THE CLOT THICKENS: UNDERSTANDING HEPARIN INDUCED THROMBOCYTOPENIA

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April 29th, 2026

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DISCLOSURE

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LEARNING OBJECTIVES

Describe the etiology and pathophysiology of Heparin Induced Thrombocytopenia (HIT) and explain clinical implications

Identify and apply diagnostic criteria for HIT using clinical scores and lab tests

Compare and select pharmacologic treatments for HIT based on patient-specific factors

Evaluate and formulate a strategy for anticoagulation rechallenge and long-term management after HIT

ABBREVIATIONS

AC: anticoagulation

aPTT: anti prothrombin time

ASH: American Society of Hematology

CHF: congestive heart failure

CT: computed tomography

Gtt: infusion

HD: hemodialysis

HIT: heparin induced thrombocytopenia

HITT: acute HIT complicated by thrombosis

HIV:

Hx: history

Kg: kilogram

LMWH: low molecular weight heparin

MAP: mean arterial pressure

mcg: microgram

MOA: mechanism of action

mmHg: millimeters of Mercury

MMR: measles, mumps and rubella

OS: per os (oral)

PF4: platelet factor 4

RR: rapid response

SBP : systolic blood pressure

UFH: unfractionated heparin

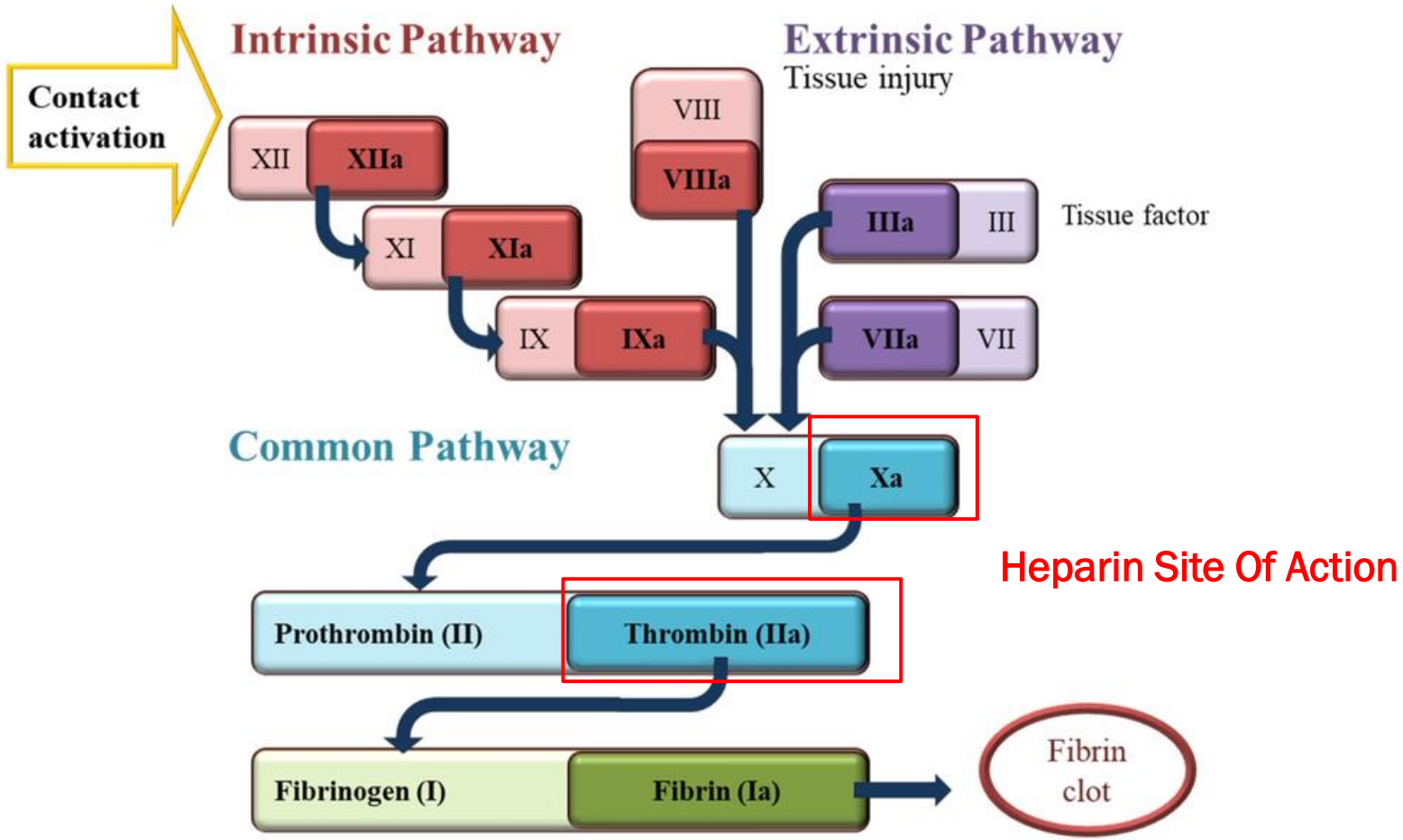
OVERVIEW OF HEPARIN

- In the United States, approximately 12 million people (one-third of hospitalized patients) are exposed to heparin each year
- Typically used for the **prevention and treatment of thrombotic events** and **prevention of clot formation during procedures**

- Both UFH and LMWH have established roles in preventing and treating venous thromboembolism and as adjuvant therapies
  - UFH is composed of long, heterogenous chains (average weight of 50,000 daltons containing 18 or more saccharide units)
  - LMWH is produced by depolymerizing UFH into smaller fragments (average molecular weight of 4000-5000 daltons containing 5-15 saccharide units)
  - **The shorter the saccharide chain** and the smaller the molecular weight, the **less likely the drug will bind to plasma proteins and cells**

Patel P, et al. StatPearls Publishing 2026
Nicolas D, et al. StatPearls Publishing; 2026

COAGULATION CASCADE



Malone, et al.Research Gate..2024

UNFRACTIONATED HEPARIN

MOA: Potentiates the action of antithrombin III and inactivates thrombin preventing the conversion of fibrinogen to fibrin

Dosing:

- Atrial Fibrillation:
  - Initial bolus of 60-80 units/kg followed by a continuous infusion of 12-18 units/kg/hour
- Hemodialysis, Anticoagulation of Circuit:
  - Bolus of 1000 units at the beginning of HD followed by a continuous infusion of 500 units/hour
- Venous Thromboembolism Prophylaxis:
  - 5000 units SC every 8-12 hours
- Venous Thromboembolism Treatment:
  - Initial bolus dose of 80 units/kg then maintenance dose of 18 units/kg/hour

Monitoring:

- For treatment dosing of venous thromboembolism obtain aPTT 6 hours after initial heparin bolus

Heparin. *Lexi-Drugs*. UpToDate Lexidrug. 2026

LOW MOLECULAR WEIGHT HEPARIN (ENOXAPARIN)

MOA: Acts as an anticoagulant by enhancing inhibition rate of clotting proteases by antithrombin III impairing normal hemostasis and inhibition of factor Xa

Dosing :

- **Injection Into Arterial Line of HD Circuit:**
  - 0.5-0.7 mg/kg administered once at the beginning of HD
- **Venous Thromboembolism Prophylaxis:**
  - 40mg SC once daily or 30mg SC once daily for CrCl < 30 mL/min
  - BMI > 40 kg/m^2 : 40mg SC twice daily
  - BMI > 50 $kg/m^{2:}$: 60 mg SC twice daily
- **Venous Thromboembolism Treatment:**
  - 1mg/kg Q12H or 1.5mg/kg Q24H
  - CrCl < 30: 1mg/kg Q24H

Monitoring : Anti-factor Xa levels are recommended in patients who are obese, pregnant, renally impaired or extremes of age. A **peak level collected 3 hours after the 3rd dose**

Enoxaparin. *Lexi-Drugs*. UpToDate Lexidrug. 2026

BACKGROUND OF HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

A severe complication that can occur in patients exposed to any form or amount of heparin products characterized by a **fall in platelet counts** and a **hypercoagulable state**

Manifests as an absolute drop in platelet count (<150 x 10^9/L) or a relative decline of 30%-50% from baseline platelet counts

