Heparin-induzierte Thrombozytopenie
Wann daran denken?
Wie behandeln?

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Thrombocytopenia

Thrombosis

HIT

Thrombin

Tissue factor

EC

B-L

Heparansulfate

Heparin

PF4
Platelet count decrease > 50% and/or new thrombotic complications between day 5-14
How to diagnose HIT?

HIT in surgical patients
Platelet fall in first 4 days is USUALLY NOT HIT.

Platelet fall on day 5-10 = HIT unless proven otherwise

Constant production of thrombopoietin in the liver

Bone marrow
megakaryocytopoiesis

(free thrombopoietin)  free thrombopoietin
romiplostim

An early fall in platelet counts to 60,000 – 100,000/µL until day 4 after major surgery is normal.

Major surgery “resets the clock“ for the 5-14 day time window.
## Diagnosis - Pretest Probability: the 4 T’s

<table>
<thead>
<tr>
<th>Scoring points:</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Thrombocytopenia</td>
<td>&gt;50% nadir ≥ 20 G/L</td>
<td>30-50% nadir 10-19 G/L</td>
<td>&lt;30% nadir ≤ 10 G/L</td>
</tr>
<tr>
<td><strong>B</strong> Timing (onset)</td>
<td>day 5-10 (d1 if recent heparin)</td>
<td>&gt; day 10, or unclear</td>
<td>before day 4</td>
</tr>
<tr>
<td><strong>C</strong> Thrombosis</td>
<td>new thrombosis</td>
<td>progressive thrombosis</td>
<td>None</td>
</tr>
<tr>
<td><strong>D</strong> Other cause for thrombocytopenia</td>
<td>no other cause</td>
<td>possible</td>
<td>definite</td>
</tr>
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</table>

0-3 low score 4-6 medium score 7-8 high score

Antigen tests
detect IgG, IgM, IgA

Functional test
detect IgG

Optimal is a combination of both tests
EIA-SRA Relationship

N = 405

PF4/heparin antigen tests have a high negative predictive value.

There is no substitute for a functional washed platelet assay to confirm the diagnosis of HIT.

HIPA test or $^{14}$C-SRA
How to diagnose HIT?

HIT for the medical expert
HIT differs from Classical Antibody Responses

Class switching

- primary antigen contact
- secondary antigenic challenge

Cumulative Percent

Day 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

IgG

Greinacher A et al Blood. 2009;113:4970-6

PF4 binds to bacteria and PF4/H abs enhance phagocytoses

HIT is a misdirected host defense.
Anti-PF4/heparin Immune Response requires additional signals

Major Surgery  n = 222  
Minor Surgery  n = 387

Lubenow et al. BLOOD 2010
• 31 year old female admitted with severe head ache.

• Upper respiratory tract infection that began 10 days earlier.

• Otherwise healthy, no medications.

• INR 1.4, aPTT 34s, fibrinogen 0.6 g/L, D-dimer >35mg/L (<0.5), platelets 31,000/µL, no bleeding, no signs of infection

• normal CT head scan (to exclude sinus vein thrombosis).
• 4 g fibrinogen and LMWH thrombosis prophylaxis.

• Next day: platelet count 15,000/µL

• New DVT; persistent headache

• Although HIT seemed implausible, platelet decrease and new thrombosis during LMWH prompted HIT testing

Greinacher A, BLOOD 2014
- Anti-PF4/heparin IgG ELISA strongly positive OD >2.5
- HIPA test strongly positive also in the sample without addition of heparin.
- Pre-LMWH admission sample: same results
- Immediate start of therapeutic-dose danaparoid anticoagulation
- She deteriorated neurologically the same day, and massive sinus vein thrombosis associated with intracerebral bleeding was demonstrated by repeat CT imaging.
Spontaneous HIT or Autoimmune HIT

- 10 patients reported in the literature
- 6 after orthopedic surgery (no heparin)
- 3 after infection
- 1 no obvious trigger

HALLMARK: positive HIPA without heparin

“HIT“ during fondaparinux, rivaroxaban, dabigatran

Warkentin et al. BLOOD 2014
Greinacher BLOOD 2014
PF4/heparin complexes on heparin-coated platelets

PF4/polyanion complexes

PF4/polyanion complexes on bacteria

PF4 complexes formed by poorly-defined non-heparin triggers

heparin-dependent HIT

(MZ) B-cells

high affinity antibodies clustering PF4

danger

heparin-independent HIT

Greinacher A, BLOOD 2014
<table>
<thead>
<tr>
<th></th>
<th>Heparin treatment</th>
<th>Platelet-activating IgG antibodies with heparin</th>
<th>Platelet-activating IgG antibodies without heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical HIT</td>
<td>yes</td>
<td>100%</td>
<td>acute phase (day 1-5) ~30%</td>
</tr>
<tr>
<td>Delayed onset HIT</td>
<td>5-14 days before</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Spontaneous HIT</td>
<td>No</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>or Autoimmune HIT</td>
<td></td>
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How to treat patients with HIT?
1. steady state of haemostasis

2. heparinized patient

3. HIT-patient (still on heparin)
   therapeutic dose
danaparoid/fondaparinux/
argatroban

4. HIT-patient heparin stop
   Protein C deficiency

5. acute HIT-patient
   (on compatible anticoagulant)

6. acute HIT-patient
   avoid early start of VKA
Alternative Anticoagulants in HIT

- Lepirudin
- Danaparoid (North America, intermittently in Europe)
- Argatroban
- Fondaparinux
- Bivalirudin

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
Monitoring of DTIs

Low prothrombin?

Yes

Monitor by prothrombin independent assay, e.g. ECA test

No

Monitor by aPTT

1.5-2.5x baseline, but not >80s**

liver impairment, DIC; pretreatment with vit K antagonists
Greinacher A and Warkentin TE; Thromb Haemost 2008; 99: 819–829

Diluted thrombin time

1. Coronary bypass surgery (40,000 U heparin)
2. Platelet transfusions
3. Pulmonary embolism (4 fingers, both feet)
4. Ischemic necrosis (4 fingers, both feet)
5. Diluted thrombin time
Heparin-induced Thrombocytopenia in 2014

• HIT still exists
• Major surgery, cardiac surgery
• Medical intensive care patients

• New: Autoimmune HIT/Spontaneous HIT

• Treatment: argatroban, danaparoid, fondaparinux, bivalirudin,
  (rivaroxaban, apixaban, dabigatran)