HEPARIN-INDUCED THROMBOCYTOPENIA (AND OTHER PROBLEMS)

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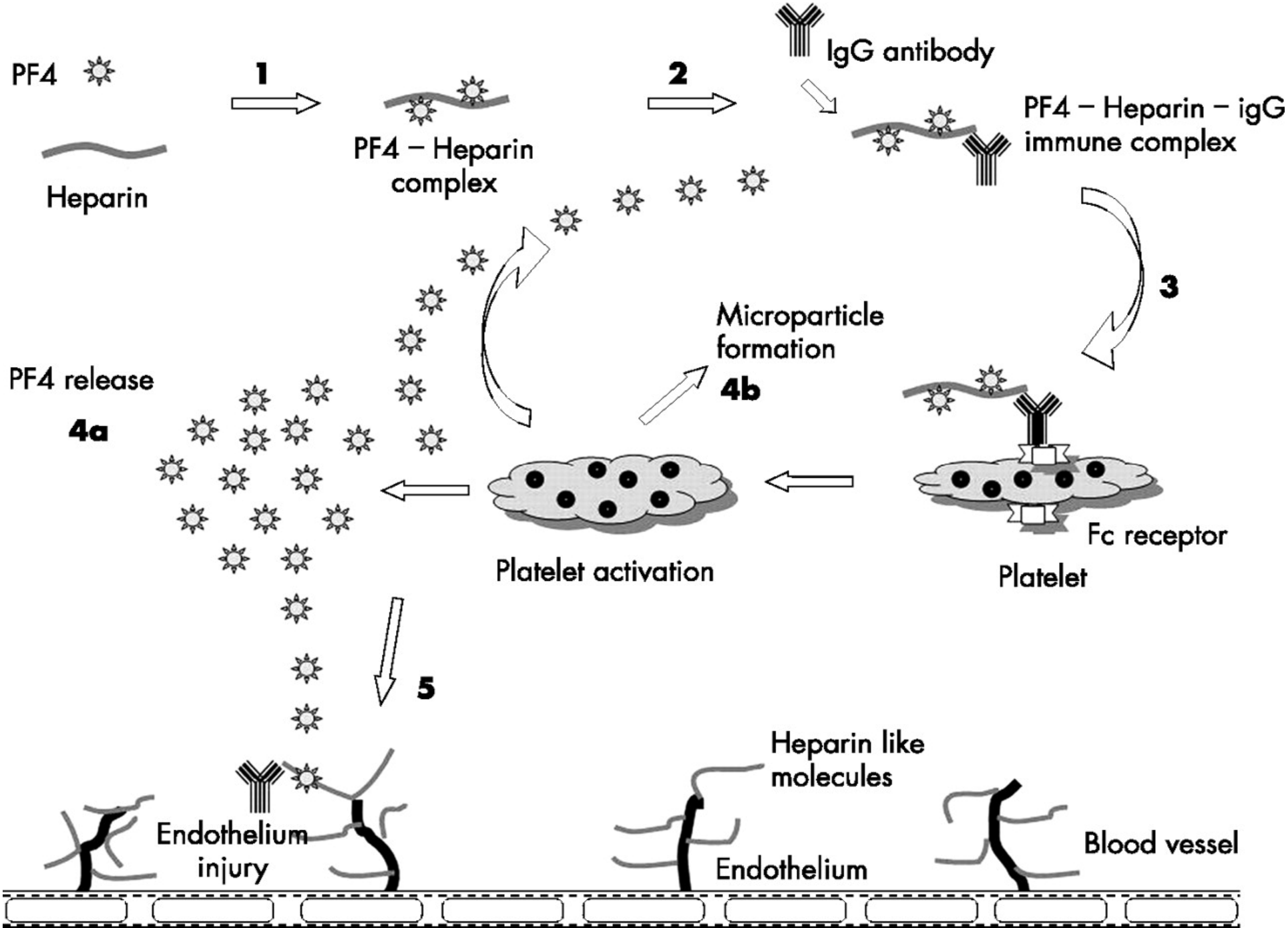
Definitions

- HIT Type I (heparin associated thrombocytopenia)
  - Non-immune interaction between heparin and platelets
  - Transient thrombocytopenia (rarely <100,000)
  - No risk of thrombosis
- HIT Type II
  - Antibody mediated reaction to iatrogenic heparin
  - Significant risk of arterial and venous thrombosis

HIT Pathophysiology

- Antibody formation of platelet factor-4 / heparin complex
- PF4-heparin-antibody complex activates platelets causing release of prothrombotic particles and platelet consumption
- Thrombocytopenia due to clearance of activated platelets and antibody coated platelets by reticulo-endothelial system