Nicolas D, et al. StatPearls Publishing; 2026

ETIOLOGY

Type I HIT: Non-immune mediated reaction

- Can occur as early as day one
- Not associated with any complications
- Platelet counts that will spontaneously normalize even if heparin is continued

Type II HIT: immune, autobody-mediated reaction

- Reaction occurs after 5-14 days of receiving heparin
- Leads to **hypercoagulable state** and life-threatening complications (ex: stroke, cardiac arrest)

Nicolas D, et al. StatPearls Publishing; 2026

EPIDEMIOLOGY

HIT is reported to occur in 0.5%-5% of patients exposed to heparin products

Occurs in 0.5%-1% of patients exposed to UFH

Occurs in 0.1%-0.5% in patients receiving LMWH

50% of patients with HIT develop thromboembolic complications

Complications are associated with a mortality rate of up to 30%

Shah NB, et al. *J Vasc Surg Venous Lymphat Disord*. 2023

Nicolas D, et al. StatPearls Publishing; 2026

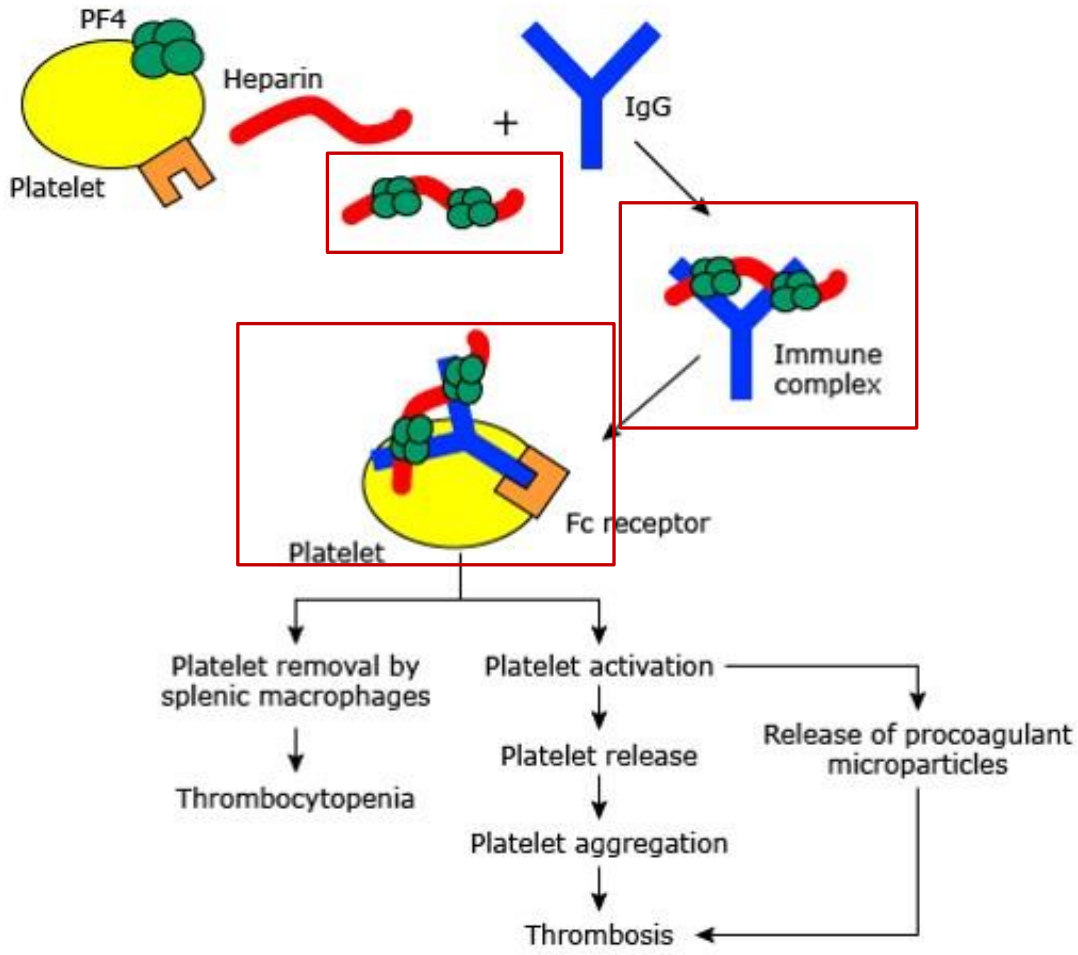
PATHOPHYSIOLOGY OF HIT : HYPERCOAGULABLE STATE

- PF4 stored in alpha-granules of platelets is released upon platelet activation and binds to **endogenous heparan** and **exogenous heparin**

- PF4 binding triggers formation of **IgG, IgA or IgM** antibodies

- Type II HIT can only occur if **IgG binds to the FC receptor** on the platelet surface -> leading to platelet activation

- **Activated platelets release pro-thrombotic substances** (thrombin and PF4)



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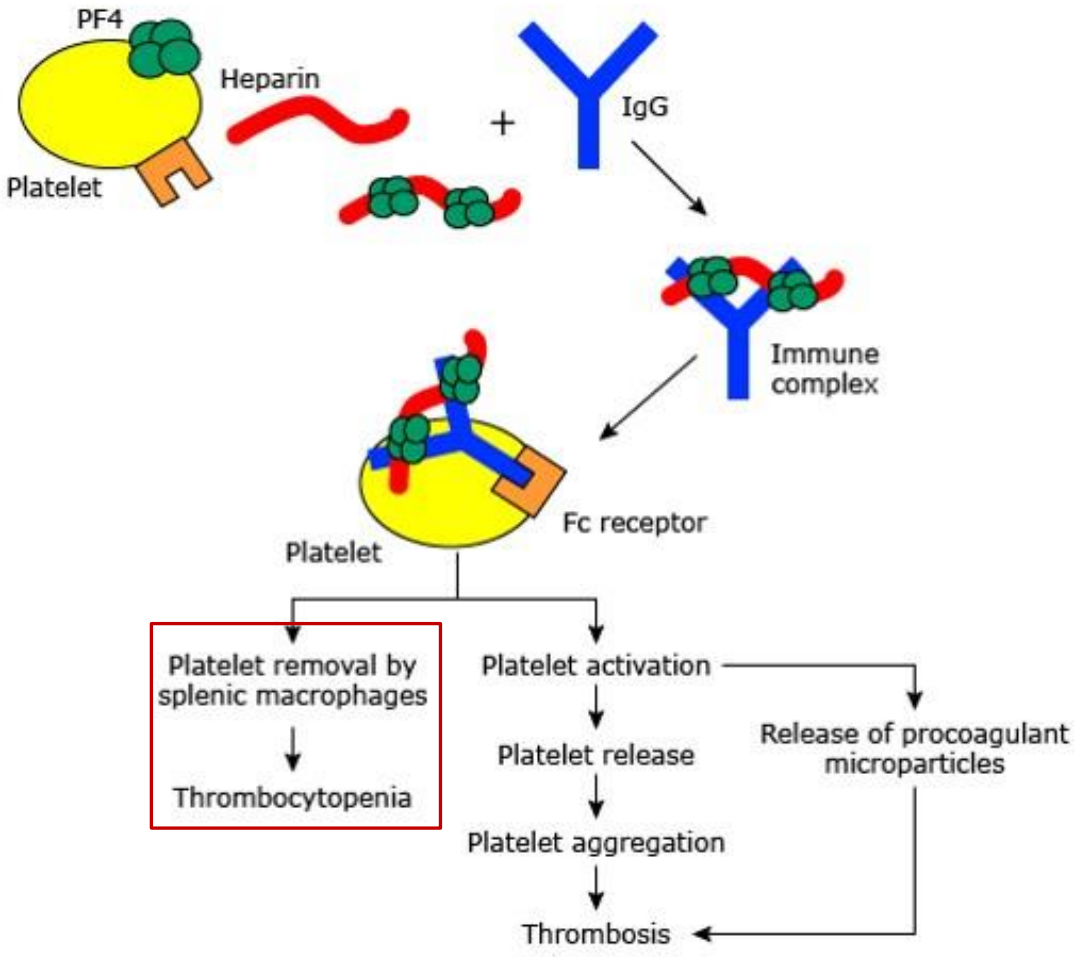
PATHOPHYSIOLOGY OF HIT: THROMBOCYTOPENIA

