Heparin-Induced Thrombocytopenia

Recent Advances in Management

Heparin-induced Thrombocytopenia

- Heparin-induced thrombocytopenia (HIT), an antibody-mediated syndrome, is associated with significant morbidity and mortality
  - considered a rarity in the past
    - unrecognized by many clinicians
    - diagnoses can be difficult to confirm
  - until recently there was no therapeutic options other than discontinuation of heparin

Epidemiology

- thrombocytopenia is one of the most common laboratory abnormalities found among hospitalized patients
- serologically proven HIT occurs in 1.5% to 3% of patients with heparin exposure

Epidemiology

- the chance of significant exposure to heparin exceeds 50% in hospitalized patients
  - acute coronary syndrome (UA / MI)
  - pulmonary embolism
  - deep venous thrombosis and prophylaxis
  - stroke / atrial fibrillation
  - heparinized pulmonary wedge catheters
  - heparin flush

Bleeding and Clotting

- present with mucocutaneous bleeding, ranging from petechiae and ecchymoses to life-threatening gastrointestinal and intracranial hemorrhage

- paradoxically, the most feared consequence in these patients with a low platelet count is not bleeding but clotting

Thrombosis

- thrombosis is mostly venous not arterial
- may result in
  - bilateral deep venous thrombosis of the legs
  - pulmonary embolism
  - venous gangrene of fingers, toes, penis, or nipples
  - myocardial infarction, stroke
  - mesenteric arterial thrombosis
  - limb ischemia and amputation

Circulation 1999;100:587-93
Am J Med 1996;101:502-7
Thromb Haemost 1993;70:554-61

Thrombosis

- thromboembolic complications
  - occurs in at least 30% to 40% of HIT cases
  - mortality estimated at 30%
  - increased length of hospital stay

Circulation 1999;100:587-93
Am J Med 1996;101:502-7
Thromb Haemost 1993;70:554-61

Differential Diagnosis of Acquired Thrombocytopenia

- **Drugs**
  - heparin
  - procainamide
  - diuretics (furosemide)
  - H_2 blockers (cimetidine)
  - thrombolytic therapy
  - GP IIb/IIIa antagonists
- **Devices**
  - membrane oxygenator
  - intra-aortic balloon pump
- **Pseudothrombocytopenia**
  - platelet clumping
  - hemodilution
- **Associated disorders**
  - hypersplenism
  - infections/sepsis
  - hypotension and subsequent disseminated intravascular coagulation
- **Other causes**
  - chronic idiopathic thrombocytopenia purpura with exacerbation
  - antiphospholipid antibody syndrome

Mechanisms of Thrombocytopenia

- Increased Platelet Destruction
  - Non-immune
  - Immune
- Decreased Platelet Production

Increased Platelet Destruction

- **Non-immune**
  - Septicemia / Inflammation
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura

Increased Platelet Destruction

- **Immune**
  - Autoimmune: idiopathic or secondary immune thrombocytopenia
  - Alloimmune: post-transfusion purpura
  - Drug-induced: **heparin**, gold, quinine, quinidine, sulfa antibiotics, rifampin, vancomycin, nonsteroidal antiinflammatory, and others

Heparin Induced Thrombocytopenia

- HIT
  (*heparin-induced thrombocytopenia)*
- HAT
  (*heparin-associated thrombocytopenia)*
- White- clot syndrome
  first noted in the surgical literature

HIT Syndrome

- **Type I**
  - associated with an early (within 4 days) and usually mild decrease in platelet count (rarely <100 x 10^9/L)
  - typically recovers within 3 days despite continued use of heparin
  - nonimmunologic mechanisms (mild direct platelet activation by heparin)
  - not associated with any major clinical sequelae
  - occurs primarily with high dose iv heparin

