Generate Knowledge

STic Expert HIT:

for a rapid and confident exclusion of Heparin Induced Thrombocytopenia

Jamal Barsheed

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Outline

- **What is HIT ?**
  - description
  - diagnosis
  - treatment
  - clinicians and labs needs
- **STic Expert® HIT**
  - product overview
  - handling
  - kit description
- **Evaluation results**
  - clinical validation
- **Conclusion**

What is HIT ?

Description of HIT

- **Heparin Induced Thrombocytopenia**
- **Adverse effect of heparin**
- **Antibody-mediated**
- **Main symptom: thrombocytopenia**
  - platelet count drop > 50% from the baseline
  - occurs 5-14 days after the start of heparin treatment
- **May affect up to 5 % of patients on UFH and 0.5- 1% of patients on LMWH**
- **Strong association with venous and arterial thrombosis**
  - High morbidity risks

➔HIT suspicion: huge stress for clinician/lab

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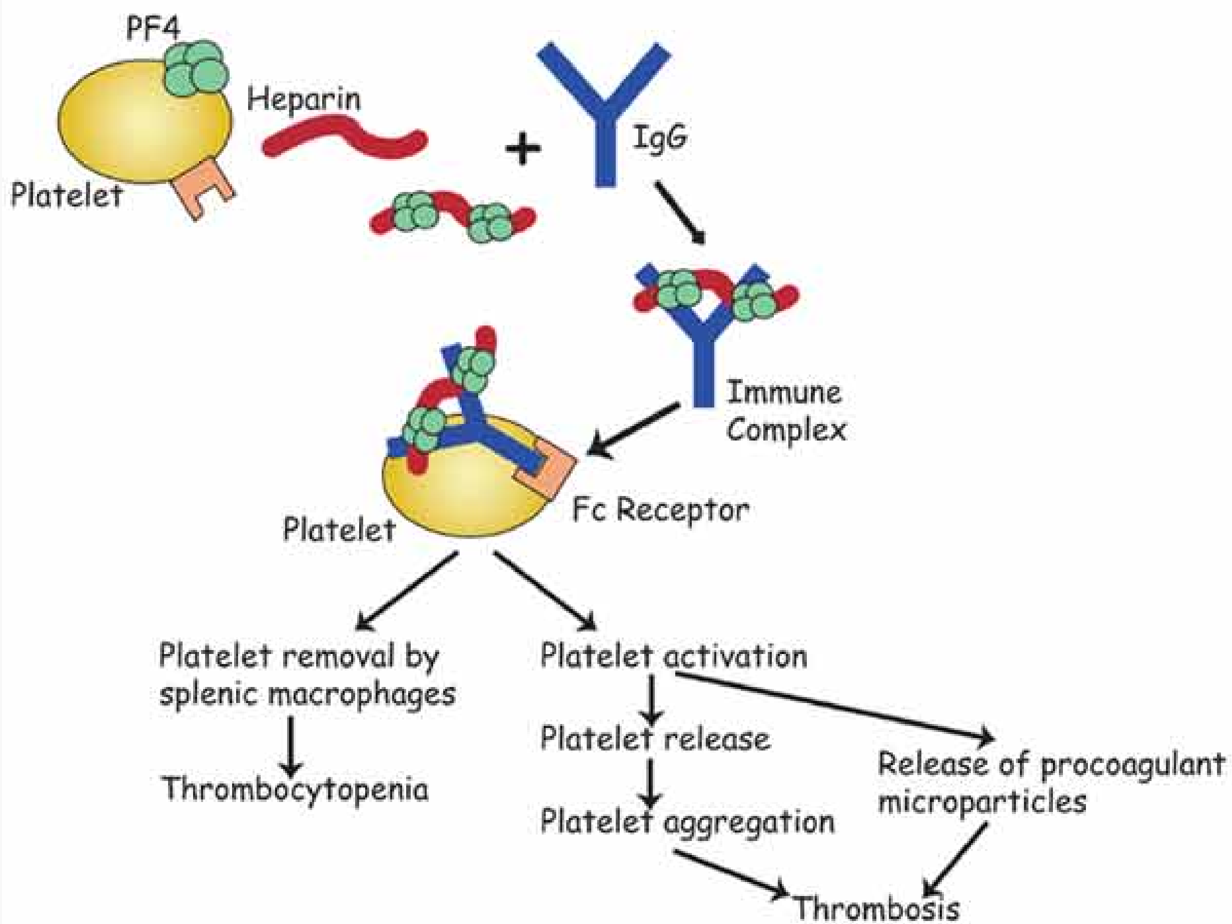
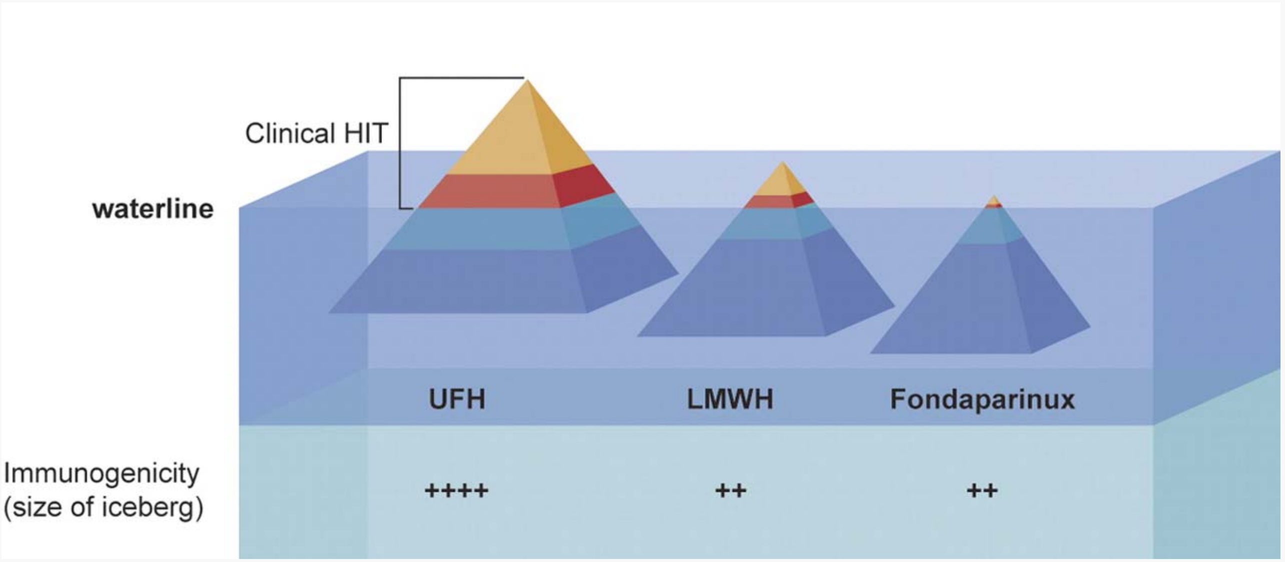
HIT pathophysiology



