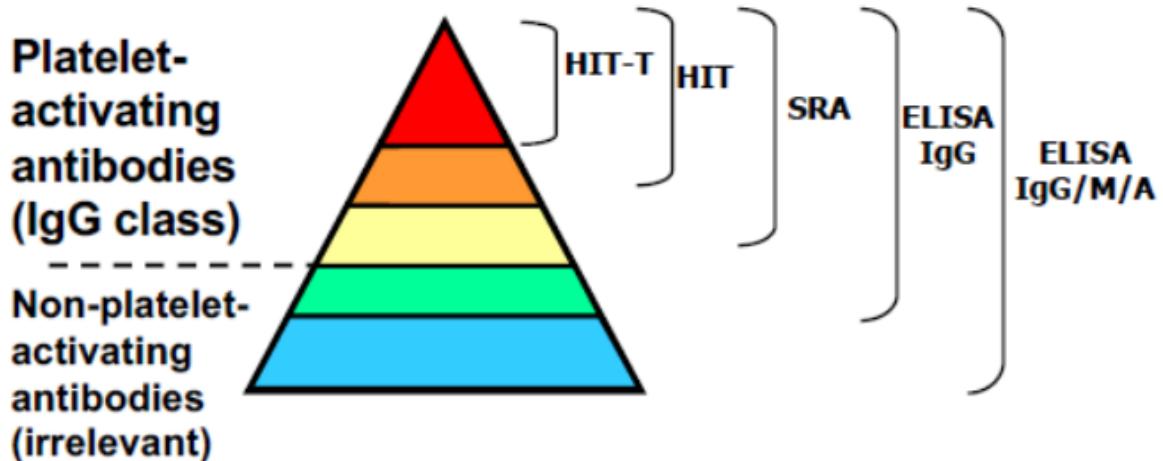


Heparin Induced Thrombocytopenia HIT HITT (fellow)

Concepts

- A clinical + pathological entity



- Clinical: onset of thrombocytopenia 5 days after exposure to heparin
- Pathological: Detect platelet activating IgG against PF4
- Thrombosis despite thrombocytopenia
- Thrombosis despite anticoagulation
- Stopping heparin is not enough
- Warfarin treatment is BAD

SUMMARY

13 PEARLS

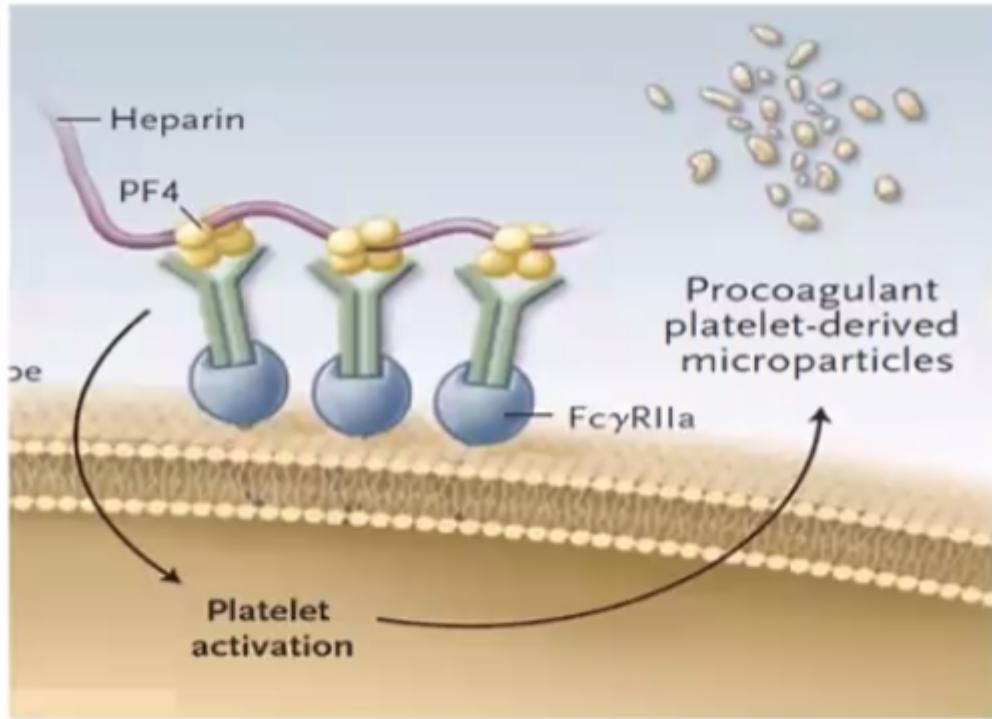
- #01 HIT is a clinical-pathological disorder
- #02 HIT is caused by IgG platelet-activating anti-PF4 antibodies
- #03 PF4 is a highly cationic, tetrameric protein (multivalent antigens)
- #04 Only a subset of anti-PF4 antibodies is plt-activating ("iceberg")
- #05 PF4-dependent ELISAs have high (>99%) sensitivity for HIT
- #06 Higher ELISA OD values predict for higher probability of HIT
- #07 Platelet activation assays (SRA) have high (>90%) specificity for HIT
- #08 PF4 supplementation increases SRA sensitivity ("SRA-negative HIT")
- #09 Heparin-independent platelet act'n (at 0 U/mL heparin) indicates aHIT
- #10 Rapid HIT assays (e.g., LIA, CLIA) provide real-time diagnostic info
- #11 Latex immunoturbidimetric assay (LIA) has ~95% Se/~95% Sp (<1hr)
- #12 VITT—resembles HIT—ELISA strong-pos and SRA-pos (added PF4)



Pathogenesis

Etiology

- Activating anti-PF4:heparin antibodies (~5 days post-exposure)
- Fc's bind same/adjacent plts via $Fc_{\gamma}RII_A$ → further activation → PF4 release
- Clearance of IgG-coated platelets via RES +/- clot thrombocytopenia



- PF4 is highly cationic++++
- Hence it can create lots of antibody-antigen complexes with anion proteins like heparin

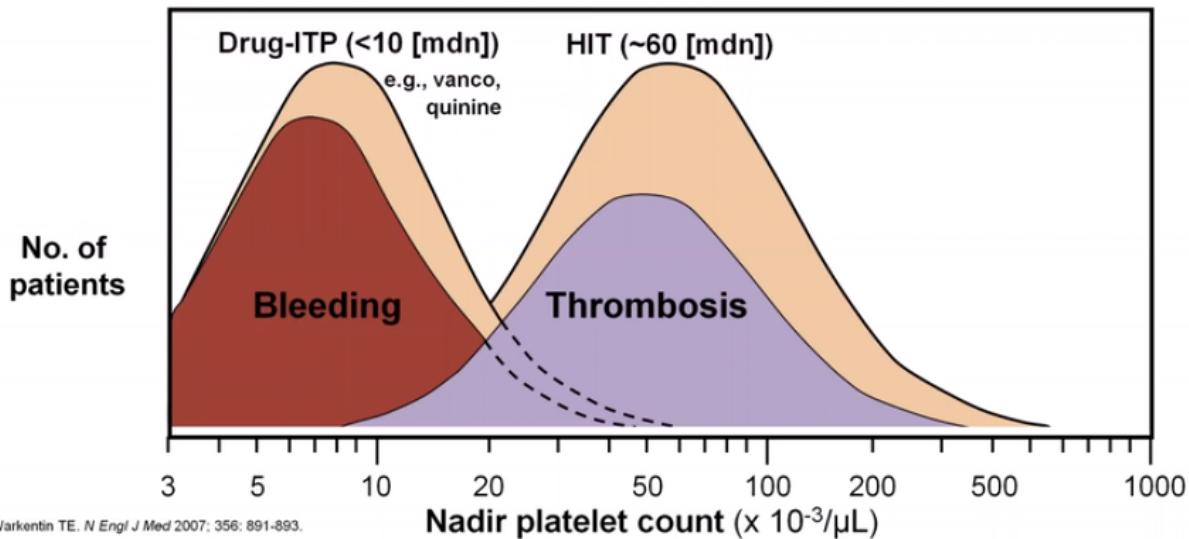
PF4 is a highly cationic (++) tetrameric protein (potential for multivalent epitopes)

- Forms multi-molecular large complexes which are intensely platelet activating

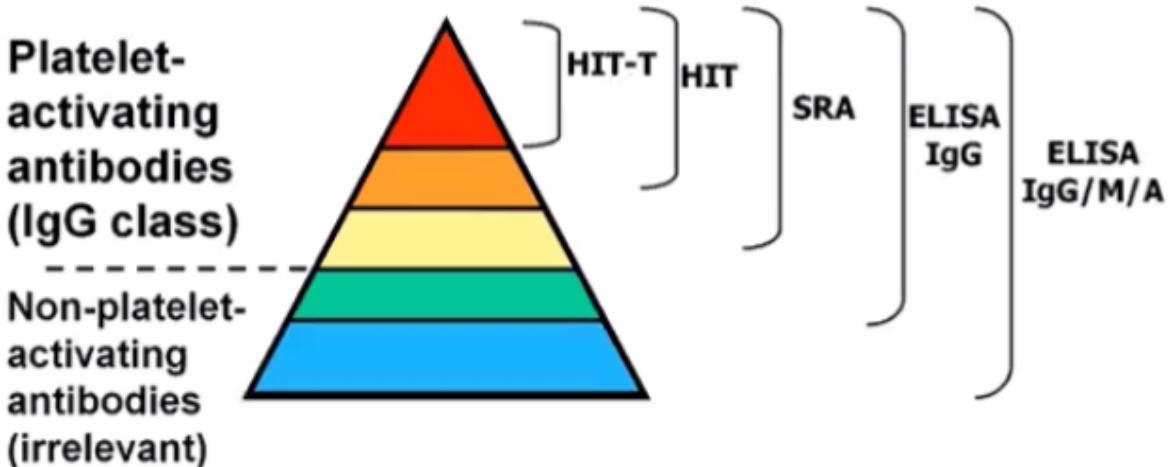


- 1:1 ratio of PF4-tetramer and Heparin is what most drives platelet activation, e.g. with supra-therapeutic levels, you may actually have a lower risk than with a bolus (so you may develop antibodies but may not develop HIT if the ratio isn't 1:1!)
- Pancellular activation, many different types of cells (monocytes, etc activated)

