/IIIa inhibitors
  - IV plt aggregation inhibitors (Abciximab, Eptifibatide)



Medications known to cause decreased plts (cont.)

- Quinine and other antimalarial drugs
- Rifampicin, sulfur drugs and other antibiotics
- Gold salts and other heavy metals
- Sedatives and anticonvulsants
- Salicylates and other analgesics

Diagnostic Approach Considerations

- Timing of onset
  - Decrease in plt count begins 5 – 14 days post start of heparin treatment
- Severity of thrombocytopenia
  - Usually mild to moderate
  - Plt count rarely <15,000/uL
- Large-vessel venous or arterial thrombosis
  - Thrombosis precedes thrombocytopenia in up to 25% of patients with HIT

Heparin Treatment Monitoring

- Baseline platelet count
- Follow-up counts based on patient risk for HIT
  - Risk >1% (UFH post cardiac or ortho surgery)
    - Plt count every 2 – 3 days from day 4 – 14 or until heparin is stopped
  - Risk <1% (LMWH)
    - ACCP suggests no plt count monitoring needed
- If count falls by >50% and/or thrombotic event occurs
  - Perform diagnostic tests for HIT
  - DC heparin ?
    - Depending on 4T score

Diagnostic Tests

- Non-functional Immunoassays
  - ELISA
- Functional assays
  - Seratonin Release Assay (SRA)
  - Heparin-Induced Platelet Aggregation assay (HIPA)
- Imaging studies

NOTE

- Really is NO Gold Standard laboratory test for diagnostic confirmation HIT
- HIT requires a *clinical diagnosis*

Immunoassays

- ELISA
  - Widely available
  - Rapid turn around time
  - High sensitivity (99%)
  - Poor specificity (30 – 70%)

ELISA Procedure

- PF4 and heparin are coated to surfaces of microplate wells
  - Patient serum or plasma is added to wells
  - Antibody (if present) adhers to PF4-Heparin complex
  - Plate wells are washed
- Enzyme-labeled monoclonal antibodies to human IgG (and IgM) are added and incubated
  - Plate is washed
- Chromogenic substrate is added
  - Color development in well is positive test for heparin induced antibodies
    - OD ≥2
      - 90% probability of strong positive SRA result
    - OD 0.4 to <1
      - 5% or lower probability of positive with SRA

ELISA (cont.)

- **Non functional assay**
  - Can detect antibodies that are not pathologic
    - ***Biologic false positive***
- Kits which detect ONLY IgG antibodies have better correlation with Seratonin Release Assays (SRA)
- Less labor intensive than SRA
- Does not require blood from healthy drug-free donors
- Can be performed in most labs

Functional Assays

- Seratonin Release Assay (SRA)
  - HIT antibodies cause platelets to aggregate and release serotonin
  - Most sensitive
  - Availability largely restricted to HIT focused research centers
- HIPA
  - Heparin-Induced Platelet Aggregation assay
    - Highly specific but less sensitive than SRA

SRA

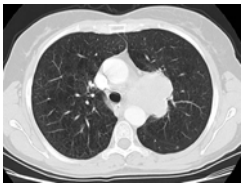
- Normal donor platelets are radiolabeled with *14-C serotonin and then washed
- Washed *14-C seratonin plts + patient serum + low (therapeutic) and high heparin concentrations
- Positive test
  - >20% serotonin release at low heparin dose (0.1 U/mL heparin)
- Considered gold standard assay
  - Sensitivity – 69% to 94%
  - Specificity – may be as high as 100%
- Technically demanding, costly, uses radioisotopes

HIPA

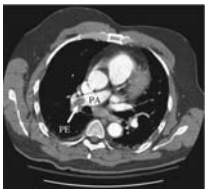
- Patient serum is mixed with donor platelets in presence of heparin
- Donor plt aggregation indicates presence of antibodies to heparin-PF4 complex
- Sensitivity varies from 39% to 81%
- Specificity varies from 82% to 100%
- One study of 146 patients
  - More sensitive than ELISA for lab confirmation of HIT
  - Neither HIPA nor ELISA predicted thrombotic risk

Imaging Studies

- DVT can be silent
- Ultrasonography even in absence of clinical evidence may be considered

