Diagnosis of Heparin-induced Thrombocytopenia (HIT)

11th Hemostasis Seminar
Instrumentation Laboratory / Werfen

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Bucharest, October 1, 2019

PD Dr Lars M. Asmis

Zentrum für perioperative Thrombose & Hämostase (ZPTH)

Worldmap. Martin Waldseemüller (1507); © public domain
see also: Toby Lester. The Fourth Part of the World

Diagnosis of HIT

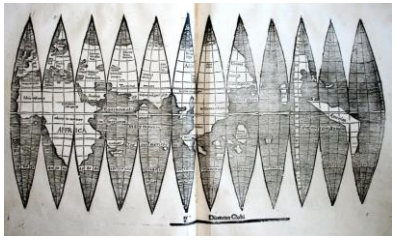
Conflict of Interest Statement

- In the past 5 years I have received honoraria for advisory boards and/or research support from the following company:
  Axon Lab, Baxalta, Bayer, Boehringer Ingelheim, CSL Behring, Siemens, Glaxo Smith Kline, Novo Nordisk, Pfizer, Roche und Sanofi Aventis
- I was free regarding the choice of this presentation's content
- My activities follow GL of the SAMW and FAMH

Introduction: a voyage

1. View of the world

- Map of the world of Hekataios of Millet (6 centur bc): world as disk
- Martin Waldseemüller and Matthias Ringmann: Worldmap, Globe und explaining text)



2. Starting point

- Where do I start from?

3. Goal

- Where do I want to go?

4. Tools

- which resources do I have available

5. The trip itinerary

- a predefined plan with starting- and endpoint that acknowledges avaliable resources and timeline (and potential alternatives)

6. Motivation

- Why am I going on this voyage?

Introduction: HIT - a diagnostic journey

1. View of the world **"model"**

- pathogenesis of HIT: an immune mediated drug-induced thrombocytopenia
- beware of overdiagnosis

2. Starting point

- **acquired thrombocytopenia**

3. Goal

- **positive patient outcome**: safe and efficient

4. Tools **4T score, antigenic and functional tests**

- patient history, clincial findings, laboratory tests (screening and confirming)

5. The trip itinerary

- a comprehensive **algorithm** defined for an individual institution with a timeline

6. Motivation

- I will get back to this

7. Outlook

- What we need in the future?

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Diagnosis of HIT

Aims of this talk:

- Provide useful information regarding HIT diagnosis
- Make you aware of (and fear) HIT overdiagnosis
- Convince you that you must establish your own local algorithm

*Warkentin TE , Seminars Thromb Hemost 2004; 30:273
HIT paradigms and paradoxes; JTH 2011; 9(Suppl 1): 105-17

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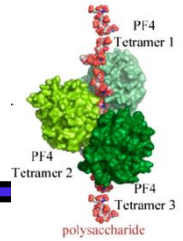
1. Model (or world view)



Definition:

- “clinicopathologic syndrome” (T. Warkentin)
- Thrombocytopenia
  - absolute <150 G/l od 150 000/µl
  - relative >50% drop in platelet count
- Exposure to heparin (in the last 100 days)
  all heparins: UFH > LMWH; bovine > porcine
- Time course: platelet drop typically after 5-10 days
  (but “early onset” and “delayed onset HIT”)

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HIT paradigms and paradoxes; JTH 2011; 9(Suppl 1): 105-17

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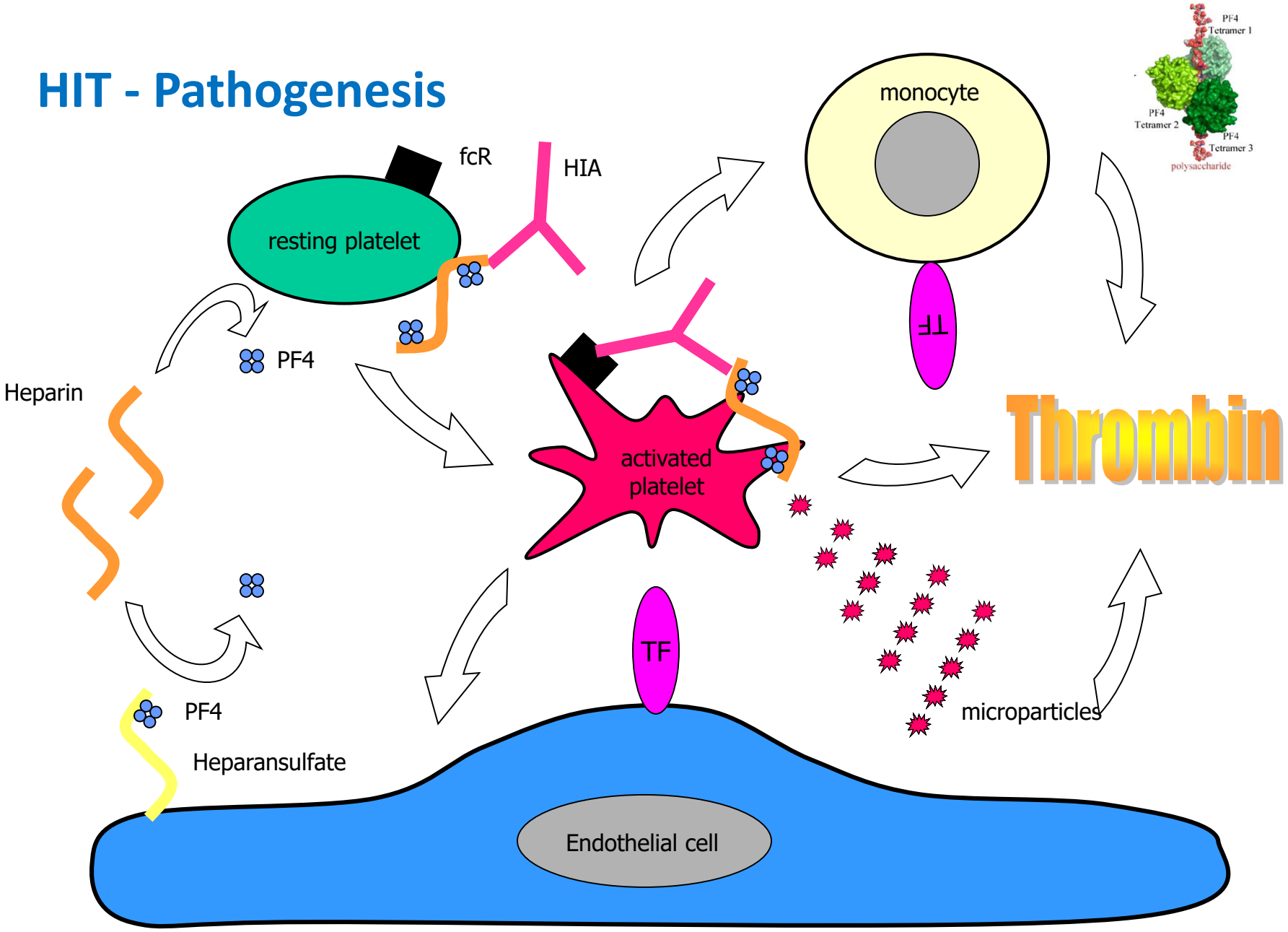
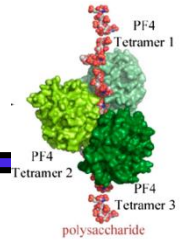
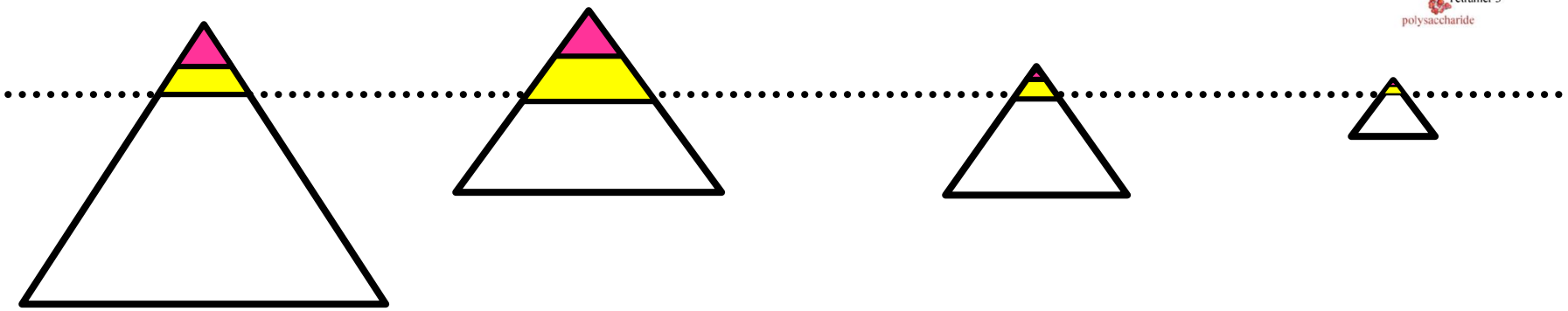
HIT - Pathogenesis