D-ITP vs HIT: clinical picture/pathogenesis



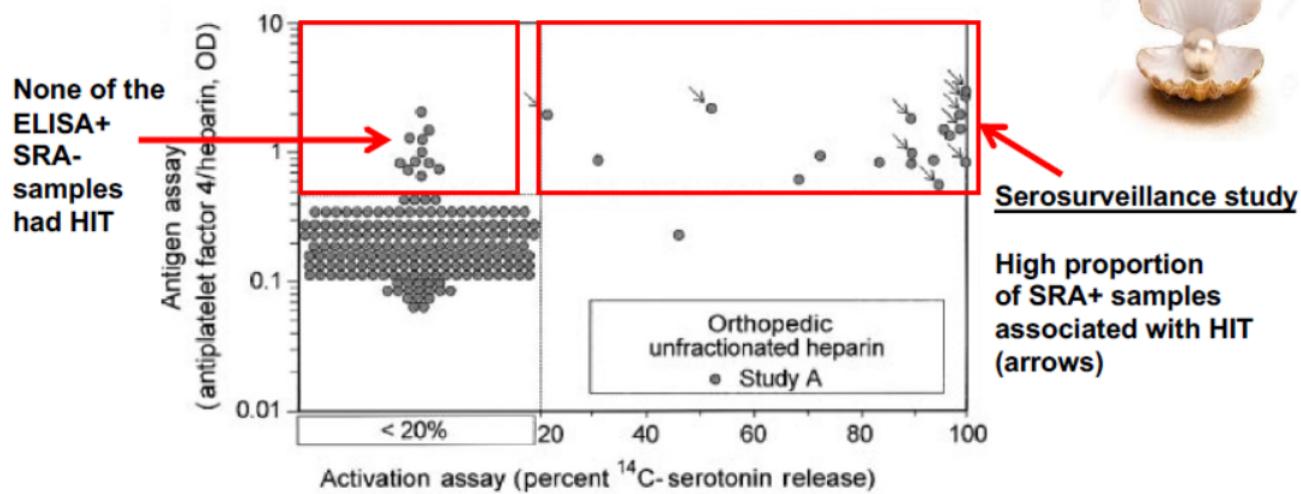
- Warkentin TE. *N Engl J Med* 2007; 356: 891-893.
- in other drug ITP, the drug-glycoprotein complex is recognized on a platelet and leads to direct clearance of platelets (not via activation, which is HIT!! and that stimulus varies in strength, same for sepsis)
- Immune mediated – Abs against heparin/plt factor 4 complex
- Type 2: Day 5-10. Binding of antibody to platelets leads to platelet activation and aggregation which leads to clearance (thrombocytopenia) and thrombosis.
- Type 1: Day 1-2. Non-immune platelet activation by Heparin binding to G2b3a. Lesser fall in plts on day 1-2 after starting treatment, counts recover even on continued heparin. Not clinically important
- Autoimmune HIT: PF4+polyanion complex, which does not have to be heparin, and these antibodies are in very high titres
- Incidence – 0.2-5% if on UFH >4days
- Thrombosis in 50%, bleeding is rare
- ICEBERG model



- Lots of PF4 antibodies don't cause HIT!
- Only 10% of people with HIT antibodies develop HIT

Platelet activation assays (e.g., SRA) have high (>90%) diagnostic specificity for HIT

#7



Can cause DIC and therefore schistocytosis!

Types of HIT

**

**

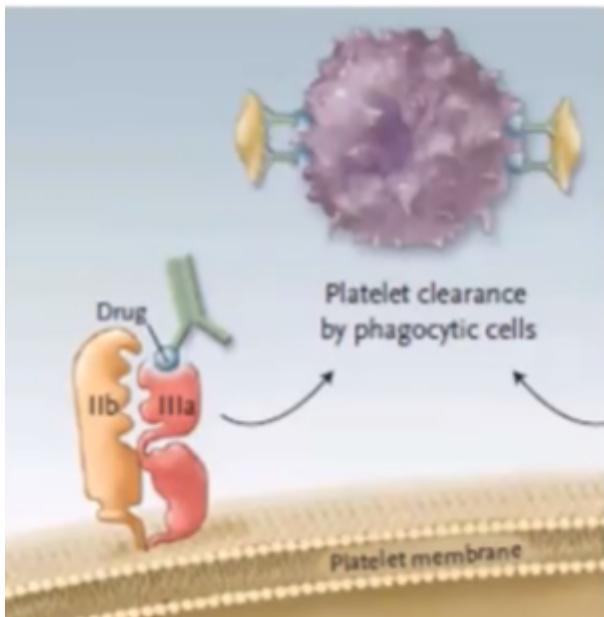
Subtypes:

**

**

Type 1 HIT = non-immune platelet aggregation (mild), occurs within 2 days of heparin start

Type 1 HIT has macrophagic clearance of platelets



Type 2 HIT = antibody associated, more severe

Type 1 HIT

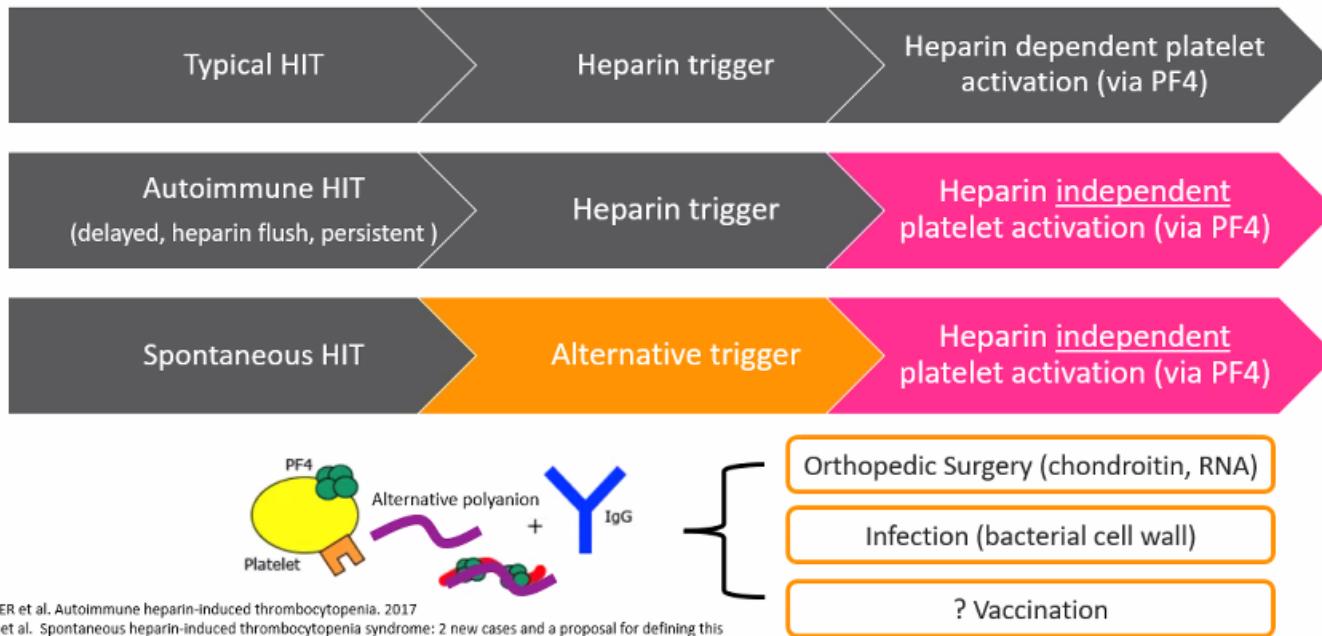
- Non-immune platelet aggregation
- Mild transient platelet drop
- Occurs within 2 days of heparin start
- Platelet counts normalize with continued heparin
- Not clinically significant

Type 2 HIT

- Antibodies against PF4/heparin
- Mean platelet drop to 60s
- Occurs 5-10 days after heparin start
- Associated with venous and arterial thrombosis
- Requires discontinuation of heparin anticoagulant

Clinical Subtypes

Alternative HIT (AHIT, SHIT, VITT/ VIPIT)



- HIT
- Delayed onset HIT
- Persistent HIT
- Autoimmune HIT
- Spontaneous HIT
- severe HIT (platelet count of $< 20 \times 10^9 \text{ L}^{-1}$) with associated disseminated intravascular coagulation (DIC)
- Heparin Flush HIT

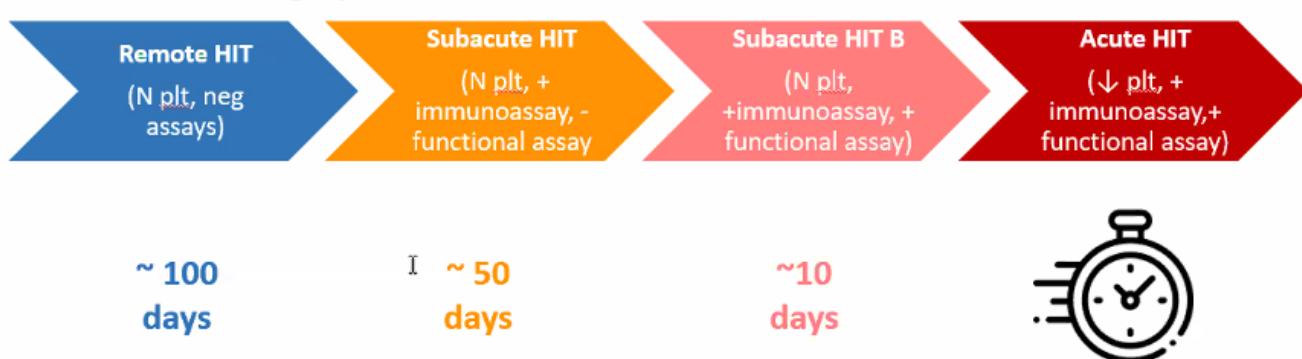
Table 1 Autoimmune heparin-induced thrombocytopenia (aHIT) syndromes