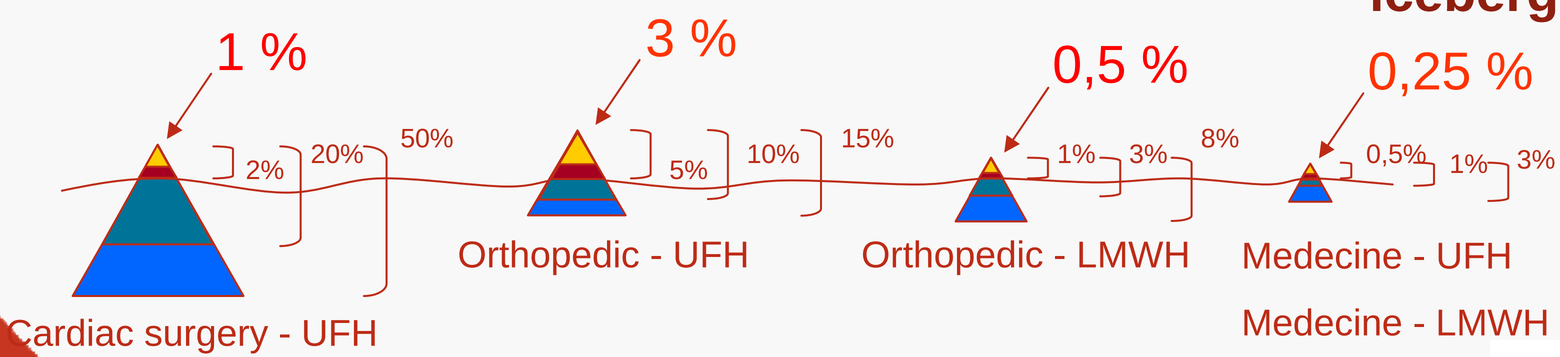
Clinical interest

HIT incidence in clinical context



Kelton J G , Warkentin T E Blood 2008;112:2607-2616

- **The type of heparin given to the patient determines the overall size of the iceberg**