- Platelet counts fall because **macrophages consume IgG-coated platelets**
  - As platelets become activated, **they aggregate and platelet count drops**



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NON-HIT CAUSES FOR THROMBOCYTOPENIA

Autoimmune Diseases	Viral Infections	Drug Induced	Nutritional Deficiencies
• SLE • Rheumatoid Arthritis • Immune Mediated Thyroid Disease	• HIV • Hepatitis C • Epstein-Barr Virus • Parvovirus • MMR	• Valproic Acid • Linezolid • Daptomycin	• Chronic Alcohol Use • Folate • B12 • Copper

Jinna S, et al. StatPearls. 2026

RISK FACTORS

Duration of Heparin Therapy (>5 days)

Type of Heparin product being used (UFH>LMWH)

Dosage of Heparin

Indication For Treatment

Gender
(Female > Male)

Comorbidities

Salter BS, et al *J Am Coll Cardiol* 2016

HEPARIN INDUCED THROMBOCYTOPENIA (HIT) : ADDITIONAL RISK FACTORS

- A retrospective matched case-control study sought to identify predictors of HIT in hospitalized adults and find additional risk factors associated with higher odds of HIT
  - Primary analysis: Hospitalized patients with/without HIT
  - Secondary analysis: Hospitalized patients with primary hypercoagulable states with/without HIT

- There are several predictors of HIT in hospitalized patients, such as **obesity, malignancy, diabetes, renal failure, major surgery, congestive heart failure, and autoimmune diseases**

Kaur J, et al. J *Hematol*. 2021

PRIMARY OUTCOME

Table 1. Univariate Analyses for Patients Without HIT Compared to Patients With HIT

Variable	Patients without HIT (N = 12,406)	Patients with HIT (N = 12,406)	P value
Age	64.8 ± 15.5	64.8 ± 15.5	1.000
Gender - female	6,091 (49.1%)	6,091 (49.1%)	1.000
Obesity	1,590 (12.8%)	2,188 (17.6%)	< 0.0005*
Solid tumor without metastases	313 (2.5%)	438 (3.5%)	< 0.0005*
Metastatic cancer	309 (2.5%)	515 (4.2%)	< 0.0005*
Lymphoma	141 (1.1%)	130 (1.0%)	0.502
Uncomplicated diabetes	2,774 (22.4%)	3,205 (25.8%)	< 0.0005*
Diabetes with chronic complications	733 (5.9%)	1,280 (10.3%)	< 0.0005*
Drug abuse	523 (4.2%)	439 (3.5%)	0.006*
Renal failure	1,875 (15.1%)	4,152 (33.5%)	< 0.0005*
AIDS	35 (0.3%)	35 (0.3%)	1.000
Primary hypercoagulable states	39 (0.3%)	416 (3.4%)	< 0.0005*
Major surgery	2,992 (24.1%)	4,533 (36.5%)	< 0.0005*
Congestive heart failure	1,304 (10.5%)	2,560 (20.6%)	< 0.0005*
Autoimmune disease	256 (2.1%)	489 (3.9%)	< 0.0005*

*P < 0.05 statistically significant. HIT: heparin-induced thrombocytopenia; AIDS: acquired immunodeficiency syndrome.

Kaur J, et al. J *Hematol*. 2021

SECONDARY OUTCOME

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	P value
Diabetes with chronic complications	1.561	0.753	3.235	0.231
Renal failure	2.955	1.994	4.380	< 0.0005*
Major surgery	1.735	1.275	2.361	< 0.0005*
Congestive heart failure	4.497	2.466	8.202	< 0.0005*
Autoimmune disease	1.712	1.120	2.618	0.013*

Kaur J, et al. J *Hematol*. 2021

CLINICAL IMPLICATIONS OF HIT

Patients who experience HIT may develop thromboembolic complications associated with morbidity and mortality

Limits the utilization of heparin products typically used for

Treatment and prophylaxis of thromboembolism	Line flushes	Coating for catheters	Blood products (ex: 4 Factor PCC)

Nicolas D, Nicolas S, et al. StatPearls Publishing; 2026

RELEVANT GUIDELINES

CLINICAL GUIDELINES | NOVEMBER 27, 2018

American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

Adam Cuker, Gowthami M. Arepally, Beng H. Chong, Douglas B. Cines, Andreas Greinacher, Yves Gruel, Lori A. Linkins, Stephen B. Rodner, Sixten Selleng, Theodore E. Warkentin, Ashleigh Wex, Reem A. Mustafa, Rebecca L. Morgan, Nancy Santesso

DIAGNOSIS OF HIT

THE 4-T'S SCORE

High probability (6-8 points) Intermediate Probability (4-5 points), low probability (≤ 3 points)

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count >50% **and** nadir ≥20 x 10^9/L	Platelet count fall 30-50% **or** nadir 10-19x 10^9/L	Platelet count fall <30% **or** platelet nadir <10x 10^9/L
Timing of Platelet Count Fall	Clear onset between 5-14 days **or** platelet fall <1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear **or** onset after day 14 **or** fall ≤1 day (prior exposure 30-100 days ago)	Platelet count fall ≤4 days without recent exposure
Thrombosis or Other Sequelae	New thrombosis confirmed; skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; non-necrotizing skin lesions; suspected thrombosis (not confirmed)	None
Other Causes of Thrombocytopenia	None apparent	Possible	Definite

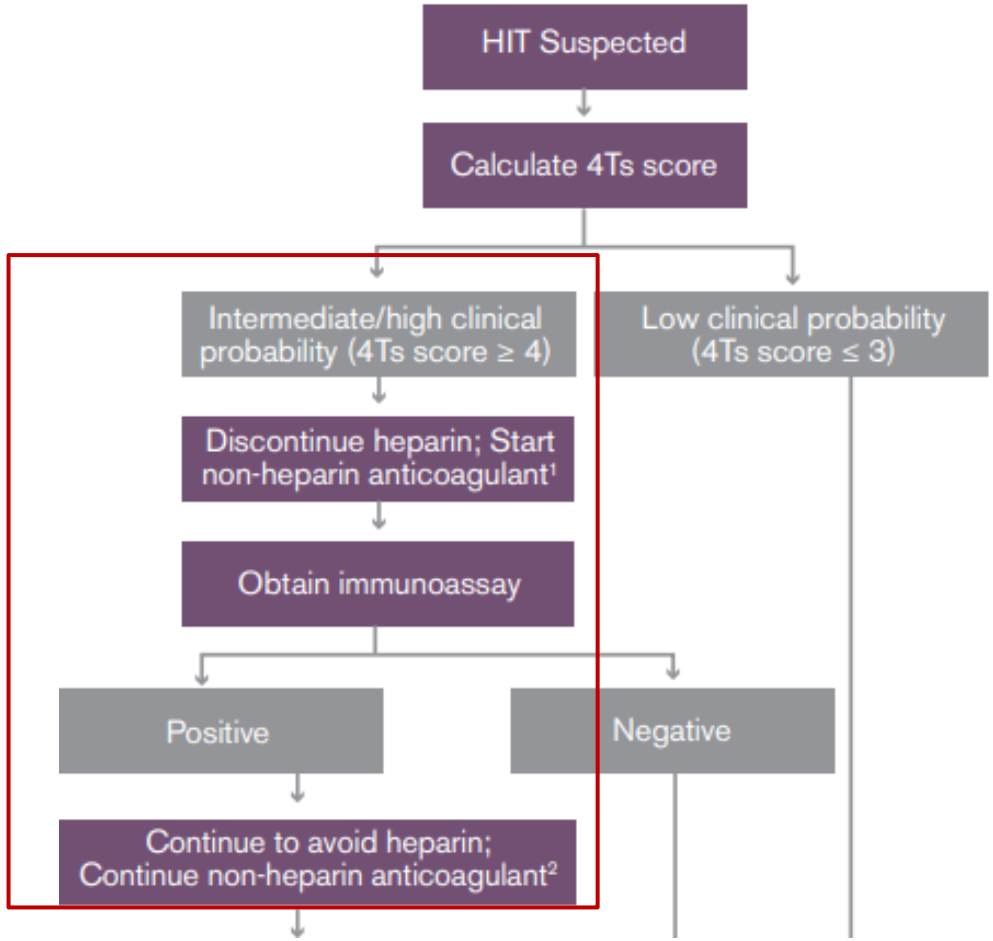
Cuker A,, et al. American Society of Hematology 2018

