Heparin-Induced Thrombocytopenia and Thrombosis: HITT Syndrome Update

Surgery Grand Rounds February 18, 2011

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Case Presentation #1

- 43 yo male with acute chest pain/ischemia
- Went for angioplasty and 5 days later CAB
- Rocky post-op course/balloon pump
- Platelet count fell significantly in 7 days
- HIT antibody test positive
- Later suffered DVT/PE; required re-intubation

Case Presentation #1

	Date	Platelet
Admit; heparin	7/18	311
Heparin	7/19	231
Heparin	7/20	228
Heparin	7/21	218
CAB; heparin	7/23	166
IABP	7/24	176
IABP removed	7/25	147
Hep Ab positive	7/26	80
	7/27	100
	7/29	158
PE/DVTs/intubated Argatroban begun	8/7	395

Ubiquity of Heparin and Heparin-based Therapies

One of the most commonly administered parenteral therapies in the hospital setting

One trillion units of heparin used per year in the US*

Approximately 12 million patients† are exposed to heparin per year

Indications for the use of heparin are increasing‡

Is heparin use always documented on patient charts?

* Fahey. *J Vasc Nurs* 1995;13:112–116.

† Data on file Texas Biotechnology Corporation and GlaxoSmithKline

‡ Kelton and Warkentin. Current Therapy in Hematology-Oncology. 5th ed. New York, NY: Mosby. 1995:149–152.

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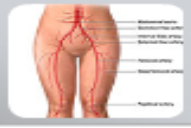


ATLANTA HEPARIN INDUCED THROMBOCYTOPENIA LAWYERS

Georgia Heparin-Induced Thrombocytopenia Attorneys

Doctors often use heparin to prevent your blood from clotting, but it can cause serious and even fatal injuries for those with

Immune- vs Nonimmune-mediated HIT

	Nonimmune-mediated	Immune-mediated
Frequency	10%- 30%	1%- 3%
Timing of onset	1- 4 days	5- 14 days
Decrease in platelets	slight	moderate/severe
Antibody mediated	no	yes
Thrombosis	no	30%- 75%
Hemorrhage	none	rare
Management	observe	stop heparin, start alternate therapy