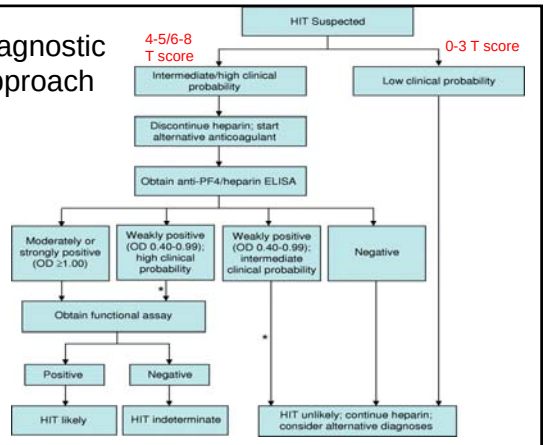


Normal lung CT



Pulmonary embolus (PE) located in the proximal pulmonary artery (PA) as seen on spiral CT.

Diagnostic Approach



Alternative Parenteral Anticoagulants (IV or injection)

- **Direct Thrombin Inhibitors**
  - *Argatroban* (Acova®)
    - FDA approved for prophylaxis and treatment of thrombosis and during coronary angioplasty in HIT patients
    - Good for dialysis patients
  - *Bivalirudin* (Angiomax®)
    - FDA approved for patients undergoing PCI or cardiac cath who have or who are at risk for HIT
  - *Lepirudin* (Refludan®)
    - Discontinued in 2012

Alternative Parenteral Anticoagulants (cont.)

- **Xa Inhibitors**
  - Fondaparinux (Atrixa®)
    - not FDA approved for use in HIT but considered to be important treatment option especially for pregnant women (doesn't cross placenta)
    - Off-label use
  - Danaparoid (Orgaran®)
    - not marketed in US since 2004

Alternative Oral Anticoagulants

- Warfarin (Coumadin)
  - Monitored with PT/INR
  - Don't start with HIT patients until platelet count >150,000/uL and adequate alternative parenteral anticoagulation has been provided
- Direct **Oral** Anticoagulants (DOACs)
  - Direct Thrombin Inhibitor
    - Dabigatran (Pradaxa®)
  - Xa Inhibitors
    - RivaroXaban (Xarelto®)
    - ApiXaban (Eliquis®)
    - EdoXaban (Savaysa®)

Note:
DOACs not fully assessed for HIT treatment
None have FDA approval for use in HIT
Can't be used for patients with kidney failure

Managing patient with history of HIT

- Treatment/prevention of VTE or management of Acute Coronary Syndrome
  - Use alternative anticoagulants in patients with persistent HIT antibodies
- However, UFH is clear anticoagulant of choice for 3 patient populations
  - Cardiac surgery
  - Vascular surgery
  - Hemodialysis

Consequenses of missed diagnosis or misdiagnosis?

- Missed diagnosis
  - Increases risk of thrombosis, amputation or death
- Misdiagnosis can result in
  - Major hemorrhage
    - Thrombocytopenic patients treated with alternative anticoagulants
  - Thrombosis
    - Heparin treatment suspended unnecessarily

Case 1

- 75 year old Hawaiian-Chinese female
- History of aortic stenosis, renal disease and hypertension
- Presented with pitting edema of lower legs
- Cardiac cath procedure
  - Showed severe aortic stenosis, aortic and mitral regurgitatio
  - Received flushes of 250 units UFH in venous and arterial sheaths
- Underwent cardiac surgery 10 days later
  - Aortic valve replacement
  - Intraaortic balloon pump (IABP)
  - Received 32,000 units UFH

J Med Case Reports. 2007; 1: 13.
Severe heparin-induced thrombocytopenia: when the obvious is not obvious, a case report
Graham M Connors and Larry J Kaufman

Case 1 (cont.)

- Pre-op platelet count – 108,000/uL
- Platelet count dropped to 25,000/uL by 3rd day post op
  - Attributed to IABP*
  - IABP was removed
- Thrombocytopenia continued
  - Refractory to plt transfusions over several days
- Renal function deteriorated
  - CVVHD**
  - Heparin-flushed dialysis catheter was placed
    - additional heparin exposure in tubing

*Intra-Aortic Balloon Pump
**Continuous VenoVenous HemoDialysis

4 T's Score

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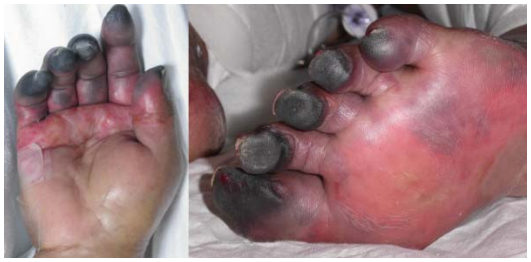
Thrombosis or other sequelae	New thrombosis OR skin necrosis; acute systemic reaction after IV UHF bolus	Progressive OR recurrent thrombosis; erythematous skin lesions	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

Case 1 (cont.)

