

Heparin Induced Thrombocytopenia

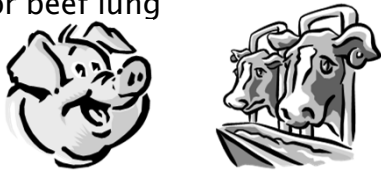
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Objectives

- ▶ 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 intestinal mucosa or beef lung

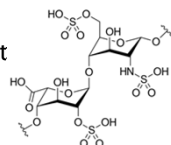


Types of Heparin

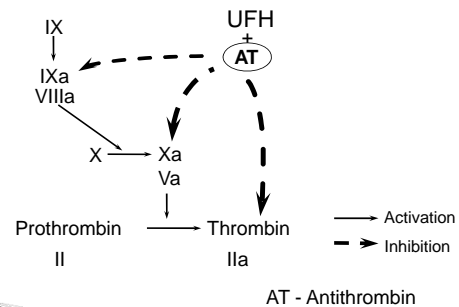
- ▶ Unfractionated Heparin (UH or UFH)
 - Isolated from liver in 1916 by Jay McLean and William Howell (Johns Hopkins University)
 - Available for medical use since 1937
- ▶ Low Molecular Weight Heparin (LMWH)
 - Derived from UFH
 - Available for medical use since 1993

Unfractionated Heparin (UFH)

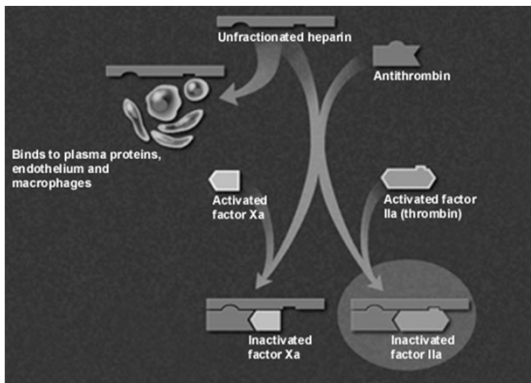
- ▶ Heterogeneous mixture of sulfated mucopolysaccharides
 - 5,000 – 40,000 Daltons
- ▶ Binds to Antithrombin (AT)
 - via unique pentasaccharide sequence
 - enhances ability of AT to inactivate Xa, IIa (thrombin), and other serine proteases
- ▶ Administered IV
 - CABG surgery, angioplasty, stent placement, orthopedic surgery



Mechanism of Unfractionated Heparin



Unfractionated Heparin Mechanism



UFH

- ▶ Anticoagulant of choice for pregnant women (does not cross placenta)
- ▶ 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



Disadvantages of UH

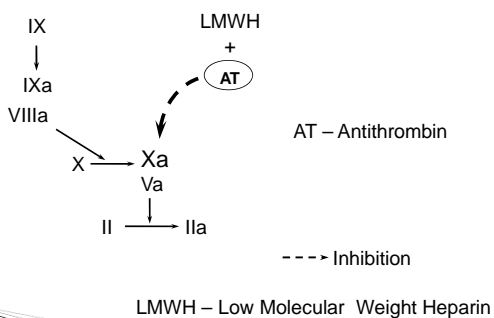
- ▶ Great variability in patient response
 - Inhibited by PF4
 - Short half-life
 - Can bind to other plasma proteins and endothelium
 - Adds to short plasma half-life problem
 - Difficult to monitor accurately with APTT
- ▶ Can be associated with
 - Osteoporosis with long-term use
 - Heparin-Induced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



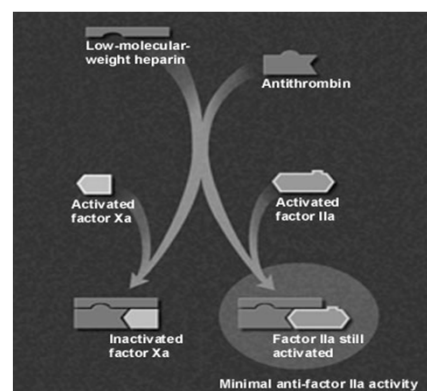
Low Molecular Weight Heparin (LMWH)

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

Mechanism of LMWH



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
- ▶ Platelet count will normalize with continued heparin therapy
- ▶ Results from direct effect of heparin on platelet activation

Type 2

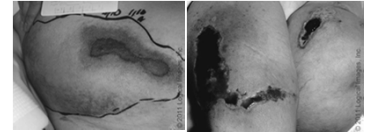
- ▶ Immune mediated
- ▶ *Typical presentation*
 - 4 - 10 days after heparin exposure
- ▶ *Rapid onset presentation*
 - Fall in platelet count in first 24 hours
 - Not a new immune response
 - Patient already has circulating HIT antibodies associated with recent heparin exposure (past 100 days)

Type 2 (cont.)

- ▶ *Delayed-onset HIT presentation*
 - Thrombocytopenia is delayed for up to 3 weeks post heparin
- ▶ Has life and limb threatening thrombotic complications
- ▶ Term HIT generally refers to Type 2

Signs of HIT

- ▶ Decrease in platelet count
 - 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
 - DVT patients with HIT who are started on warfarin
 - Can lead to severe Protein C depletion with likely loss of limb
 - Activated Protein C with cofactor Protein S are Vitamin K dependent **inhibitors** of clotting

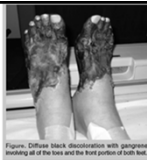
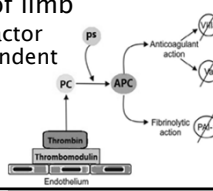


Figure: Diffuse black discoloration with progressive swelling of the toes and the first portion of both feet.



