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ILLUSTRATED REVIEW

Heparin-induced thrombocytopenia: An illustrated review

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Abstract

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug effect from unfractionated or low-molecular-weight heparin that results in thrombocytopenia and potentially catastrophic thrombosis. HIT occurs due to the development of platelet-activating antibodies against multimolecular complexes of platelet factor 4 and heparin. Given the frequency of thrombocytopenia and heparin use among hospitalized patients, calculation of the 4Ts Score is recommended to identify patients at increased likelihood of HIT and direct further evaluation. In patients with an intermediate or high probability 4Ts Score, an immunoassay and functional assay are recommended to confirm or refute the diagnosis of HIT. Heparin avoidance and initiation of nonheparin anticoagulation are the mainstays of acute HIT management. In this illustrated review, we provide visual summaries of the diagnosis and management of HIT, highlighting connections between pathophysiology and clinical care as well as summarizing efforts in quality improvement in the field. We further emphasize common pitfalls and pearls in diagnosis and management to encourage evidence-based care. We include graphical representation of the unique challenges of HIT with cardiopulmonary bypass and also delineate autoimmune HIT and its subtypes.

KEYWORDS
anticoagulants, drug-related side effects and adverse reactions, heparin, quality improvement, thrombosis

Essentials

- Heparin-induced thrombocytopenia (HIT) is an immune adverse drug effect that results in low platelets and risk of thrombosis.
- Use of the 4Ts Score is recommended to assess patient risk of HIT.
- Sequential specialized testing is required to diagnose HIT.
- Heparin avoidance and use of nonheparin anticoagulation are the mainstays of HIT management.

Heparin-induced thrombocytopenia (HIT)

Definition: An immune-mediated adverse drug event to heparin that results in **thrombocytopenia** and potentially **catastrophic thrombosis**.

This illustrated review will discuss the ***diagnosis and management*** of HIT, highlighting connections between **Pathophysiology** and clinical care, and emphasizing central **Pitfalls** and **Pearls** to encourage evidence-based care.

Incidence

↑ incidence with **major surgery**, particularly cardiac[2]

1 in 1500 hospitalizations[1] in the United States

↑ incidence with **unfractionated heparin** (3%) vs. low molecular weight (<1%)[3,4]

↓ incidence with **shorter duration of exposure** to heparin, specifically <5 days[5]

Clinical manifestations & outcomes[1]

Compared to hospital discharges without HIT

Thrombosis	Bleeding	Amputation	Mortality	Length of stay
30-60%[6-8]	**6.2%**	aOR **5.1** (4.3-6, 95% CI)	aOR **4.1** (3.8-4.3 95% CI)	**>3** fold

Single institution reports[9]

ratio Venous:Arterial		
1:1 to 4:1	3-8%	6-50%

Rare manifestations

- Disseminated intravascular coagulation (DIC)[10]
- Injection site necrotizing skin lesions[11]
- Anaphylactoid reactions to IV heparin bolus[11]

aOR, adjusted odds ratio; CI, confidence interval

Pathophysiology

The Key Players

1 Heparin

Unfractionated heparin (UFH)

Low molecular weight heparin (LMWH)

Heparin is a negatively charged polysaccharide chain with anticoagulant activity.

2 Platelet factor 4 (PF4)

PF4 is a positively charged chemokine released from α-granules of activated platelets.

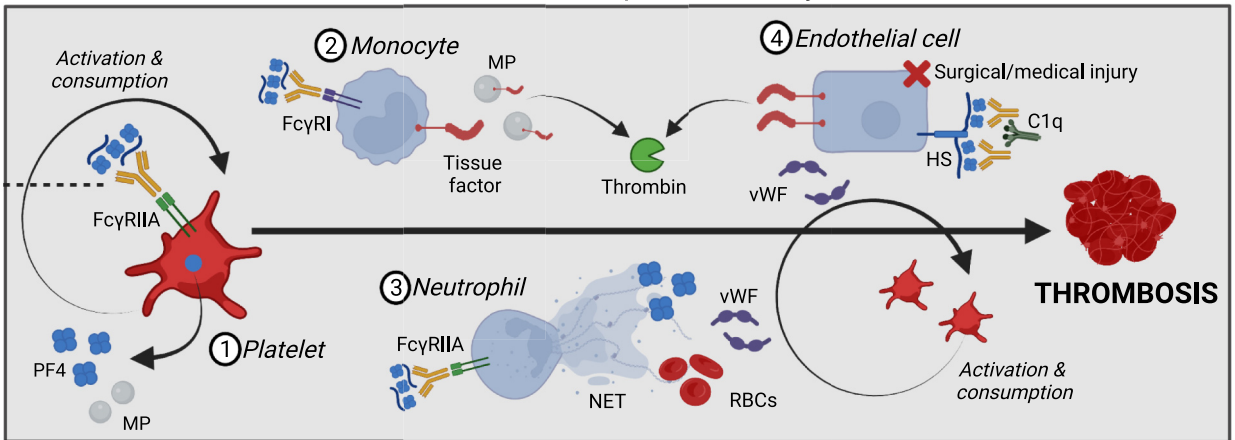
3 The HIT antigen

Via electrostatic interactions, PF4 and heparin bind to form a multimolecular complex.[12]

4 The anti-PF4/heparin antibody

Immune cells recognize the PF4/heparin complex and produce antibodies.

How does the anti-PF4/heparin antibody cause HIT?

