

Update:
Heparin-Induced
Thrombocytopenia

Jeremy D Graham, MA, DO

Dr. Graham has indicated that he does not have any relevant financial relationships or affiliations that may have a direct bearing on the subject matter of this CME activity.

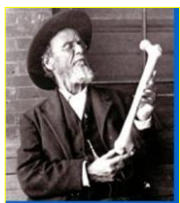
Update:
Heparin-Induced
Thrombocytopenia

Jeremy D Graham, MA, DO
Spokane Society of Internal Medicine
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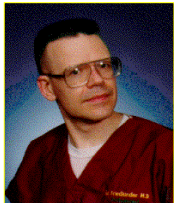
OBJECTIVES:

- Basics of HEPARIN(oid)S
- Define HIT Patholophysiology
- Diagnostic Considerations
- Basics of NON-heparin therapy
- Note key points of ACCP 2008 Guidelines:
 - Monitor for HIT- How and Who
 - Understand warfarin in HIT patients

Heparin and HIT

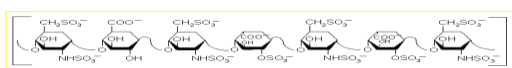


All Drugs Are Poisons

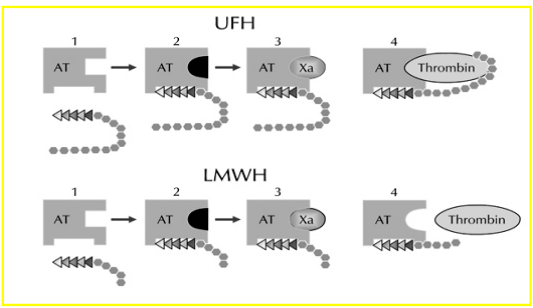


All Poisons are (Potentially) Drugs

Heparin: "Miracle Lubricant?"



Heparins at Work



H.I.T.

Heparin-Induced Thrombocytopenia

Type 1:

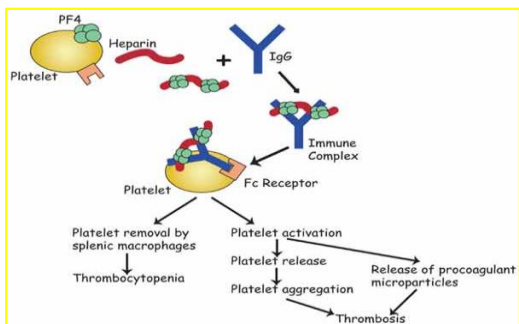
- mild, 2-3 days after starting Heparins
- probably (?) from direct marrow effects

Type 2: True HIT=

Heparin-Induced *THROMBOSIS* Disease

- Antibody-mediated event (usually IgG)
- Much more than just thrombocytopenia!

HIT: Mechanism



HIT: Beyond the low platelets

Of 408 sero-confirmed cases:

- 26% had a clot found *on the day* plts dropped.
- 38% had clot *BEFORE* the plts dropped.

Gruenacher and Warkentin, J Thrombosis, 2005

VENOGRAMS in HIT-Ab(+) patients= 8:1 clot (+)

Warkentin et al NEJM, 1995

Patient has a new clot while on heparin? Think HIT.

Levine et al, Chest, 2006

HIT: Clots and More

Clots may be the *first* sign of HIT

Venous : Arterial = 4:1

Amputate a limb: 20%

Thrombosis → Death: 30%

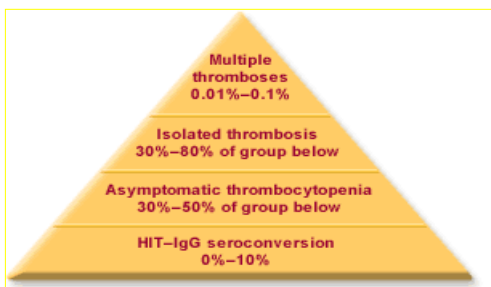
Local injection site destruction present?

= 25% go on to full thrombocytopenia

Acute *systemic* reaction to a dose? (Chills, HTN)

= 25 % go on to full thrombocytopenia

Warkentin et al, Brit J Hematology, 1996



“NON-CLASSIC” HIT

Rapid Onset

Requires prior heparin exposure

Abrupt

Anaphylactoid event upon dosing

Delayed Onset

Poorly understood

Clots / Platelet-drops days to weeks after the exposure

“CLASSIC” HIT RISKS

- A. 5-7 days after starting Heparins
- B. More exposure time → higher occurrence rate
- C. Patient Type Influences Risk:
 1. Ortho Surgery
 2. Cardiac Surgery
 3. FEMALES : MALES (2:1)
 4. Surgical : Medical (7:1)

Warkentin et al, Blood, 2006

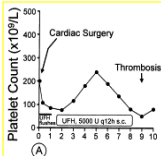
H.I.T. DIAGNOSIS

More difficult than the books suggest...

LOTS of things confound platelets:



- Other drugs
- Infections
- Hemodilution
- Hypercoag state
- Marrow disease
- &
- Post-Op PLT *rises*



RISKS by PATIENT TYPE

RISK CLASS	Rx Type	Dose Level	Ward / Casemix type	% RISK HIT
High	UFH	Proph	Ortho-Trauma	3-5
	UFH	Proph	Cardiac	1-3
	UFH	Therap	Thrombosis TX	1
Intermediate	LMWH	Proph	Post-Sx, Medical	0-0.9
	LMWH	Therap	Thrombosis TX	<1
	UFH	Prophy	Med / ObG	0.8-1
	UFH	FLUSHES	Post-Sx	0.1-1
	UFH <small>(w. LMWH) / UFH<sup>0.06</sup></small>	Prophylactic	Post-Sx, Med, Ob	0.1-1
Low	UFH or LMWH	Proph	Gen PEDS, long-term HD	<0.1
	LMWH	Prophylactic	Medical Obstetric	<0.1
	UFH	FLUSHES	Medical	<0.1

Greinacher, Warkentin et al Blood, 2005

A SCORE SYSTEM: FOUR T'S

Thrombocytopenia

Timing

Thrombosis (or other sequelae)

other causes possible?