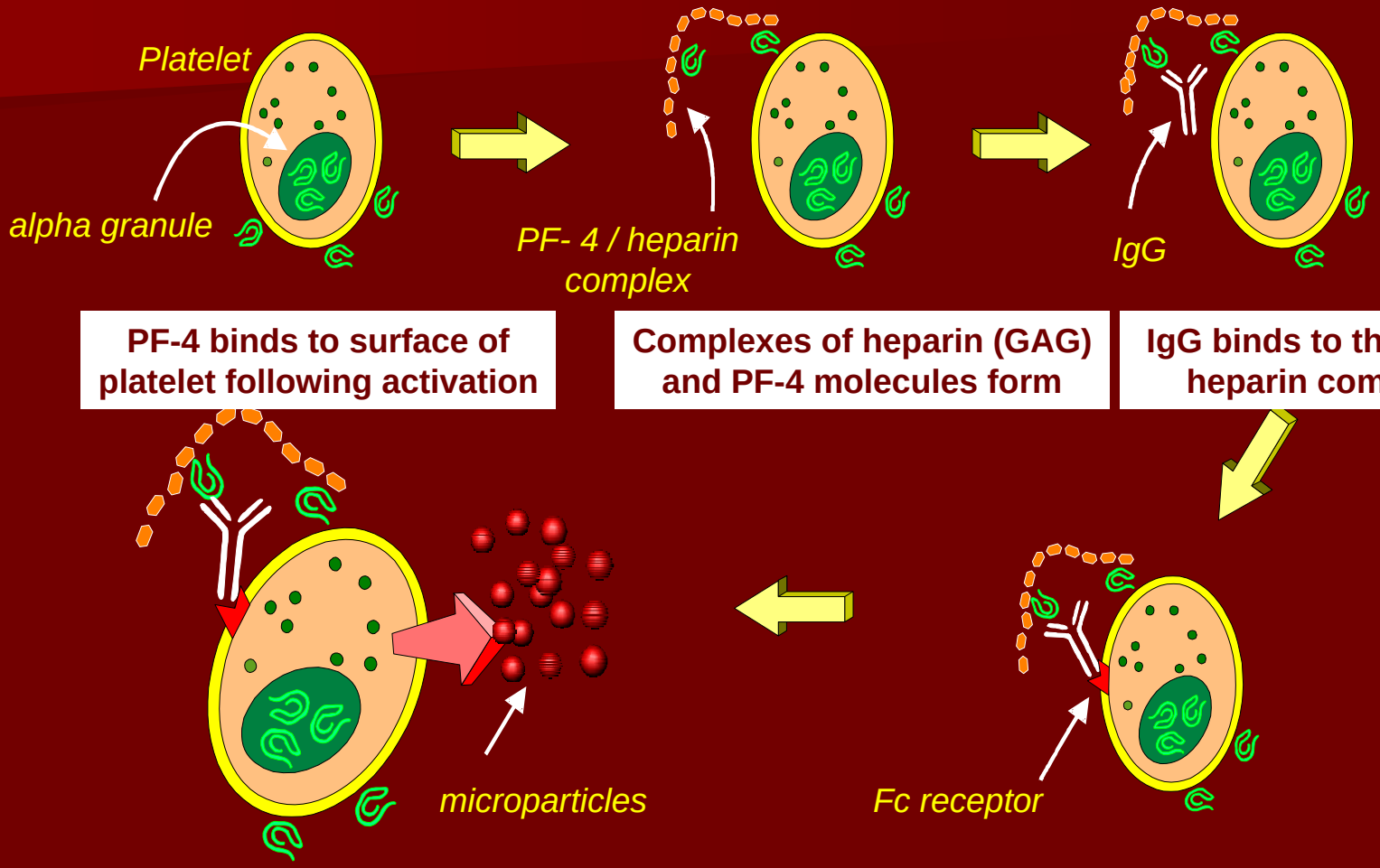
Classic HIT

1. Thrombocytopenia
   - <150,000 or a 50% drop in platelet count from baseline
   - Onset 5–14 days after starting any dose, any type, or any route of heparin exposure
2. Exclusion of other causes of thrombocytopenia
3. With or without thrombotic complications

plus

A positive serologic test for HIT

Pathophysiology



PF-4 binds to surface of platelet following activation

Complexes of heparin (GAG) and PF-4 molecules form

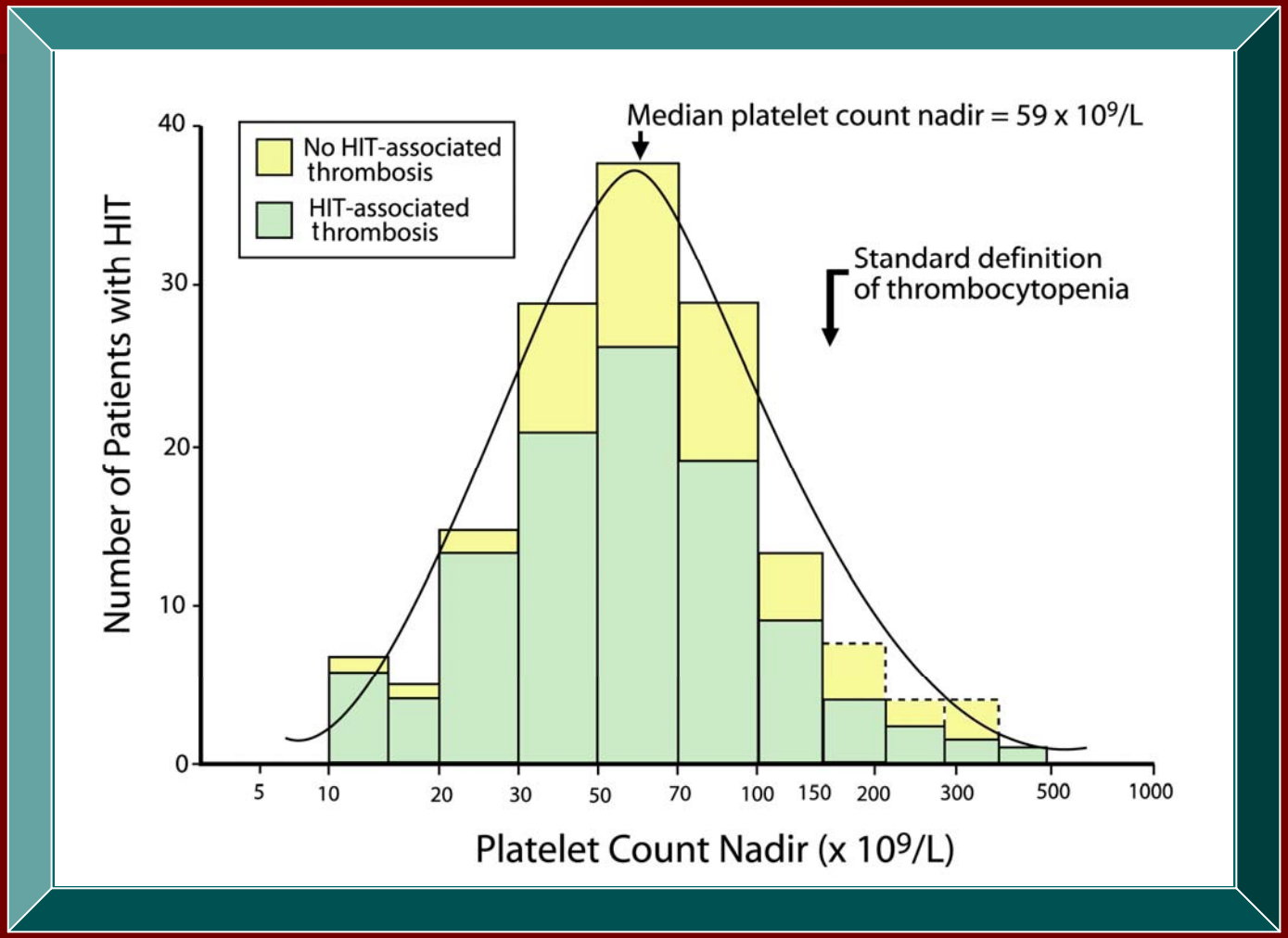
IgG binds to the PF-4/ heparin complex

IgG/PF- 4/heparin complex activates via the Fc receptor

Fc stimulation leads to the generation of procoagulant-rich microparticles

Dr. John G. Kelton, McMaster University

Patients With HIT vs Platelet Counts



Warkentin. *Semin Hematol* 1998;35(4):9–16.