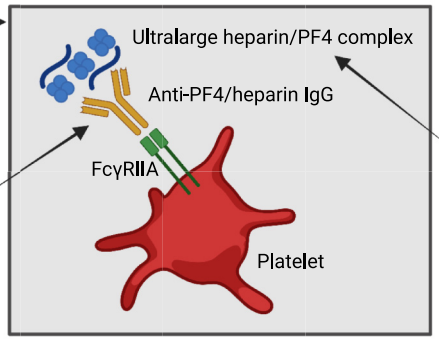


The anti-PF4/heparin IgG antibody binds Fc receptors (FcR), leading to FcR clustering which stimulates (1) platelet activation, consumption, and granule and microparticle (MP) release, (2) expression and release of tissue factor (TF) and TF-containing MPs by monocytes, generating thrombin, and (3) release of neutrophil extracellular traps (NETs) that engage platelets, red blood cells (RBCs), PF4, and von Willebrand factor (vWF).[9,13,14] There is also FcR-independent activation of (4) endothelial cells via direct injury causing TF expression and vWF release as well as binding of anti-PF4/heparin IgG to complexes of PF4 and surface heparan sulfate (HS), triggering complement activation via C1q.[9,15]

Why don't all anti-PF4/heparin antibodies cause HIT?

1 Antibody class

Almost all HIT is caused by anti-PF4/heparin IgG antibodies because IgG is able to engage the platelet-activating FcγR.[16,17] IgM and IgA rarely cause HIT.



2 PF4/heparin complex size

Even among anti-PF4/heparin IgG antibodies, only a subset cause HIT. This subset of antibodies recognize and facilitate generation of ultralarge molecular complexes of PF4/heparin that have increased immunogenicity.[18-20]

Diagnosis, Step 1: **The 4Ts Score**

4Ts Score[21] = Pre-test scoring system to assess the probability of HIT
Calculated as a sum of points from 4 components:

① Thrombocytopenia

Points:

- 2 — Platelet fall > 50% *and* platelet nadir ≥ 20 × 10^9/L
- 1 — Platelet fall 30%-50% *or* Platelet nadir 10-19 × 10^9/L
- 0 — Platelet fall < 30% *or* Platelet nadir < 10 × 10^9/L

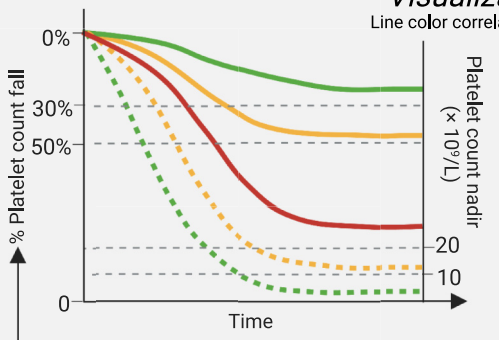
② Timing of platelet count fall

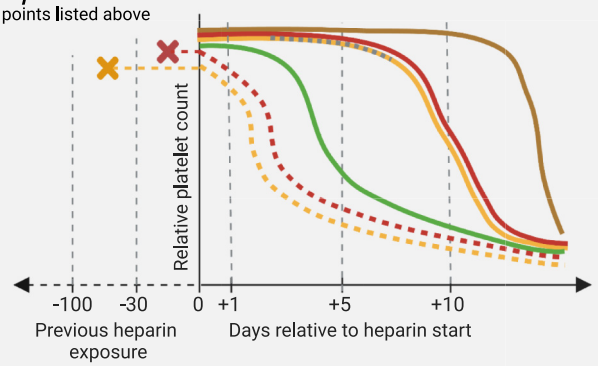
Points:

- 2 — Fall starts days 5-10 (timing is clear) *or* Fall starts ≤ 1 day + heparin exposure within 30 days
- 1 — Fall starts days 5-10 (timing is unclear) *or* Fall starts after day 10 *or* Fall starts ≤ 1 day + heparin exposure 30-100 days ago
- 0 — Fall starts ≤ 4 days without recent heparin exposure

Visualization of points:

Line color correlates with # points listed above





! Calculate using *peak* platelet count *after* heparin started (i.e., not necessarily the day heparin started)

% decline is used, not an absolute platelet threshold, as HIT can occur without thrombocytopenia if the peak count is high (e.g., after surgery, myeloproliferative neoplasm).[21]

! Calculated based on the *first day* of consistent platelet fall.

! In many patients, platelet fall can be *biphasic*, with an initial decline due to a non-HIT insult (e.g. surgery), followed by a rebound and a second, HIT-induced decline.

It takes 5-10 days to produce new IgG antibodies. Immediate HIT onset can occur in those with recent exposure due to presence of previously formed antibodies.[23,24]

Total 4Ts Score
= probability of HIT[22]

- ≥6 **High** (64%)
- 4-5 **Intermediate** (14%)
- ≤3 **Low** (0.2%)

③ Thrombosis or other sequelae

Points:

- 2 — New thrombosis; skin necrosis; acute systemic reaction post-intravenous UFH bolus
- 1 — Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions at heparin injection sites; suspected thrombosis (not proven)
- 0 — None

! Includes thrombosis that occurs or progresses in the period of platelet count decline *after* heparin exposure (i.e., not thrombosis that occurred before heparin exposure)

④ OTher causes of thrombocytopenia

Points:

- 2 — None apparent
- 1 — Possible
- 0 — Definite

! This variable can be challenging to determine and leads to variation between providers in score determination.[25]