Clinical entity	Description
Delayed-onset HIT	HIT that begins or worsens after stopping of heparin
Persisting HIT	HIT that persists for > 1 week despite stopping of heparin
Spontaneous HIT syndrome	HIT without proximate heparin exposure
Flush heparin HIT	HIT induced by exposure to heparin flushes
Fondaparinux-associated HIT	HIT that is believed to be triggered by exposure to fondaparinux
Severe HIT (e.g. platelet count of $< 20 \times 10^9 \text{ L}^{-1}$ with overt DIC)	Overt HIT-associated DIC defined as proven HIT with one or more of the following: relative/absolute hypofibrinogenemia, elevated INR (without another explanation), and normoblastemia (circulating nucleated red blood cells)

DIC, disseminated intravascular coagulation; INR, International Normalized Ratio.

Natural History

- Suspected HIT
 - Platelets low
 - Testing pending
- Acute HIT
 - Platelets low
 - Testing positive
- Subacute HIT
 - Platelets recovered
 - Testing remains positive
- Remote HIT
 - Platelets recovered
 - Testing returns negative



Platelets recover by 3-4 days, recovery by 7-10 days

Platelets have a median of 60 in HIT

Risk Factors

- UFH >LMWH by 5-10x, extremely rare with fondaparinux
- Some dose dependency
- Post-op > medical > pediatric/obstetric
 - 3-5% with 10 + days of heparin
- Cardiovascular surgery
- Female 2x
- LOW incidence in ICU: ~0.5%

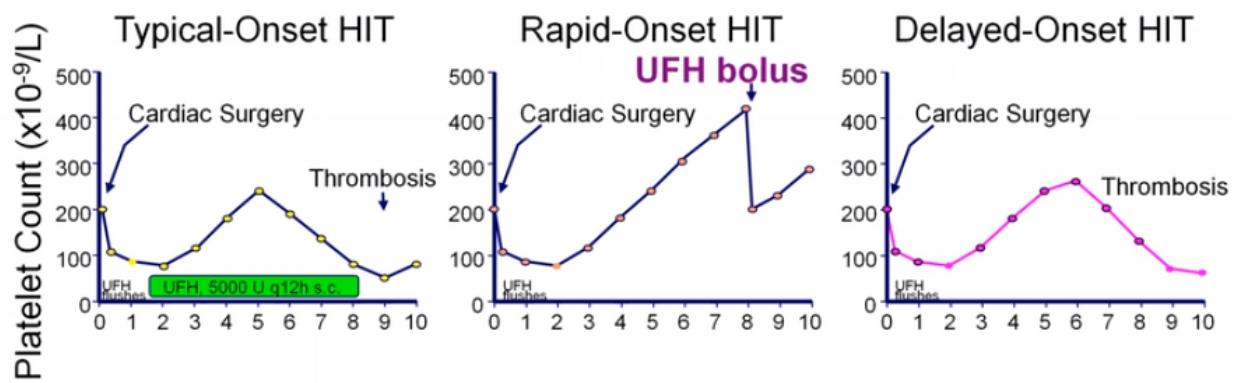
Sources of Heparin in Hospital

- Stem Cells suspended in Heparin
- PCC

- TPN
- Flushes for IV lines and flows
- Therapeutic heparin / prophylactic heparin

Clinical Features – A Clinico-Pathological Diagnosis

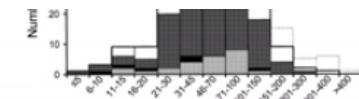
- **Onset** – usually 5-10 days after initiation, day 0 is day of heparin exposure
 - Typical onset of HIT, even with prior exposure, is the SAME, 5-10 days, i.e. no immune memory for HIT! (HIT ab's are transient, and not detectable on SRA after about 100 days), so it's not *necessarily* that it will recur in the future. *Repeat heparin exposure is generally SAFE!!*
 - Risk of repeat HIT in a patient is about 5%
 - Rapid Onset HIT = abruptly within 1 day! But, does not have to do with immune memory, but rather **recent** (within 100 days) exposure to heparin. *check if the patient got heparin within the past few weeks*



- Unusual >14 days , but delayed onset possible, especially with long term LMWH
- Exceptions: rapid-onset HIT in patients with recent exposure and pre-existing HIT, which manifests within hours of re-exposure
- Exception: 2-3 weeks after prior exposure, even after heparin is not present (antibody auto-reactivity)
- **Platelet count –**
 - large drop, but to a moderate degree, generally >20 , median nadir 60. (unlike ITP and post transfusion)....***classically 50%**** drop but nadir $> 20^*$
 - The baseline is the 'highest platelet count RIGHT before platelet count fall', i.e. after getting heparin, but before platelet drop, to account for post-op thrombocytosis/etc
 - Begins day during 5-10 window
 - Bleeding uncommon
- **Thrombosis** – venous, arterial, external circuits 1100-1400% increase in baseline risk of thrombosis
 - 75% of all patients get thrombosis!! 50% at first diagnosis, 50% of the remaining will develop it without treatment
 - 4:1 ratio of venous to arterial thrombosis
 - watch for bilateral adrenal necrosis!

- VENOUS: Deep-vein thrombosis (~50% of HIT)
 - Lower-limb (most common HIT event) ~30-50%
 - Upper-limb (catheter-associated) ~5-10%
 - Adrenal necrosis/hemorrh. ~2-3% (adrenal vein thrombosis; bilat → adrenal failure)
 - Cerebral venous (sinus) thrombosis (CVST) ~1%
 - Mesenteric/portal vein thrombosis ~1%
- VENOUS: Pulmonary embolism (~25% of HIT)
- ARTERIAL (10-15% of HIT)
 - Limb artery ~5-10%
 - Cerebral artery (stroke) ~3-5%
 - Myocardial infarction ~2-3%
 - Miscellaneous (mesenteric, radial, renal, etc. artery) ~1%
- Necrotizing skin lesions (at heparin injection sites) rare

• Warkentin et al. Br J Haematol 2003; 121: 535-555.



Ratio
Venous:Arterial
~4:1



- Skin necrosis – heparin-dependent abs present, often plt normal.
 - Usually in fat rich areas, also distal extremities or nose.
- Anaphylactoid reactions (post-UFH bolus)
 - 5-30 minutes post-bolus
 - can actually result in abrupt platelet count fall post-bolus, with symptoms of tachycardia, rigors.
 - can be severe with ARDS, cardiac arrest, transient global amnesia
- Fevers
- Unusual complications – adrenal hemorrhage, transient global amnesia

Rule out other causes

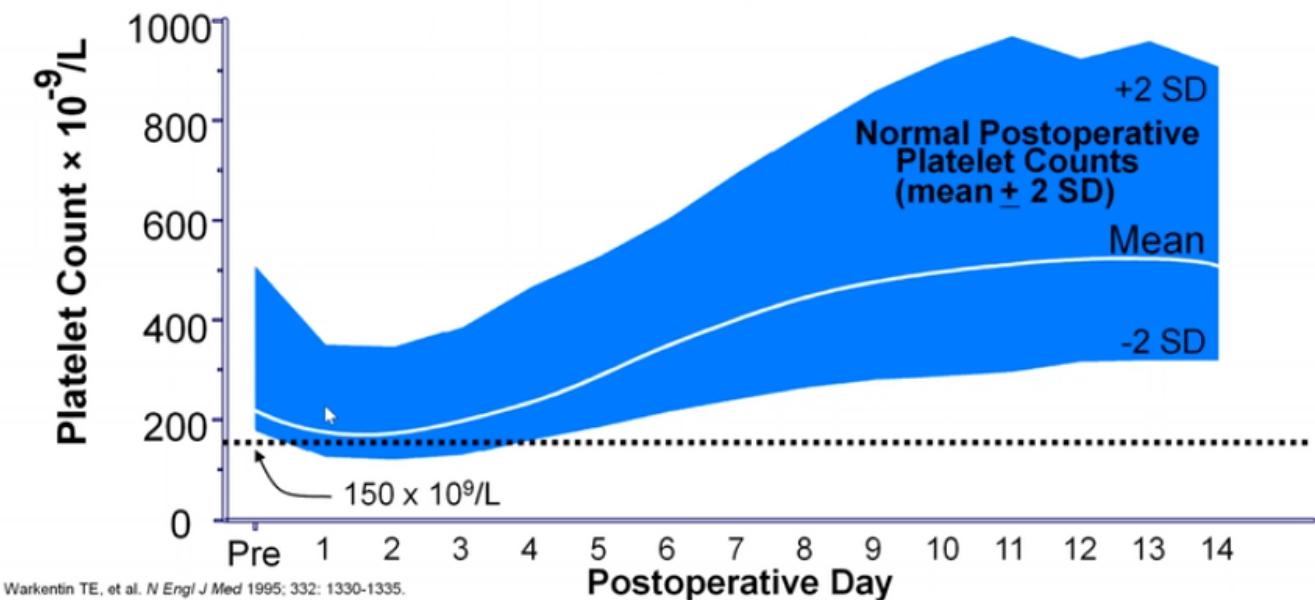
Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*

Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immuno-suppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