Acc. to T.E. Warkentin in Warkentin & Greinacher, eds. 2004

Diagnosis

Combination of clinical and biological criteria

- pre-test scoring (4T's)
- biological assays

- **Pre-test scoring: 4 T's**
  - **T**hrombocytopenia
    - level of platelet fall
  - **T**iming
    - time after heparin exposure
  - **T**hrombosis
    - occurrence after heparin exposure
  - o**T**her cause of thrombocytopenia
    - need to be reliably excluded

- Identification of 3 levels of risks
  - 0-3: low
  - 4-5: intermediate
  - 6-8: high

How to calculate the 4T score?

points	2	1	0	Score
Thrombocytopenia	- Platelet count fall > 50% and nadir ≥ 20 G/L	- Platelet count fall 30 à 50% or - nadir between 10 and 19 G/L	- Platelet count fall < 30% or - nadir< 10 G/L	/2
Timing of platelet count fall	- Clear onset between days 5 to 10 after the start of treatment or - at day 1 (if prior heparin exposure within -30 days)	- Thrombocytopenia after day 10 of the start of treatment - at day 1 (if prior heparin exposure within -30-100 days ago) - after day 10.	- Platelet count fall < 4 days without recent exposure	/2
Thrombosis or other sequelea	- New thrombosis - Skin necrosis (injection point) - Acute systemic reaction after bolus IV	- Progressive or recurrent thrombosis - thrombosis suspicion - skin necrosis at the point of injection	- None	/2
oTher causes of thrombocytopenia (drugs etc…)	- None apparent	Possible	Definite other causes - Infections - Chemo / radiotherapy - DIC	/2
			Total	

Probability :
- High: Score 6 to 8
- Medium : Score 4 to 5
- Low : Score 0 to 3

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Diagnosis

- **Combination of clinical and biological criteria**
  - pre-test scoring (4T's)
  - biological assays

Functional assays	**Immunoassays**
(SRA, HIPA, PA)	
= detect platelets activating antibodies	*= detect antibodies against [Heparin/PF4]*
☺ highest sensitivity/specificity	☺ better standardization
☹ complex, expensive, time consuming	😐 easier to use
☹ not standardised	☹ lower specificity
☹ not widespread use	

→ No perfect test, room for improvement

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Treatment of HIT

HIT: SEVERE clinical impacts
Suspicion of HIT = stress for clinician/lab

Clinician does not wait for lab results
→switch to alternative anticoagulant

Alternative anticoagulants
→high risk of bleeding (no antidote)
→much more expensive

Real frequency of HIT

6~12% of patients investigated for HIT have really HIT*

88~94% of patients suspected of HIT don't have HIT

*Warkentin T.E. HIT paradigms and paradoxes. J Thromb Haemost 2011; 9 (Suppl. 1): 105-117

ISTH recommendations

JTH Dec-11

Journal of Thrombosis and Haemostasis, 9: 2498–2500

DOI: 10.1111/j.1538-7836.2011.04536.x

OFFICIAL COMMUNICATION OF THE SSC

Laboratory testing for heparin-induced thrombocytopenia: a conceptual framework and implications for diagnosis

T. E. WARKENTIN,* A. GREINACHER,† Y. GRUEL,‡ R. H. ASTER§ and B. H. CHONG,¶ ON BEHALF OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

**Department of Pathology and Molecular Medicine and Department of Medicine, McMaster University, Hamilton, Canada; †Department of Immunology and Transfusion Medicine, Ernst-Moritz-Arndt University-Greifswald, Greifswald, Germany; ‡Department of Hematology, Hôpital Trousseau, Tours, France; §Blood Research Institute, Blood Center of Wisconsin, and Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; and ¶Department of Medicine, St George Clinical School, University of New South Wales, and St George Hospital, Sydney, Australia*

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Heparin-induced thrombocytopenia (HIT) is a 'clinicopathologic' syndrome (i.e. diagnosis depends on both clinical and pathologic criteria being present) [1]. The 'clinical' criteria include the presence of thrombocytopenia and/or thrombosis bearing a temporal relationship to an immunizing exposure to heparin. The 'pathological' criterion is the detectability of 'HIT antibodies' in acute patient serum or plasma. HIT is caused by heparin-dependent platelet-activating antibodies that in almost all patients recognize complexes of platelet factor 4 (PF4) bound to heparin [2]. Sensitivity of solid-phase enzyme-immunoassays (EIAs) for anti-PF4/heparin antibodies is very high (approximately 99%), due to certain unique properties of HIT antigens; they are expressed on large, stable multimolecular complexes comprised of PF4 and polyanions [3]. This differs from other drug-induced, immune-mediated thrombocytopenic disorders, where laboratory tests for drug-dependent antibodies often lack high diagnostic sensitivity. The antigens in these other disorders are labile complexes of drug (or drug metabolites) and platelet glycoproteins [4].