INTERPRETING THE 4 T'S SCORE

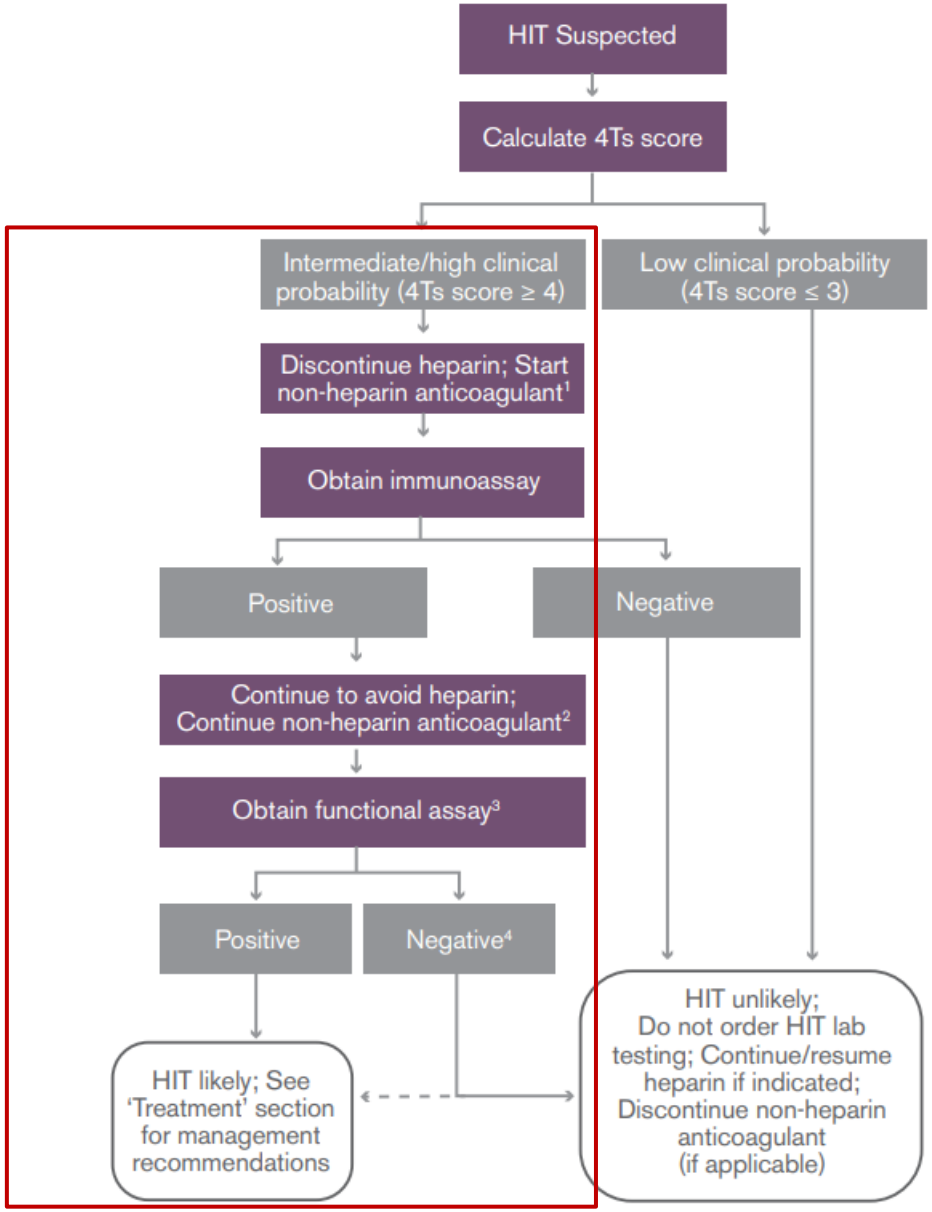
Score	Probability	Risk of HIT	Action
<3 Points	Low	<1 %	Additional HIT laboratory testing is not needed Heparin therapy may be continued, and other causes of thrombocytopenia should be evaluated
4-5 Points	Intermediate	~10%	All forms of heparin should be discontinued and treatment with an alternative anticoagulant
6-8 Points	High	~50%	

Cuker A, Arepally GM, et al. American Society of Hematology 2018

PERFORMING DIAGNOSTIC WORKUP



Cuker A, Arepally GM, et al. American Society of Hematology 2018



Cuker A, Arepally GM, et al. American Society of Hematology 2018

FUNCTIONAL ASSAY

Mechanism	Examples	Normal Range	Diagnostic Range	Comments
Detects the antibodies that induce heparin dependent platelet activation	Serotonin Release Assay (SRA)* Heparin Induced Platelet Antibody (HIT) PF4-Dependent P-Selection Expression Assay	Low Dose Heparin: <20% serotonin release High Dose Heparin: No significant release	Low Dose Heparin: >20% serotonin release High Dose Heparin: Release is inhibited and falls below 20% threshold	• High sensitivity • High specificity • Requires referrals to outpatient laboratories with a turnaround time of 5-7 days

*Gold standard test

Cuker A, Arepally GM, et al. American Society of Hematology 2018

PHASES OF HIT

Phase	Platelet Count	Functional Assay	Immunoassay
Suspected HIT	Decreased	N/a	N/a
Acute HIT Complicated by thrombosis (HITT) Not complicated by thrombosis (Isolated)	Decreased	Positive	Positive
Subacute HIT A	Normal	Positive	Positive
Subacute HIT B	Normal	Negative	Positive
Remote HIT	Normal	Negative	Negative

Cuker A, Arepally GM, et al. American Society of Hematology 2018

KNOWLEDGE CHECK

The PF4 ELISA Immunoassay has _____ sensitivity but _____ specificity

A) High, High

B) Low, Low

C) High, Moderate

D) Low, Moderate

KNOWLEDGE CHECK

The PF4 ELISA Immunoassay has _____ sensitivity but _____ specificity

A) High, High

B) Low, Low

C) High, Moderate

D) Low, Moderate

- The lower specificity is due to the **nonpathogenic antibodies being indistinguishable from the true HIT-causing antibodies.**
- **IgG, IgA, and IgM antibodies against the H-PF4 complex can be detected**, but **only the IgG antibody class can bind to the Fc receptor and cause subsequent platelet activation**, thrombocytopenia, and the clinical prothrombotic state

PATIENT CASE

MEET PATIENT HS

CC: Feeling weak for the past few days, feverish with nausea and vomiting, left arm elbow pain

HPI: Endorsing weakness, poor PO intake and fevers over the past few days. Experiencing left elbow pain and swelling after manipulation trying to get out of bed

PMH: CAD (prior MI s/p 3v CABG- 2019), **HFpEF**, HTN, HLD, pAF, **DM2**, Basal Cell Carcinoma, **Obesity** and remote TIA

Vitals: BP: 132/80, Temp. 36.5 C , HR 93, RR 18 and SP02: 95 %, Lactate of 2.5 mmol/L. WBC of 0.17

