CEEA

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TROMBOCITOPENIA INDUSA DE HEPARINA (Sindromul HIT)

TROMBOCITOPENIA INDUSA DE HEPARINA

- Heparin-induced thrombocytopenia (HIT), sindrom mediat de anticorpi
  - Considerat o raritate in trecut
    - Nerecunoscut de multi clinicieni
    - Dificil deseori de diagnosticat/confirmat
  - Pana de curand, fara alta optiune terapeutica decat sistarea heparinoterapiei

HIT: Epidemiology

- More than 1 trillion units of heparin are used yearly in the United States; a third of hospitalized patients are exposed (12 million)[1]
- HIT occurs in up to 1% to 3% of patients receiving unfractionated heparin (UFH)[2]
- HIT is a serious condition, with roughly 50% of patients at risk of life- or limb-threatening thromboses if they remain untreated[3]
- Risk of developing thromboembolism after HIT diagnosis is 30% to 75%[3]
- HIT is known to occur in 0.2% of patients who receive low-molecular-weight heparin (LMWH)[4]

1. Fahey. *J Vasc Nurs*. 1995;13:112-116.
2. Warkentin et al. *N Engl J Med*. 1995;332:1330-1335.
3. Warkentin, Kelton. *Am J Med*. 1996;101:502-507.
4. Martel et al. *Blood*. 2005;106:2710-2715.

Epidemiologie

- „Sansa” de a primi heparina este de peste 50% la pacientii spitalizati:
  - Sindrom coronarian acut (IMA)
  - Embolie pulmonara
  - TVP si profilaxie
  - stroke / fibrilatie atriala
  - Catetere Swan-Ganz heparinizate
  - Spalarea cateterelor venoase cu heparina

Sangerarea/Coagularea

- Sangerari cutanate sau la nivelul mucoaselor, petesii, echimoze…..hemoragii gastro-intestinale sau intracraniene

- Paradoxal, teama cea mai mare nu este de sangerare ci de…coagulare.

Tromboza

- Tromboza este mai ales venoasa, nu arteriala
- Apare ca si:
  - TVP bilaterala a membrelor inferioare
  - Embolie pulmonara
  - Gangrena venoasa a degetelor, penis
  - IMA, stroke
  - Tromboza arteriala mezenterica
  - Ischemie de membru, amputatie

Circulation 2009;100:587-93
Am J Med 2006;101:502-7
Thromb Haemost 2013;70:554-61

Tromboza

- Complicatii tromboembolice
  - Apar in cel putin 30% - 40% din HIT
  - Mortalitate estimata la 30%
  - Creste durata spitalizarii

Circulation 2009;100:587-93
Am J Med 2006;101:502-7
Thromb Haemost 2013;70:554-61

Diagnostic diferential in trombocitopenia dobandita

- **Droguri**
  - heparina
  - procainamida
  - diuretice (furosemid)
  - Blocanti H_2 (cimetidina)
  - Terapia tromboltica
- **Dispozitive medicale**
  - oxigenatori de membrana
  - intra-aortic balloon pump
- **Pseudotrombocitopenia**
  - Agregarea plachetara
  - hemodilutia
- **Boli asociate**
  - hipersplenism
  - infectii/sepsis
  - CID
- **Alte cauze**
  - Exacerbarea purpurei trombocitopenice idiopatice
  - Sdr. Anticorpilor fosfolipidici

Mecanismele trombocitopeniei

- Cresterea distrugerii de trombocite
  - Non-imuna
  - Imuna
- Scaderea productiei de trombocite

Cresterea distrugerii de trombocite

- **Non-imuna**
  - Sepsis / Inflamatie
  - CID
  - Purpura trombocitopenica

Cresterea distrugerii de trombocite

- **Imună**
  - Autoimuna: idiopatic sau trombocitopenia imuna secundara
  - Alloimuna: purpura post-transfusionala
  - Drug-induced: **heparina**, aur, chinine, chinidine, antibiotice (rifampicina, vancomicina), NSAID