Diagnosis

- Clinical Assessment
  - **Inclusion criteria**
  - **Exclusion criteria**

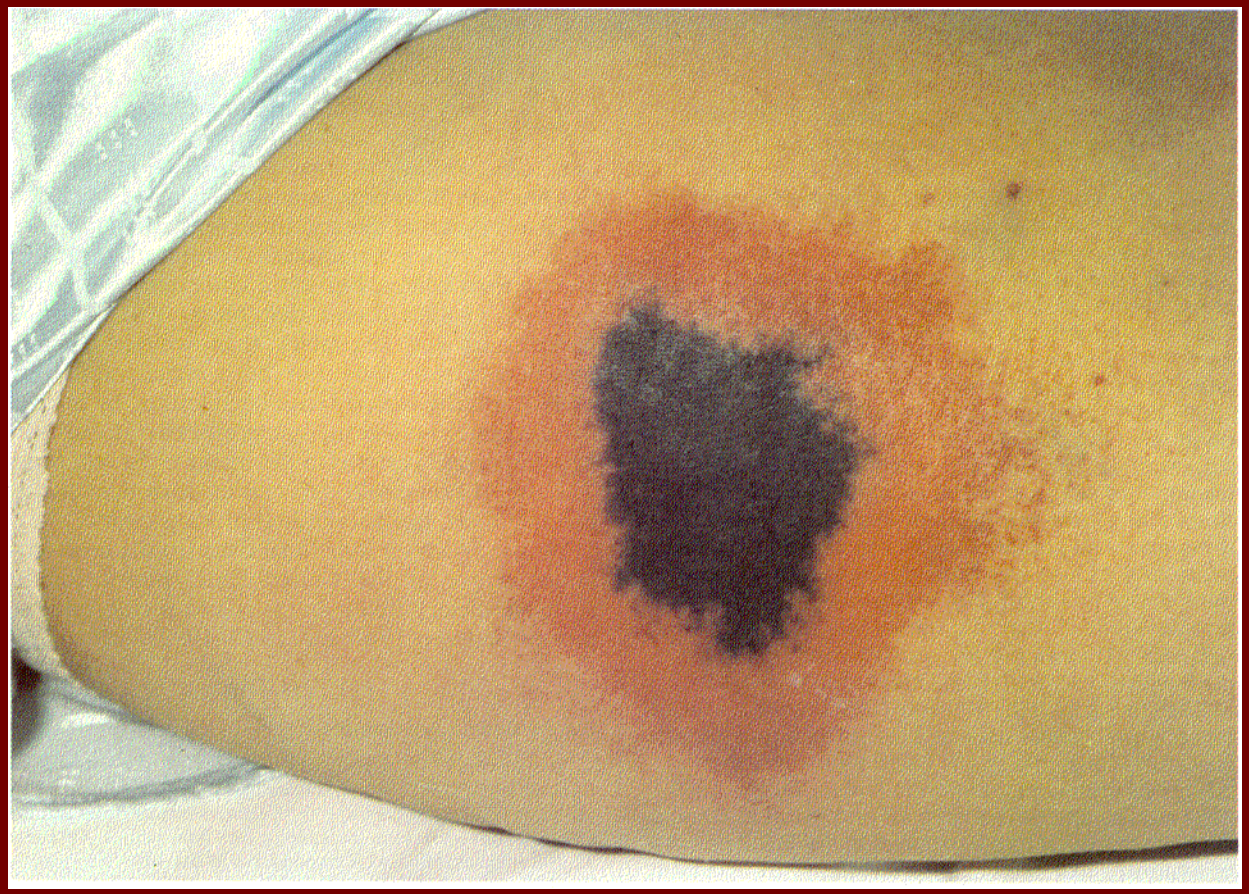
- Laboratory Assessment

Key: A high index of suspicion
An increased awareness and vigilance

Clinical Assessment: Inclusion Criteria---Thrombocytopenia

- Thrombocytopenia during and after heparin exposure (<150,000)
  - Drop in platelet count (>50%) rather than absolute thrombocytopenia
    - Smaller drop in platelets (especially skin necrosis)
    - Early-onset of thrombocytopenia with heparin re-exposure caused by circulating antibodies
    - Platelet count may rarely be normal when patient presents with thrombosis (delayed-onset HIT)
  - Thrombocytopenia recovers after heparin withdrawal
    - Median time to platelet count recovery after heparin withdrawal is 4 days

Rare Complications of Heparin
Skin Necrosis



Clinical Assessment: Inclusion Criteria---Timing

- History of heparin exposure
  - Usually occurs within 5–14 days after initiation
  - May occur within hours to days if patient had recent (within 3 months) heparin exposure
  - May occur after hospital discharge (9–30 days) with delayed-onset HIT

NOTE: Heparin exposure may be through virtually any preparation (including LMWH), any dose, or any route of heparin (including flushes and coated lines)

Clinical Assessment: Inclusion Criteria---Thrombosis

- Thrombotic complications (arterial or venous)
  - During or after heparin therapy
    - **Localization of thrombosis is influenced by independent acute and chronic factors, such as postoperative state, atherosclerosis, or the location of intravascular catheters in central veins or arteries**