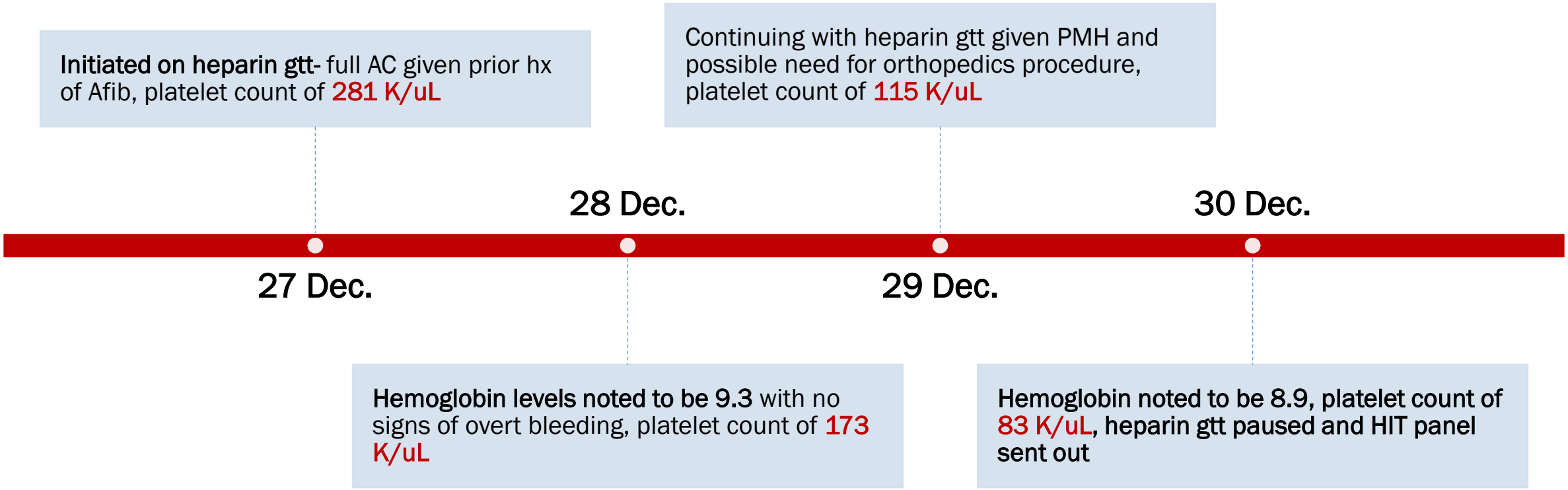
At 15:29 Admitted for evaluation of fever, leukopenia and ruling out septic response

LABS AT INITIAL PRESENTATION

Lab	Value	Reference Range
WBC Count	0.17	4.5-11.0 x 10^9/L
RBC Count	3.62	Male: 4.3-5.9 x 10^{12}/L
Hemoglobin	9.3	13 to 17 g/dL
Hematocrit	28.2	40% to 55%
Mean Cell Volume	77.9	80 to 100 fL
Platelet Count	288	150-400 x 10^9/L
Sodium	133	136 to 144 mmol/L
Potassium	4.2	3.7 to 5.1 mmol/L
Chloride	98	98 to 107 mmol/L
Carbon Dioxide	24	22 to 30 mmol/L
Anion Gap	11	<12
Blood Urea Nitrogen	27	7 to 21 mg/dL
Creatinine	1.50	0.58 to 0.96 mg/dL
Glucose	378	74 to 99 mg/dL
Calcium	8.6	8.5 to 10.2 mg/dL

CONTINUING WITH HS

- At 03:27 a RR was called for hypotension SBP 74 -> completed 1 L bolus and BP unresponsive, SBP remained in the 70's mmHg with a MAP of 50 mmHg, repeat lactate of 2.6 mmol/L
- Upgraded to ICU level of care



CALCULATING 4T'S SCORE FOR HS

Thrombocytopenia: >50% fall, nadir ≥20 K/μL ⟶ 2 points

Timing of fall: Onset within 4 days and heparin exposure within 30 days: ⟶ 2 points

Thrombosis or other sequelae: unknown ⟶ 0 points

Other causes of thrombocytopenia: Possibly sepsis related 1 point

KNOWLEDGE CHECK

The 4-T's score for HS is calculated to a 5, what is the probability of HIT and the next appropriate course of action?

A) Low probability of HIT, resume heparin infusion

B) High probability of HIT, increase the infusion rate on the heparin infusion

C) Intermediate probability of HIT, stop heparin infusion and select a non-heparin anticoagulant

D) High probability of HIT, stop heparin infusion and initiate a DOAC

KNOWLEDGE CHECK

The 4-T's score for HS is calculated to a 5, what is the probability of HIT and the next appropriate course of action?

A) Low probability of HIT, resume heparin infusion

B) High probability of HIT, increase the infusion rate on the heparin infusion

C) Intermediate probability of HIT, stop heparin infusion and select a non-heparin anticoagulant

D) High probability of HIT, stop heparin infusion and initiate a DOAC

A score of 4-5 on the 4-T's score represents **intermediate probability of HIT.**

All forms of heparin should be discontinued and treatment with an **alternative anticoagulant**

HIT PANEL FOR PATIENT HS

PF4/heparin ELISA IgG: **Positive; OD 1.85**

0.1 U/mL (low dose) heparin: **82% release**

100 U/mL (high dose) heparin: **2% release**

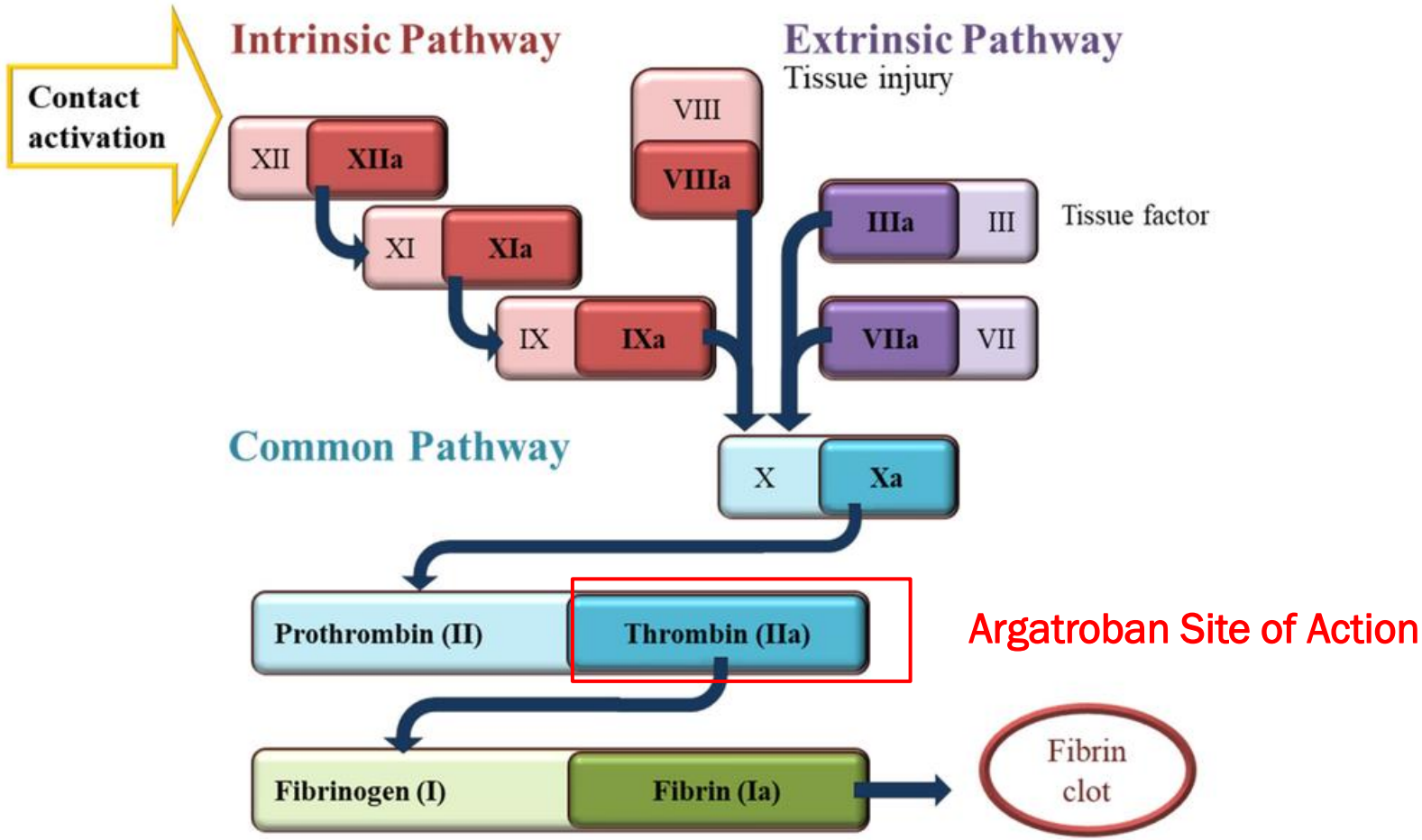
- HS was initiated on **argatroban 0.5 µg/kg/min**, **titrating aPTT 1.5-3x** control not to exceed 100 second, checking aPTT 2 hours after start of infusion and every 6 hours thereafter