Heparin Induced Thrombocytopenia

- HIT (*heparin-induced thrombocytopenia)*
- HAT (*heparin-associated thrombocytopenia)*
- White - clot syndrome

HIT Syndrome

- **Tip I**
  - Asociat cu scaderea precoce (sub 4 zile) si moderata a nr. trombocitelor (rar <100 x 10^9/L)
  - Tipic, recuperare in 3 zile chiar daca se continua utilizarea heparinei
  - Mecanisme non-imunologice (activare directa moderata a trombocitelor de catre heparina)
  - Nu se asociaza cu urmari clinice severe
  - Apare dupa doze mare de heparina IV

HIT Syndrome

- **Tip II**
  - Scadere semnificativa a nr trombocitelor (> 50%)
  - Nr. trombocite: 50,000 - 80,000 /mm
  - Instalare in 4-14 zile
  - Independenta de doza si cale de adm
  - Indus de mecanisme imunologice
  - Rar determina sangerari
  - Potential de dezvoltare a complicatiilor letale de tip tromboembolic

Risc de HIT

- **Tip I**
  - **Doza mare intravenoasa de heparina**
- **Tip II**
  - **Variaza cu doza de heparina**
  - **Heparina nefractionata > LMWH**
  - **bovine > porcine**
  - **Pacienti chirurgicali > medicali**

HIT - fiziopatologie

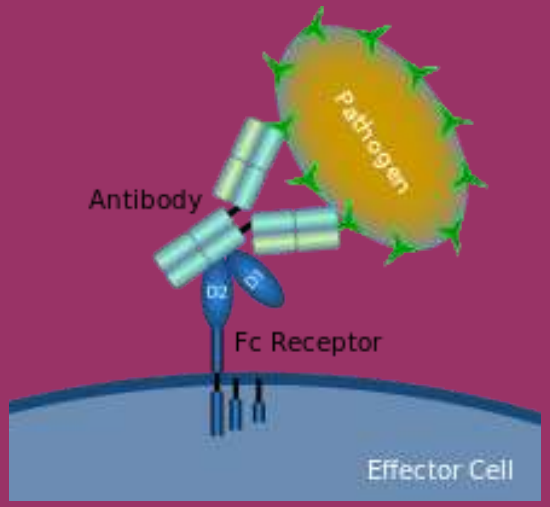
- **Reactie adversa mediata de imunoglobuline, caracterizata prin:**
  - **Activarea trombocitelor**
  - **Trombocitopenia**
  - **Complicatii trombotice**

Patogeneza
Drug-induced thrombocytopenia

- Anumite medicamante (quinine, quinidine, sulfa antibiotics) se leaga non-covalent cu glicoproteinele membranare ale trombocitelor.
- Rar, IgG antibodies – recunosc aceste complexe drug-glycoprotein
- Macrofagele elimina complexele care cauzeaza trombocitopenia severa.