HEP score:[26] An alternate score with similar criteria but better performance with less experienced clinicians, likely due to inclusion of defined "other causes of thrombocytopenia:"[27]

1. Chronic thrombocytopenia
2. Newly initiated non-heparin med known to cause thrombocytopenia
3. Severe infection
4. Severe disseminated intravascular coagulation (DIC)
5. Indwelling intra-arterial device
6. Cardiopulmonary bypass within 96 hours

Diagnosis, Step 2a: **Laboratory diagnosis, *Immunoassays***

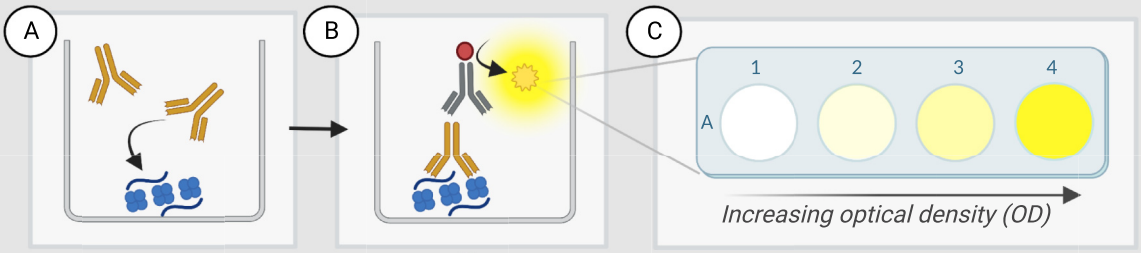
The laboratory diagnosis of HIT is classically divided into 2 steps:
(a) an **immunoassay** and (b) a **functional assay.**

Enzyme Immunoassay (EIA)

The EIA is the prototypical immunoassay, and is used as the standard immunoassay throughout this manuscript

Purpose: Determine if anti-PF4/heparin antibodies are *present*, and if so, their abundance
Performance: High sensitivity (0.97, 95% CI 0.95-0.99), limited specificity (0.82, 95% CI 0.90-0.84)[28]

Specificity varies based on assay used, increasing with IgG-specific assays[28,29] and higher OD thresholds.[30]



Higher OD correlates with higher HIT likelihood[30] and thrombotic risk.[31]

How it works: (A) The plate well is coated with multimolecular complexes of PF4/heparin (or PF4/heparin-like polyanions). Patient serum or plasma is added and anti-PF4/heparin antibodies bind to the complex. (B) Tagged anti-human antibody is added and binds anti-PF4/heparin antibodies. A substrate is added to elicit color change. (C) Degree of color change (optical density, OD) increases with increasing concentration of anti-PF4/heparin antibodies.

***If EIA is positive**, proceed with functional assay (see next page, "Laboratory diagnosis, Functional assays").*
If EIA is negative, HIT is essentially excluded.

Additional immunoassay options: Rapid Immunoassays

Multiple types of immunoassays exist, all with different performance characteristics and different international availability. Selected examples of rapid immunoassays are included below.

Purpose: Similar to EIA but provide results in ≤30 minutes (EIA is often batched, takes hours to perform)
Performance: Varies by assay

		Sensitivity (95% CI)	Specificity (95% CI)	How it works: Method of anti-PF4/heparin detection		Ab class detected
Particle gel immunoassay[32]	PaGIA	0.98 (0.94-1.00)	0.88 (0.91-0.96)		Polymers coated with PF4/heparin complexes	IgG1
IgG-specific chemiluminescence assay[32]	IgG CIA	0.95 (0.90-1.00)	0.94 (0.89-0.99)		Magnetic particles coated with PF4/polyvinyl sulfonate	IgG
Lateral flow immunoassay[32]	LFIA	0.97 (0.92-1.00)	0.91 (0.86-0.96)		PF4-polyanion complexes	IgG
Latex immunoturbidimetric assay[33]	LIA	0.974	0.94		Competitive inhibition of nanoparticles coated with HIT-like antibodies	IgG, IgA, IgM

There is limited guidance on how rapid immunoassays should be incorporated into diagnostic algorithms, and whether additional confirmatory laboratory testing is needed.[32-33]