Asmis LM SMF 2004; 4:997-1002

1. HIT Iceberg modell (~ Warkentin)





CardiacSx-UFH:
50%-2%-1%

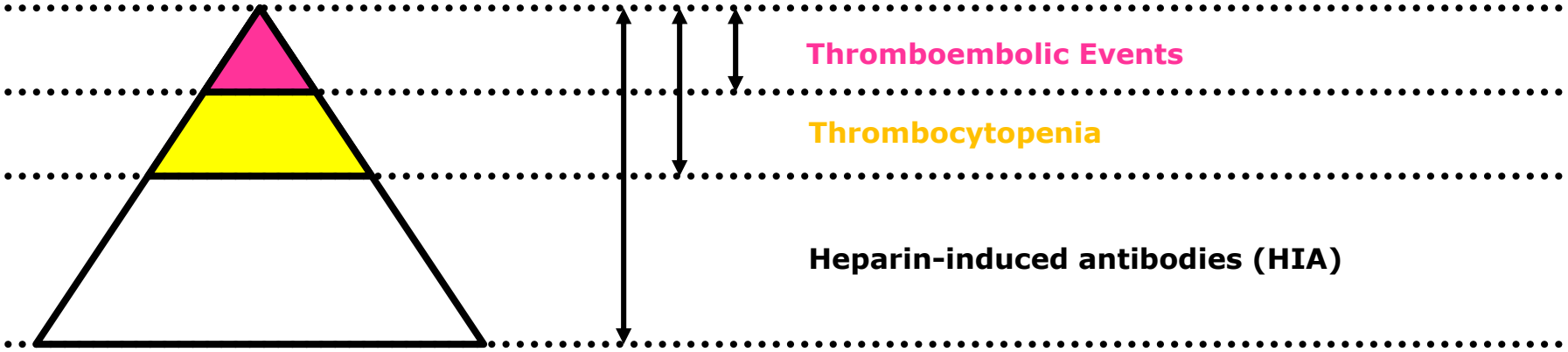
OrthoSx-UFH:
15%-5%-3%

OrthoSx-LMW:
8%-1%-0.5%

MedicalPt-UFH:
3%-0.5%-0.25%

Surgery (Sx)

Medical



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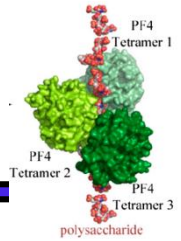
1. Over-Diagnosis of HIT



Acquired TCP in ICU setting[1,2,3]

- acquired TCP (HIT+/?/?): occurs in 30-50% of patients
- true positive HIT (HIT+/+/+): occurs in 0.3-0.5% of these patients

1:100!

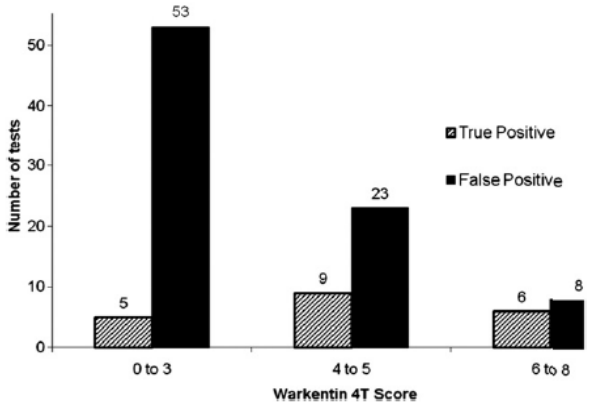


Figure 2. Heparin-induced thrombocytopenia (HIT) results, grouped by Warkentin score (0 to 3, HIT unlikely; 4 to 5, intermediate suspicion; 6 to 8, high suspicion) (x-axis), from 104 Warkentin tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with SRA ≥ 20%. False positive, black bar, patients with a serotonin releasing assay < 20%.