Pathogenesis of HIT

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



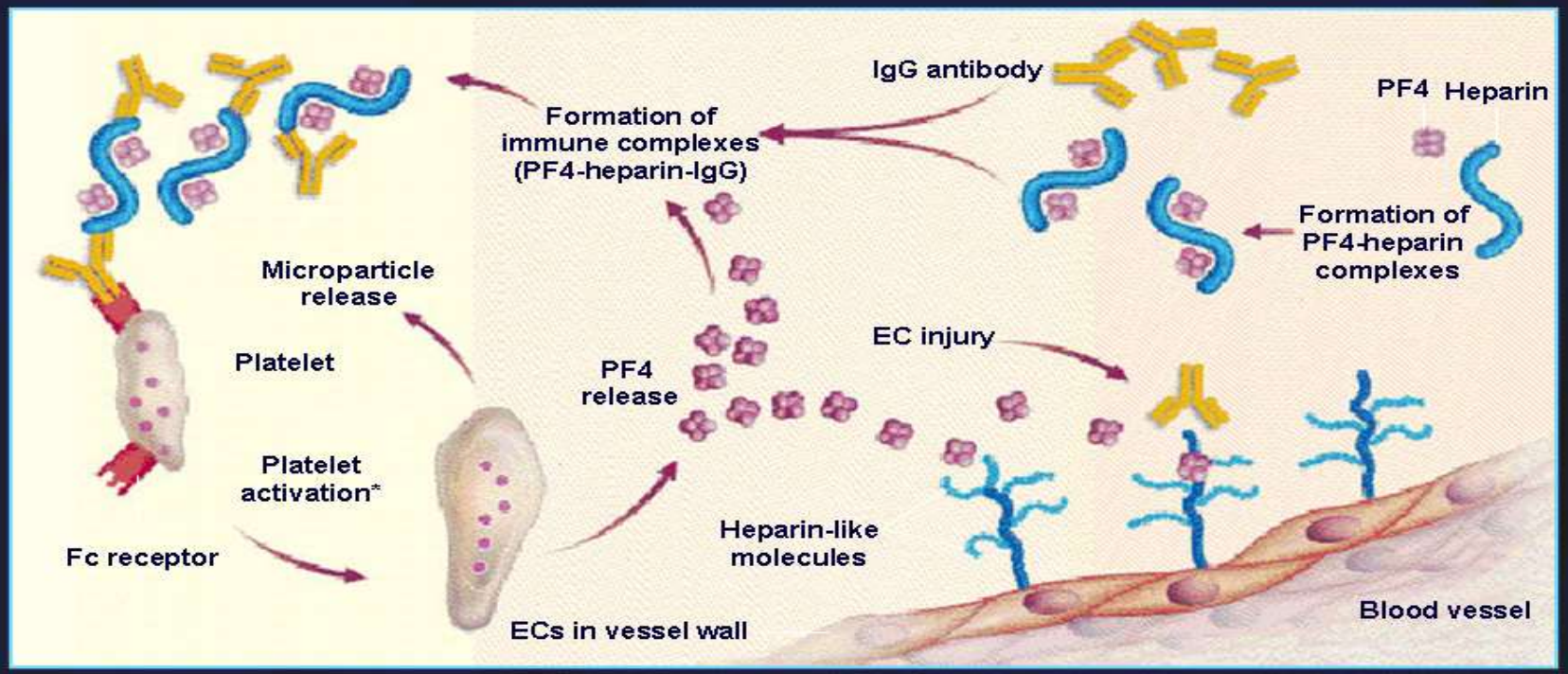
Antigenic Heparin/PF4 Complex

- Antigen in HIT complex:
  - “-” charged heparin polysaccharide
  - “+” charged protein tetramer (platelet factor 4/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



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 2008;79:1-7
2. NEJM 2005;332:1330-1335