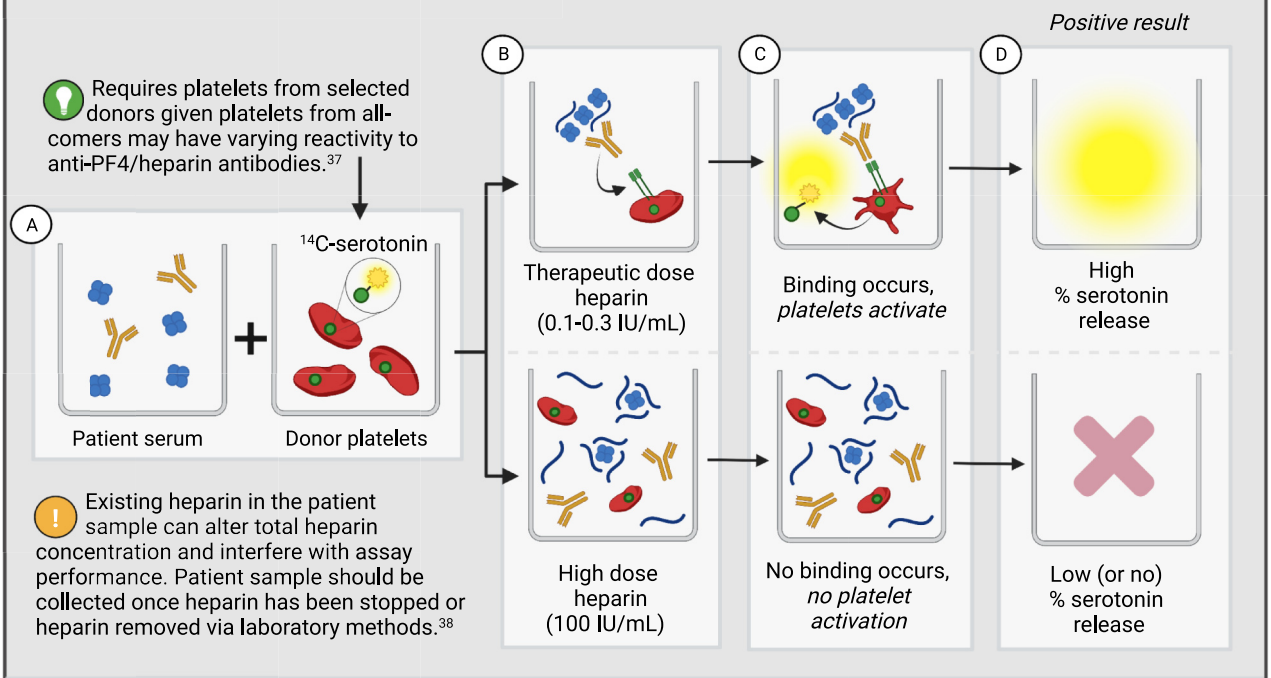
Diagnosis, Step 2b: **Laboratory diagnosis, *Functional assays***

^{14}C-serotonin release assay (SRA)

The SRA is the "gold standard" functional assay[34,35] and is used as the standard functional assay throughout this manuscript

Purpose: Determine if anti-PF4/heparin antibodies are *pathogenic* (i.e. activate platelets)
Performance: High sensitivity (~0.95), high specificity (~0.95)[35]

Due to variation in assay performance and reporting practices,[36] real-world performance may vary from literature reports.



How it works:[34,35] (A) Patient serum is combined with washed donor platelets radiolabeled with ^{14}C-serotonin. (B) At least two different doses of heparin are added. At therapeutic dose, the HIT antigen forms and is recognized by the anti-PF4/heparin antibody. At high dose, heparin disrupts the multimolecular HIT antigen[34,39] so the anti-PF4/heparin antibody cannot bind. (C) When the antigen/antibody complex binds to the platelet Fc receptor, platelets activate and release granules containing ^{14}C-serotonin. Radioactivity is measured and converted to a % ^{14}C-serotonin release. (D) A diagnosis of HIT (i.e. positive SRA) is generally characterized by strong activation (high % serotonin release) with therapeutic dose heparin *plus* inhibited activation (low % serotonin release) with high dose heparin. A negative SRA shows no activation at either concentration. An indeterminate SRA shows activation at both heparin concentrations.

Additional functional assays

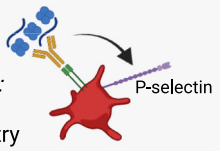
Multiple functional assays exist that differ by the method used for measuring platelet activation:

Heparin-induced platelet activation assay (HIPA)[40]

Measurement of activation: Visual assessment of decreased turbidity with platelet activation

P-selectin expression assay (PEA)[41-43]

Measurement of activation: Platelet P-selectin (CD62p) expression by flow cytometry



Diagnosis: **Putting it all together**

Why use risk scores before laboratory testing?

- Thrombocytopenia is common in hospitalized patients, and it is rarely due to HIT[44]
- The 4Ts Score has excellent *negative* predictive value (can exclude HIT)[22]
- EIA is sensitive, not specific. False positives are common.

Choosing Wisely recommendation to avoid laboratory testing in patients with low probability 4Ts Score[45,46]

Why not wait for the laboratory results to change anticoagulation?

Without appropriate therapy in a patient with HIT, the daily risk of complications (combined risk of thromboembolism, amputation, and death) is 6.1%.[47]

Risk of HIT can be further stratified based on EIA optical density (OD) and 4Ts Score:

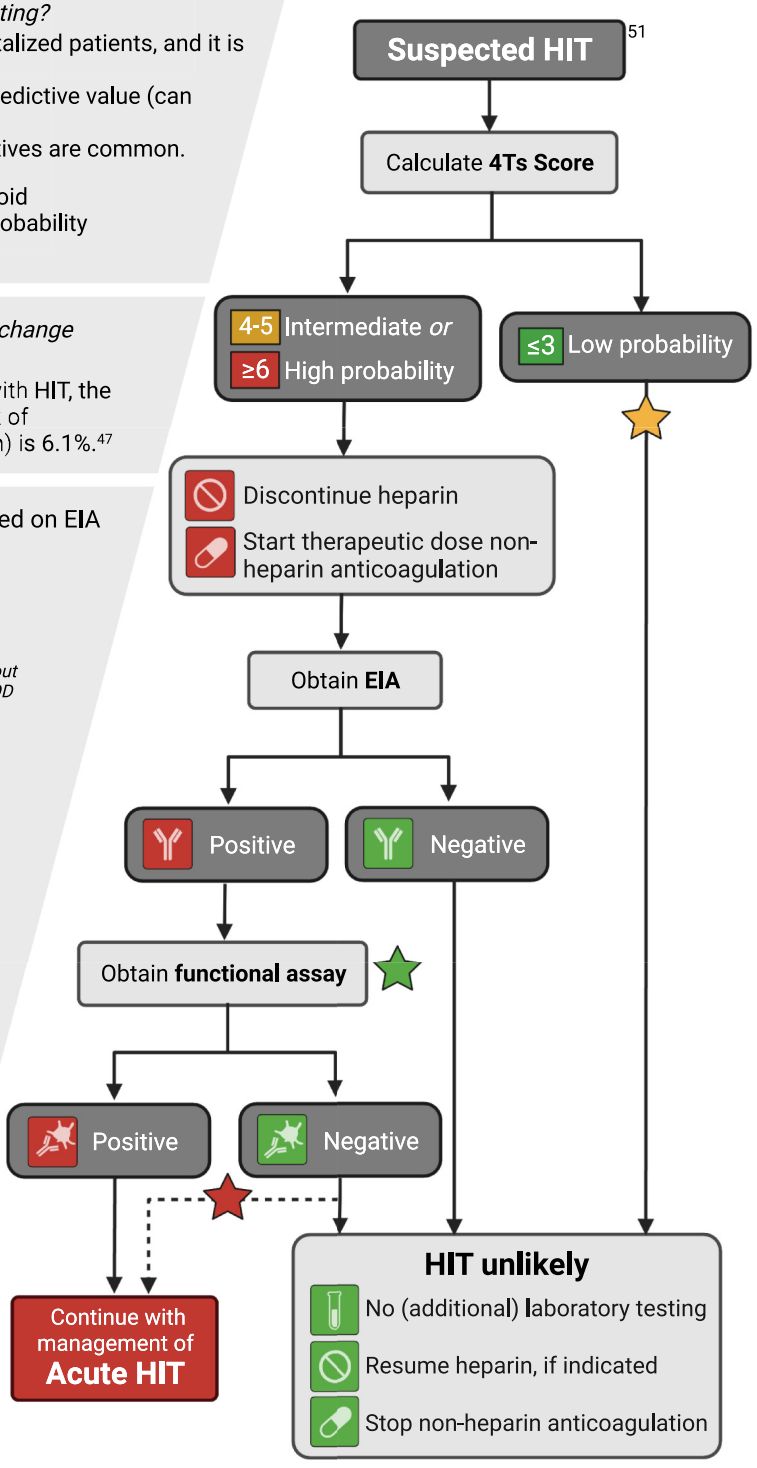
EIA OD	4Ts Score 4-5	4Ts Score 6-8
	14%	64%
<0.6	0%	0%	0%
0.6-1.49	5-25%	16%	68%
1.5-1.99	50%	53%	93%
2+	90%	92%	99%

without 4Ts Score — *without EIA OD*

Lighter shades indicate probability of the individual component (4Ts Score without EIA OD,[22] EIA OD without 4Ts Score[48]). Darker shades indicate probability accounting for combination of 4Ts Score and EIA OD.[49,50] *Exact probabilities will vary with different EIA assays.*

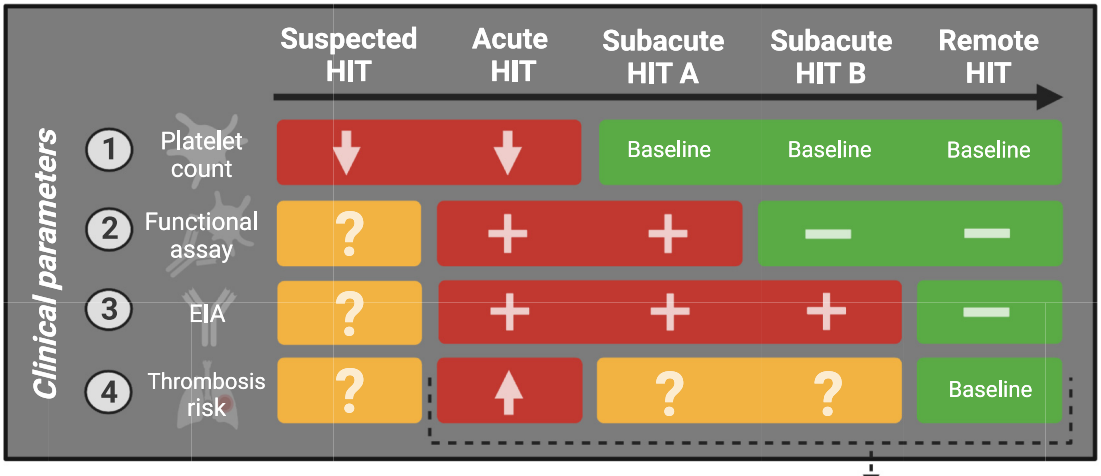
In patients with a high probability 4Ts score and a strongly positive EIA, a functional assay may not be necessary.[51]

Rarely, functional assays are falsely negative.[52] In patients with a high 4Ts score and high EIA OD, treatment for HIT can be considered despite a negative functional assay.[51]



HIT **phases** & **management**

The phases of HIT: The timeline of HIT diagnosis and progression can be defined in phases.[53] Phases are defined by 4 clinical parameters: (1) platelet count, (2) functional assay result, (3) EIA result, and (4) risk of thrombosis. Red indicates the feature is abnormal, yellow indicates the feature is unclear (e.g., in suspected HIT, EIA result is unknown), and green indicates the feature has returned to baseline.



Who requires **platelet monitoring** for HIT?