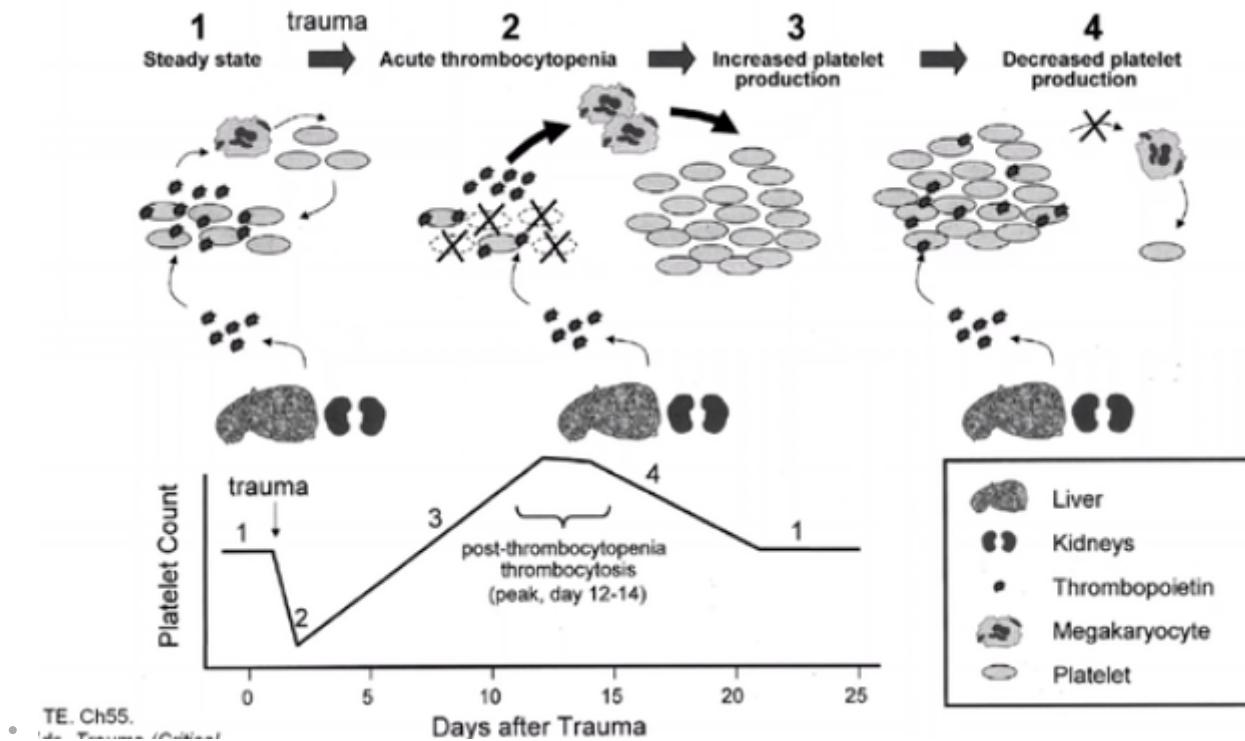
* For a more extensive list, see Aster,² Warkentin,¹² and George et al.¹³ and the University of Oklahoma Web site (<http://moon.ouhsc.edu/jgeorge/DITP.html>).

HIT vs. Post-Op Thrombocytosis

Postoperative Thrombocytosis



- Surgery leads to plt count drop, followed by TPO production increase, followed by platelet production and thrombocytosis
- TPO level are elevated usually around 5-10 days, leading to an 'overshooting' of platelet levels



Diagnosis

**

**

- Suspect if thrombocytopenia (absolute or drop >50%), new clot, necrotic skin lesions, anaphylactoid reaction after IV heparin

- Clinical diagnosis initially given high morbidity and slow testing
- Potential clues

Risk factors

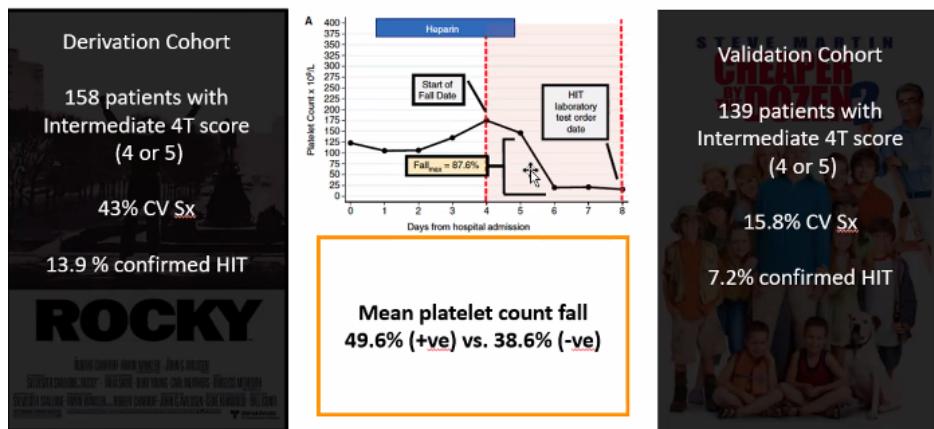
- UFH > LMWH
- therapeutic dose > prophylaxis dose
- surgery > medicine > OB
- Old > young
- Female > Male

Speed of platelet decline

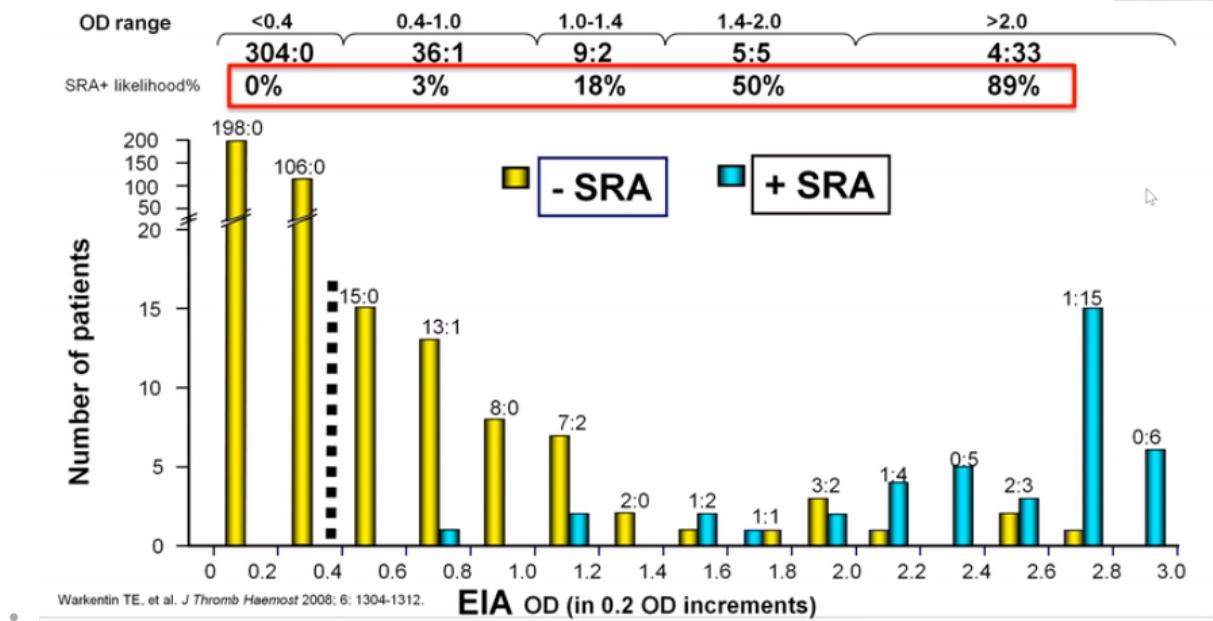
- 24h drop greater than 30%

Maximum 24-hour platelet count fall: Metric for improving the diagnosis of heparin-induced thrombocytopenia among patients with intermediate probability 4Ts scores

Daniel S. Lefler¹ | Adam Cuker^{1,2} | Lori-Ann Linkins³ | Theodore E. Warkentin^{3,4} | Allyson M. Pishko¹ |  



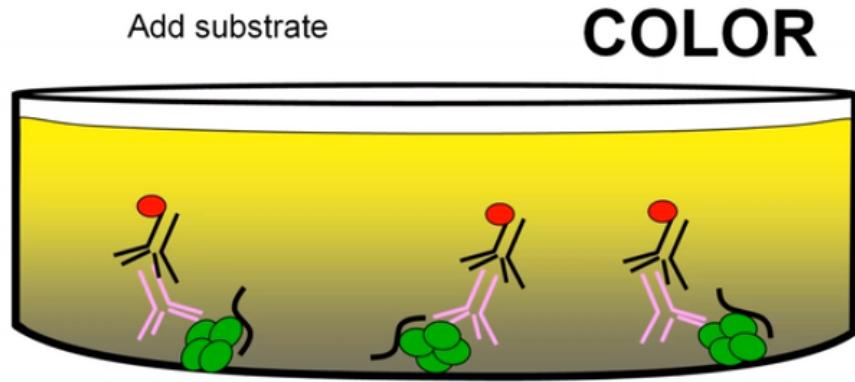
- HIT assay (antibody test)
 - Only tests if antibody present
 - 80% specific
 - ELISA/EIA test – Heparin/PF4 complexes react with heparin dependent Abs from pt.
 - Detects the antibody, doesn't tell you if it's platelet activating
 - Strongly positive ELISA makes it more likely to have a + SRA!