The high diagnostic sensitivity of the PF4/heparin EIAs is accompanied by a parallel problem in diagnostic specificity for HIT. This arises because EIAs also have high sensitivity for detecting clinically insignificant anti-PF4/heparin antibodies, which can be present coincidentally in patients with thrombocytopenia caused by non-HIT factors. This leads to the potential for HIT 'over-diagnosis,' especially in critically-ill patients. Systematic serosurveillance studies show that only a minority (2–15%) of heparin-treated patients who form anti-PF4/heparin antibodies develop clinically evident HIT [5,6]. Even among those who form platelet-activating antibodies, no more than half develop HIT. This Subcommittee statement provides a framework on when to perform and how to interpret laboratory tests for HIT diagnosis.

Patients should not be routinely screened for anti-PF4/heparin antibodies (other than for research studies). Patients should only undergo testing if clinical features reasonably suggest a diagnosis of HIT. Scoring systems can be helpful to estimate the pretest probability of HIT [7–9]. HIT antibodies are transient, however [10], and thus testing should be performed using acute serum or plasma.

Laboratory diagnosis of HIT differs fundamentally from other antibody-mediated cytopenias, such as autoimmune thrombocytopenia or hemolysis, because free HIT antibodies are readily detectable in patient serum/plasma even during the earliest phase of the platelet count decline indicating HIT [11]. Therefore, a negative result of an HIT antibody test performed because of thrombocytopenia or thrombosis generally rules out HIT. Routine repeat testing a few days later is not indicated (unless a new platelet count decline or thrombosis occurs) because such testing risks detecting clinically irrelevant antibodies (as demonstrated in serosurveillance studies). Overdiagnosis of HIT is potentially dangerous because it may lead to withholding of certain diagnostic and therapeutic interventions during the acute event and in future admissions, and because it usually prompts treatment with alternative anticoagulants, which may increase bleeding risk (approximately 1% risk of major bleeding per treatment day for direct thrombin inhibitors) [12].

Diagnostic accuracy for HIT is optimized by combining the anti-PF4/heparin EIA with a functional (platelet activation)

Correspondence: Theodore (Ted) E. Warkentin, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences, Hamilton General Hospital, 237 Barton Street East, Room 1-270B, Hamilton, Ontario, Canada L8L 2X2.
Tel.: +1 905 527 4322; fax: +1 905 577 1421.
E-mail: twarken@mcmaster.ca

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Overdiagnosis of HIT is potentially dangerous

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How to exclude HIT ?

Therefore, a negative result of an HIT antibody test performed because of thrombocytopenia or thrombosis generally rules out HIT. Routine repeat testing a few days later is not indicated

How to improve specificity ?

ity of EIAs. Patients should be tested for IgG class antibodies, as only this isotype class activates platelets [2,6,16,17] (rare

Clinicians and labs needs ?

Clinicians and labs needs

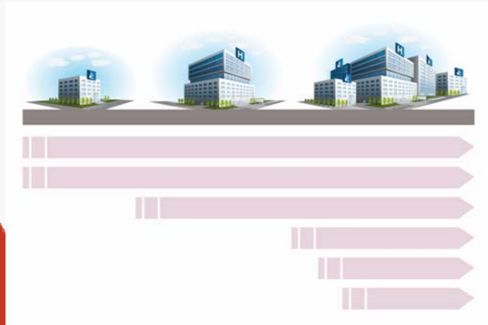
Clinician

Huge interest to **quickly RULE-OUT HIT**

→ avoid alternative treatment, maintain heparin

- less bleeding risks
- costs savings
  - ✓treatment
  - ✓less additional expensive testing, labor cost

From the lab perspective



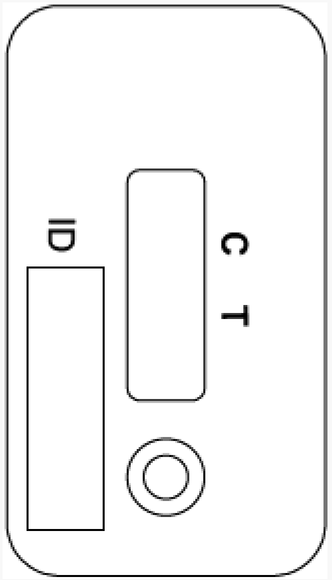
Unitary test
Rapid
Easy to use
24/7, STAT adapted
Negative Predictive Value 100%
High specificity