Recommendations[51] based on risk influenced by (1) type of heparin product and (2) patient population

Estimated risk of HIT	Platelet count monitoring*
Low <0.1%	None
Intermediate 0.1-1%	Consider every 2-3 days
High >1%	Consider at least every other day

Schedule assumes no heparin exposure within 30 days. If monitoring, includes day 4-14 after heparin exposure (day 0). Consider a platelet count before day 4 to identify baseline in case of decline.

	LMWH	UFH*	Fondaparinux
Medical			
Obstetric			
Minor surgery			
Major surgery			
Minor trauma			
Major trauma			

*If exposed to LMWH and UFH, follow guidance for UFH

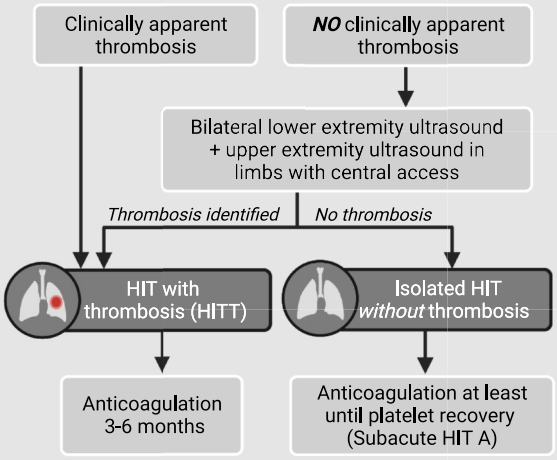
2 key principles of **HIT management**

1 Avoid heparin

Duration of heparin avoidance: Indefinite avoidance is recommended. Brief exposure can be considered in Subacute HIT B and Remote HIT in specific scenarios (See *HIT in cardiopulmonary bypass*).

2 Use non-heparin anticoagulation

Duration of non-heparin anticoagulation: Depends on the presence or absence of thrombosis.[51] For details of agent selection, see *Selection of non-heparin anticoagulation & other therapies*



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

		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*	Agent is not recommended	Agent is not recommended	Agent is not preferred, but can be considered based on availability, risk/benefit	Agent is not preferred, but can be considered based on availability, risk/benefit
Oral	Vitamin K antagonist (VKA)	Agent is not recommended	Agent is not recommended	Agent is not recommended	Agent is not recommended
IV	Argatroban	Agent is preferred	Agent is preferred	Agent is preferred	Agent is not recommended
IV	Bivalirudin	Agent is preferred	Agent is preferred	Agent is not recommended ^	Agent is preferred
SQ	Danaparoid	Agent is preferred	Agent is preferred	Agent is preferred	Agent is preferred
SQ	Fondaparinux°	Agent is not preferred, but can be considered based on availability, risk/benefit	Agent is preferred	Agent is not recommended ~	Agent is preferred

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

* 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]

Oral anticoagulation pearls[51,59]

VKA

Initial decline in protein C can exacerbate the prothrombotic state of HIT, with potential to cause venous limb gangrene and/or skin necrosis.[60,61]

Do not use. If already started, administer vitamin K with initiation of alternative anticoagulant. → Initiate VKA with parenteral anticoagulation bridge after platelet count recovery →

Acute HIT → Subacute HIT A →

Oral Xa inhibitors

- **Isolated HIT** Lead-in dose* → Convert to therapeutic dose* after platelet count recovery →
- **HITT** VTE dose** →

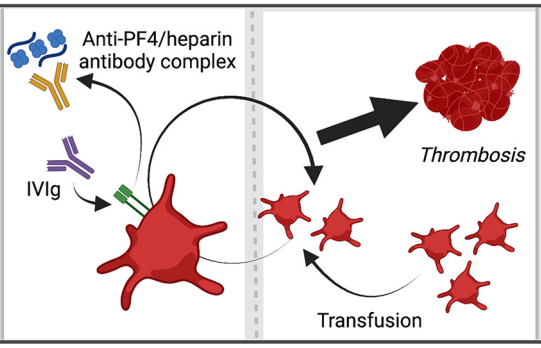
Oral Xa inhibitors provide immediate anticoagulant effect. Dosing strategies are based on reported use, which attempt to maximize dose in periods of presumed highest thrombotic risk.

*Lead-in dose: apixaban 10mg twice daily, rivaroxaban 15mg twice daily
Therapeutic dose: apixaban 5mg twice daily, rivaroxaban 20mg daily
**VTE dose: apixaban 10mg twice daily x7 days, then 5mg twice daily; rivaroxaban 15mg twice daily x21 days, then 20mg daily

Additional treatment considerations

Intravenous immunoglobulin (IVIg)

- Hypothesized to competitively inhibit binding of anti-PF4/heparin antibody to platelet FcR.[62]
- Can be considered in cases of **severe and/or refractory thrombosis or thrombocytopenia**.



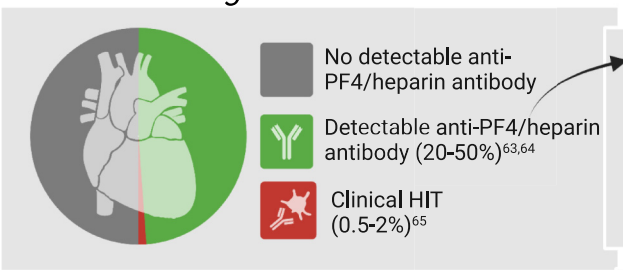
STOP Platelet transfusion?