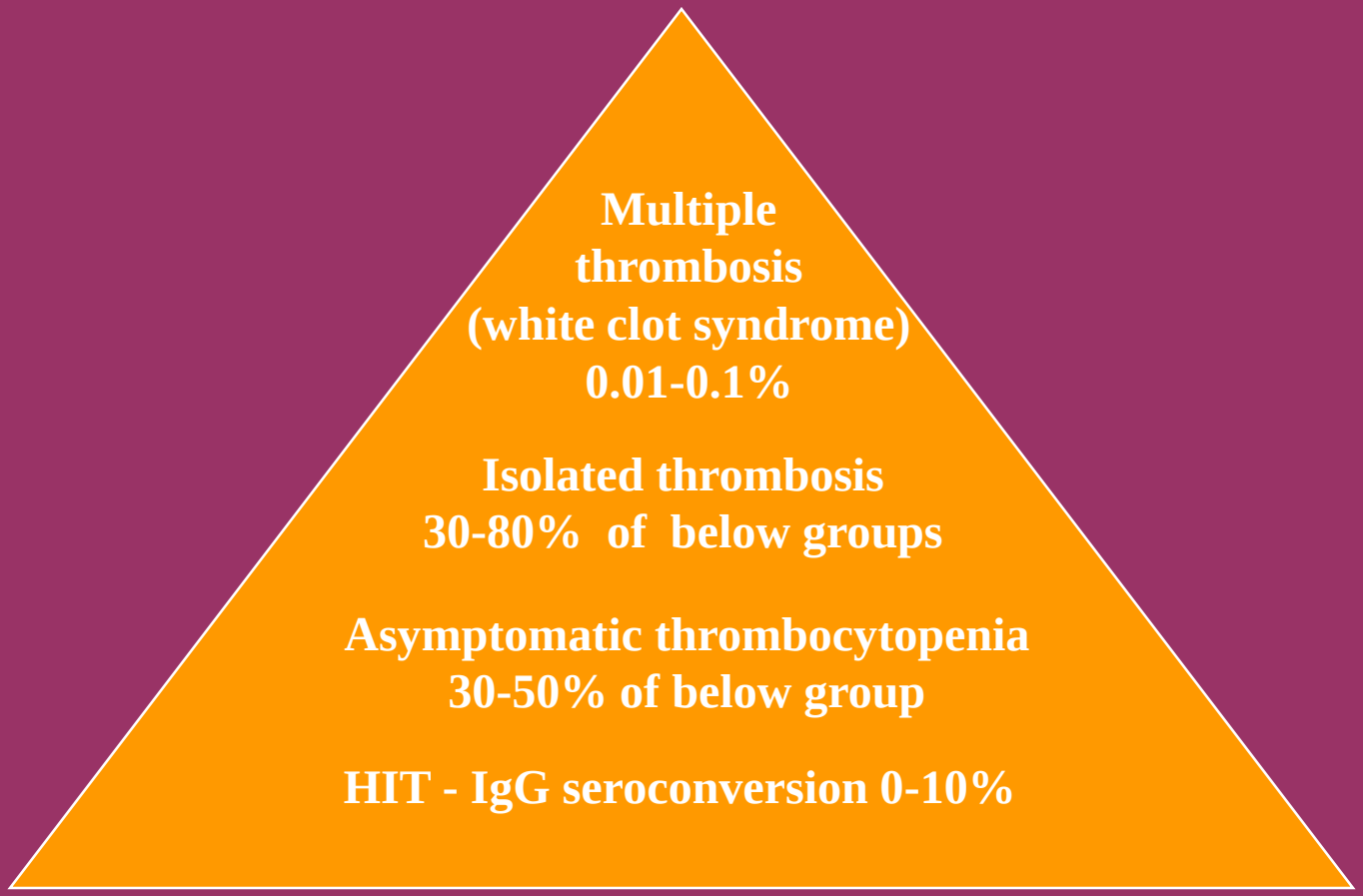
HIT-associated thrombosis

- **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 2005;332:1330-1335

Iceberg Model



Warkentin TE, et al. 2004;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)