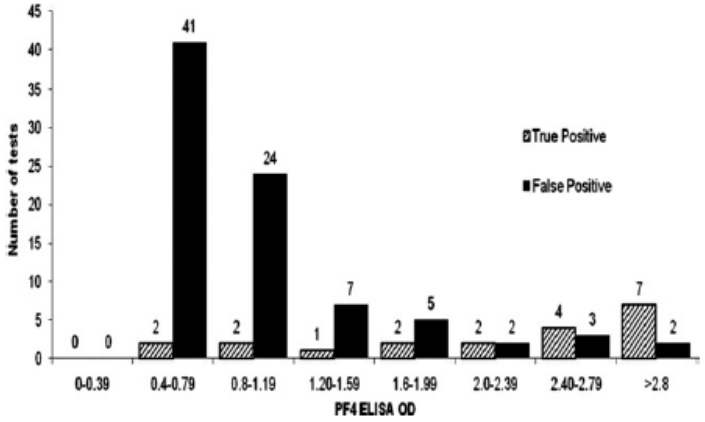
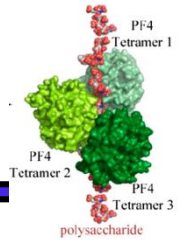


Figure 3. Heparin-induced thrombocytopenia (HIT) results, grouped by 0.4 optical density (OD) (x-axis), from 104 PF4 ELISA tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with serotonin releasing assay (SRA) ≥ 20%. False positive, black bar, patients with a SRA < 20%.

1. Warkentin HIT in critically ill patients. Critical Care 2011; 805-23 2. Berry et al JAMCollSurg 2011; 213;10-17. 3. Demma LJ Anasth Analg 2011; 113:697.

1. Over-Diagnosis of HIT



Acquired TCP in ICU setting[1,2,3]

- acquired TCP (HIT+/?/?): occurs in 30-50% of patients
- true positive HIT (HIT+/+/+): occurs in 0.3-0.5% of these patients

1:100!

Heparin-induced thrombocytopenia (HIT) in 2011: An epidemic of overdiagnosis

Adam Cuker
Department of Medicine and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

- 2000's educational activity +++
  "Think of HIT", "Don't miss HIT"
- lack of specificity of diagnostic tests
  (many positives: true and false positives)
- tests can be very sensitive (to rule out disease)

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2. Where do I start from?
DD of acquired thrombocytopenia

1. Consumption TCP

- SIRS, Sepsis
- DIC (PT, aPTT, Fibrinogen, D-Dimere, Tc)
- Medications
- uncontrolled bleeding
- hemofilters, dialysis
- IABP
- TTP/HUS
- ITP

2. Production TCP

- Medications (chemo therapy)
- Toxins (alcohol)
- BM infiltration a/o necrosis
- (ITP)

3. Pooling TCP

- Splenomegaly (portal hypertension)

LoE: Low

Lars' rule of thumb (not-evidence based):
consider a HIT test (4T and ELISA/EIA),
when HIT is in #1 or #2 position of your DD

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2. Where do I start from?
Severity of acquired thrombocytopenia

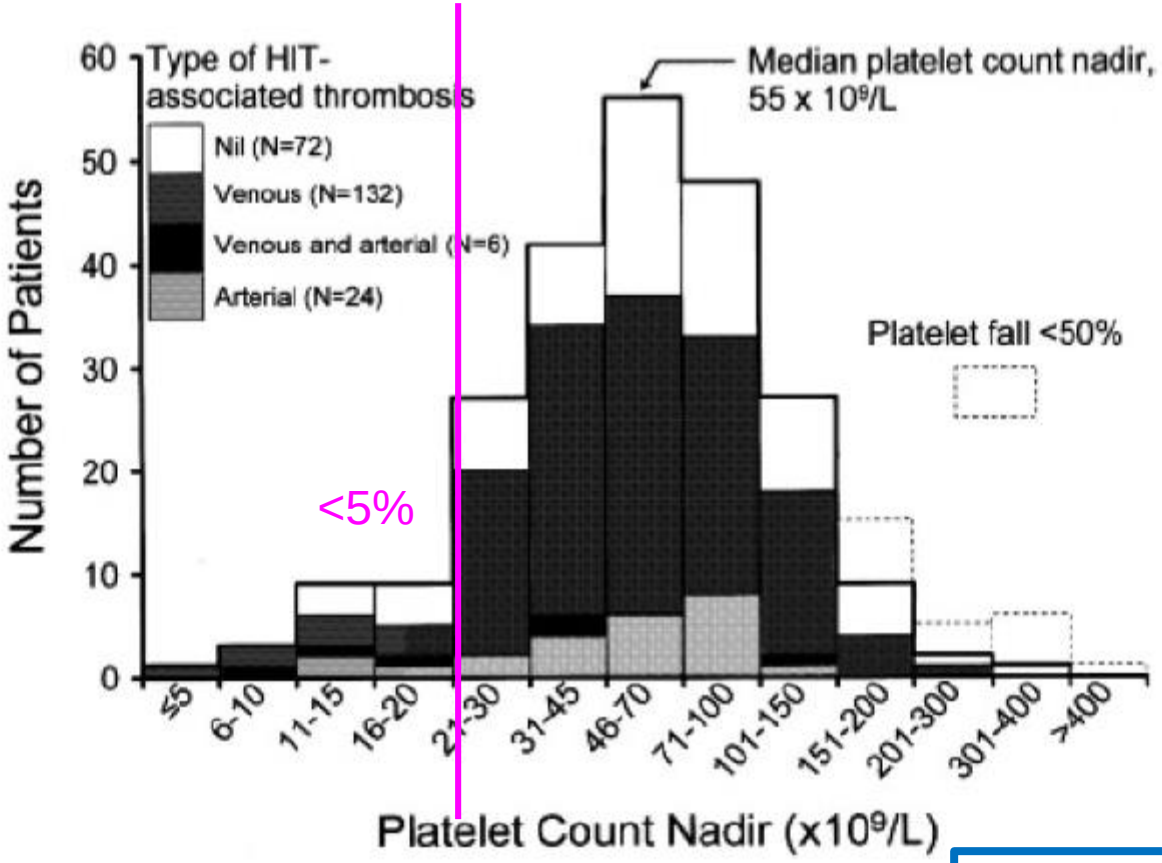

Fig. 1. Platelet counts at the time of diagnosis in 234 patients with heparin-induced t

LoE: Med

Lars' rule of thumb (partially-evidence based):

if you have acquired TCP <20 G/l HIT is unprobablle

(unless you have HIT plus another etiology)

3. Where do I want to go?

1. Fast and adequate diagnosis

- true positives — HIT+/+/+ — functionally active HIA
- false positives — HIT+/+/-
- true negatives — HIT+/-/- or nd
- false negatives — HIT+/-/+

2. Efficient and safe treatment

- true positives — require alternative anticoagulation
- false positives — – cave: anticoagulation in acquired TCP
- true negatives — continue heparin
- false negatives — – cave: thromboembolic risk

HIT status: 3 parmeters, each + or -
HITacquired thrombopenia/HIA status/functional status

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4. Tools

Methods of diagnosis

- HIT definitions have varied over time
  - 1957 clinical salmon colored emboli or white (arterial) clots under heparin therapy
  - 1980's functional tests (heparin-induced antibodies that clot with normal platelets)
  - 1990's antigenic tests (heparin/PF4/HIA complexes)

Weismann RE Tobin RW Arch surg 1958; 76:219-27.
Silver D. Annals Surg 1983 198:301-6.
Amiral J. Thromb Haemost 1995; 73: 21-8.