NEGATIVE predictive value for low-score patients was good
 POSITIVE predictive value for high-scores unclear (100 vs 21 % !!!)
 * PPV/NPV for intermediate-patients are uninterpretable.

Lo, Juhl, Warkentin et al, J Thromb Hemost, 2006

RISKS by SCORE SYSTEM:
 FOUR T'S

	POINTS		
	0	1	2
Thrombocytopenia	Fall <30% or by <10x10 ⁹ /L	Fall 30-50% or by 10-19x10 ⁹ /L	Fall >50% or by 20-100x10 ⁹ /L
Timing	PLT count fall doesn't follow HEP exposure	Consistent but not clear, or missing data, or AFTER Day 10	Clearly noted between days 5-10, or less than 1 day if HEP exposed in last 100 days
Thrombosis (or other sequelae)	None	Progressive/Recurrent RED skin lesions Suspected clot.	New Clot Skin NECROSED Acute Bolus Reaction
Other causes not apparent.	Definite other cause.	Possible other cause present.	No other cause at all evident.

Warkentin et al, Brit Jrn Hem, 2003

MONITOR FOR HIT:
 ACCP-2008 GUIDELINES

High Risk: PLT Q 2-3 Days from day 4-14.

Intermed: PLT count *if* skin / systemic reactions

Low Risk: PLT monitor "Not Recommended"

ACCP Guidelines (2008)

A. Monitor PLT count if HIT risk > 1% *

B. Suspect HIT if:

1. Heparin in last 2 weeks

AND

2. PLT %50 drop

OR

Clot within 14 days of Heparin start

(even if the Heparin is stopped now!)

Diagnostic Bottom-Line:

IN PTS WITH HEPARIN EXPOSURE:

- **New-onset thrombocytopenia**
- **Arterial/venous clots despite thrombocytopenia**
- **50% drop in platelets**
- **Necrosing skin lesions**
- **Anaphylactoid dose-events**

Should trigger DX concern for HIT

LABS

HIT ANTIBODIES:

For Diagnosis... NOT for screening

ACCP: Don't "screen" with HIT labs.

CAP: Use the lab only when HIT "suspected":

Commercial Solid-Ph assay = inadequately SENSITIVE

Reacts to PF4 plus other anion = inadequately SPECIFIC

Easy to inappropriately DX the presence of HIT!

OTHER LABS: use only to clarify uncertain DX

Serotonin-Release Assay (**preferred*)

Platelet Aggregation

HIT DX / SUSPECTED:

1. STOP the heparins (duh)
 ...but around 50% will clot without further tx!

(38-76%) Warkentin et al, Arch Int Med, 2004

2. Put the HEPARIN on their "ALLERGY" List
3. Replace with a NON-HEPARIN
 ACCP 2008: EVEN if PLTs still over 150
4. ULTRASOUND LEGS (same day!)

NON-Heparin Therapy:



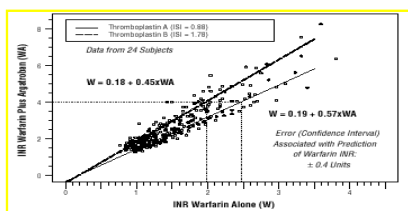
NON-Heparin Options:

DTPs Lepirudin Argatroban Bivalirudin	Fondaparinux	Gp2a3b TPA Plasmapheresis Arvin ASA/Clotpidigrel	Warfarin

Notes on WARFARIN

- New HIT DX while **ON** Warfarin?
 ACCP-2008 : **REVERSE** WITH Vit K 10mg PO
- Start Warfarin **ONLY AFTER** PLTs Normalize
- Overlap warfarin with the DTI by probably 5 days
 (overlap at a **therapeutic INR** * > 48 hrs)

*DTIs and INR:



BOTTOM LINE -- WHEN COUMADINIZING:

1. Overlap with DTI for at LEAST 48 hours on an adequate INR
2. For Argatroban: use the prescribing formula to correct the INR, OR:
 just dose to an **INR = 4** before stopping the Argatroban.

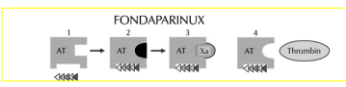
Direct Thrombin (Xa) Inhibitors

Drug	Indication	Metabolism
Lepirudin	HIT	Renal
Argatroban	HIT PCI in HIT-risk pts	Liver
Bivalirudin	PCI in HIT-risk pts	Plasma

Notes on DTIs:

- Titrate to a goal PTT 1.5-2xNL for Lepirudin, or 1.5-3xNL for Argatroban
- HAVE NO ANTIDOTES! Especially important for Lepirudin.

FONDAPARINUX



Pentasaccharide heparin(oid)
Evidence Level: Case reports/ Anecdotal
H.I.T. = off-label use at present



THE BOTTOM LINE:

- Keep High **SUSPICION**
- Consider the **4T Score**
- Consider the **Pt-Risk Category**
- Consider using lab testing
- But realize their **inadequacies.**
- Track **PLTS QOD** on Heparins on intermediate & high risk pts
- Suspect **HIT?**
- STOP ALL** heparins
- ADD** an active substitute
- Start Warfarins **Thoughtfully**