HIT Syndrome

- **Type II**
  - substantial fall in platelet count (> 50%)
  - count in the 50,000 - 80,000 /mm range
  - typical onset of 4-14 days
  - occurs with any dose by any route
  - induced by immunologic mechanisms
  - rarely causes bleeding (think of alternative Dx)
  - potential for development of life-threatening thromboembolic complications

Risks for HIT

- **Type I**
  - **intravenous high-dose heparin**
- **Type II**
  - **varies with dose of heparin**
  - **unfractionated heparin > LMWH**
  - **bovine > porcine**
  - **surgical > medical patients**

HIT

- An **immunoglobulin-mediated** adverse drug reaction characterized by:
  - platelet activation
  - thrombocytopenia
  - thrombotic complications

Pathogenesis of Drug-induced thrombocytopenia

- Certain drugs (quinine, quinidine, sulfa antibiotics) link non-covalently to platelet membrane glycoproteins
- very rarely, IgG antibodies are produced that recognize these drug-glycoprotein complexes
- macrophages remove the complexes causing severe thrombocytopenia

Pathogenesis of HIT

- Most commonly caused by IgG antibodies (designated HIT-IgG) that activate platelets through their Fc receptors

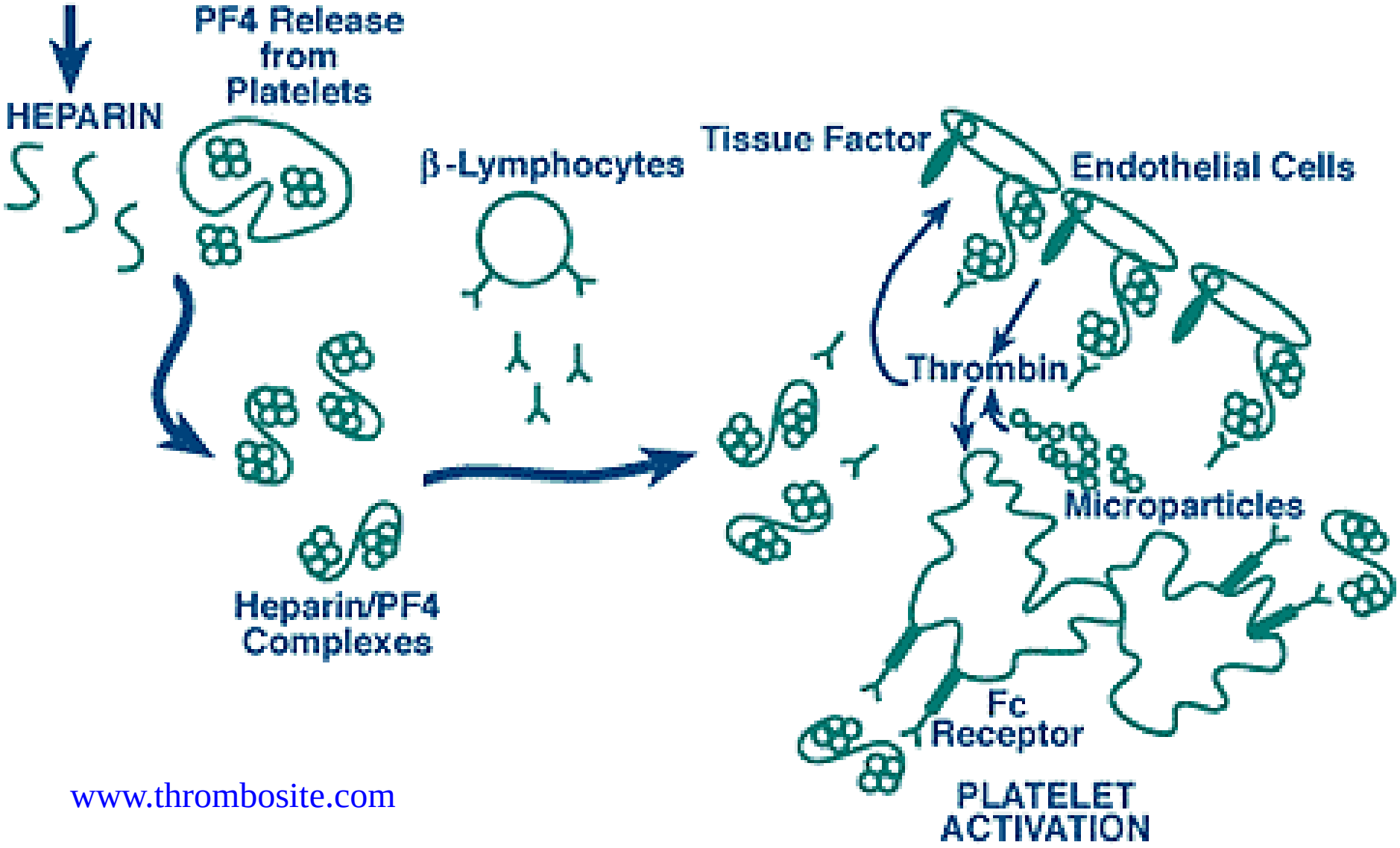
Antigenic Heparin/PF4 Complex

- antigen in HIT is a complex of "-" charged heparin polysaccharide and "+" charged protein tetramer (platelet factor 4 or PF4)
- PF4 is released from platelet storage granules during platelet activation
- unfractionated heparin wraps around PF4 to a greater extent than LMWH

Effects on the coagulation system

- Binding of heparin to PF4 neutralizes the anticoagulant effect of heparin
- Immune complexes composed of heparin, PF4, and IgG binds to platelet Fc receptors, resulting in strong platelet activation, and ultimate increase in thrombin generation

Cascade of events leading to formation of HIT antibodies and prothrombotic components



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Frequency of HIT

- Unfractionated heparin [1]
  - 1% and 3% orthopedic patients who received UFH for one and two weeks, respectively
- Low molecular weight heparin [2]