Clinical Assessment: Inclusion Criteria---Other sequelae

- Unexplained resistance to anticoagulation
- Unexpected acute systemic event within 5–30 minutes of IV heparin bolus
  - Fever and chills
  - Tachycardia, hypertension
  - Flushing, headaches
  - Chest pain, dyspnea
  - Nausea, vomiting, diarrhea
  - Sudden anaphylactoid death

Clinical Assessment: Exclusion Criteria---Other causes

- Early thrombocytopenia (<5 days) is unlikely to be HIT in a patient without previous heparin exposure (<3 months)
- Obvious other causes for thrombocytopenia
- Recovery of platelet count during heparin therapy

HIT Antibody Testing

- The Four "T" Score
- Thrombocytopenia
- Timing
- Thrombosis
- oTher causes of thrombocytopenia

Probability of HIT: the 4 T's

Category	0 points	1 point	2 points
Thrombocytopenia	<30% fall, nadir <10K	30-50% fall, nadir 10-19K	>50% fall, nadir >20K
Timing of decrease	<Day 1; no recent heparin	>Day 10 or ? <1D if recent exposure 30-100 days	Day 5-10 <1D if recent exposure
Thrombosis or other	None	Thrombosis, red skin lesions	Proven clots, skin necrosis, bolus reaction
oTher causes thrombocytopenia	Definite	Possible	None evident

Warkentin, Aird, Rand; Hematology Education Program ASH 2003: 497

4T scores

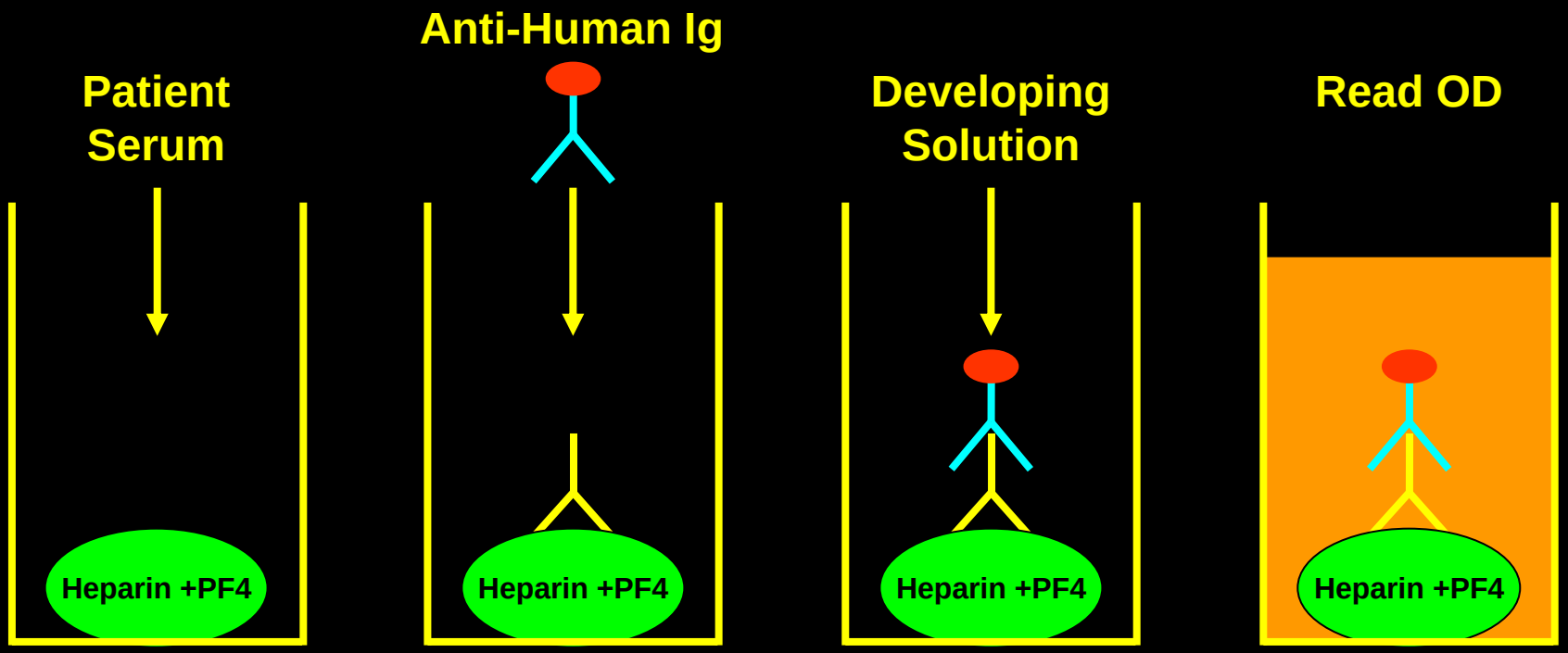
- High: 6-8 Must test and treat
- Intermediate: 4-5 Must test; treat until negative test
- Low: 0-3 Don’t test

4T scores and ruling out HIT

- Using 4T *a priori* scoring and specific IgG anti-PF4/heparin Ab ELISA with hi-dose heparin added in second step to show heparin dependence
- Negative predictive value of low 4T score (0-3) 100%
- No need for testing/DTI use