MANAGEMENT OPTIONS IN THE SETTING OF HIT

In patients with acute HIT complicated with/without thrombosis the ASH guideline panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant

Cuker A, et al. American Society of Hematology 2018

ARGATROBAN ACTION ON COAGULATION CASCADE



Malone, et al.Research Gate..2024

ARGATROBAN

- **MOA**: Direct, highly-selective thrombin inhibitor, binds to the active thrombin site of free and clot-associated thrombin and inhibits fibrin formation; activation of coagulation factors V,VIII and XIII, activation of Protein C and platelet aggregation

- **Dosing Adjustments:**
  - **Altered Kidney Function/Hemodialysis:** No dosage adjustment necessary
  - **Altered Liver Function**: In patients with Child-Pugh class B or C -> **consider use of alternative agents**
- **Half-life**: 39-51 minutes
- **Clinical Considerations**: IV infusion, on formulary, use actual body weight (ABW) in patients with obesity

Argatroban. *Lexi-Drugs*. UpToDate Lexidrug. 2026

ARGATROBAN (CONTINUED)

- **Dosing: Continuous IV Infusion**
  - **Non-Critically Ill:** Initial 2 mcg/kg/minute adjusting dose based on aPTT results (Not exceeding 10 mcg/kg/minute)
  - **Moderate Hepatic Dysfunction (Bilirubin >1.5 mg/dL), Heart Failure, Anasarca, Post Cardiac Surgery**: 0.5 mcg/kg/minute
  - **Critically Ill (Multiple Organ Dysfunction)** Initial: 0.2 mcg/kg/minute, adjusting dose based on aPTT results
- **Monitoring:**
  - Provider adjusts infusion rate based on aPTT results
  - Results should be measured 2 hours after initiation then every 6 hours until two consecutive therapeutic readings
  - Target aPTT should be 1.5-3x the initial baseline value, not exceeding 100 seconds

Argatroban. *Lexi-Drugs*. UpToDate Lexidrug. 2026

HIT PANEL FOR PATIENT HS

PF4/heparin ELISA IgG: **Positive; OD 1.85**

0.1 U/mL (low dose) heparin: **82% release**

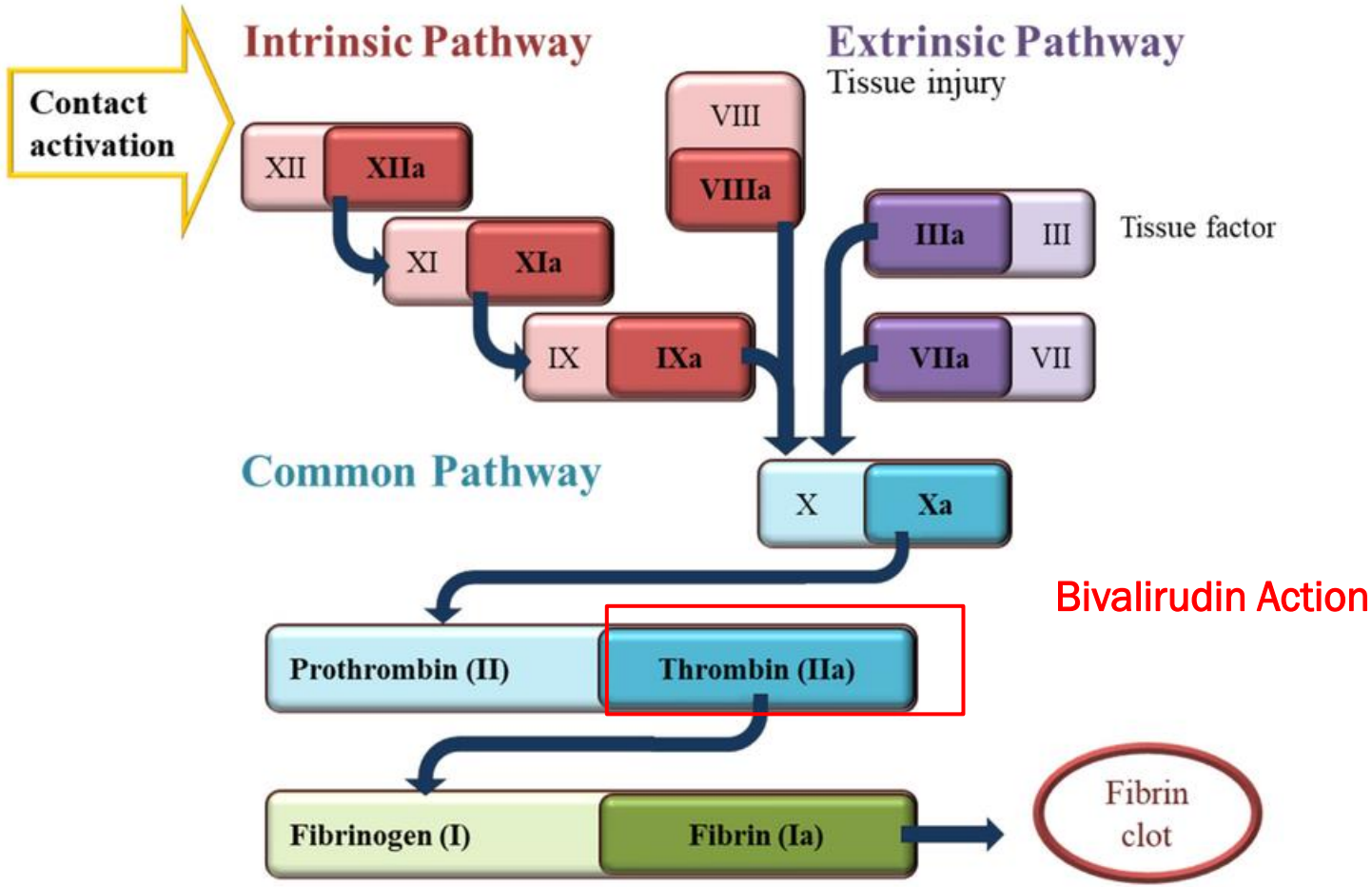
100 U/mL (high dose) heparin: **2% release**

- HS was initiated on **argatroban 0.5 µg/kg/min**, **titrating aPTT 1.5-3x** control not to exceed 100 second, checking aPTT 2 hours after start of infusion and every 6 hours thereafter

Was this the correct action?

- SCr 3.90 mg/dL, eGFR of 15, BUN 46 mg/dL
- Albumin 1.2 g/dL
- Total bilirubin 1.0 mg/dL