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4. Tools: First step

Acquired thrombocytopenia

- Relative — drop by 30-50% (depending on publication)
- Absolute — local reference values! (often 150 G/l)

4. Tools: Second step – Scoring (pretest probability)

“Gut feeling”

- f.e. low/medium high
- few publications
- works astonishingly well (try yourself)

Hit Expert Probability Score (Cuker et al)

- 8 clinical and laboratory criteria

Simple scoring system (Messmore et al)

- low or probable possibility ~ HIT manifestations

4T Score (Warkentin T or Greinacher A)

- <4 low, 4-5 = medium, 6-8 = high pprobaility

Bakchoul T. Int Jnl Lab Hem 2014; 36:296;
Raschke RA. JTH 2017; 15:1640-5.

4. Tools: Sec … bability)

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4T Score

- <4 low, 4

Table 1 Bayesian diagnostic algorithm for HIT that employs the 4Ts score and stratified interpretation of HIT ELISA, with recommendations for reasonable clinical actions based on post-test probability of HIT

Four-T score	Pretest probability of HIT	Anti PF4/H ELISA (OD)	Post-test probability of HIT	Recommendation
0–3	1%	≥ 2.000	42%	Order SRA*
		1.500–1.999	7%	Order SRA*
		0.600–1.499	1%	HIT ruled out†
		< 0.600	0	
4–5	10%	≥ 2.000	91%	HIT ruled in‡
		1.500–1.999	44%	Order SRA*
		0.600–1.499	11%	Order SRA*
		< 0.600	0	HIT ruled out†
6–8	50%	> 2.000	99%	HIT ruled in‡
		1.500–1.999	87%	HIT ruled in
		0.600–1.499	54%	Order SRA*
		< 0.600	0	HIT ruled out/ Order SRA***

anti-PF4/H, anti-platelet factor 4/heparin; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; SRA, serotonin release assay; OD, optical density. We suggest that the final recommendation in this algorithm should be modified to 'Order SRA' (see Discussion). *Stop heparin and start alternative antithrombotic therapy for HIT pending SRA results. †No need for SRA. ‡Stop heparin, begin treatment, no need for SRA. *** Original algorithm recommendation: HIT ruled in, modified algorithm recommendation: Order SRA (see discussion).

Bakchoul T. Int Jnl Lab Hem 2014; 36:296;
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4T Score (Warkentin T or Greinacher A)

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LoE: Hi

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4. Tools: 4T S

Suspicion of HIT based upon the "4 T's"	Score	Pre-test Probability Score Criteria 2	1	0
Thrombocytopenia	☐	nadir 20-100, or >50% platelet fall	nadir 10-19, or 30-50% platelet fall	nadir <10, or <30% platelet fall
Timing of onset of platelet fall	☐	day 5-10, or ≤day 1 with recent heparin*	>day 10 or timing unclear (but fits with HIT)	≤day 1 (no recent heparin)
Thrombosis or other sequelae	☐	proven thrombosis, skin necrosis, or ASR†	progressive, recurrent, or silent thrombosis; erythematous skin lesions	none
OTher cause of platelet fall	☐	none evident	possible	definite

Bitte bestimmen Sie bei HIT-Verdacht den Score. Wir wollen diesen Score prospektiv evaluieren, um die Diagnose einer HIT an Hand klinischer Symptome zu vereinfachen.

der HIT-Verdacht basiert auf folgenden Kriterien	Score	Wahrscheinlichkeitskriterien 2	1	0
Thrombozytopenie	☐	niedrigster Wert ≥20 GPT und >50% Abfall	niedrigster Wert 10-19 GPT oder 30-50% Abfall	niedrigster Wert <10 GPT oder <30% Abfall
Tag des Auftretens des Thrombozyten-Abfalls	☐	Tag 5-10 oder ≤1bei früherer Heparintherapie (innerhalb der letzten 30 Tage)	unbekannt, aber könnte zur HIT passen bzw. >Tag 10 bzw. ≤Tag 1bei früherer Heparintherapie (innerhalb der letzten 30 bis 90 Tage)	Tag <4 (keine frühere Heparintherapie)
Thrombosen oder andere Komplikationen	☐	gesicherte neue Thrombose, Hautnekrosen, anaphylaktische Reaktion (anaph. Reaktion nach Heparinbolus)	Fortschreitende oder rezidivierende Thrombose, Verdacht auf Thrombose (noch nicht bestätigt) oder nicht nekrotisierende Hautläsionen	keine Komplikationen
andere Gründe für Thrombozytenabfall	☐	keine	denkbar	definitiv
Wahrscheinlichkeits-Score	☐			

*Warkentin TE , Seminars Thromb Hemost 2004; 30:273

treat isolated HIT (0.1 mg/kg/h, adjusted by aPTT); to avoid overdosing and anaphylaxis, it may be preferable to omit the bolus, and begin as *i.v.* infusion (except when facing life-or limb-threatening thrombosis); reduce dose for renal insufficiency
naparoid: usual *i.v.* bolus, 2,250 U (body weight 60-75 kg) followed by infusion (400 U/hr for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-factor Xa levels); this therapeutic-dose regimen is appropriate both for isolated HIT and for HIT complicated by thrombosis (though higher than approved dose in some jurisdictions); withdrawn from U.S. market (2002)
†† bivalirudin: no bolus, *i.v.* infusion 0.15 mg/kg/h adjusted by aPTT; limited experience (off-label)
‡‡ fondaparinux: dosing for HIT not established; limited experience (off-label)
¶¶ delay coumarin pending substantial platelet count recovery (at least >100, preferably >150); begin coumarin in low doses, with at least 4-5 day overlap, stopping alternative anticoagulant when INR therapeutic for 2 days and platelets recovered
depending on physician confidence in the laboratory's ability to rule out HIT antibodies (usually, negative PF4-dependent enzyme-immunoassay and/or washed platelet activation assay performed by an experienced laboratory)
*** some thrombi may require special treatment, e.g., thrombectomy for large limb artery thrombosis
††† routine ultrasound of lower-limb veins recommended, since many HIT patients have subclinical deep-vein thrombosis (DVT)

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4. Tools: Third step – antigenic tests

Sytematic review and meta analysis of immunoassays for HIT

- 2716 references
- 2261 screened
- 258 assessed for eligibility
- 49 included
- Quadas-2 criteria

Nagler M. Blood 2016; 127:546-57.