- Routine use **NOT** recommended due to concern it may "fuel the fire" and increase thrombotic risk, particularly arterial
- Can be considered in patients with active bleeding or prior to urgent procedures.[51,5]

HIT in **cardiopulmonary bypass (CPB)**

CPB is associated with a higher risk of HIT than other surgeries because (1) it requires high doses of anticoagulation, most commonly unfractionated heparin, and (2) it causes intense platelet activation and PF4 release.

Incidence & diagnosis

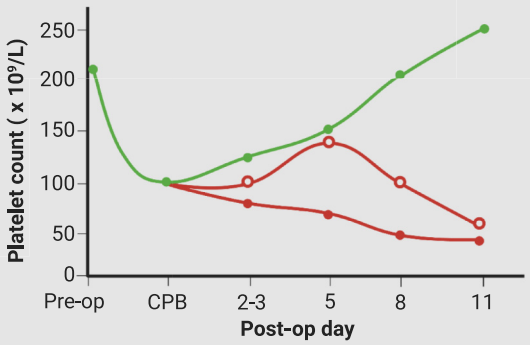


In CPB, the diagnostic algorithm is unchanged (see *Diagnosis: Putting it all together*). Assessing pre-test probability before laboratory testing is even more important given the frequency of anti-PF4/heparin antibodies.

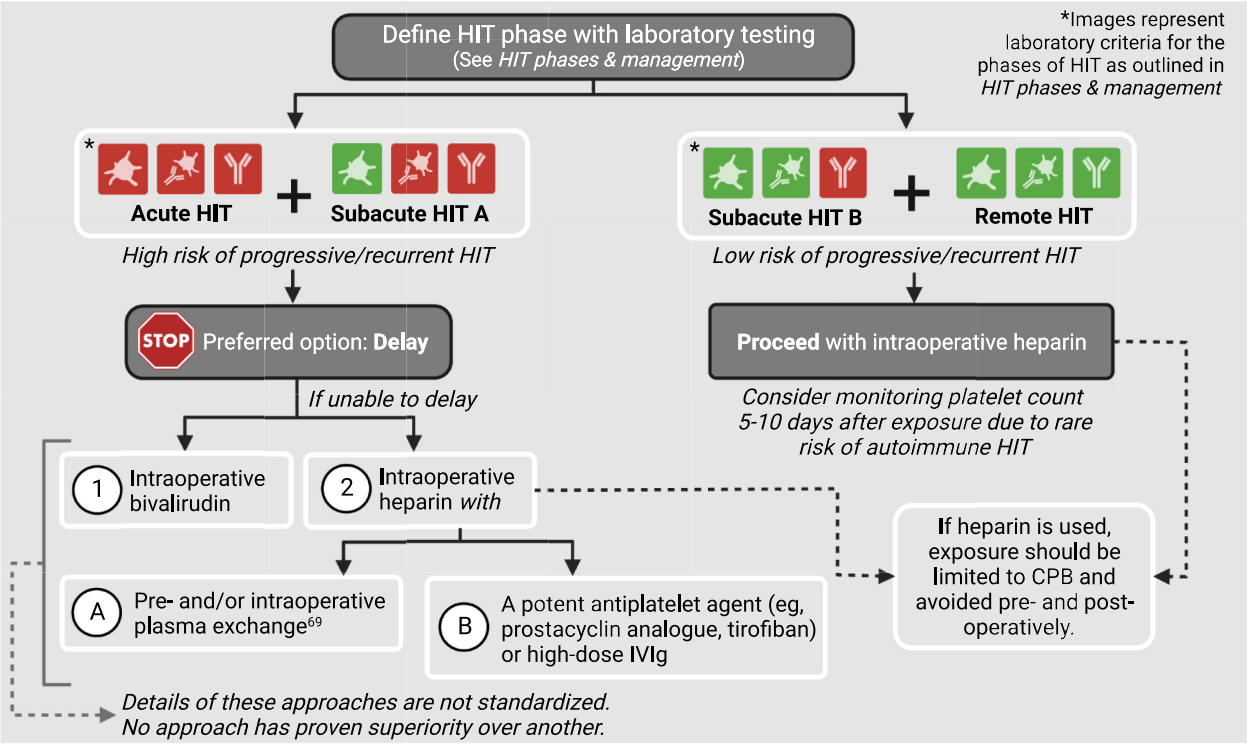
Lilllo-Le Louet Score was developed in CPB,[66] but has not been extensively validated, so 4Ts Score is preferred.

Platelet count trajectory in diagnosis

- **Expected** trajectory in the absence of HIT: Mean ↓ 50% with nadir 48-72h after CPB, with nadir <100 x 10^9/L in approximately 50% of patients[67]
- **Biphasic** trajectory in HIT after CPB, highly suggestive of HIT
- **Non-recovery** trajectory after CPB, rarely due to HIT (rare to develop HIT intraoperatively[68])