- 7 days post-op
  - Plt count 43,000/uL despite 48 units of plts
- Differential diagnosis
  - Sepsis related DIC
  - Accelerated plt removal 2^0 to CVVHD
- Right hand cyanosis developed
  - Attributed to right radial arterial catheter
  - Removed
- All toes and fingers showed severe ischemic changes
- 2 days later
  - Plt count dropped to 8,000/uL

Gangrenous right hand and left foot as they appeared on hospital day #15.



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Case 1 (cont.)

- **FINALLY**
  - Critical care specialist joined team
  - Ordered heparin-PF4 ELISA test
    - Strongly POSITIVE
  - Patient started on argatroban
  - 6 days post argatroban
    - Platelet count was >100,000/uL
  - Started on warfarin with goal of INR of 2 – 3
  - Argatroban discontinued after 5 day overlap

Case 1 (cont.)

- 27 days in intensive care
- No additional thromboses
- Required bilateral mid-foot amputations and amputations of all fingers of right hand

Case 1 (cont.)

- Reasons for misdiagnosis
  1. Plausable alternative explanations for thrombocytopenia
     - Presence of the IABP
     - Presence of sepsis, CVVHD*
  2. Rapid-onset presentation
     - Usually platelet count drop happens 5 – 10 days after heparin initiation
     - Drop occurred on day 3 of heparin reexposure

Case 1 (cont.)

- Should have
  - Immediately ceased all heparin including flushes and LMWH
  - Started argatraban
    - lepirudin (available at this time) was contraindicated due to acute renal failure

Case Study 2 – Patient with remote history of HIT requiring urgent cardiac surgery

- 51 year old male with history of Hereditary Erythroblastic Multinuclearity associated with a Positive Acidified Serum Test (HEMPAS)
- Developed severe HIT (heparin reexposure)
  - Strongly positive for HIT antibodies
- Treated successfully with danaparoid
- 3 years later
  - Developed acute pulmonary edema 2^0 to flail mitral valve
  - Required urgent cardiac surgery
  - No time to perform repeat HIT antibody testing prior to surgery

What treatment was recommended?

- HIT antibodies are remarkably transient
  - Non-detectable 40 – 100 days post HIT episode (SRA vs ELISA-IgG)
- Probability of HIT antibodies being present after 3 years negligible
- Recommendation
  - Usual intraoperative anticoagulation with UFH
  - Post-op anticoagulation with danaparoid (Orgaran)
    - Xa inhibitor
    - Not available in US since 2012
    - This patient was treated in Canada

Case 3

- 70 year old woman
- 4 days post discharge following laparotomy for perforated duodenal ulcer with peritonitis
- Complaints of right-sided pleuritic chest pain
  - Started day after discharge
  - Associated with productive cough of whitish sputum
- Chills but no fever
- SOB

Case 3(cont.)

- Physical exam revealed obese woman in mild distress
- Lung fields had decreased air entry bilaterally, right side>left
- Metabolic panel – essentially normal
- CBC
  - WBC – 16,000/uL with 83% neutrophils
  - Hgb – 10 g/dL
  - Hct – 29.5%
  - Plt ct – 170,000/uL
- Ct scan – pleural effusion
- Chest X-ray – pneumonia in right lung

Case 3(cont.)

- Diagnosed with hospital acquired pneumonia
- Treated with IV fluids and antibiotics
- Day 2
  - Improved symptoms
  - CBC
    - WBC – 8,000/uL
    - Hgb – 8.6g/dL
    - Hct – 26%
    - Plt ct – 118,000/uL
  - CT scan – improving pleural effusion
  - In evening – patient complained of left knee pain

Case 3(cont.)