4. Tools: Third step – antigenic tests

Table 2. Pooled diagnostic accuracy measures of different classes of immunoassays for diagnosis of HIT

Type of test	No. studies; no. patients*	Statistical model	Sens. (%)	Spec. (%)	LR		Posttest probability of pos. test result			Posttest probability of neg. test result		
					Pos. (95% CI)	Neg. (95% CI)	1% Prev.	7% Prev.	15% Prev.	1% Prev.	7% Prev.	15% Prev.
Polyspecific ELISA												
LT[16,19,20,28,39,41,43,44,46,47,49-54,59-61,63,64,68,69,71,74,75,77-79]	31; 8933	Unified†	96.7 (89.7, 99.0)	86.8 (82.0, 90.5)	7.3 (5.4-10.0)	0.04 (0.01- 0.12)	6.9 (5.1, 9.2)	35.5 (28.9, 42.9)	56.3 (48.9, 63.8)	0.0 (0.0, 0.1)	0.3 (0.1, 0.9)	0.7 (0.2, 2.1)
IT[19,47,61,65,77]	5; 2334	Unified†	98.4 (90.8, 99.7)	94.9 (90.5, 97.3)	19.3 (10.4-36.0)	0.02 (0.00-0.1)	16.3 (9.5, 26.7)	59.2 (43.9, 73.0)	77.3 (64.7, 86.4)	0.0 (0.0, 0.1)	0.1 (0.0, 0.7)	0.4 (0.0, 1.7)
HT[19,39,47]	3; 1014	Fixed effects‡	15.0 (14.5, 15.5)	100 (99.3, 100)	73.4 (28.2-190.9)	0.3 (0.2-0.5)	42.6 (22.2, 65.9)	84.7 (68.0, 93.5)	92.8 (83.3, 97.1)	0.3 (0.2, 0.5)	2.2 (1.5, 3.6)	5.0 (3.4, 8.1)
IgG-specific ELISA												
LT[19,20,44,55,63,64,66,69-72,77]	12; 3116	Unified†	98.3 (95.1, 99.4)	85.4 (78.2, 90.6)	6.7 (4.5-10.2)	0.02 (0.01-0.05)	6.3 (4.3, 9.3)	33.5 (25.3, 43.4)	54.2 (44.3, 64.3)	0.0 (0.0, 0.1)	0.2 (0.1, 0.4)	0.4 (0.2, 0.9)
IT[19,20,77]	4; 2545	Unified†	91.2 (86.2, 94.5)	93.5 (89.1-96.2)	14.1 (8.1-24.5)	0.09 (0.05-0.15)	12.5 (7.6, 19.8)	51.5 (38.0, 64.8)	71.3 (58.9, 81.2)	0.1 (0.1, 0.2)	0.7 (0.4, 1.1)	1.6 (1.0, 2.6)
HT[19]	2; 1958	Fixed effects‡	60.9 (59.7, 62.1)	99.4 (97.6-100)	97.0 (53.0-177.6)	0.4 (0.3-0.5)	49.5 (34.9, 64.2)	88.0 (80.0, 93.0)	94.5 (90.3, 96.9)	0.4 (0.3, 0.5)	2.9 (2.2, 3.6)	6.6 (5.0, 8.1)
PaGIA												
LT[20,36,42,45,46,53,58,64,68,70,72,75,79]	12; 2205	Unified†	96.5 (89.8, 98.9)	93.7 (83.1, 97.8)	15.3 (5.5, 42.3)	0.04 (0.01, 0.11)	13.4 (5.3, 29.9)	53.5 (29.3, 76.1)	73.0 (49.3, 88.2)	0.0 (0.0, 0.1)	0.3 (0.1, 0.8)	0.7 (0.2, 1.8)
IT[65]	1; 1291	None§	98.9	95.9	24.1	0.01	19.6	64.5	81.0	0.0	0.1	0.2
Lateral flow immunoassay[54-56,58,66,70,72]	7; 1163	Unified†	98.4 (85.3, 99.9)	90.3 (84.4, 94.1)	10.1 (6.2, 16.5)	0.02 (0.00, 0.18)	9.3 (5.9, 14.3)	43.3 (31.9, 55.4)	64.2 (52.4, 74.5)	0.0 (0.0, 0.2)	0.1 (0.0, 1.3)	0.3 (0.0, 3.0)
PIFA[28]	1; 88	None§	0.0	70.1	2.3	0.5	2.3	14.8	28.9	0.5	3.6	8.1
Latex agglutination assay[37]	1; 119	None§	100.0	84.3	3.7	0.0	3.6	21.8	39.5	0.0	0.0	0.0
Polyspecific CLIA												
LT[37,38,57,61,62,77]	7; 1008	Unified†	98.9 (92.7, 99.8)	85.6 (79.3, 90.3)	6.9 (4.7-10.0)	0.01 (0.00-0.09)	6.5 (4.5, 9.2)	34.2 (26.1, 42.9)	54.9 (45.4, 63.8)	0.0 (0.0, 0.1)	0.1 (0.0, 0.7)	0.2 (0.0, 1.6)
IT[37]	2; 448	Fixed effects‡	97.9 (94.6, 100.0)	93.1 (90.4, 95.8)	13.5 (9.5-18.9)	0.0 (0.0-0.1)	12.0 (8.8, 16.0)	50.4 (41.7, 58.7)	70.4 (62.6, 76.9)	0.0 (0.0, 0.1)	0.0 (0.0, 0.7)	0.0 (0.0, 1.7)
HT[37,61,62,77]	5; 755	Unified†	98.3 (69.5, 99.9)	97.5 (94.4, 98.9)	39.5 (17.5-89.2)	0.0 (0.0-0.40)	28.5 (15.0, 47.6)	74.8 (56.8, 87.1)	87.5 (75.5, 94.1)	0.0 (0.0, 0.4)	0.1 (0.0, 2.9)	0.2 (0.0, 6.6)
IgG-specific CLIA												
LT[37,57,61,77]	5; 741	Unified†	98.8 (69.2, 100.0)	94.6 (90.7, 96.9)	18.3 (10.6-31.5)	0.01 (0.00- 0.40)	15.6 (9.7, 24.1)	57.9 (44.4, 70.3)	76.3 (65.2, 84.8)	0.0 (0.0, 0.4)	0.1 (0.0, 3.2)	0.2 (0.0, 7.2)
IT[37]	2; 448	Fixed effects‡	78.6 (75.9, 81.2)	98.7 (94.6, 100)	42.3 (20.1-88.7)	0.2 (0.1-0.3)	29.9 (16.9, 47.3)	76.1 (60.2, 87.0)	88.2 (78.0, 94.0)	0.2 (0.1, 0.3)	1.5 (0.7, 2.2)	3.4 (1.7, 5.0)
HT[37,61]	3; 552	Fixed effects‡	74.2 (71.9, 76.5)	99.1 (95.4, 100)	47.8 (23.2-98.7)	0.2 (0.1-0.4)	32.6 (19.0, 49.9)	78.3 (63.6, 88.1)	89.4 (80.4, 94.6)	0.2 (0.1, 0.4)	1.5 (0.7, 2.9)	3.4 (1.7, 6.6)

Nagler M. Blood 2016; 127:546-57.