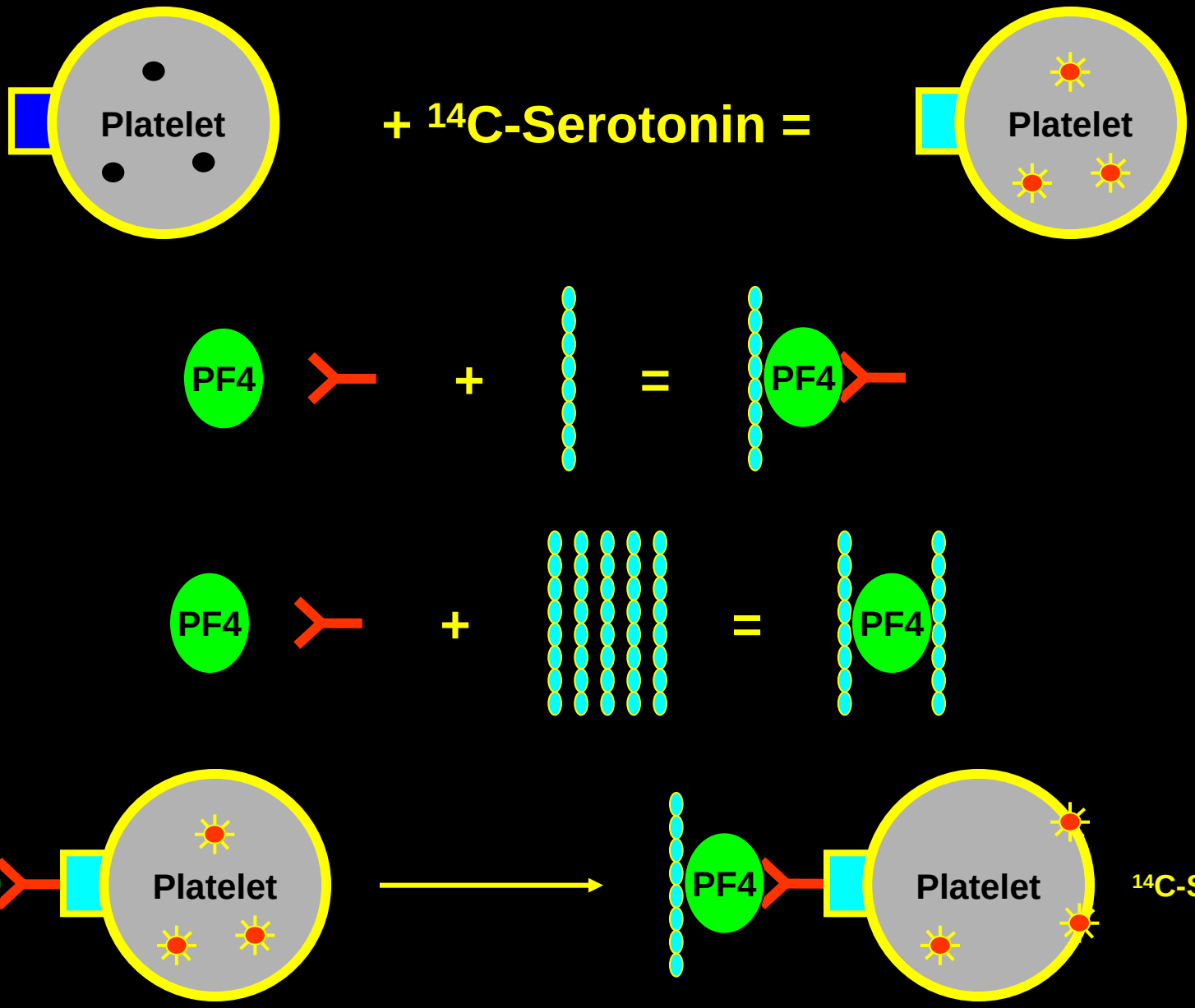
Blood 2009; 114: 543 Abstr #1328

Enzyme-Linked ImmunoSorbent Assay



- Positive typically > 0.4 OD units 405 nm.
- There are signals < 0.4 OD units that are clearly not negative, and are from patients who clinically have a strong likelihood of having HIT.
- Has lead to an “Equivocal” category (0.2 - 0.4 OD units), and many of these patients are treated as if they have HIT. Many do not have a subsequent rise in titer.