	HIT antibodies	HIT syndrome
UFH	7.8%	3%
LMWH	2.2%	0%

1. Thromb Hemost 1998;79:1-7
2. NEJM 1995;332:1330-1335

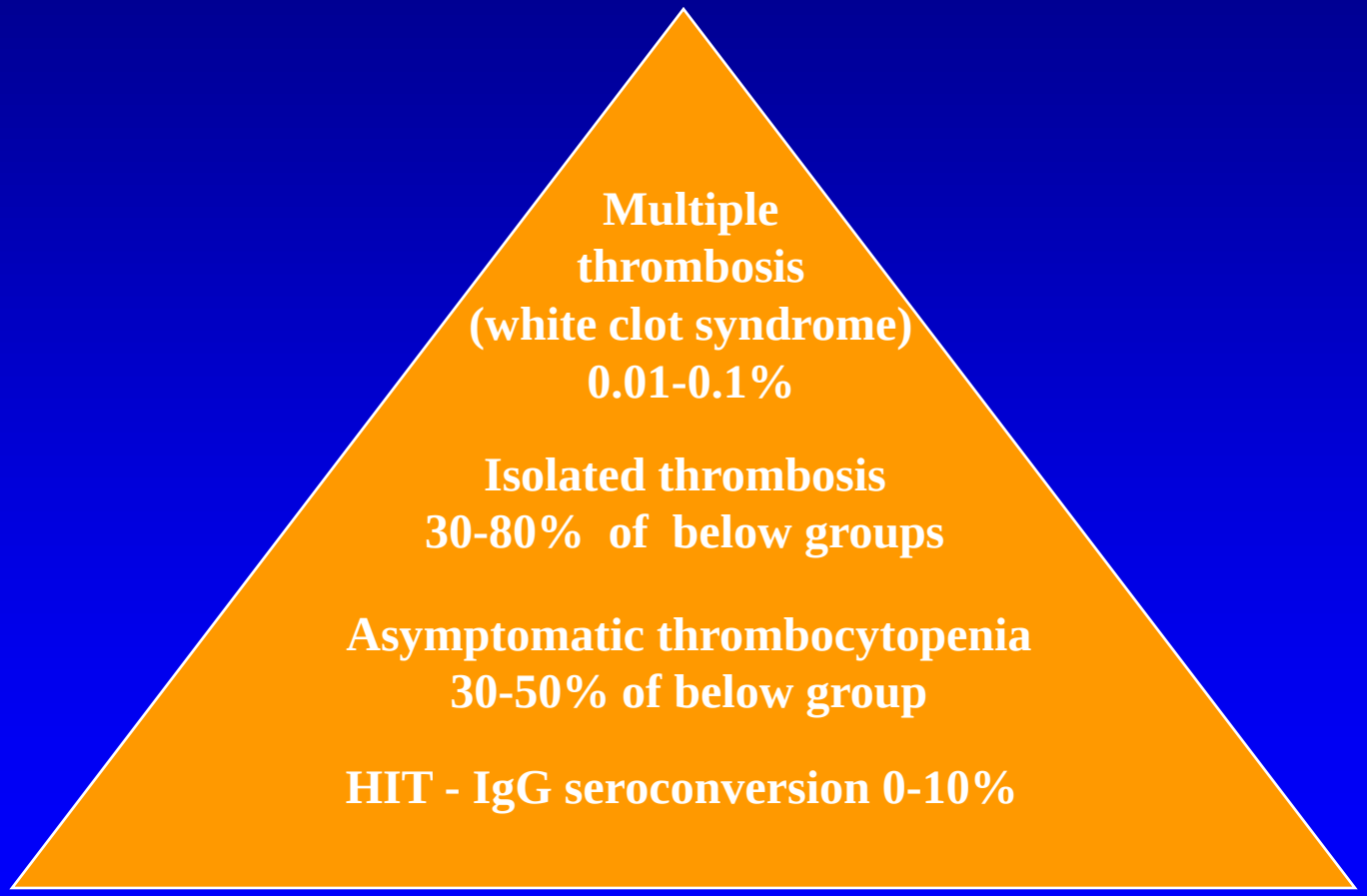
HIT-associated thrombosis

- **HIT is prothrombotic**
  - **89% with HIT developed thrombosis**
  - **18% without HIT developed thrombosis**

"increased risk for thrombosis was seen only in the patients who developed thrombocytopenia, and not in the patients who developed HIT antibodies without thrombocytopenia"

NEJM 1995;332:1330-1335

Iceberg Model



Warkentin TE, et al. 1994;75-127

Diagnosis of HIT

- absence of another clear cause for thrombocytopenia
- the timing of thrombocytopenia
- the degree of thrombocytopenia
- adverse clinical events (most often thrombocytpenia)
- positive laboratory tests for HIT antibodies

Characteristic features of HIT

- platelet count typically begin to fall 5-8 days after heparin therapy is started
- may develop within the first day with repeat exposure
- consider other causes if occurs after 2 wks of therapy
- thrombocytopenia is usually mild to moderate, with platelet counts ranging from 20 to 150 x 10^9/L (threshold for thrombocytopenia)

Comparison of HIT and other Drug-Induced Thrombocytopenia

	HIT	Quinine/Sulfa
Frequency	~1/100	~1/10,000
Onset	5-8 days	≥ 7 days
Platelet count	20-150x10^9/L	<20x10^9/L
Sequelae	Thrombosis	Bleeding
Laboratory	Immunoassay (heparin/PF4 antigen)	Platelet-associated IgG

Clinical Features Suspicious for HIT

- a rapid drop in platelets may also be indicative of HIT, particularly if the patients received heparin within the previous 3 months
- a fall in platelet count of >50% that begins after 5 days of heparin therapy, but with the platelet count > 150 x 10^9/L, should also raise the suspicion of HIT