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4. Tools: Third step – antigenic tests

Meta analysis of rapid immunoassays for HIT

- 171 references
- 126 screened
- 63 assessed for eligibility
- 23 included
- Quadas-2 criteria

Sun L. Thromb Haemost 2015; 127:546-57. – remark: meta analysis!

4. Tools: Third step – antigenic tests

Assay name	Abbreviation	Principle	Turn-around time	Antibody classes detected	Regulatory approval
Particle Gel Immunoassay	PaGIA	Red-dyed polymer particles coated with PF4/heparin complexes agglutinate at top of gel chamber if bound by anti-PF4/heparin antibodies	20 min	IgG1	Asia Australia Canada Europe
IgG-specific Chemiluminescent Assay	IgG-CA	1. PF4-coated magnetic particles capture anti-PF4/heparin antibodies in sample 2. Isoluminol-labeled secondary anti-IgG antibody is added and emits light with intensity proportional to concentration of anti-PF4/heparin antibodies in sample	30 min	IgG	Europe
Polyspecific Chemiluminescent Assay	Poly-CA	Same as IgG-CA, but secondary luminescent antibodies are mixture of anti-human IgG, IgA, and IgM	30 min	IgG, IgA, IgM	Europe
Lateral Flow Immunoassay	LFIA	1. PF4-polyanion complexes in buffer migrate through test strip and bind patient anti-PF4/heparin antibodies 2. IgG anti-PF4/heparin antibodies are bound by immobilized anti-IgG antibody and form a red test line	15 min	IgG	Europe
Latex Particle-Enhanced assay	HemosIL-Ab	1. Latex beads coated with PF4/polyvinyl sulfonate bind anti-PF4/heparin antibodies 2. Monoclonal anti-PF4/heparin antibody is added; if human anti-PF4/heparin antibodies are present, agglutination of latex beads is inhibited	15 min	IgG, IgA, IgM	Europe
Particle Immunofiltration Assay	PIFA	Blue PF4-coated microparticles aggregate if bound by anti-PF4/heparin antibodies; cannot pass through permeable membrane and yield no color change if positive	15 min	IgG, IgA, IgM	United States

PF4, platelet factor 4. 1PaGIA is technically able to detect IgG, IgM, and IgA antibodies, but the presence of anti-human-IgG in the gel card allows for preferential detection of IgG.

4. T

Table 2: Characteristics of eligible studies.

Index Test/ Reference	Setting (n)	Population (%)	Median age	No (%) female	Reference standard
Particle Gel Immunoassay					
Alberio 2003 (13)	Switzerland (148)	NR	62.5 (F) 65 (M)	62 (43)	PAT > 50 % aggregation
Bakchoul 2009 (16)	Germany (500)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min) AND 4T score ≥ 4
Bryant 2008 (17)	Australia (246)	CT surgical (43) Other surgical (8) Cardiac medical (22) Other medical (27)	62	92 (37)	SRA > 20 % release
Denys 2008 (19)	Belgium (102)	Surgical and Medical (NR)	NR	4 (40 %) for 10 HIT+ pts – NR for all pts	Functional Flow (% platelet activation ≥ 2 times control)
Kapadia 2013 (21)	India (217)	Medical ICU and Surgical ICU (NR)	NR	NR	SRA > 20 % release
Legnani 2010 (24)	Italy (102)	Medical (49) Cardiac surgical (10) General surgical (32) Thrombosis treatment (29)	73	47 (46)	PAT > 20 % aggregation AND 4T score ≥ 4
Leroux 2014 (25)	France (124)	NR	NR	NR	SRA>20*% release AND ELISA absorbance ≥ 11.5 % of control AND 4T score ≥ 4
Linkins 2015 (26)	Canada (526)	Cardiac surgical (23) Other surgical (23) ICU (51) Medical (48) Oncology (13)	66.5	256 (49)	SRA > 50 % mean release AND positive in-house ELISA
Meyer 1999 (27)	Germany (109)	NR	NR	NR	HIPA (loss of turbidity in 30 min)
Nellen 2012 (29)	Switzerland (1291)	Medical (54) Surgical (24) ICU (20) OB/Gyn (1.2) Pediatric (0.5) Unknown (1)	68	566 (44)	PAT > 50 % aggregation
Pouplard 2007 (30)	France (213)	Medical (42) Cardiac surgical (14) General surgical (19) Other (25)	69	73 (34)	SRA > 20 % release
Sachs 2011 (31)	Germany (452)	NR	NR	NR	HIPA (loss of turbidity in 30 min) AND 4T score ≥ 4
Solano 2013 (32)	Australia (37)	Medical (59) Surgical (41)	63	14 (38)	Functional Flow (% platelet activation ≥ 2 times control)
Tawfik 2011 (33)	Egypt (50)	Medical (40) Surgical (60)	64*	19 (38)	SRA (radioactivity > 2-fold standard deviation of control)

Sun L. Thromb Haemost 2015; 127:546-57. – remark: meta analysis!

4. T

Table 2: Continued

Chemiluminescent Assays†					
Althaus 2013 (14)	Italy, England, Germany (448)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min)
Legnani 2010 (24)	Italy (102)	Medical (49) Cardiac surgical (10) General surgical (32) Thrombosis treatment (29)	73	47 (46)	PAT >20% aggregation AND 4T score ≥ 4
Minet 2013 (28)	Belgium (45)	NR	NR	NR	SRA >20% release
Van Hoecke 2012 (34)	Belgium (87)	Cardiac surgical and Medical (NR)	NR	NR	Functional Flow (% plt activation ≥ 2 times control)
Vianello 2015 (35)	Italy (96)	Medical, orthopedic, surgical, ICU (NR)	NR	NR	HIPA (loss of turbidity) AND 4T score ≥ 4
Lateral Flow Immuno					
De Cooman 2015 (18					
Kolde 2011 (22)					
Kolde 2014 (23)					
Leroux 2014 (25)					
Sachs 2011 (31)					
Vianello 2015 (35)					
Latex Particle Enhano					
Althaus 2013 (14)		(119)			
Jourdy 2015 (20)	France (100)	NR	69 (F) 73 (M)	42 (35)	+/- HIPA (≥ 30% aggregation between spontaneous curve and 0.5 or 1IIU/mL curve and inhibited with 100 IU/ml UFH) +/- SRA >20% release ‡
Particle Immunofiltration Assay					
Andrews 2013 (15)	United States (92)	MICU (100)	54 *	34 (37)	SRA >20% release AND 4T score ≥ 4

*Mean. † The first four studies investigated both the IgG-specific and polyspecific chemiluminescent assays; Vianello et al. investigated only the IgG-specific chemiluminescent assay. ‡ HIPA was only performed on patients with at least intermediate pretest probability; SRA was only performed as confirmatory testing in patients with discrepant immunoassay and HIPA test results. CT, cardiothoracic; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet activation assay; ICU, intensive care unit; NR, not reported; PAT, platelet aggregation test; SRA, serotonin release assay.