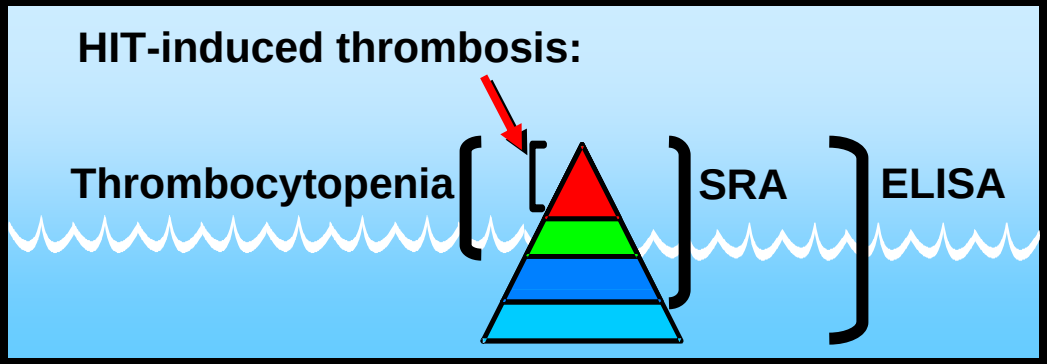
Serotonin Release Assay for HIT

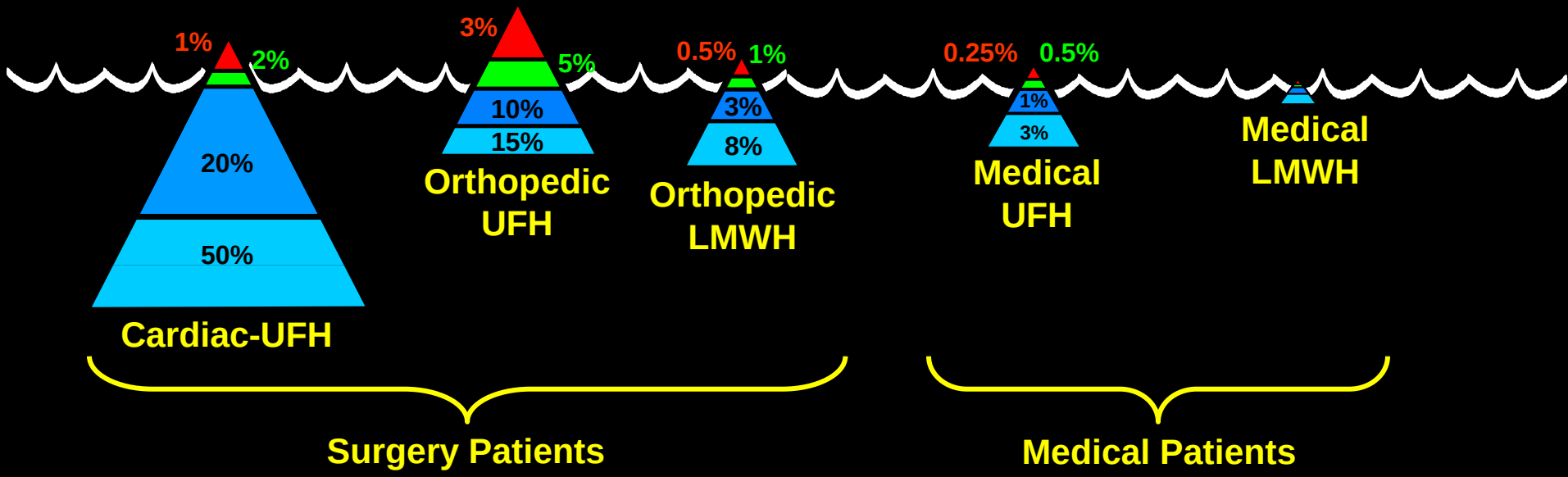


The "Ideal" HIT Test

- Relevant to pathophysiology of HIT
- High sensitivity and specificity
- Predictive of HIT
- Differentiates HIT and HIT with thrombosis
- Technically simple
- Rapid turnaround time
- Does not exist . . .yet

Iceberg Model for HIT





Lee and Warkentin. *Heparin-Induced Thrombocytopenia.* New York: Marcel Dekker; 2000:81–112.

Treatment Goals Based on Pathophysiology and Clinical Observations

- Interrupt the immune response
  - Discontinue heparin
- Inhibit thrombin generation
  - Treat active thrombosis
  - Prevent new thrombosis

Preventive Strategies and Measures

- Diagnose HIT early
- STOP ALL HEPARIN—EVERY MOLECULE—
  when platelet count falls 50% from baseline or $<150,000/mm^3$
- Disciplined application of alternative anticoagulants for patients with HIT to prevent thrombotic morbidity
- Avoid platelet transfusions in HIT except in instances of major hemorrhage

Management of Suspected HIT

- Monitor carefully for thrombosis
- Follow platelet counts until recovery
- Avoid prophylactic platelet transfusions
- Medic-alert bracelets, heparin “allergy” education
- Document HIT in medical records

Treatment Recommendations for HIT

- STOP all heparin
- Begin alternative anticoagulation
  - Direct thrombin inhibitor
  - Factor Xa inhibitor
- Do NOT use warfarin until platelets normal
  - Reverse any warfarin on board with Vit K
  - Overlap with DTI for minimum 5 days

Warkentin & Greinacher, Chest 2008;133:340-380S

Direct Thrombin Inhibitors

Inhibitor	Type	HIT indication
Argatroban	synthetic	prophylaxis or treatment
Lepirudin	hirudin analog	treatment
Bivalirudin	hirudin analog	PCI in HIT/T
Dabigatran	oral synthetic	none

- Contraindications to the direct thrombin inhibitors
  - Hypersensitivity
  - Active bleeding
  - Recent puncture of large vessels or organ biopsy
  - Recent cerebrovascular accident, intracerebral surgery, or other neuraxial procedure
  - Severe uncontrolled hypertension

Argatroban vs Lepirudin

	Argatroban	Lepirudin
Half-life	**40–50 minutes**	**1.3 hours**
Antigenicity	**no**	**yes** **? clinical importance**
Elimination	**hepatic**	**renal**
Thrombin binding	**strong**	**strongest**
Pregnancy category	**B**	**B**