- weakly positive elias's are not therefor so important
- Monospecific** assays for IgG are more specific (than **polyspecific** which look at all of IgG, IgA, IgM)

PF4/polyanion EIA

IgG/IgA/IgM
or IgG
(more
specific)



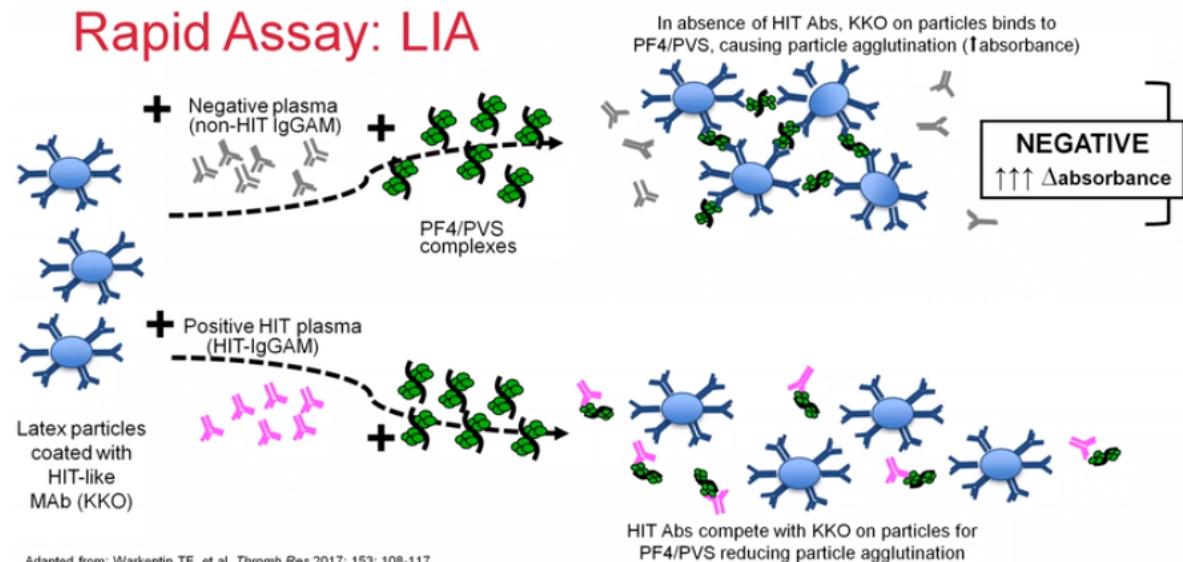
- Sensitive >97%, less specific
- False positive: Vancomycin
- SRA (functional assay)
 - serotonin release assay....labelled plt's exposed to pt's serum can cause plt activation and release of labelled serotonin
 - Gold standard – Sn > 95%, sp >95%

CONCEPT:

adding PF4 enhances detection of platelet-activating anti-PF4 antibodies

- RAPID assays

- Latex immununoturbidimetric assay - LIA - latex agglutination, requires plasma, highly sensitive and specific, semi-quantitative (units per ml)



- Chemiluminescent immunoassay - CLIA (IgG specific, extremely sensitive and specific, semi-quantitative)

Rapid HIT assays (LIA, CLIA) provide real-time diagnostic information

**Results within 1 hour (if instrument available in hospital)
— on demand**

Werfen (Instrumentation Laboratory)

LIA = latex-enhanced immunoturbidimetric assay

CLIA = chemiluminescence immunoassay (IgG-specific)

- sensitivity and specificity of about 95%!

HIT SCORE or 4T score

- Thrombocytopenia
 - 50% drop and nadir >20: 2 points
 - 30-50% or nadir 10-19: 1 point
 - <30% or nadir <10: 0 points
 - Typically no lower than 20ish, which can happen in PTP, ITP
 - Can be overall a normal count!!

- Timing
 - Clear Onset of fall at day 5-10 (or day <=1 if prior heparin within last 30 days) : 2
 - c/w Onset of fall at day 5-10 (or day <=1 if prior heparin within last 30-100 days), or onset >day 10: 1 point
 - fall <4 days with no recent exposure: 0 points
- Thrombosis
 - confirmed new thrombosis, skin necrosis or anaphylactoid infusion rxn: 2 points
 - Progressive/recurrent clot, non necrotizing skin lesion, suspected clot: 1 point
 - None: 0
- Other causes of low plt
 - None: 2 points
 - Possible: 1
 - Definite: 0

Table 3. Estimating the pretest probability of heparin-induced thrombocytopenia: the four Ts

	Point		
	2	1	0
Thrombocytopenia	> 50% fall or nadir 20 to 100	30% to 50% fall or platelet nadir 10 to 19 $\times 10^9/L$	Fall < 30% or platelet nadir < 10 $\times 10^9/L$
Timing of platelet count fall or other sequelae	Clear onset between days 5 to 10 or less than 1 day (if recent heparin exposure [past 100 days])	Consistent with immunization but not clear (eg, missing platelet counts) or onset of thrombocytopenia after day 10	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (eg, skin lesions)	New thrombosis; skin necrosis; post-heparin bolus ASR	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
Pretest probability score:	6 to 8 = high; 4 to 5 = intermediate; 0 to 3 = low		

*Points 0, 1, or 2 for each of four categories; maximum score possible is 8.

[†]First day of immunizing heparin exposure considered day zero; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1 to 3 more days until an arbitrary threshold that defines thrombocytopenia is passed).

ASR—acute systemic reaction.

The author acknowledges the contribution of Professor Ben H. Chong (Chairman, Platelet Immunology Scientific and Standardization Committee, International Society on Thrombosis and Haemostasis) in initiating this discussion toward developing a scoring system that takes into account clinical and laboratory criteria in arriving at a diagnosis of heparin-induced thrombocytopenia.

- Warkentin TE, Heddle NM. *Curr Hematol Rep* 2003; 2: 148-157; 4Ts validation study = Lo GK, Juhl D, Warkentin TE, et al. *J Thromb Haemost* 2006; 4: 759-765.

Score:

- 0-3 =low (1%)
- 4-5 = intermediate (10%)
- 6-8 = high (35%)

HEP Score (Better for ICU)

Select Criteria:

Fall in Platelet Count from Peak Platelet Count to the Nadir Platelet Count since Heparin Exposure	
<input type="radio"/> <30%	-1 Point
<input type="radio"/> 30% - 50%	1 Point
<input type="radio"/> >50%	3 Points
Timing of the Fall in Platelet Count	
i. For patients in whom typical onset HIT is suspected	
<input type="radio"/> Fall in platelet count occurs <4 days after exposure to heparin	-2 Points
<input type="radio"/> Fall in platelet count occurs 4 days after exposure to heparin	2 Points
<input type="radio"/> Fall in platelet count occurs 5-10 days after exposure to heparin	3 Points
<input type="radio"/> Fall in platelet count occurs 11-14 days after exposure to heparin	2 Points
<input type="radio"/> Fall in platelet count occurs >14 days after exposure to heparin	-1 Point
ii. For patients with previous Heparin exposure within 100 days and in whom rapid onset HIT is suspected	
<input type="radio"/> Fall in platelet count occurs <48 hrs after exposure to heparin	2 Points
<input type="radio"/> Fall in platelet count occurs >48 hrs after exposure to heparin	-1 Point
Nadir Platelet Count	
<input type="radio"/> $\leq 20 \times 10^9/L$	-2 Points
<input type="radio"/> $>20 \times 10^9/L$	2 Points
Thrombosis	
i. For patients in whom typical onset HIT is suspected	
<input type="radio"/> New venous or arterial thrombosis ≥4 days after heparin exposure	3 Points
<input type="radio"/> Progression of venous or arterial thrombosis whilst receiving heparin	2 Points
ii. For patients with previous Heparin exposure within 100 days and in whom rapid onset HIT is suspected	
<input type="radio"/> New venous or arterial thrombosis ≥4 days after heparin exposure	3 Points
<input type="radio"/> Progression of venous or arterial thrombosis whilst receiving heparin	2 Points
Skin necrosis at subcutaneous Heparin Injections site[s]	
<input type="radio"/> Yes	3 Points
<input type="radio"/> No	0 Points
Acute Systemic Reaction after iv Heparin infusion	
<input type="radio"/> Yes	2 Points
<input type="radio"/> No	0 Points
Bleeding [Bleeding/petechiae or bruising]	
<input type="radio"/> Yes	-1 Point
<input type="radio"/> No	0 Points
Other causes of Thrombocytopaenia not evident [Select all that apply]	
<input type="radio"/> Presence of a chronic thrombocytopenic disorder	-1 Point
<input type="radio"/> Newly commenced treatment [non-heparin] known to cause thrombocytopaenia	-2 Points
<input type="radio"/> Severe infection	-2 Points
<input type="radio"/> DIC [Fibrinogen <1g/L & D-dimer >5.0µg/mL]	-2 Points
<input type="radio"/> Indwelling arterial device	-2 Points
<input type="radio"/> Cardiopulmonary bypass within 96hr	-1 Point
<input type="radio"/> No other cause identified	3 Points

Treatment

**

**

General

- Treat if intermediate or high pretest probability
- DON'T
 - Don't give Warfarin, and REVERSE if already on it. **HIT is a risk factor for coumadin induced necrosis**
 - Warfarin reduces protein C (so absence of natural anti-coagulant). It meanwhile does not turn off thrombin, raises PTT (confounds treatment) so you confound anticoagulation, **and long half life**

- No prophylactic platelet transfusions
- **Check for bilateral lower limb DVTs**
- **Stop all heparin containing products** (consider line locks, dialysis etc as other sources)

Anticoagulation

- **Initial treatment**

- Uncomplicated → Fondaparinux full dose
- Need for rapid reversal → Argatroban
- Bleeding risk and acute clot → Argatroban
- Bleeding risk and no clot → Fondaparinux prophylaxis → Argatroban if HIT confirmed
- Pregnancy → Danaparoid