Table 4: Predictive values of rapid immunoassays for HIT.

Assay	PPV (95 % CI)	NPV (95 % CI)
PaGIA	0.45 (0.33–0.57)	1.00 (0.99–1.00)
IgG-CA	0.71 (0.49–0.93)	0.99 (0.98–1.00)
Poly-CA	0.42 (0.30–0.53)	1.00 (0.98–1.00)
LFIA	0.66 (0.41–0.90)	1.00 (0.99–1.00)

NPV, negative predictive value; PPV, positive predictive value; PaGIA, particle gel immunoassay; IgG-CA, IgG-specific chemiluminescent assay; Poly-CA, polyspecific chemiluminescent assay; LFIA, lateral flow immunoassay.

Sun L. Thromb Haemost 2015; 127:540-57. = remark: meta analysis!

ZFTH

4. T

Table 2: Continued

Chemiluminescent Assays†					
Althaus 2013 (14)	Italy, England, Germany (448)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min)
Legnani 2010 (24)	Italy (102)	Medical (49) Cardiac surgical (10) General surgical (32) Thrombosis treatment (29)	73	47 (46)	PAT >20% aggregation AND 4T score ≥ 4
Minet 2013 (28)	Belgium (45)	NR	NR	NR	SRA >20% release
Van Hoecke 2012 (34)	Belgium (87)	Cardiac surgical and Medical (NR)	NR	NR	Functional Flow (% plt activation ≥ 2 times control)
Vianello 2015 (35)	Italy (96)	Medical, orthopedic, surgical, ICU (NR)	NR	NR	HIPA (loss of turbidity) AND 4T score ≥ 4
Lateral Flow Immunoassay					
De Cooman 2015 (18)	Belgium (153)	NR	NR	NR	Functional Flow CD62p
Kolde 2011 (22)	Germany (60)	NR	NR	NR	HIPA (loss of turbidity in 30 min)
Kolde 2014 (23)	Germany, Austria (211)	NR	NR	NR	HIPA (loss of turbidity in 30 min)
Leroux 2014 (25)	France (334)	Medical (31) Cardiac Surgical (20) General Surgical (16) Other (33)	70	148 (44)	SRA>20% release AND ELISA absorbance ≥ 11.5 % control AND 4T score ≥ 4
Sachs 2011 (31)	Germany (452)	NR	NR	NR	HIPA (loss of turbidity in 30 min) AND Intermediate-high 4T
Vianello 2015 (35)	Italy (114)	Medical (39) Orthopedic (7) Cardiac surgical (20) ICU (17) Other (7)	70* (F) 62.2* (M)	60 (53)	HIPA (loss of turbidity) AND 4T score ≥ 4
Latex Particle Enhanced Assay					
Althaus 2013 (14)	Italy and England (119)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min)
Jourdy 2015 (20)	France (100)	NR	69 (F) 73 (M)	42 (35)	+/- HIPA (≥ 30% aggregation between spontaneous curve and 0.5 or 1IU/mL curve and inhibited with 100 IU/ml UFH) +/- SRA >20% release ‡
Particle Immunofiltration Assay					
Andrews 2013 (15)	United States (92)	MICU (100)	54 *	34 (37)	SRA >20% release

	n	Quadas-2	Sensitivity	Specificty	NPV
Althaus	119	Hi: 6/7	1.00 (0.83-1.00)	0.76 (0.66-0.84)	0.99
Jourdy	110	Hi: 6/7	1.00 (0.66-1.00)	0.91 (0.83-0.96)	0.99

4. Tools: Third step – antigenic tests

Which test to use?

- Study 1850 patients, single center, divided in 2 periods
  period 1: PaGIA (particle gel immune assay) and
  ELISA (IgG only)
  period 2 CLIA (lateral flow immune assay)

test	n	pos	%	cost/test
PaGIA	892	281	31.5%	12.27
ELISA	901	83	9.2%	26.17
CLIA	1174	71	6.0%	37.51

LoE: Low

Lars' rule of thumb (not-evidence based):
you want to chose a antigenic HIA test
that produces few positive results (<10%)
(less positives result in less false positives)

4. Tools: Third step – antigenic tests

IgG (specific) vs IgGAM (polyspecific)

Table 2 Study quality assessment by QUADAS-2 criteria

	Risk of bias				Applicability concerns		
References	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Warkentin* 2013 [19]	Low	Unclear	Low	Low	Low	High	High
Cuker 2013 [20]	High	Unclear	High	Low	Low	Low	High
Galea 2013 [21]	Low	Unclear	Unclear	Low	Low	Low	High
McFarland 2012 [22]	High	Unclear	High	High	Low	High	High
Van Hoecke 2012 [13]	Low	Unclear	High	Low	Low	Low	High
Morel-Kopp 2010 [23]	Low	Low	High	High	Low	Low	High
Pouplard 2010 [24]	High	Unclear	Low	Low	Low	Low	High
Bakchoul 2009 [25]	Low	Unclear	Unclear	Low	Low	High	High
Warkentin 2008 [15]	Low	Unclear	High	High	Low	High	High

*Determined from data reported in original article, the PROTECT trial, and discussions with Dr. Theodore Warkentin.

LoE: Hi

Lars' rule of thumb (not-evidence based): 2 alternatives

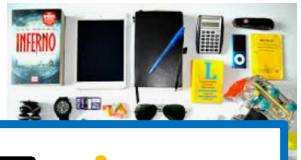
only one test: then use IgG specific test

if more than one test then use IgGAM unspecific test next to IgG

LoE: Low

Husseinzadeh HD. JTH 2017; 1203-12.