Thrombin Inhibitors: Monitoring

- aPTT
  - Target range for treatment ratio=1.5–2.5 for lepirudin
  - Target range for treatment ratio=1.5–3.0 for argatroban
  - Obtain a baseline aPTT before initiation of therapy
  - Check aPTT 2 hours (for argatroban)/4 hours (for lepirudin) after initiation of therapy
    - Frequent monitoring should be done in patients with renal impairment (for lepirudin) and hepatic impairment (for argatroban)
  - Monitor aPTT daily during the course of therapy
  - Concomitant thrombolytics may considerably enhance the effect of thrombin inhibitors and should be avoided

Factor Xa Inhibitors

- Danaparoid
  - Heparan sulfate/dermatan sulfate
  - Some anti-thrombin activity
  - Very low-level cross-reactivity in vitro with HIT antibodies
  - Not currently available in the USA
- Fondaparinux
  - Pentasaccharide
  - No cross-reactivity in vitro
  - Very minimal data in patients with HIT; case reports; case series only
  - Renal elimination 17-20h

Oral Direct Thrombin inhibitor

- Dabigatran/Pradaxa®
- Just approved for use in chronic atrial fibrillation
- NO studies for acute HIT
- NO dosing recommendations for HIT
- NO outcome data for acute HIT
- Approved outside USA for ortho prophy

Warfarin in HIT

- Warfarin is considered contraindicated in patients with acute HIT until the platelet count has recovered (or >100,000)
- Use during acute HIT only with an agent that reduces thrombin generation or inhibits thrombin
  - Associated with progression of deep venous thrombosis to venous limb gangrene
  - Caution if INR >4

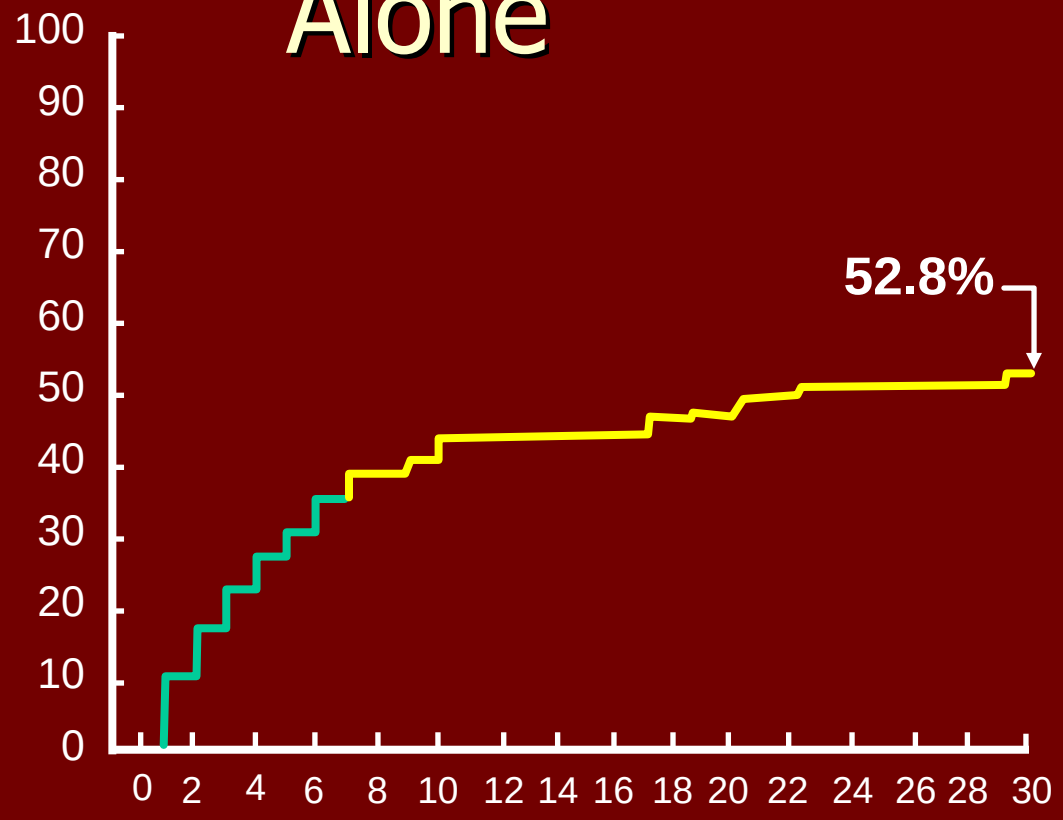
Thrombotic Complications of HIT

~50% of untreated HIT patients with isolated thrombocytopenia progress to thrombosis

~4:1 Incidence Ratio Venous to Arterial

Venous	Arterial
Deep vein thrombosis	Aortic occlusion
Pulmonary embolism	Acute thrombotic stroke
Cerebral dural sinus thrombosis	Myocardial infarction
Adrenal hemorrhagic infarction	Cardiac intraventricular thrombosis
	Thrombosis in upper limb, lower limb, mesenteric, renal, and spinal arteries

Frequency of Thrombosis: Failure of Heparin Cessation Alone



Warkentin and Kelton. *Am J Med* 1996;101.