I

- **Subacute treatment**

- Uncomplicated → DOAC
- Arterial disease or other high risk features → Warfarin

Treating HIT in the ICU

Approved doses are generally WAY to high

- **Argatroban** (2 mcg/kg/min): I start at ~0.2 mcg/kg/min
 - Titrate to aPTT 1.5-2.5x baseline (60 to 99 ish)
- **Bivalirudin** (0.15 mg/kg/hr): I start at ~0.08 mg/kg/hr
 - Titrate to aPTT 1.5-2.5x baseline (60 to 99 ish)
- **Fondaparinux** - Use limited in ICU due to renal clearance and long half life



Selection of non-heparin anticoagulation & other therapies

Anticoagulation selection in Acute HIT

Dependent on 4 clinical criteria

- Agent is preferred
- Agent is not preferred, but can be considered based on availability, risk/benefit
- Agent is not recommended

Laboratory monitoring required

* Existing data with rivaroxaban, apixaban

^ If argatroban not available, can use with close monitoring due to accumulation risk

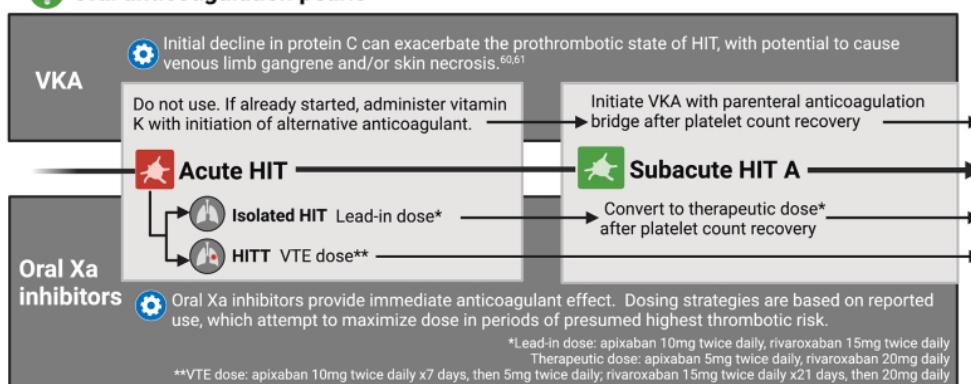
* Trivial risk of reported HIT,⁵⁴ but has been demonstrated to be safe for use in acute HIT^{55,56}

~ Use in renal dysfunction has been reported^{57,58}

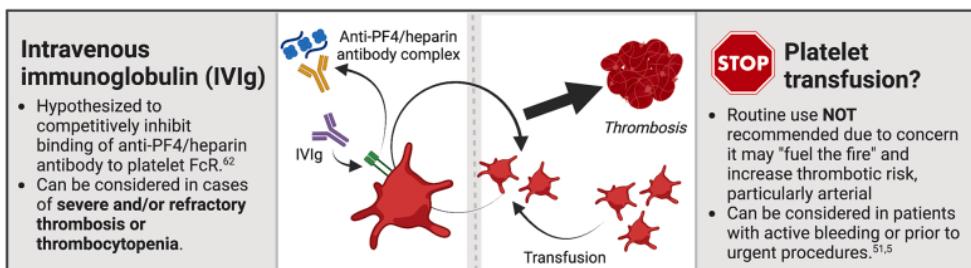
	1) Clinically unstable	2) Life- or limb-threatening ischemia	3) Renal dysfunction CrCl <30ml/min	4) Liver dysfunction Bili >1.5mg/dL
Oral	Oral Xa inhibitors*	●	●	●
	Vitamin K antagonist (VKA)	●	●	●
IV	Argatroban	●	●	●
	Bivalirudin	●	●	^
SQ	Danaparoid	●	●	●
	Fondaparinux ^o	●	●	~

Bili, bilirubin; CrCl, creatinine clearance; IV, intravenous; SQ, subcutaneous

Oral anticoagulation pearls^{51,59}



Additional treatment considerations



- Agents

Anticoagulant (mechanism, route)	Dosing	Clearance & Monitoring
Argatroban (direct thrombin inhibitor) IV	Bolus: None Infusion: STANDARD (2 mcg/kg/min), REDUCED DOSE for liver dysfunction, CHF, post-cardiac surgery (0.5-1.2 mcg/kg/min)	<ul style="list-style-type: none"> Hepatobiliary clearance Adjusted to aPTT 1.5-3.0 times baseline
Bivalirudin (direct thrombin inhibitor) IV	Bolus: None Infusion: STANDARD (0.15 mg/kg/hr); consider REDUCED DOSE for renal or liver dysfunction	<ul style="list-style-type: none"> Enzymatic clearance Adjusted to aPTT 1.5-2.5 times baseline
Danaparoid (indirect Xa inhibitor) IV	Bolus: Weight-based (1500-3750 units) Infusion: INITIAL ACCELERATED (400 units/hr x 4 hr, then 300 units/hr x 4 hr), then MAINTENANCE (150-200 units/hr)	<ul style="list-style-type: none"> Renal clearance Adjusted to anti-Xa activity 0.5-0.8 units/mL
Fondaparinux (indirect Xa inhibitor) SC	< 50 kg → 5 kg daily 50-100 kg → 7.5 mg daily > 100 kg → 10 mg daily	<ul style="list-style-type: none"> Renal clearance No monitoring
Rivaroxaban (direct Xa inhibitor) PO	HITT: 15 mg twice daily x 3 weeks, then 20 mg daily Isolated HIT: 15 mg twice daily until platelet count recovery (≥ 150)	<ul style="list-style-type: none"> Renal clearance No monitoring

- **Use direct thrombin inhibitors** (even if no clot as risk of thrombosis high) -- downside is they are all PTT adjusted (but can be unreliable due to liver disease, DIC, etc)
 - Lepirudin (direct thrombin inhibitor) – avoid in renal failure, follow PTT
 - Argatroban (direct thrombin inhibitor)– avoid in hepatic failure, short t1/2. Easy on-off

Ok for ESRD
Very short t1/2

Hepatic elimination
Variable pharmacodynamics/ kinetics → risk of under and over dosing
Expensive and resource intensive

- Danaparoid (heparinoid) – long t1/2, SC, not available
- Fondaparinux – long t1/2, renal excretion (lasts 24 hours) -- higher dose and weight based. CRRT you can use Fonda 2.5 mg q48h

Management of HIT:

Anticoagulant Choice:

- IV: Argatroban, Danaparoid
- SC: Fondaparinux
 - . <50 kg → 5 mg SC daily
 - . 50-100 kg → 7.5 mg SC daily
 - . >100 kg → 10 mg SC daily
 - . CrCl 30–50 ml/min → caution
 - . CrCl <30 ml/min → do not use
- PO: Warfarin, DOACs
 - Warfarin: start when PLT ≥ 150 + overlap with non-heparin anticoagulation ≥5d once INR 2 – 3
 - DOACS “may be effective” upfront, appropriate for long term anticoagulation
- Pregnancy: Danaparoid preferred

Duration:

- No thrombosis = 1 month
- Thrombosis = 3 months

Bilateral Leg Dopplers: r/o silent DVT in all pts

Platelet Transfusion: AVOID

- Avoid warfarin *until the thrombocytopenia resolves (>150)* and on another anticoagulant to avoid increased risk of venous gangrene (initial use of warfarin alone increases risk of limb gangrene in pts with DVT due to rapid lowering of protein C)
 - When starting warfarin Overlap for 5 days with another agent
 - **Duration:** Continue for **2-3 months** total A/C if no clot, **3-6 months** if clot present
 - UHN book says treat X 1 mo with no thrombosis and HIT with thrombosis treat X 3 months or longer.....so consensus is can treat X 1 mo if no thrombosis and then R/A (if plts still low or at risk for thrombosis tx longer X 2-3 mo) while if thrombosis tx X at least 3 mo (and up to 6m)
- Can consider DOACs as well! at therapeutic doses

<u>For</u>	<u>Debate</u>	<u>Against</u>
<ul style="list-style-type: none"> • Not APTT dependent • Familiar • Cheapish • Easy • Benefit in non HIT population • No cross reactivity 		<ul style="list-style-type: none"> • Concern for prevention of arterial disease in non HIT population • Limited evidence even for HIT

Regular Article



CLINICAL TRIALS AND OBSERVATIONS

Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review

Theodore E. Warkentin,¹⁻³ Menaka Pai,¹⁻⁴ and Lori-Ann Linkins^{2,4}

Key Points

- New data plus a literature review documented new thrombosis in only 1 (2.2%) of 46 patients with acute HIT who were treated with rivaroxaban.
- The literature review found similarly favorable results, albeit with fewer patients, when apixaban and dabigatran were used to treat acute HIT.

Warkentin TE, et al. *Blood* 2017; 130: 1104-1113.