4. Tools: Third step – antigenic tests



LoE: Low

What is a good antigenic (or immunological) test

- sensitivity >99 (98)%
  negative predictive value (NPV) >99 (98)%

- Low absolute and relative number of positive tests
  few positives = few to follow up on with a functional test
  my view: should be below 10%
- Rapid turn around time (20-30 minutes! vs hours to days)
- Low absolute and relative number of false positive tests

Asmis LM, personal opinion

4. Tools: Fourth step – functional tests

Serotonin relase assay

- Functionally active HIA induce secretory response in healthy donor platelets
- Considered one of two gold standards

Heparin-induced platelet activation

A positive functional test is sufficient condition to
prove the HIA's "danger"
- functional HIA (HIT+/+/+) require alternative anticoagulation
(in therapeutic dose)

PS: the presence of an acquired TCP and HIA positivity (HIT+/+/?)
are the necessary condition

- n.b: platelet count should normalize after 3-5 days, same goes for D-dimers
- Not considered to be "gold standard"

Asmis LM, personal opinion

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5. The plan

Algorithm*:

- "unambiguous specifications for performing a task"*
- Common features

background	HIT pathogenesis
starting point	acquired TCP
end point or goal	preventing complications
equipment and tools	scores, tests, (medications)
periodic reevaluation!	
motivation	

- abundance of examples/data from other fields indicating things start improving once you define a plan/algorithm

*wikipedia

5. The Algorithm

< Day 1!

	Pre Test Pb - 4T score - Other scores	Post Test 1 - EIA Test - other Ag Tests	Post Test 2 - HIPA / SRA - Tc evolution, D-Dimers
High	Stop Heparin Alternative AC	Stop Heparin Alternative AC	Alternative AC
Medium	Stop Heparin? Alternative AC?	+ Stop Heparin Alternative AC	+ Alternative AC
Low	No test	- Reevaluate diagnosis	- Reevaluate diagnosis

5. The Algorithm

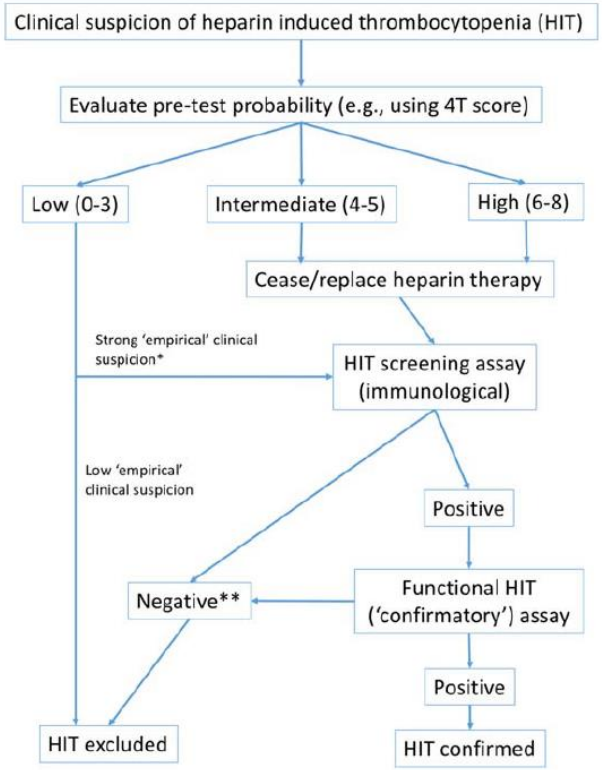
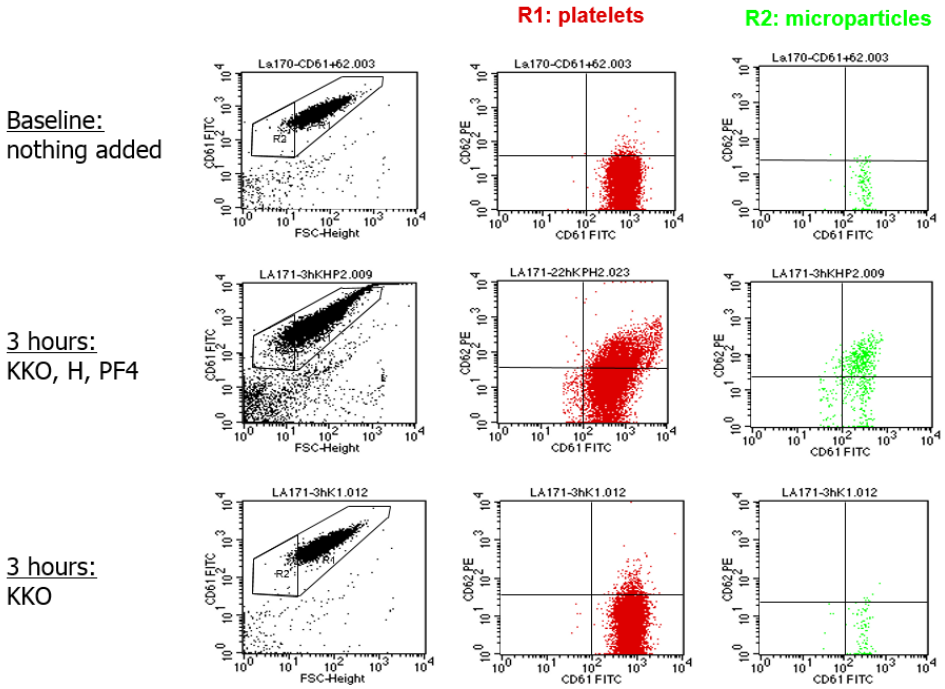


FIGURE 1 An algorithm that reflects a recommended approach to the investigation of individuals with potential heparin induced thrombocytopenia (HIT), based on local[3,9] and other published experience. Notes: *Strongly recommended that the decision to perform HIT testing in cases with low **4Ts** only progress after consultation with a local hematology expert. **Be aware that

Favaloro EJ. Am J Hematol 2018; 93:308-14

7. Outlook – what we need?



Time limiting factor: functional tests:

- (1) or 3 to 5 days: this needs to be improved
- shorter delays might decrease mortality

Asmis LM: unpublished data

Conclusions: HIT - a diagnostic journey

1. View of the world **"model"**

- pathogenesis of HIT: an immune mediated drug-induced thrombocytopenia
- beware of overdiagnosis

2. Starting point

- **acquired thrombocytopenia** (median plt count 55 G/l)

3. Goal

- **positive patient outcome**: safe and efficient

4. Tools **4T score, antigenic and functional tests**

- patient history, clincial findings, laboratory tests (screening and confirming)

5. The trip itinerary

- a comprehensive **algorithm** defined for an individual institution with a timeline

6. Motivation

- 365 day mortality↑; HIT+/+/+ vs con: ≈, HIT+/+/- and HIT+/+/nd vs con: ↑

7. Future

- we need quicker confirmation!

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Conclusions: HIT - a diagnostic journey

1. View of the world **"model"**

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- **acquired thrombocytopenia** (median plt count 55 G/l)

3. Goal

- **positiv**

4. Tools

- patient

Thank you, for Your attention!

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- a comprehensive **algorithm** defined for an individual institution with a timeline

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