STic Expert® HIT

Product overview

STic Expert HIT 5, Cat. Nr. 01058
STic Expert HIT 20, Cat. Nr. 01059

- **Intended use: qualitative detection of IgG antibodies against PF4/polyanion complexes**
- **Test principle: immunochromatography / lateral flow**
- **Unitary test, extremely simple handling**
- **Results in 10 min**
- **Validated with PLASMA and serum**



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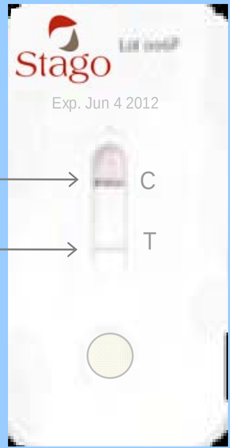
Handling: simple and quick



Control line

Test line

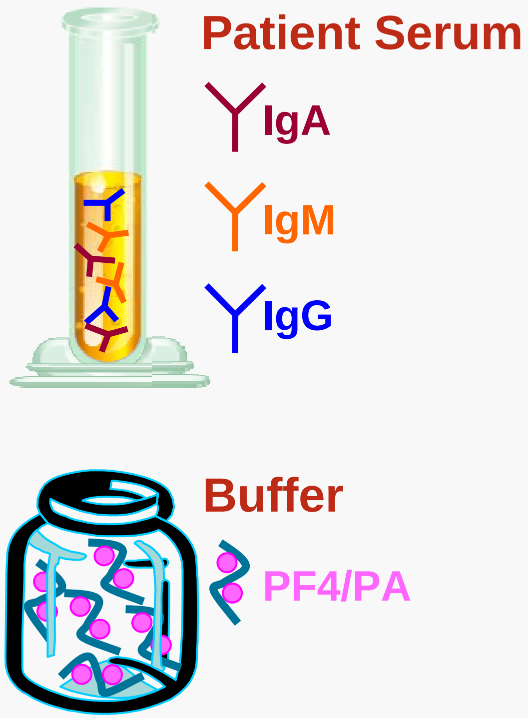
1 5 µl serum

2 2 drops of buffer

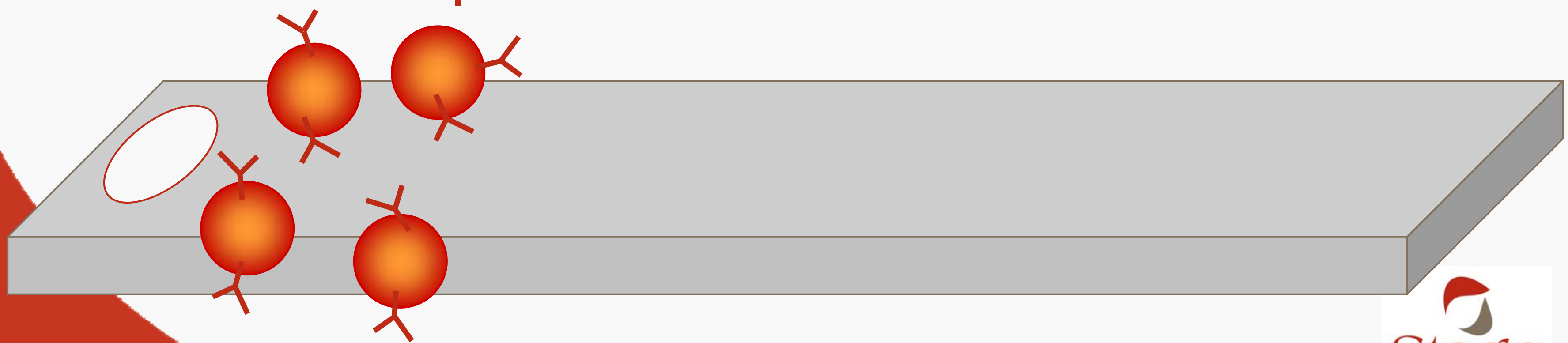
3 Visual inspection endpoint after 10 min