- Rivaroxaban preferred out of the DOACs

Anticoagulant Options for Patients with Heparin-Induced Thrombocytopenia (HIT)

Parameter	Argatroban Argatroban®	Bivalirudin Angiomax®	Fondaparinux Arixtra®
Recommended Uses and Prescribing Restrictions at SHSC	Thromboembolism (TE) Service for treatment of selected patients with HIT (agent of choice in renal insufficiency). In hepatic impairment, argatroban is not recommended or major dose reduction and close monitoring is recommended.	<ul style="list-style-type: none"> Cardiology for patients undergoing PCI (with or without HIT) TE Service for treatment of selected patients with HIT (patients with both renal and hepatic insufficiency; also when use of an agent with a short half-life is desirable) TE with Cardiac Anesthesia for HIT patients requiring urgent CV Surgery 	<ul style="list-style-type: none"> TE service for prevention/ treatment of VTE in HIT patients Cardiology & Emergency Medicine for treatment of Non-ST Elevation Acute Coronary Syndrome (NSTACS)
Mechanism & Immunogenicity	Direct thrombin inhibitor Antibodies do not develop	Direct thrombin inhibitor	Selective Factor Xa Inhibitor No antibody development
Half-Life	45 min	25 min (approx. 60 min if CrCl < 30)	17 hr
Clearance	Hepato-biliary	80% proteolysis; 20% Renal	Renal
Renal and hepatic dosing precautions	Avoid, or reduce initial dose, in hepatic impairment	Half-life is doubled in patients with CrCl < 30 mL/min	Clearance is reduced 25% if CrCl 50-80 mL/min; 50% if CrCl < 50 mL/min
Monitoring aPTT or ACT	Target aPTT is 1.5 to 2.5 times patient baseline level. If warfarin is started, target INR is 4.0 * Check INR 4-6 h after stopping argatroban; target INR is 2 - 3	Target aPTT (for treatment of HIT) is 1.5 to 2.5 times patient baseline level. Target INR during co-therapy with warfarin is 3.5 * Check INR 4-6 h after stopping bivalirudin; target INR is 2 - 3	None required
Dose	No bolus dose. Initial infusion rate: 0.75 mcg/kg/min (range: 0.5 to 1 mcg/kg/min)	Dose in PCI (normal Renal Function) IV bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/hr Dose for HIT (normal Renal Function) No bolus dose. Initial infusion rate: 0.1 to 0.2 mg/kg/hr Dose for HIT (CrCL<30 mL/min or patient on dialysis or CRRT) No bolus dose. Initial infusion rate: 0.05 mg/kg/hr	Prophylaxis of VTE: 2.5 mg SC once daily Treatment of VTE: <50 kg 5 mg SC daily 50-100 kg 7.5 mg SC daily >100 kg 10 mg SC daily NSTACS: 2.5 mg SC once daily
Cost/ day (75 kg)	\$633	PCI: \$410 HIT: \$450 to \$600	VTE Prophylaxis: \$14 VTE Treatment: \$28 - \$56 NSTACS: \$14

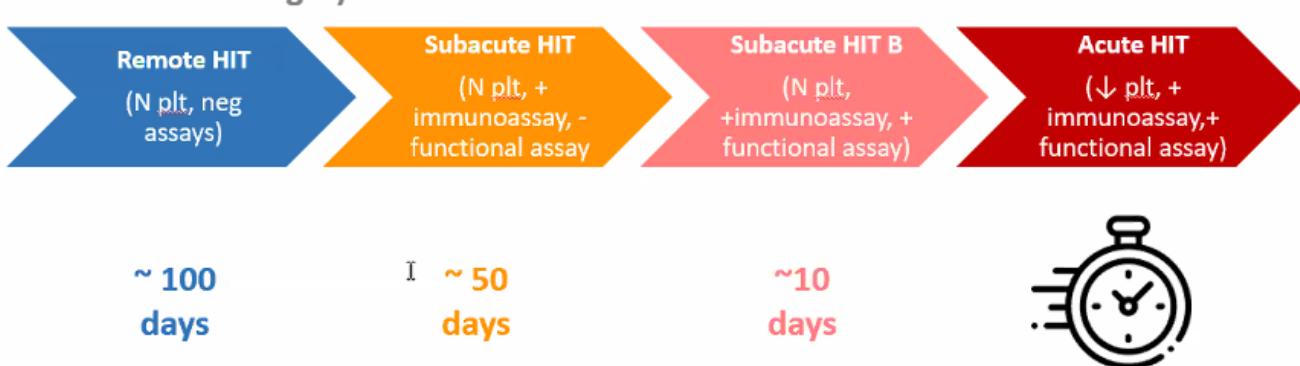
Anticoagulation for Urgent Cardiac Surgery:

**

**

**

**



- IntraOp
 - Within 100 days, need PLEX then heparin

1) Can the surgery be delayed?



2) Is the surgeon comfortable with another anticoagulant? (Can the lab provide required monitoring quick enough?)



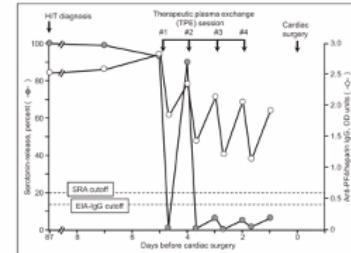
3) Mitigate HIT antibodies

- Removal (PLEX to SRA neg)
- Inhibition (IVIG)*needs to be timed in relation to PLEX

• patients with a history of heparin-induced thrombocytopenia

• In this setting, follow OD (functional assay doesn't matter)

• After 100 days, HIT assay, and limit Heparin for cardiac surgery only



In patients with **subacute HIT B (immunoassay positive but normal platelet count and negative functional assay) or remote HIT (normal platelet count, negative immunoassay and negative functional assay)** who require cardiovascular surgery, the panel suggests intraoperative anticoagulation with heparin rather than treatment with a non-heparin anticoagulant, plasma exchange and heparin, or heparin combined with antiplatelet agent (*conditional recommendation, very low certainty*)

- Post-Op:
 - Monitor platelet counts, if change, then OD

Antibody Treatment

- High-Dose IVIG to Treat HIT; Indications
 - For autoimmune persisting HIT
 - Idea is to 'turn off' HIT antibodies in autoimmune HIT

Supportive

- **Platelet Transfusions**
 - avoid, but can be effective if bleeding or high risk for bleeding
- Non-Pharm
 - Counsel patient
 - Add to allergy list
 - ?Medic alert

Monitoring

- Therapeutic-dose UFH, prophylactic LMWH or UFH: q2days from day 4-14
- UFH in the past 100 days and are starting UFH or LMWH, a baseline platelet count should be obtained and repeated within 24 hours.
- For medical/obstetric patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH "flushes", in whom the incidence of HIT is expected to be <0.1 percent, routine platelet count monitoring is not suggested

- If previous HITT can never use heparin again (exception CABG and then only if plts normal preop and HIT assay negative preop....theory is that if no Abs present at time of CABG will take at least 3 days to develop so using during CABG should not affect anything; NB – use alternative anticoagulant than heparin postop)
 - If CABG urgent and Abs still present can use Bivalirudin

Other Concepts

Post-Op Thrombocytopenia

- Occurs Day 1-3 of surgery
- Followed by post-op thrombocytosis day 4+, if not present, this is **abnormal!**
- Even if HIT is present, sometimes the platelet counts continue to drop even after stopping heparin in **autoimmune HIT**

**
**
**
**

"Alternative HIT"

Label Used for autoimmune/refractory HIT etc

- Typical HIT timeline but can take longer to recover
- Often more severe as requires very high affinity antibodies
 - Very high OD
 - Severe thrombocytopenia (often see below 20)
 - Multiple thrombotic events
 - DIC
- Unclear if more prevalent in patients with autoimmune history



Autoimmune HIT

- HIT which continues even after Heparin is stopped!
- It is a heparin-independent release of serotonin release! (as well as being heparin dependent)
- Explains heparin flush HIT, delayed-onset hit, persistent refractory HIT and Fonda HIT
- Lasts much longer

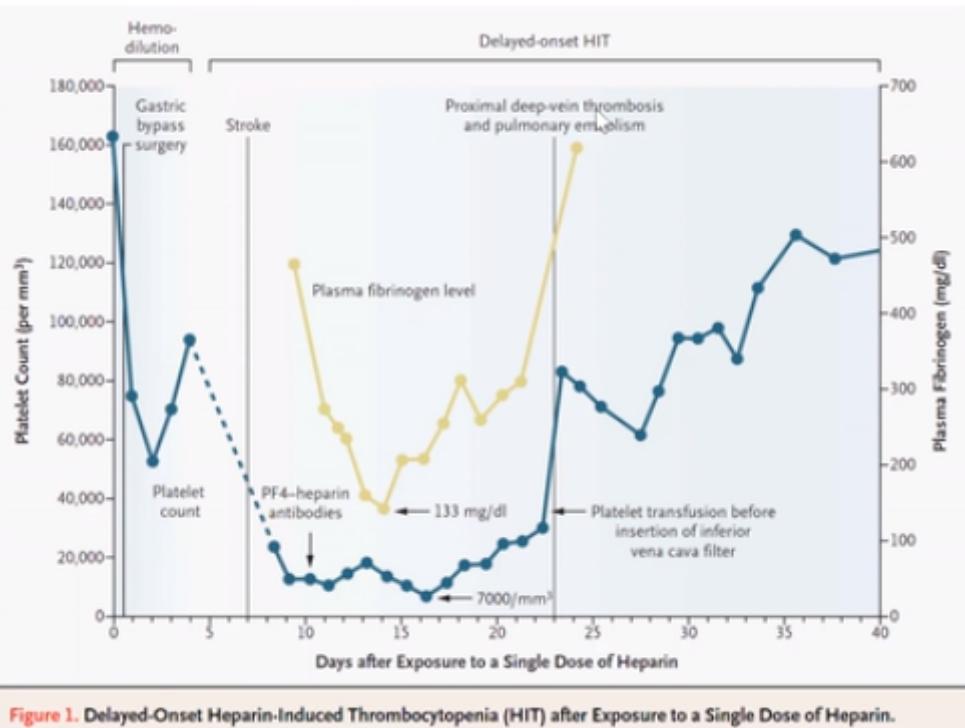
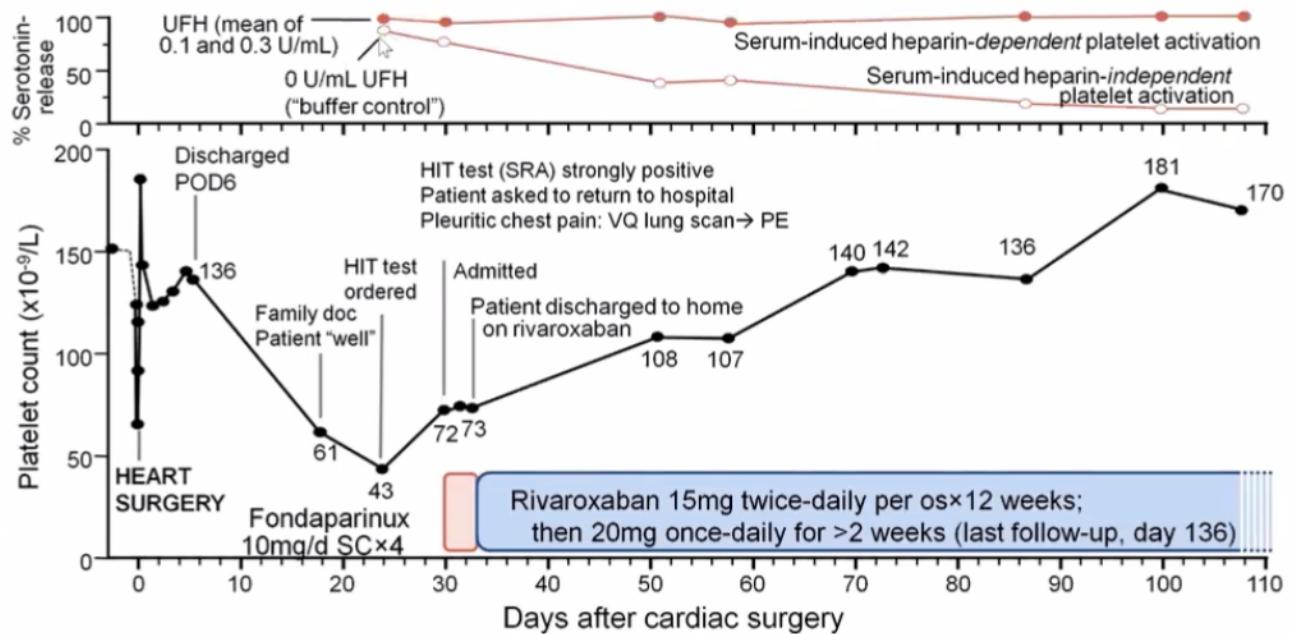