BIVALIRUDIN ACTION ON COAGULATION CASCADE



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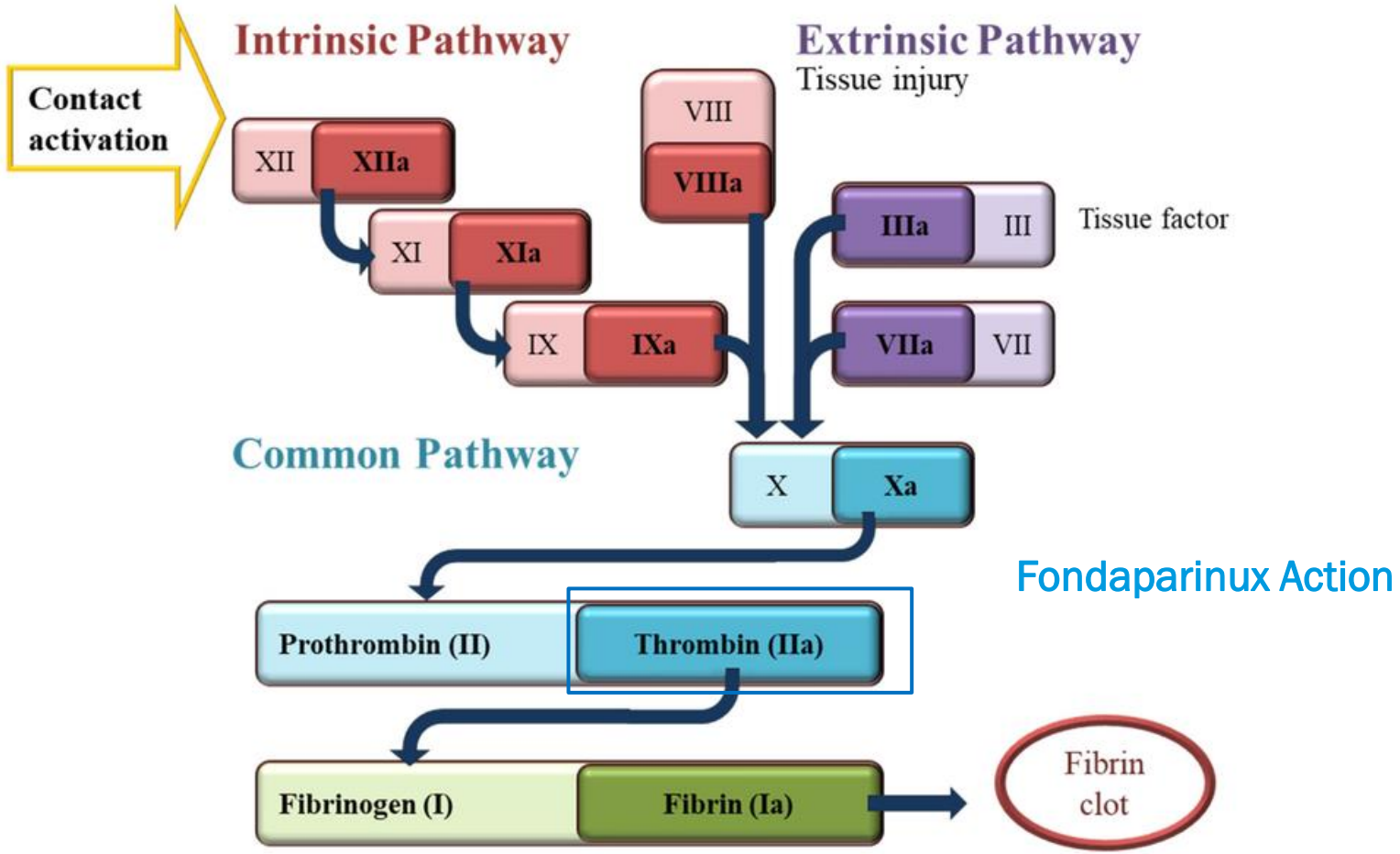
BIVALIRUDIN

- **MOA:** Specific and reversible direct thrombin inhibitor, prevents thrombin-mediated cleavage of fibrinogen to fibrin and activation of factors V, VIII and XIII
- **Dosing: (Off-label Use)**
  - IV: Initial dose of 0.15-0.2 mg/kg/hour; adjust to aPTT 1.5-2x baseline
- **Dosing Adjustments:**
  - **Altered Kidney Function/Hemodialysis:**
    - CrCl >60: No adjustment necessary, can consider range of 0.13-0.16 mg/kg/hour
    - CrCl 30-60: IV Initial dose of 0.08-0.12 mg/kg/hour
    - CrCl <30: IV initial dose of 0.04-0.07 mg/kg/hour
    - Hemodialysis: IV initial dose of 0.04-0.08 mg/kg/hour
  - **Altered Liver Function**: No dose adjustment necessary
- Duration of action: Coagulation times return to baseline in ~1 hour, half life of 25 minutes
- Clinical Considerations: IV infusion, on formulary, costly, use ABW in patients with obesity

Bivalirudin. *Lexi-Drugs*. UpToDate Lexidrug. 2026

FONDAPARINUX ACTION ON COAGULATION CASCADE



Malone, et al.Research Gate..2024

FONDAPARINUX

- **MOA:** Synthetic pentasaccharide that causes an antithrombin III-mediated selective inhibition of factor Xa -> interrupts thrombin formation and thrombus development
- **Dosing: HIT Treatment (Off-label Use) and VTE Treatment**
  - **< 50 kg: 5 mg subcutaneous (SC) once daily**
  - **50 to 100 kg: 7.5 SC once daily**
  - **>100 kg: 10mg SC once daily**
- **Dosing: VTE Prophylaxis**
  - < 50 kg: Contraindicated
  - Medical patients with acute illness at risk for thromboembolism: 2.5 mg SC once daily
- Time to peak: ~2 to 3 hours, half life of 17-21 hours
- Clinical Considerations: **SC administration**, **no aPTT monitoring**, on formulary, use ABW in patients with obesity

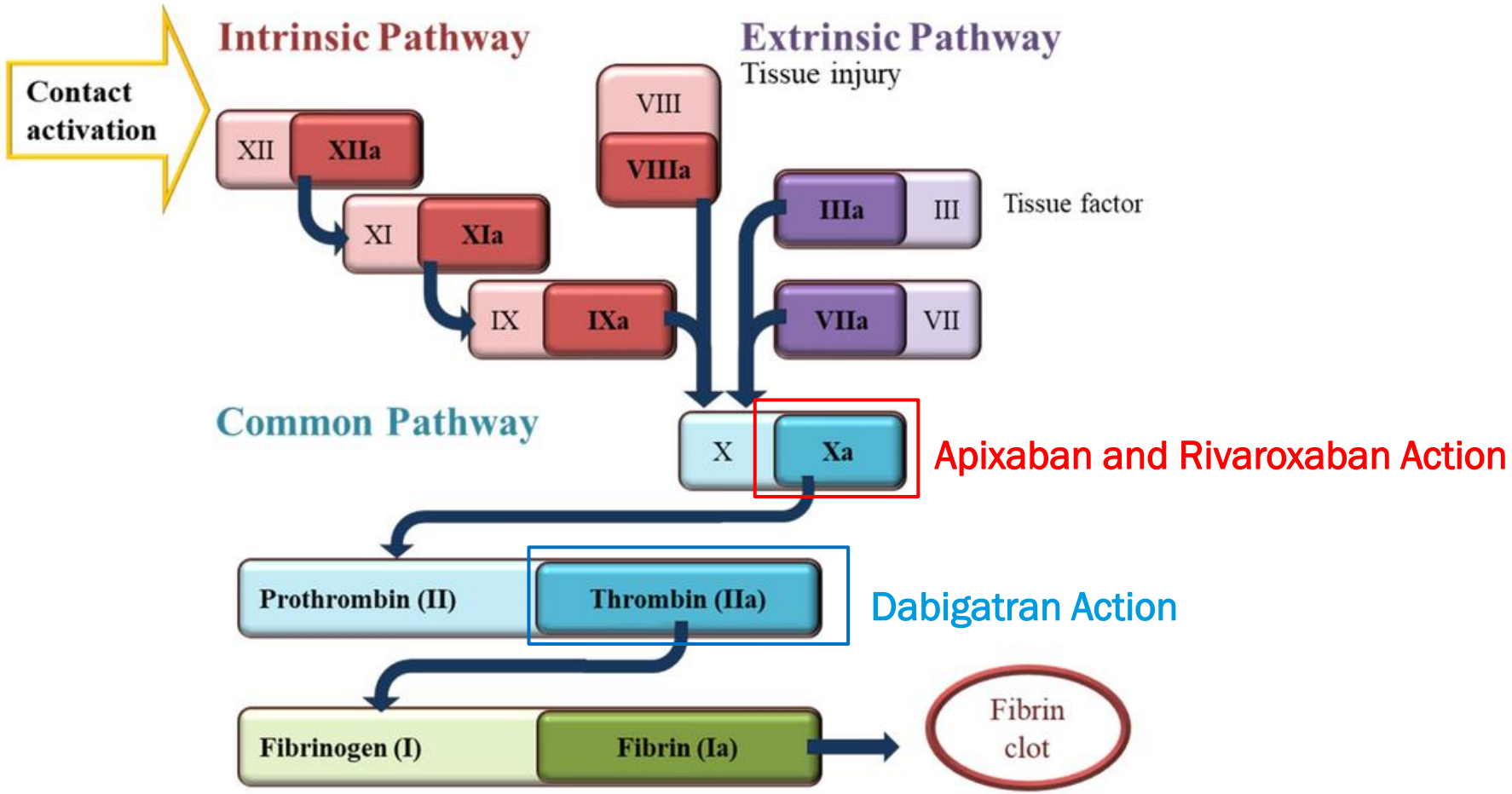
Fondaparinux. *Lexi-Drugs*. UpToDate Lexidrug. 2026