Principle

Figure



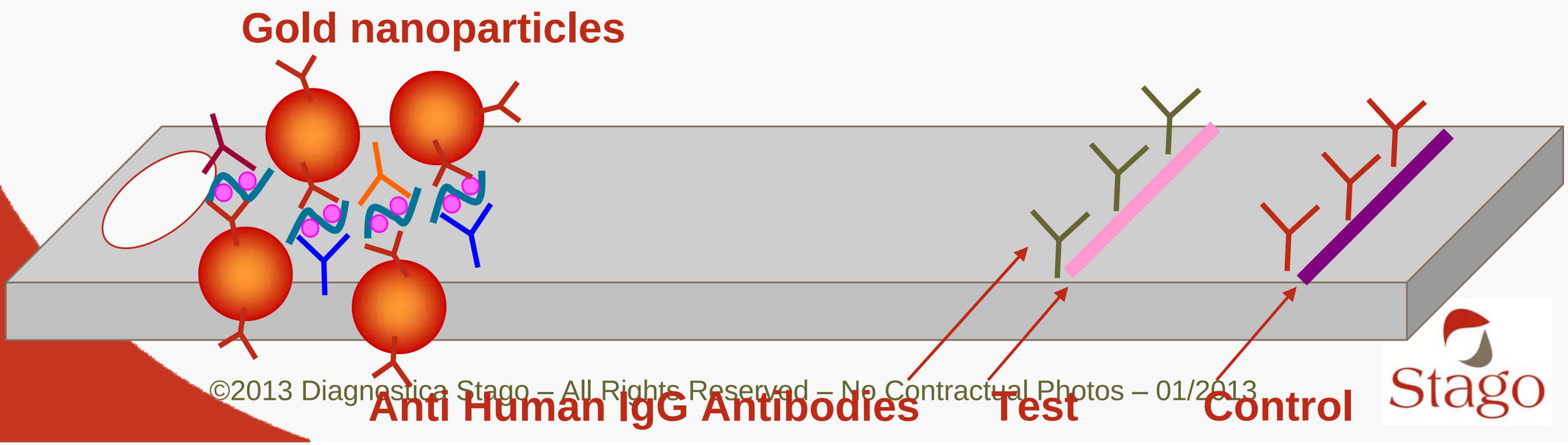
- Lateral-flow immunoassay principle (LFI-HIT) is based on the capillary action which induces a flow of the test sample along a solid phase (test strip).
- The test strip contains a conjugate which is a gold nanoparticle coated with an anti-ligand.
- To the sample pad, 5 µl of the patient's serum/Plasma and two drops of a reagent are added.
- The buffer contains biotynilated human PF4/polyanion (PA) complex.



Principle

Figure

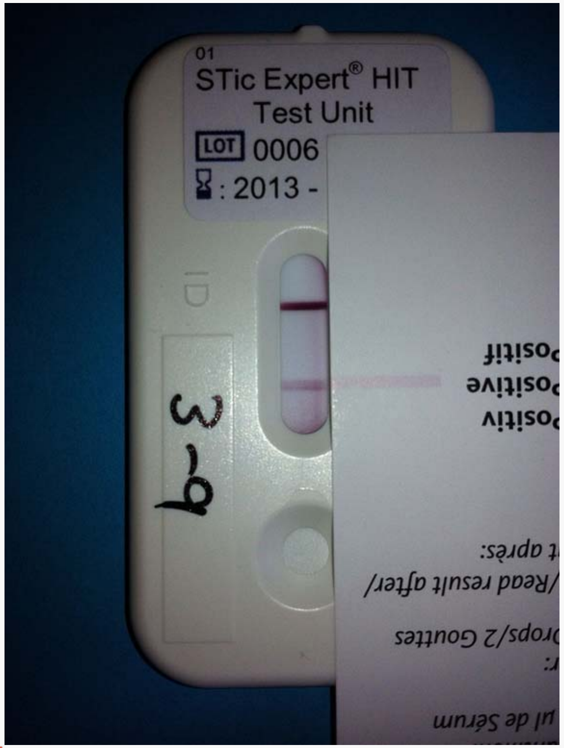
- At the same time, anti-PF4/PA human antibodies (if present) bind to the PF4/PA complexes.
- When the fluid passes the location of the test line on the strip, complexes containing biotinylated PF4/PA, anti-biotin coated gold nanoparticle(s) and human antibodies are retained by an immobilised goat antibody.
- This goat antibody was chosen to allow specific immobilisation of human IgG antibodies (which serves as the capture antibody printed onto the membrane).
- A positive reaction becomes visible as an intensively coloured line can be read visually (test line).
- The test strip also includes a second line (control line). At this location an antibody, which binds specifically to the biotin within the conjugate, is coated onto the test strip. The presence of the control line confirms that the test has performed properly.