Unusual Clinical Events Suspicious for HIT

- mild to moderate thrombocytopenia, often in conjunction with thrombosis
- adrenal hemorrhagic infarction (caused by adrenal vein thrombosis)
- warfarin-induced venous limb gangrene
- fever, chills, flushing, or transient amnesia beginning 5 to 30 minutes after an IV heparin bolus
- heparin-induced skin lesions associated with HIT antibodies, even in the absence of thrombocytopania

Clinical Syndromes Associated with HIT

- Venous thromboembolism
- Arterial thrombosis
- Skin lesions at heparin injection site
- Acute platelet activation syndromes

Venous Thromboembolism

- Deep vein thrombosis *
- Pulmonary embolism *
- Venous limb gangrene
- Adrenal hemorrhagic infarction
- Cerebral sinus thrombosis

* most common complication of HIT

Arterial thrombosis

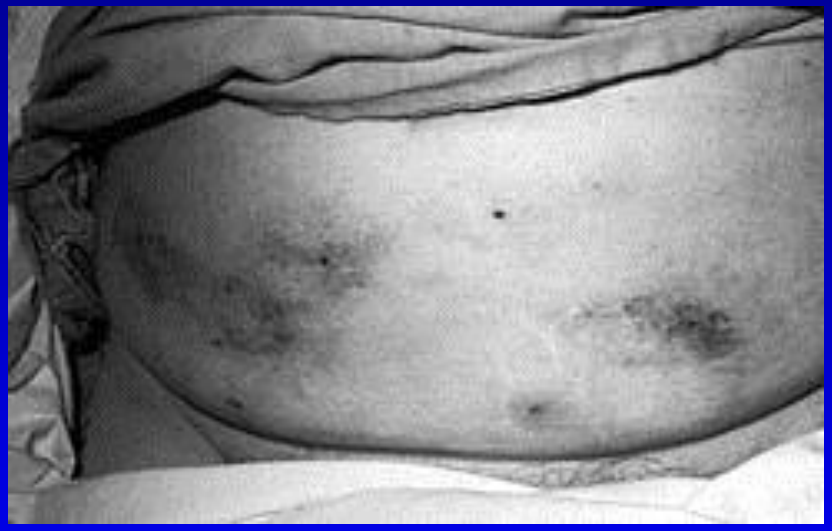
- **Lower limb involvement**
- **Stroke**
- **Myocardial infarction**
- **Other**

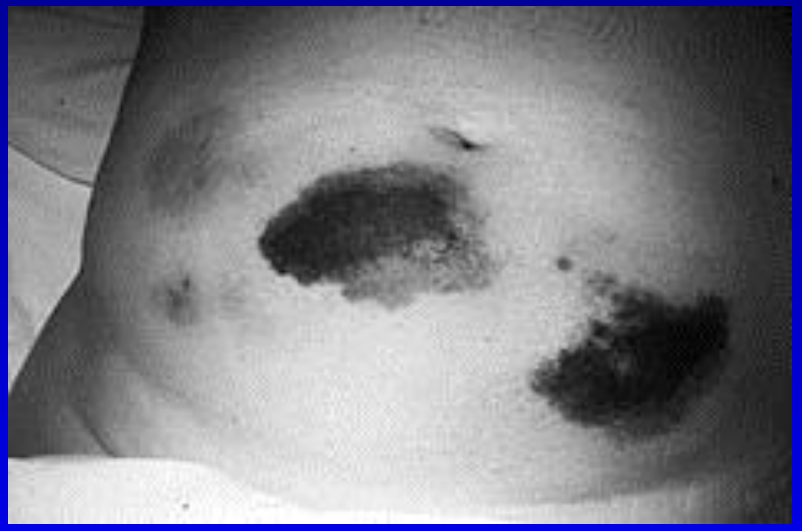
Venous thrombotic events predominate over arterial events by 4:1 ratio. Usually involving large vessels.