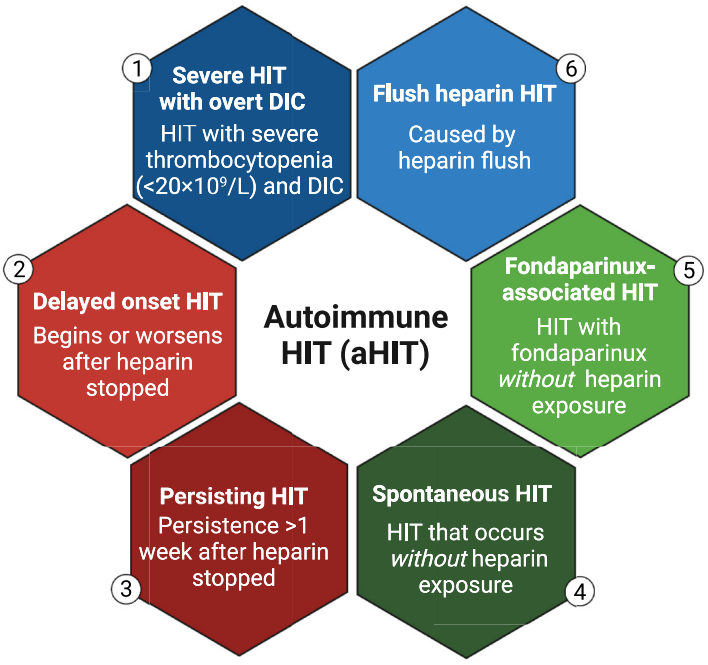
Performing CPB in patients with a history of HIT [51,65]



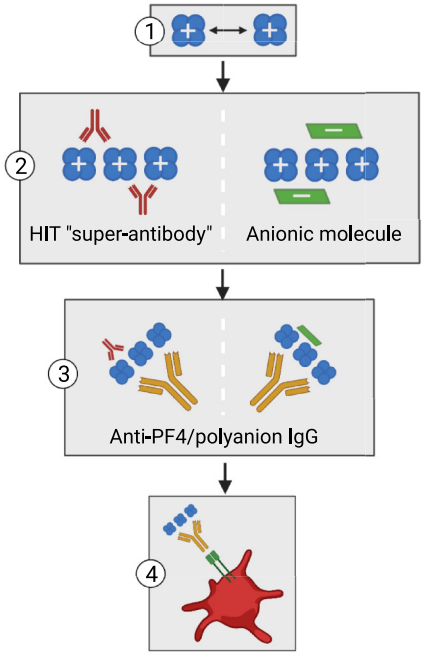
Autoimmune HIT (aHIT)

What is autoimmune HIT?

- Rarely, the clinical manifestations of HIT can develop via **heparin-independent platelet activation**.
- Autoimmune HIT (aHIT) refers to any HIT-related platelet count fall that begins or persists in the absence of heparin.[70,71]
- Six subtypes of aHIT have been described.
- Notably, spontaneous HIT has been reported to occur most commonly after knee replacement or infection.[71]



Pathophysiology



(1) Positively charged PF4 tetramers repel one another. (2) In aHIT, a non-heparin molecule overcomes this electrostatic repulsion, bringing individual PF4 tetramers together to form large multimolecular PF4 complexes. The exact non-heparin molecule able to perform this action is debated and may vary based on aHIT subtype, but proposed examples include HIT "super-antibodies" that bridge two PF4 tetramers and/or highly anionic molecules which could include chondroitin sulfate (released from joint cartilage in joint surgery), polyphosphate, and/or nucleotides such as DNA and RNA.[70,71] (3) The PF4 complexes then serve as antigens bound by anti-PF4/polyanion IgG, which (4) trigger activation of platelets and other cell types.

Principles of diagnosis & management of aHIT syndromes are ***the same as classical HIT,*** with some unique considerations:

When to suspect?

- Thrombosis *and*
- Thrombocytopenia

that is otherwise unexplained *even in the absence of heparin exposure*

→

Diagnosis

- Immunoassay +
- Functional assay +

Functional assay may show platelet activation in the absence of heparin, but a non-heparin control is not performed in all laboratories.

→

Management

- Avoid heparin
- Use non-heparin anticoagulation

Experts recommend consideration of high-dose IVIg in severe cases.[70,71]

Quality improvement in diagnosis & management

The diagnosis and management of HIT are ripe for opportunities to improve the delivery of evidence-based, cost-effective care. Below are examples of successful initiatives, with discussion of the details of the intervention and its impact.

	Goal	Intervention	Impact
Heparin exposure	Decrease exposure to unfractionated heparin (UFH) to decrease incidence of HIT	**The Avoid Heparin Initiative:**[72] Replacement of UFH with LMWH for prophylactic and therapeutic indications	↓ **total HIT incidence** by 79% (10.7 to 2.2 per 10,000 admission) ↓ **HITT incidence** by 91% (4.6 to 0.4 cases per 10,000 admissions) ↓ **HIT-related costs** by $266,938 per year
Suspected HIT	Decrease unnecessary testing for HIT	**Clinical decision support** requiring 4Ts Score calculation with all HIT assay[73,74]	↓ proportion of tested patients with **low 4Ts scores** from 66% to 56%[73] ↓ screening and functional assay **testing** by 37.5% and 85%, respectively[74]
Acute HIT	Increase appropriate use of non-heparin anticoagulants	Creation of an **anticoagulation stewardship program,**[75] with a focus on anticoagulation in HIT	↓ median duration of **IV direct thrombin inhibitor use** from 9.9 days to 7.3 days ↓ **time from diagnosis to discharge** in acute HIT from 12.8 days to 9.2 days ↑ **fondaparinux and oral Xa inhibitor prescribing** rates in acute HIT from 40.7% to 62.2%

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AUTHOR CONTRIBUTIONS

J.M. conceptualized the manuscript and created the initial content and visualization. B.W. and A.C. provided critical review and revision.

RELATIONSHIP DISCLOSURE

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