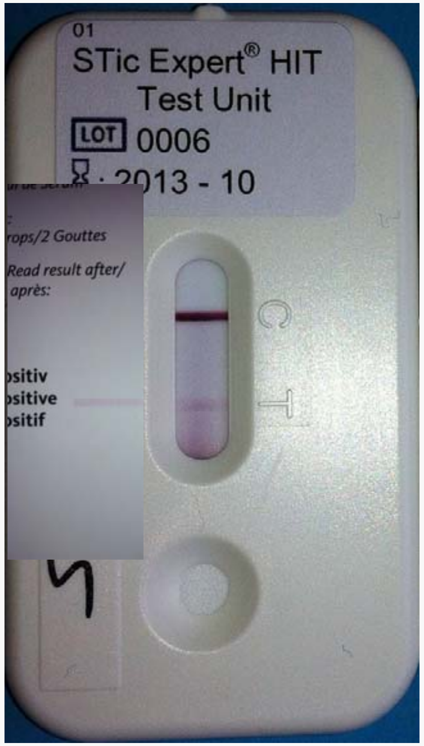
Result interpretation

Compare the test line to the evaluation card

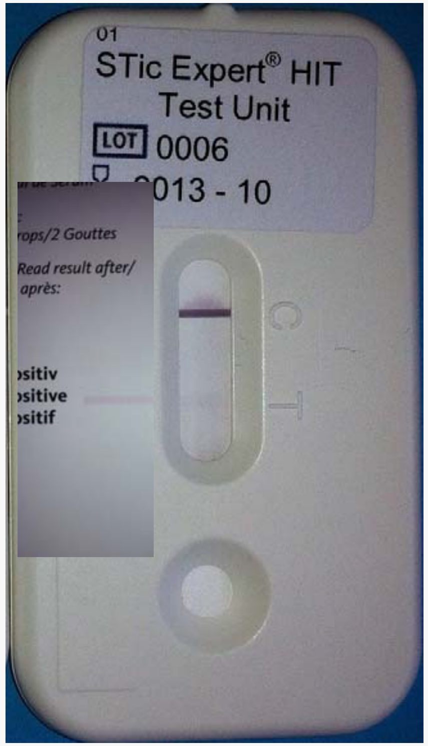
- intensity of the test line a evaluation card → positive
- intensity of the test line ≤ evaluation card → negative



Positive result



Low positive result



Negative result

Evaluation results

Clinical validation

Institute for Clinical Immunology and Transfusion Medicine - University of Giessen, Germany

- **452 surgical and medical patients suspected of HIT (prospective)**
- **Clinical pretest probability**
  - 4T score
- **Immunoassays**
  - ❖ IgG ELISA (GTI & Hyphen)
  - ❖ PaGIA Biorad/Diamed
  - ❖ STic Expert® HIT
- **Functional assay**
  - ❖ HIPA

Results

Test	Negative results		Positive results		Sensitivity	Specificity	NPV	PPV
	true	false	true	false				
STIC Expert	389	0	34	29	1	**0.93**	**1**	0.54
GTI-IgG ELISA	373	0	34	45	1	0.892	1	0.43
Hyphen-IgG ELISA	365	0	34	53	1	0.873	1	0.39
PaGIA	361	3	31	55	0.912	0.868	0.992	0.36
HIPA	**418**		**34**					

- **STic Expert® HIT showed the best performances**
  - NPV: 100 %
  - higher specificity (93%)

Conclusion of the study

- **With STic Expert® HIT***
  - negative individuals do not require additional laboratory testing in order to exclude the diagnosis of HIT
  - enhanced specificity may help to avoid unnecessary confirmatory testing in referral laboratories

***Sachs UJ et al. Evaluation of a new nanoparticle-based lateral-flow immunoassay for the exclusion of heparin-induced thrombocytopenia (HIT). Thromb Haemost. 2011; 106:1197-1202**

Key features summary

Key features

- **Unitary test**
- **Rapid**
- **Easy to use**
- **24/7, STAT adapted**
- **NPV 100%**
- **High specificity**

- *Suitable for **any hospital/lab size***
- *Results in 10 minutes*
- ***No long training** needed*
  Easy interpretation
- *Allows running the test **before deciding** to stop or continue heparin*
- ***Full exclusion of HIT***
  Avoids unnecessary changes of heparin
  *➔**Lower risk** of bleeding*
  *➔**Costs savings** (treatment, add. tests)*
- *Less false positive*
  Reduces over-diagnosis