Other Clinical Syndromes

- **Skin lesions at heparin injection site**
  - **Skin necrosis**
  - **Erythematous plaques**
- **Acute platelet activation syndrome**
  - **Acute inflammatory reactions (fever, chills, etc.)**
  - **Transient global amnesia**

Skin lesions associated with HIT





LEFT: Heparin-induced erythematous plaques.
RIGHT: Heparin-induced skin necrosis

Morbidity and Mortality

- HIT-associated mortality is high (about 18%)
- 5% of affected patients require limb amputation
- Overt bleeding or bruising is rare even with severe thrombocytopenia
- Appropriate management can limit morbidity and mortality

Common Laboratory Tests for HIT

Test	Advantages	Disadvantages
PAA	Rapid and simple	Low sensitivity - not suitable for testing multiple samples
SRA	Sensitivity >90%	Washed platelet (technically demanding), needs radiolabeled material ^{14}C
HIPA	Rapid, sensitivity >90%	Washed platelets
ELISA	High sensitivity, detects IgA and IgM	High cost, lower specificity for clinically significant HIT

Functional Assays

- exploits the ability of HIT antibodies to activate normal platelets
  - platelet aggregation assay (PAA)
  - serotonin release assay (SRA)
  - heparin induced platelet activation (HIPA)
- use of washed donor platelets increase sensitivity and specificity to >90% for SRA and HIPA

Functional Assay

- **Platelet aggregation assay (PAA)**
  - performed by many laboratories
  - incubate platelet-rich plasma from normal donors with patient plasma and heparin
  - limited by poor sensitivity and specificity because heparin can activate platelets under these conditions, even in the absence of HIT antibodies

Antigen Assay

- Antibodies against heparin/PF4 complexes (the major antigen of HIT) are measured by colorimetric absorbance
- Two ELISA have been developed
  - Stago
  - GTI
- limited by high cost

Management of HIT

- risk for thrombosis is high in HIT, prevention of thrombosis is the goal of intervention
- heparin is contraindicated in patients with HIT
- **discontinuation of heparin** - all sources of heparin must be eliminated
- most patients will require treatment with an alternate anticoagulant for
  - initial clinical problem
  - HIT induced thrombosis

Antithrombotic Treatment

- **LMWH (enoxaparin and dalteparin)**
  - in vitro studies showed virtually 100% cross-reactivity with HIT antibodies
  - lack large, controlled studies
  - anecdotal reports of persistent or recurrent thrombocytopenia during treatment

Antithrombotic Treatment

- **Ancrod**
  - a defibrinogenating snake venom
  - slow onset of action (must be given over 12 to 24 hours)
  - does not ↓ thrombin generation which is important in the pathogenesis of HIT
  - HIT and DIC patients may already be hypofibrinogenemic

Antithrombotic Treatment

- **Warfarin**
  - caution if INR >4
  - high INR corresponds to a marked reduction in protein C levels, i.e., there is insufficient protein C activity to regulate the ↑ thrombin generation found in HIT
  - associated with progression of deep venous thrombosis to venous limb gangrene
  - considered contraindicated in acute HIT, but reasonable to use in longer-term anticoagulation

Thromb Haemost 1998;79:1-7
Ann Intern Med 1997;127:804-812

New Antithrombin Drugs

Agents that reduce or inhibit thrombin

- lepirudin (Refludan)
- danaparoid sodium (Orgaran)
- argatroban (Novastan)

Lepirudin (Refludan®)

- A direct thrombin inhibitor
  - recombinant form of the leech anticoagulant hirudin, the most potent direct thrombin inhibitors yet identified
- Rapid anticoagulant effect with IV bolus
- Relatively short half-life (1.3 hours)
- Relatively contraindicated in renal failure
- Anticoagulant effect readily monitored with aPTT (target range 1.5-3.0 times normal)

Lepirudin (Refludan®)