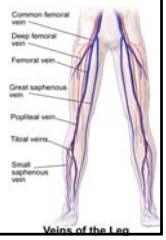
- PE revealed erythema around left knee
- Patient denied trauma
  - Stated flow-tron was a little tight
  - Flow-tron was loosened
- Tylenol given for pain
- One hour later
  - Entire left leg noted to be swollen and tender
  - Diagnosed with DVT
  - Started on heparin infusion

4 T's Score

Feature	2 points	1 point	0 points
Thrombocytopenia	>50% drop AND nadir >20,000	30%-50% drop OR nadir 10-19,000	>30% drop OR nadir <10,000
Timing of platelet count fall	5-10 days OR fall ≤1 day if heparin exposure in past 30 days	5 -10 days fall but not clear; OR ≤1 day fall if heparin exposure 30-100 days ago	Platelet count fall in <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis OR skin necrosis; acute systemic reaction after IV UHF bolus	Progressive OR recurrent thrombosis; erythematous skin lesions	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

Case 3(cont.)

- Day 5
  - Acute thrombosis of left common femoral, superficial femoral, popliteal, tibial and saphenous veins with absence of flow
  - Right popliteal vein also showed chronic re-canalized thrombosis
  - CBC
    - WBC – 9900/uL
    - Hgb – 8.5 g/dL
    - Hct – 24.7%
    - Plt ct – 89,000/uL
      - 170,000 on admission
  - SRA – 100%



Veins of the Leg

Case 3(cont.)

- Patient diagnosed with HIT
- Started on Lepirudin (Refludan®)
  - DTI
  - Not available since 2012
- Leg swelling improved
- Platelet count rose to 197,000/uL

Case 3(cont.)

- Diagnosis of HIT
  - Thrombocytopenia post heparin exposure
  - DVT
  - Positive SRA
  - HIT score of 7 – High probability

Case Study 4

- 55 year old female
- Admitted to hospital for coronary artery bypass surgery
- Had mild myocardial infarction 3 years previously and was treated with heparin therapy for 5 days without complications

Pre-op Lab Results

WBC	8200/μL
RBC	4.8 x 10^6/μL
Hgb	13.5 g/dL
Hct	41%
Plt	265x10^3/μL
PT	11.5 sec
APTT	36 sec

Case Study 4

- Patient underwent bypass surgery with associated heparin therapy
- 2 days post surgery patient complained of left leg pain and chest discomfort
- Thrombotic evaluation revealed DVT
- Ventilation-perfusion scan indicated a perfusion defect in right lung suggesting possible PE

4 T's Score

Feature	2 points	1 point	0 points
Thrombocytopenia??	>50% drop AND nadir >20,000	30%-50% drop OR nadir 10-19,000	>30% drop OR nadir < 10,000
Timing of platelet count fall	5-10 days OR fall ≤1 day if heparin exposure in past 30 days	5 -10 days fall but not clear; OR ≤1 day fall if heparin exposure 30-100 days ago	Platelet count fall in <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis OR skin necrosis; acute systemic reaction after IV UHF bolus	Progressive OR recurrent thrombosis; erythematous skin lesions	None
oTher causes of thrombocytopenia??	None apparent	Possible	Definite

Case Study 4

- Heparin was continued
- 7 days post-op
  - Left lower leg became blue and swollen
  - Platelet count dropped to 50 x$10^3/\mu L$
  - Diagnosis?

4 T's Score

Feature	2 points	1 point	0 points
Thrombocytopenia??	>50% drop AND nadir >20,000	30%-50% drop OR nadir 10-19,000	>30% drop OR nadir < 10,000
Timing of platelet count fall	5-10 days OR fall ≤1 day if heparin exposure in past 30 days	5 -10 days fall but not clear; OR ≤1 day fall if heparin exposure 30-100 days ago	Platelet count fall in <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis OR skin necrosis; acute systemic reaction after IV UHF bolus	Progressive OR recurrent thrombosis; erythematous skin lesions	None
oTher causes of thrombocytopenia??	None apparent	Possible	Definite

HIT

Case Study 4 (cont)

- Left leg was determined to be nonviable and was amputated below the knee
- Maintenance therapy with warfarin was started
- Patient was discharged

What Should Have Happened?

- Platelet count should have been more carefully monitored
- Heparin probably should have been discontinued immediately when DVT was diagnosed
- Alternative anticoagulation started
  - Bilvalirudin or Argatraban
- ELISA ordered

References

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