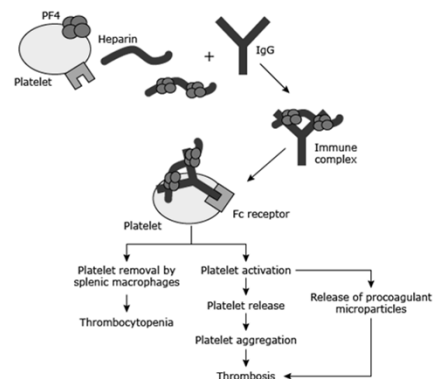
Consequences of Type 2 HIT

- ▶ 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



HIT in absence of heparin

- ▶ HIT antibodies recognize PF4 on platelet chondroitin sulfate
 - Activate platelets even when no heparin is present
- ▶ Explains
 - Delayed-onset HIT
 - Thrombosis and thrombocytopenia without proximate heparin exposure
 - Spontaneous HIT syndrome
 - Persistent HIT

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

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

Characteristic Features

- ▶ 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 may precede 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

Diagnostic Tests

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

NOTE

- ▶ Really 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) adheres 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

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 Serotonin 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

- ▶ Serotonin 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 ¹⁴C serotonin and then washed
- ▶ Washed ¹⁴C serotonin 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 - as high as 100%
- ▶ Technically demanding, costly, uses radioisotopes

HIPA

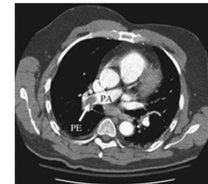
- ▶ Patient serum is mixed with donor platelets in presence of heparin
- ▶ Donor plt aggregation indicates presence of antibodies to heparin-PF4 complex
- ▶ Sensitivity varies from 30% to 81%
- ▶ Specificity varies from 82% to 100%
- ▶ One study of 146 patients
 - More sensitive than ELISA for lab confirmation of HIT
 - Neither HIPA nor ELISA predicted thrombotic risk

Imaging Studies

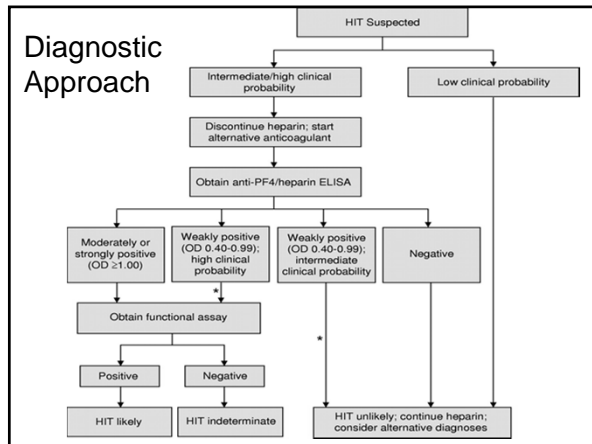
- ▶ DVT can be silent
- ▶ Ultrasonography even in absence of clinical evidence may be considered



Normal lung CT



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



- ### Alternative Parenteral Anticoagulants (IV or injection)
- **Direct Thrombin Inhibitors**
 - *Argatroban (Acova®)*
 - FDA approved for prophylaxis and treatment of thrombosis 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®)*
 - No longer available

- ### 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 available in US

- ### Alternative Oral Anticoagulants
- ▶ *Warfarin (Coumadin)*
 - Monitored with PT/INR
 - Don't start with HIT patients until platelet count >150,000/uL
 - ▶ **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

- ### Long-term Monitoring
- ▶ HIT patients with isolated thrombocytopenia
 - Give alternative anticoagulants until platelet count recovers to stable plateau
 - Continue for up to 4 weeks with the alternative agent or warfarin
 - ▶ HIT patients with thrombosis
 - Give alternative anticoagulant followed by transition to warfarin only after plt counts have recovered to >150,000/uL
 - Overlap with DTI until INR is therapeutic for at least 48 hrs
 - Continue for 3 months

Long-term Monitoring (cont.)

- ▶ HIT patients who no longer have thrombocytopenia but need cardiac intervention
 - Heparin can be used short term for cardiac surgery
 - Bivalirudin or argatroban for cardiac cath or PCI(angioplasty with stent)
- ▶ HIT patients with persistent antibodies who need cardiac surgery
 - Should NOT receive heparin

Consequences 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 Study 1

- ▶ 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/ μ L
RBC	4.8×10^6 / μ L
Hgb	13.5 g/dL
Hct	41%
Plt	265×10^3 / μ L
PT	11.5 sec
APTT	36 sec

Case Study 1

- ▶ 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 \leq 1 day if heparin exposure in past 30 days	5–10 days fall but not clear; OR \leq 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 1

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

HIT

Case Study 1 (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
 - Bivalirudin or Argatroban

Case 2 – 2005

- ▶ 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 regurgitation
 - 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
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1804000/

Case 2 (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

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

Case 2 (cont.)

- ▶ 7 days post-op
 - Plt count 43,000/uL despite 48 units of plts
- ▶ Differential diagnosis
 - Sepsis related DIC
 - Accelerated plt removal 2^o 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 2 (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 2 (cont.)

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

Case 2 (cont.)

- ▶ Reasons for misdiagnosis
 1. Plausible 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 2 (cont.)

- ▶ Should have
 - Immediately ceased all heparin including flushes and LMWH
 - Started argatroban
 - lepirudin (available in 2005) was contraindicated due to acute renal failure

Case Study 3 – 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^o 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 FDA approved in US
 - This patient was treated in Canada

Case 4

- ▶ 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 4(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 4(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 4(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

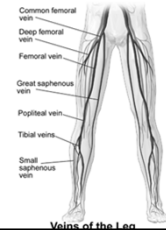


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Case 4(cont.)

- ▶ 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%



Case 4(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 4(cont.)

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

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