Ahmed, I et al. Postgrad Med J 2007;83:575-582

Two Step Model

- Following tissue injury, PF4 is released
- PF4-heparin immune complex causes antibody formation
- Platelets aggregate and thrombocytopenia ensues
- Platelets are activated and and release more PF4
- Once a certain concentration is reached, monocytes produce tissue factor and coagulation ensues

Hematology. 2008 (13)

Pathophysiology

- Activated platelets
- Excessive thrombin
- Tissue Factor Production
- Antibody mediated endothelial injury

- Ultimately, thrombocytopenia with paradoxic thrombosis

Epidemiology

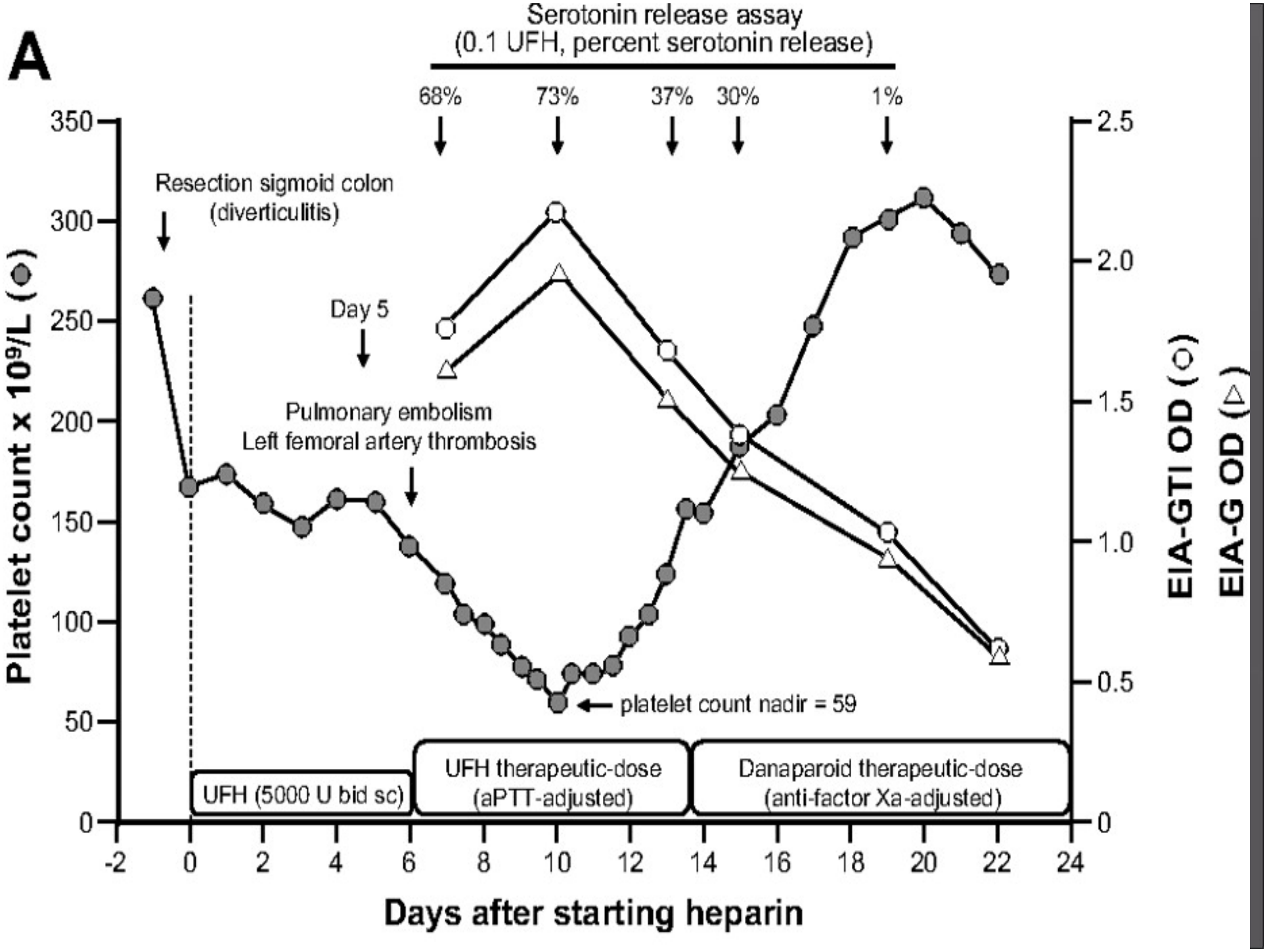
- Incidence varies among patient populations

Therapy	Risk	Patient Population	Incidence of Abs	Incidence of HIT
Unfractionated Heparin	High	Orthopedic Surgery	14	3-5
	Intermediate	Cardiac Surgery	25-50	1-2
	Intermediate	Medical patients	8-20	0.8-3
LMWH	Intermediate	Surgical patients	2-8	0-0.9

NEJM. 2006. 355;8.