Unusual Complications of HIT

- Warfarin-associated venous limb gangrene
- Bilateral adrenal hemorrhagic infarction
- Disseminated intravascular coagulation (DIC)
- Acute systemic reactions following IV bolus

Alternate Presentations of HIT

- Small drop in platelet count (especially skin necrosis)
- Earlier onset of thrombocytopenia with heparin re-exposure
- Delayed-onset of thrombocytopenia after stopping heparin
- Thrombosis after heparin exposure

Case Presentation #3

Event	Date	Platelet Count
Stents placed	1/23/02	217
Recurrent stenosis	7/18/02	231
Elective CAB	7/25/02	194
	7/26/02	143
	7/27/02	154
	7/30/02	251
RLE edema/ DVT	8/8/02	251
Tx heparin/coumadin; d/c	8/13/02	---
Extension RLE DVT; tx heparin	8/22/02	274
Heparin tx continues	8/25/02	108
Hematology Evaluation/+HIT test	11/19/02	210

Delayed-Onset HIT

- Previous heparin exposure was uncomplicated
- Patient often discharged home, off heparin for days
- Patient readmitted to hospital
  - New thrombosis (usual)
  - Unexpected thrombocytopenia (uncommon)

Clinical Sequelae in HIT

Sequelae	Incidence
New thrombosis	30%–75% ◆ Clinical situation dependent
Amputation	10% ◆ Associated with arterial thrombosis ◆ Associated with venous limb gangrene
Death	10%–20%

Heparin Re-exposure in Patients With History of HIT

- Re-exposure soon after the diagnosis of HIT associated with a high risk of thrombocytopenia and thrombosis
- However, heparin antibodies generally disappear within 100 days of last exposure
- Re-exposure may be safe if heparin-dependent antibody is no longer present and exposure time is limited

Heparin re-exposure in prior +HIT

- 5 uremic patients with hx of HIT with new-onset dialysis had no recurrence with later re-exposure
  - J Thromb Haemost 2010; 8: 616-8
- 7 patients re-exposed after documented HIT did not manifest recurrent Abs
  - NEJM 2001; 344: 1286-92

Immune Response Profile

- IgG, IgM, and even IgA antibodies form about the same time, 4-14 days after exposure. No IgM to IgG class switching
  - Blood 2009; 113: 4963-4969
- Anamnestic response upon re-exposure and re-development of HIT is lacking; Abs still form 4-14 days later
  - Blood 2009; 113:4970-4976

Other Influencing Risk Factors

- Type of surgery; timing of first injection
  - Post-op > pre-op
  - Knee > hip fracture
  - BMI quartiles; drug stoichiometry
    - J Thromb Haemost 2010; 8: 504-12
- Severity of Trauma
  - Higher risk with major v minor surgery
  - UFH > LMWH
    - Blood 2010; 115: 1979-1803

Platelet Monitoring Recommendations

- At least every other day monitoring days 5-14
  - Patients on therapeutic dose UFH, post-operative patients on UFH prophylaxis
- At least every other day monitoring days 5-14
  - Cardiac surgery where plts fall ≥50% of original
  - Thrombosis develops day 5-14
- No routine monitoring
  - Pts receiving fondaparinux

Warkentin, et al, Chest 2008; 133: 340S

Preventive Strategies and Measures

- Remember, heparin use is ubiquitous in hospitals
  - Often, the drug is not even charted
- Careful history and physical examination
- Don't use heparin if it can be avoided
  - Eliminate unnecessary exposures (eg, line flushes)
  - Minimize heparin exposure; use porcine instead of bovine
  - Consider early ambulation, employ anti-DVT exercises, and pneumatic compression stockings
  - Consider early transition to warfarin
  - Consider use of alternate anticoagulant drugs
  - Use of LMWH instead of UFH
- Monitor platelet counts

Comment on Martel et al, page 2710

HIT as a preventable disease?

Theodore E. Warkentin MCMASTER UNIVERSITY

Martel and colleagues report their meta-analysis of thromboprophylaxis studies comparing the frequency of heparin-induced thrombocytopenia (HIT) between patient groups receiving unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Their study supports the view that HIT is a preventable disease.

Relative Risk of HIT with LMWH v UFH

- Odds Ratio of developing HIT with LMWH compared to UFH
  - 0.1
- Absolute Risk of developing HIT
  - 0.2% LMWH
  - 2.6% UFH
- Orthopedic surgery patients
- Receiving prophylactic dosing

Blood 2005; 106: 2713

Economic Consequences of HIT

- 130 HIT cases with 4T scores of >4 and +HIPA test analyzed
  - Prolonged stay 70.3%
  - Costs alternative drugs 19.7%
  - Worse in surgical patients
  - Worse if thrombosis developed
  - Early institution of DTIs did NOT increase costs; save complications
  - Mean additional costs 9008€

Wilke, et al; J Thromb Haemost 2009; 7: 766

Additional Frightening Stories

- Fondaparinux HIT
  - At least 2 cases of HIT-like syndrome with only fondaparinux use, including thrombosis

- "Spontaneous HIT"
- HIT-syndrome without any heparin exposure
  - 4 Cases of HIT antibodies induced in inflammatory/infectious settings
  - ?autoimmune phenomenon

J Throm Haem 2008; 6: 1598

Summary

- Think of HIT in any patient with thrombocytopenia or progressive thrombosis on heparin
- Assess the need for testing with the 4T score evaluation
- Stop all heparin exposures
- Treat the patient with a direct thrombin inhibitor until platelets return to normal; convert to warfarin or anti-Xa drug
- Avoid re-exposures while antibodies are still active