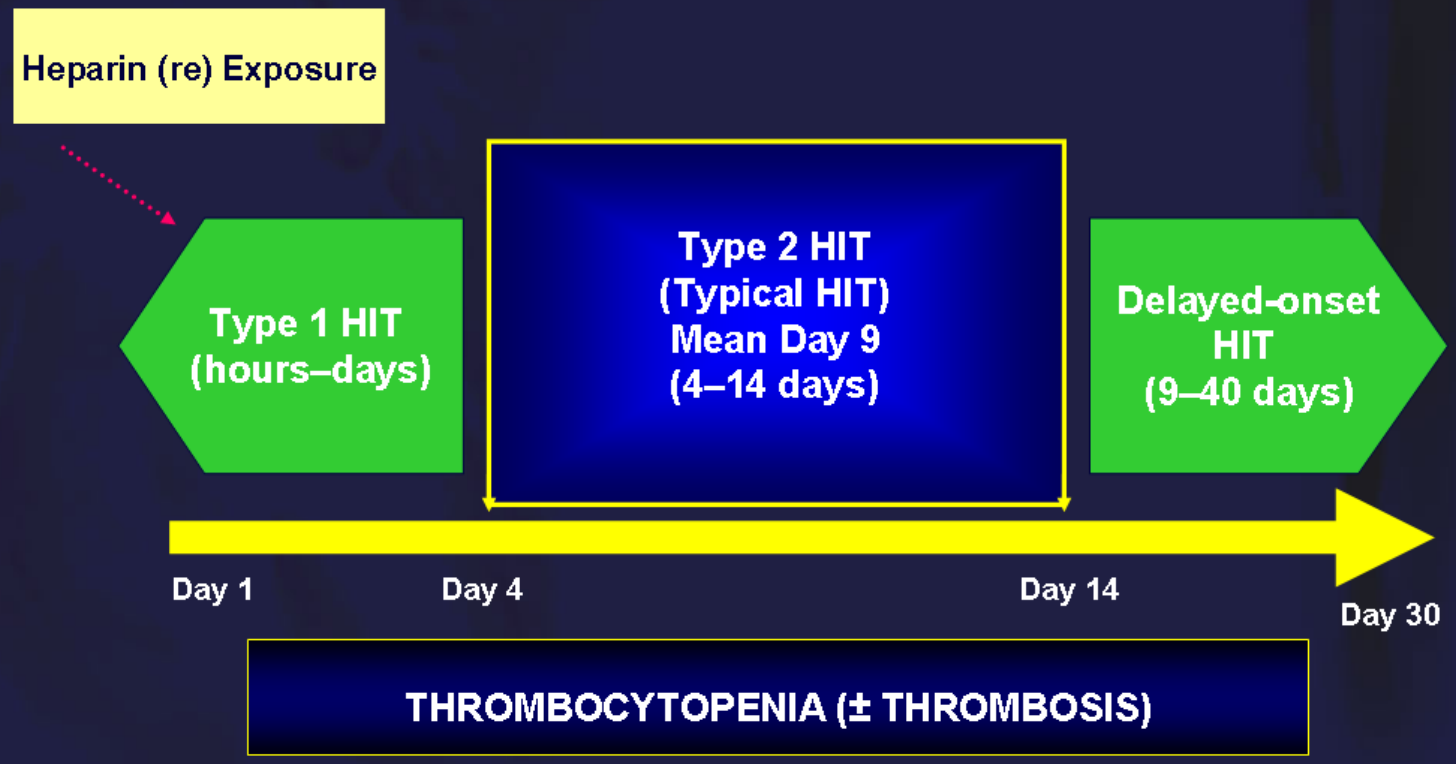
Comparison of HIT and other Drug-Induced Thrombocytopenia

	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

Temporal Patterns of Thrombocytopenia in HIT



Warkentin, Greinacher. *Chest*. 2004;126(Suppl):311S-337S.