Diagnosis

- Clinical Diagnosis (warranting laboratory testing)
- Usually between day 5 and 14 of heparin therapy (or can be immediate if exposed to heparin in last 100 days)
  - Platelet count drop drop of 30 to 50% or <150,000
  - Venous thrombosis, PE, arterial thrombosis, CVA, MI, etc.
  - Skin lesions at heparin injection site
  - Anaphylactoid reactions


A
Serotonin release assay
(0.1 UFH, percent serotonin release)
68%
73%
37%
30%
1%
Resection sigmoid colon
(diverticulitis)
Day 5
Pulmonary embolism
Left femoral artery thrombosis
platelet count nadir = 59
UFH (5000 U bid sc)
UFH therapeutic-dose
(aPTT-adjusted)
Danaparoid therapeutic-dose
(anti-factor Xa-adjusted)
Platelet count x 10⁹/L (●)
EIA-GTI OD (○)
EIA-G OD (△)
Days after starting heparin
350
300
250
200
150
100
50
0
2.5
2.0
1.5
1.0
0.5
0
-2
0
2
4
6
8
10
12
14
16
18
20
22
24

Laboratory Diagnosis

- Many tests available- both functional and serologic
- At UCH-> use ELISA for PF4-heparin antibody
  - High sensitivity, but lower specificity
    - Significant number of people can have antibodies present but do not have the diagnosis of HIT
- Functional assays available that measure platelet activation

Laboratory Testing

	Functional tests	Immunologic assays
Pros	Highly sensitive and specific Detect pathogenic antibodies Can detect other antigens besides PF4 ^{14}C-serotonin release assay is gold standard test	Highly sensitive Less operator dependent than functional tests Readily available
Cons	^{14}C-serotonin release assay requires radioisotopes Performed in only a few reference laboratories Operator dependent	Low specificity Detect nonpathogenic IgA and IgM antibodies Many IgG antibodies detected are nonpathogenic

Abbreviations: HIT, heparin-induced thrombocytopenia; Ig, immunoglobulin; PF4, platelet factor 4.

Pretest Probability is Key

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count decrease >50% and platelet nadir ≥20 × 10^9/L	Platelet count decrease 30–50% (or >50% decrease resulting from surgery) or platelet nadir 10–19 × 10^9/L	Platelet count decrease <30% or platelet nadir <10 × 10^9/L
Timing of platelet count decrease	Clear onset between days 5 and 10 or platelet decrease within 1 day (heparin exposure within 30 days)	Consistent with immunization but unclear history; onset after day 10; decrease <1 day (heparin exposure 1–3 months ago)	Platelet count decrease <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous UFH bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis not yet proven	None
oTher causes for thrombocytopenia	None apparent	Possible	Definite

Low Risk	<3 point
Intermediate Risk	4-5 points
High Risk	6-8 pints

Crit Care Med. 2007. 35 (4)

Platelet Monitoring

- American College of Chest Physicians Guidelines 2008
  - Platelet count monitoring recommended if probability of HIT is >0.1% (Grade 2C)
  - Baseline platelet count and platelet count every 2 to 3 days during day 4 through 14 of therapy (Grade 1C)
  - For post-operative patients (risk >1%), platelet count every other day (Grade 2C)

Treatment

- Stop Heparin
- Need therapeutic anticoagulation
  - Danaparoid (Grade 1B)- best studies
  - Lepirudin (Grade 1C)- caution in renal failure; can develop antibodies to lepirudin; monitor PTT
  - Argatroban (Grade 1C)- safe in renal failure
  - Fondaparinux (Grade 2C)
  - Bivalrudin (Grade 2C)
    - All directly inhibit thrombin

2008 Treatment Guidelines

- All carry significant bleeding risk, 2.4-18 % (NEJM 2006)
  - No antidote (such a protamine or Vit K)
- Select Tx based on experience and center availability
- Routine lower limb ultrasonography
- If thrombosis is present, warfarin for four weeks after platelet count normalizes

Conclusions

- Maintain a high index of suspicion for HIT
- Order tests when high degree of suspicion
- Therapy should be started empirically if suspicion is high

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