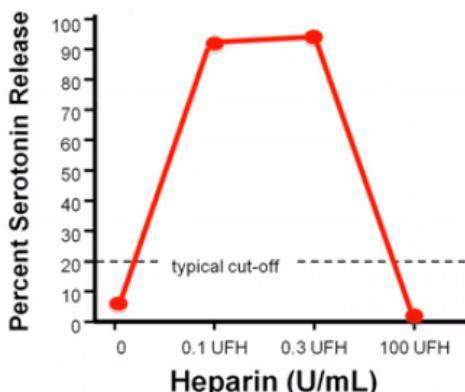
Figure 1. Delayed-Onset Heparin-Induced Thrombocytopenia (HIT) after Exposure to a Single Dose of Heparin.

Warkentin TE, Bernstein RA. *N Engl J Med* 2003; 348: 1067-1069.

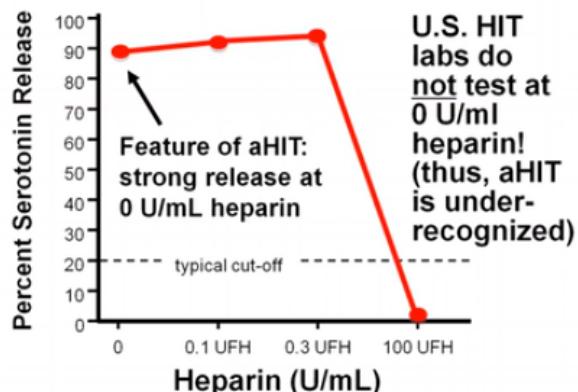
Classic

Autoimmune

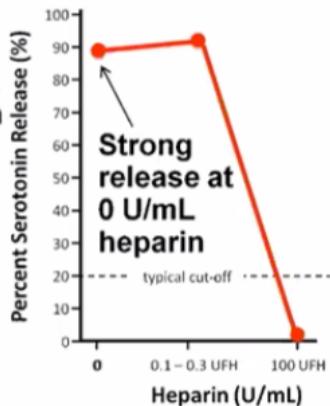
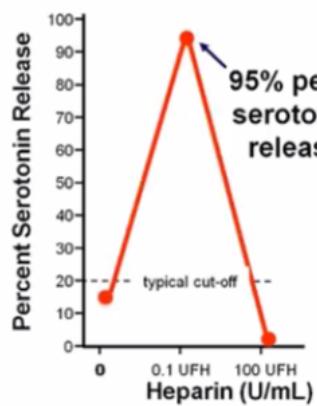
Heparin-dependent Abs



+Heparin-independent Abs



Heparin-independent serotonin-release (at 0 U/mL heparin) indicates aHIT disorders #9



Positive SRA (heparin-dependent Abs) Positive SRA (heparin-independent Abs)



Autoimmune HIT (aHIT) disorders

- Delayed-onset HIT
- Persisting (refractory) HIT
- Heparin "flush" HIT
- Fondaparinux-induced HIT

Greinacher A, Selleng K, Warkentin TE. *J Thromb Haemost* 2017; 15 (11): 2099-2114.

Spontaneous HIT Syndrome

- HIT without proximate heparin exposure
- Strong HIT antibodies
- Clinical settings
 - Knee replacement
 - Post-infection
 - No trigger
- Treatment: identical to standard HIT but risk of failing direct thrombin inhibitor
 - High dose IVIG

Treatment

Treatment pearls for alternative HIT



1) Ensure effective anticoagulation

- Avoid heparin (while not the trigger, may still accentuate platelet activation)
- Watch for PTT confounding with Argatroban (e.g. if DIC)
- Cross reactivity? (Danaparoid & Fondaparinux may theoretically cause HIT)

2) Block HIT antibodies

- IVIG 1 g/kg x 2 days

I

3) Remove HIT antibodies

- PLEX

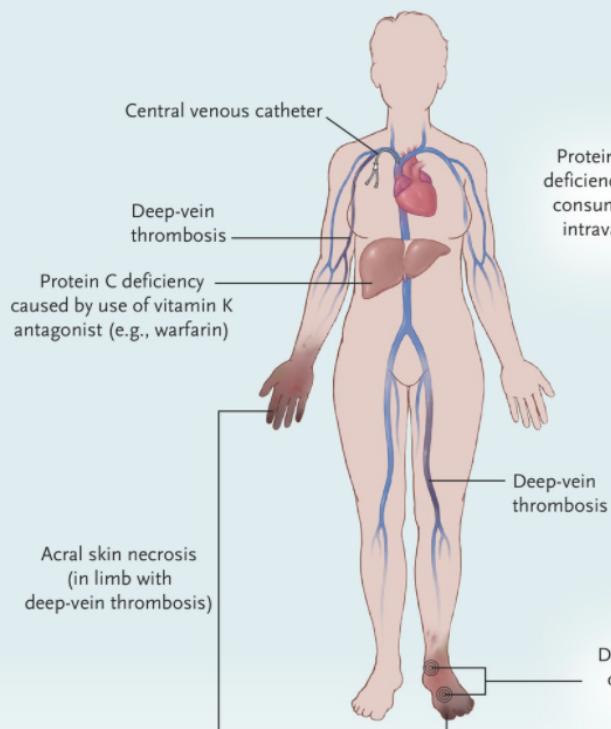
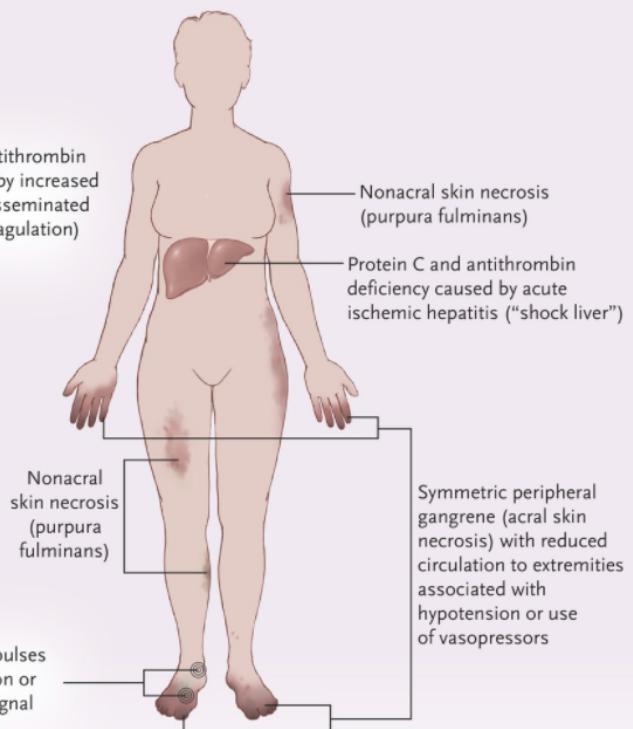
HIT Mimicking Disorder -- Symmetric Peripheral Gangrene

- Symmetrical peripheral gangrene, SPG
- Do vasopressors cause microthrombosis? NO!



- Natural anticoagulant depletion from **Shock Liver!!**
- Bloodwork:
 - CBC, blood films, d-dimer, fibrinogen
 - Check serial liver enzymes
 - 2-5 days warning

[Ischemic Limb Gangrene with Pulses | NEJM](#)

A Phlegmasia Cerulea Dolens (Prodrome), Venous Limb Gangrene**B Symmetric Peripheral Gangrene, Purpura Fulminans****Disseminated Intravascular Coagulation Disorders with Deep-Vein Thrombosis**

Heparin-induced thrombocytopenia
Adenocarcinoma
Antiphospholipid syndrome

Disseminated Intravascular Coagulation Disorders Usually without Deep-Vein Thrombosis

Septic shock
Cardiogenic shock