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Conclusion

- **6~12% of patients investigated for HIT really have HIT**
- **Ruling-out HIT quickly avoids unnecessary changes of heparin**
  - ~90% of suspected patients
  - reduce bleedings risks
  - reduce costs
- **Stago offers a comprehensive range**
  - STic Expert® HIT
  - Asserachrom® HPIA-IgG

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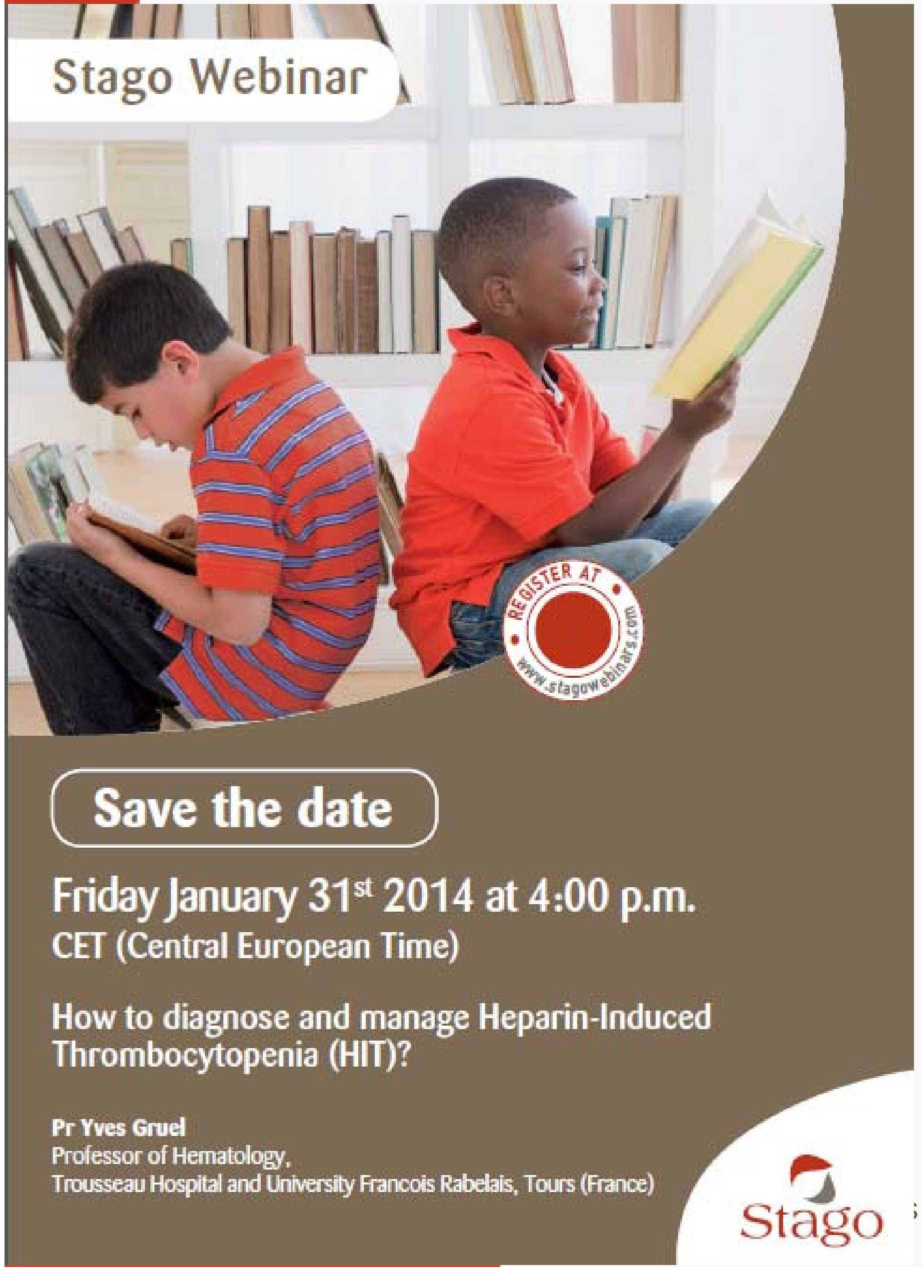
Webinar


Stago Webinar
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Friday January 31st 2014 at 4:00 p.m.
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How to diagnose and manage Heparin-Induced Thrombocytopenia (HIT)?
Pr Yves Gruel
Professor of Hematology,
Trousseau Hospital and University Francois Rabelais, Tours (France)
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CET (Central European Time)
How to diagnose and manage Heparin-Induced Thrombocytopenia (HIT)?
To attend this webinar, please register at www.stagowebinars.com
This 30-minute presentation will be followed by a 15-minute live chat with the speaker

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