- The only direct thrombin inhibitor approved for use and for treatment of HIT in the U.S.
- German trial of 200 patients with HIT
  - 75% to 81% effectively anticoagulated
  - significant reduction in composite endpoints (death, limb amputation, new thrombotic complications) compared with historical control

7 day	10% vs 23%
35 day	25% vs 52%

Blood 1996;88(suppl):281a

Lepirudin (Refludan®)

Lepirudin for Parental Anticoagulation in Patient with Heparin-induced Thrombocytopenia

- a prospective, historically controlled trial
- by five weeks after laboratory diagnosis of HIT, the incidence of death, limb amputation, or new thromboembolic events was 52.1% in the historical controls and 30.9% in the Lepirudin-treated group

Danaparoid (Orgaran®)

- a low-molecular-weight heparinoid
  - mixture of anticoagulant glycosaminoglycans (heparin sulfate, dermatan sulfate, and chondroitin sulfate) with predominant anti-factor Xa activity
- rapid anticoagulant effect with IV bolus
- long half-life (~25 hours) for anti-Xa activity
- in vitro cross-reactivity with the HIT antibody (10% to 40%) does not predict development of thrombocytopenia or thrombosis

Blood 1996;88(Suppl 1):626a
Thromb Haemost 1993;70:554-561

Argatroban (Novastan®)

- a small synthetic non-polypeptide molecule
- a direct thrombin inhibitor
- FDA approved June30, 2000
- has the same theoretical advantages of lepirudin
  - short half-life (< 1hr)
  - lack of cross-reactivity for HIT antibodies
  - potent antithrombin activity
- metabolized predominantly by the liver, may require dose adjustment
- excreted normally even in severe renal failure

Adjunctive Therapies for HIT

- Plasmapheresis
  - can reduce the concentration of HIT antibodies
  - replace deficient plasma anticoagulant factors
- Aspirin/Clopidogril/Gp2b3a inhibitors
  - can inhibit platelet activation by HIT antibodies

Treatment Options for HIT

Drug	Dose	Comments
IV Lepirudin	0.4 mg/kg load	preferred therapy, if available adjust those for renal insufficiency check aPTT 4hr after dose adjustment
IV Danaparoid	400 U/hr x 4 hr → 300 U/hr x 4hr → 100 - 370 U/hr	direct thrombin inhibitor cannot be used monitor anti-factor Xa levels adjust those for renal insufficiency
SC Danaparoid	750 U every 12 hr	may be used for low-risk cases must have ability to monitor anti-fact Xa levels if renal insufficiency is present
Warfarin		consider for long-term anticoagulation do not start war for without concurrent alternative anticoagulation

Do's and Don'ts of HIT Management

Drug	Do	Don't	Comments
Warfarin		x	warfarin in the absence of an anticoagulant can precipitate venous limb gangrene
Platelet		x	infusing platelets merely "adds fuel to the fire"
Vena caval filter		x	often results in devastating caval, pelvic, and lower leg venous thrombosis
LMWH		x	low molecular weight heparin usually cross-react with unfractionated heparin after HIT or HITTS (HIT thrombosis syndrome) has occurred
Ancrod		x	not readily available; difficult to titrate dose
Danaparoid	x		cross-reacts with UFH in about 10-15% of cases; titrate with unwieldy anti-factor Xa levels
Hirudin	x		Beware renal insufficiency, antibody formation
Plasmapheresis	x		removes micro-particles formed from platelet activation; not a standard indication
Argatroban	x		FDA approved June 30, 2000

Steps to Prevent HIT

- porcine heparin preferred over bovine heparin
- LMWH preferred over unfractionated heapirn
- oral anticoagulation should be started as early as possible to reduce the duration of heparin exposure
- intravenous adapters should not be flush with heparin
- monitoring serial plate counts for developing thrombocytopenia

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World Wide Web

- www.thrombosite.com