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

AM J Med 2006;101:502-507

Arterial thrombosis

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

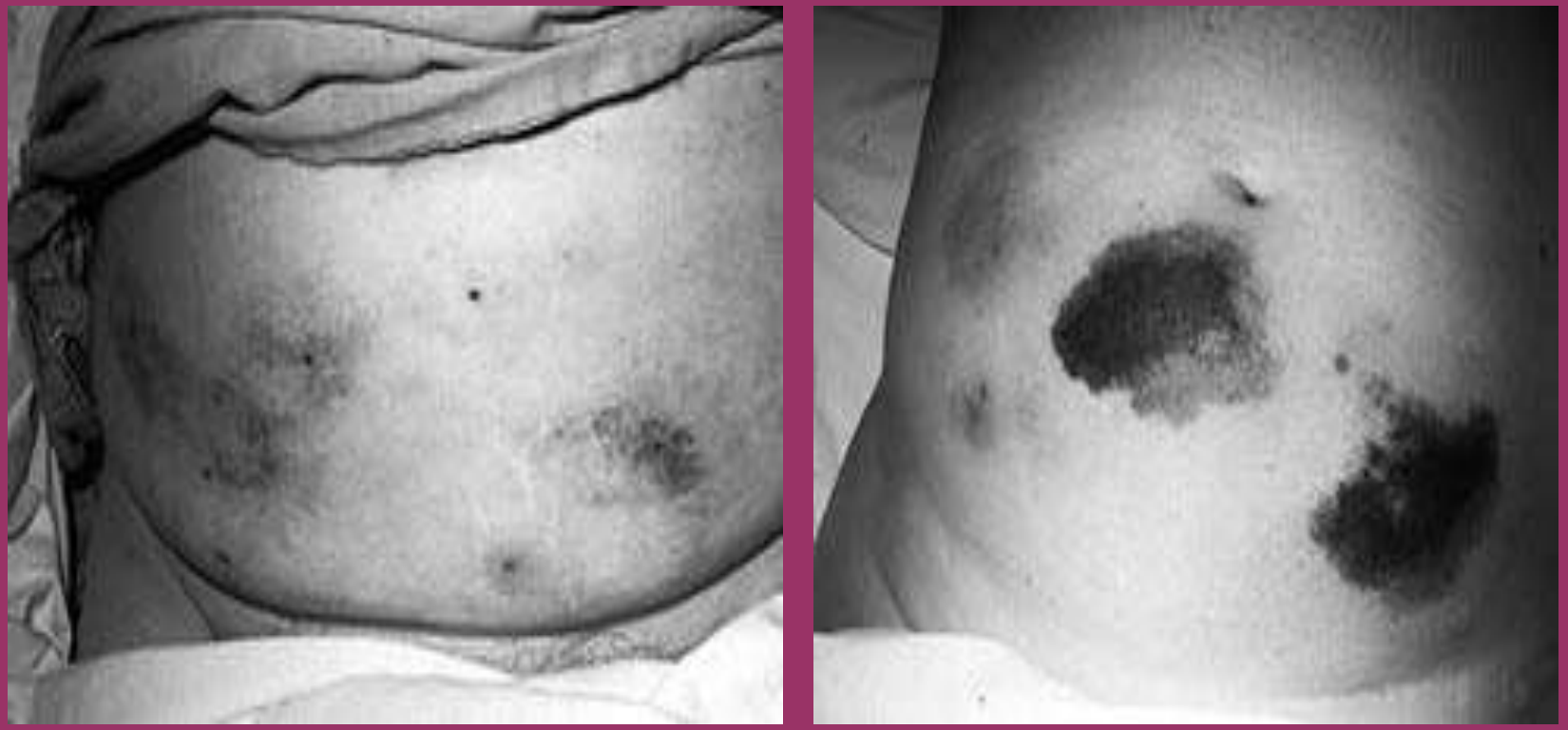
Venous thrombotic events predominate over arterial events by 4:1 ratio. Usually involving large vessels.

AM J Med 1996;101:502-507

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 are rare even with severe thrombocytopenia
- Appropriate management can limit morbidity and mortality

Common Laboratory Tests for HIT

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

Thromb Haemost 2008;79:1-7

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

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

- **Ancrod (Viprinex)**
  - 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

Blood 1996;88(Suppl 1):626a

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 2008;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

- 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)

Blood 1996;88(suppl):281

Lepirudin

- 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 2006;88(suppl):281a

Lepirudin

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

Circulation 1999;100:587-93

Danaparoid

- 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 2006;88(Suppl 1):626a
Thromb Haemost 2013;70:554-561

Argatroban

- a small synthetic non-polypeptide molecule
- a direct thrombin inhibitor
- 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

Xa inhibitor Fondaparin- off-lebel

Steps to Prevent HIT

- porcine heparin preferred over bovine heparin
- LMWH preferred over unfractionated heparin
- 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