FONDAPARINUX (CONTINUED)

- **Dosing Adjustments**:
  - **Altered Kidney Function/Hemodialysis**:
    - CrCl 50-80: No adjustment necessary, total clearance reduced by ~25%
    - CrCl 30- 50: No adjustment necessary, use with caution/**50% reduction if using for thromboprophylaxis**
    - CrCl <30: Contraindicated as per manufacturer labeling
    - Hemodialysis **Avoid use**
  - **Altered Liver Function**: No dose adjustment necessary, caution in Child-Pugh Class C
- **Duration for HIT without thrombosis:** 4 weeks to 3 months, may discontinue after platelet count recovery
- **Duration for HIT with thrombosis:** Typically 3 to 6 months

Fondaparinux. *Lexi-Drugs*. UpToDate Lexidrug. 2026

DOACS ACTION ON COAGULATION CASCADE



Malone, et al.Research Gate..2024

DIRECT ORAL ANTICOAGULANTS (DOACS)

Apixaban

Dabigatran

Rivaroxaban

- DOACs are considered reasonable options in **clinically stable patients** with an average risk of bleeding
- Most of the published literature involves the use of rivaroxaban

Cuker A, Arepally GM, et al. American Society of Hematology 2018

RIVAROXABAN FOR TREATMENT OF SUSPECTED OR CONFIRMED HIT

Study Design	Outcomes	Results	Clinical Findings/ Outcome
A Canadian multicenter single-arm, prospective cohort study of patients with confirmed or suspected HIT Rivaroxaban 15mg PO BID until platelet recovery then stepped down to 20mg PO QD until day 30 <u>Patients with acute thrombosis:</u> 15mg PO BID until day 21 then 20mg PO QD until day 30	<u>Primary</u>: - Incidence of new symptomatic thromboembolism at Day 30 <u>Secondary</u>: - Incidence of symptomatic thromboembolism while on Rivaroxaban - Incidence of thromboembolism - Major bleeding - Time to platelet recovery	The study was terminated early due to poor recruitment - 1 HIT positive participant had possible symptomatic recurrent VTE (4.5%, 95% CI: 0 to 23.5%) - 1 HIT positive participant had major bleeding (9 days after rivaroxaban was held) - 11 patients achieved platelet recovery with a mean time of 9 days	Rivaroxaban appears to be safe and effective for treating patients with confirmed HIT Small sample size and a lack of comparator warranted additional evaluation

DIRECT ORAL ANTICOAGULANTS FOR TREATMENT OF HIT: HAMILTON REVIEW

Study Design	Outcomes	Results	Clinical Findings/ Outcome
A systematic review for published reports on the use of DOACs for the treatment of HIT **Group A:** - Patients who received DOAC therapy for acute HIT **Group B:** - Treatment using a non-DOAC/non-heparin anticoagulant with transition to a DOAC	**Primary:** - Incidence of new symptomatic thromboembolism at Day 30 **Secondary:** - Incidence of symptomatic thromboembolism while on Rivaroxaban - Incidence of thromboembolism - Major bleeding - Time to platelet recovery	Thrombosis rate of 1 of 46 patients (2.2%; 95% CI, 0.4%-11.3%) in patients treated with rivaroxaban during acute HIT No major hemorrhage seen in 0 of 46 patients **Similar outcomes** in smaller numbers of patients were observed with apixaban and dabigatran	Evidence supporting efficacy and safety of DOACs for acute HIT is increasing, with the most experience reported for rivaroxaban

Warkentin, et al. *Blood. 2017*

SELECTING A NON-HEPARIN ANTICOAGULANT

Critical illness, increased bleeding risk or potential need for urgent procedure	Argatroban or bivalirudin preferred If moderate or severe hepatic dysfunction may avoid or use reduced dose
Life or limb threatening thrombosis (Massive PE or venous limb gangrene)	Argatroban or fondaparinux preferred
Clinically stable patients at average bleeding risk	Argatroban, fondaparinux or rivaroxaban, apixaban or dabigatran reasonable

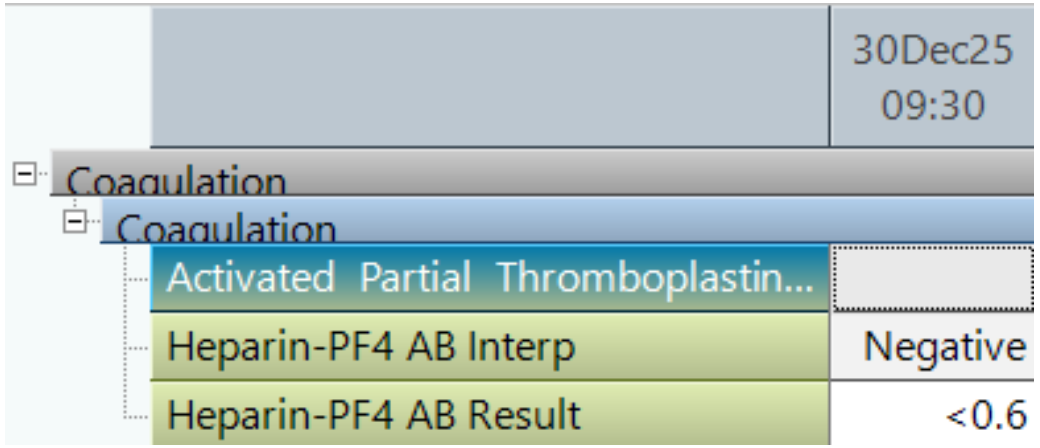
Cuker A, Arepally GM, et al. American Society of Hematology 2018

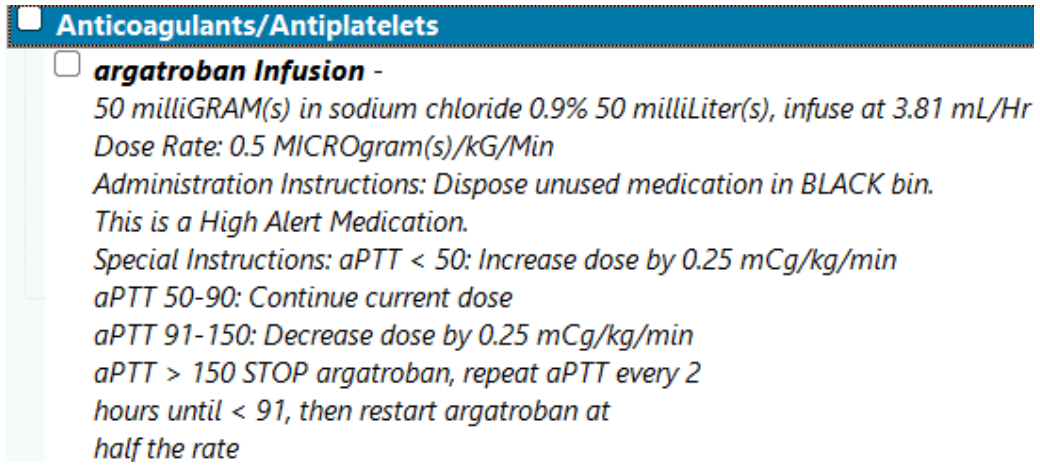
TRANSITIONING TO AN ORAL AGENT

Transition	Timing of Initiation of Oral Agent	Overlap	Additional Comments
Parenteral agent to warfarin	Initiate warfarin once platelet count has recovered (Usually >150 x 10^9/L)	5 days of parenteral agent overlap until INR has reached intended target	• Patients receiving <2mcg/kg/minute of argatroban, stop argatroban when INR is >4 • Repeat INR in 4-6 hours • If INR <2, restart argatroban • Repeat procedure daily until INR >2 Patients receiving >2 mcg/kg/minute of argatroban, reduce to rate of 2 mcg/kg/minute first and adjust
Parenteral agent to DOAC	Transition when patient is clinically stable	**No overlap,** Start DOAC within 2 hours of stopping argatroban or bivalirudin infusion Or 24 hours after last dose of fondaparinux	

Cuker A, Arepally GM, et al. American Society of Hematology 2018

KNOWLEDGE CHECK





Based on the Heparin-PF4 AB results what is the appropriate course of action?

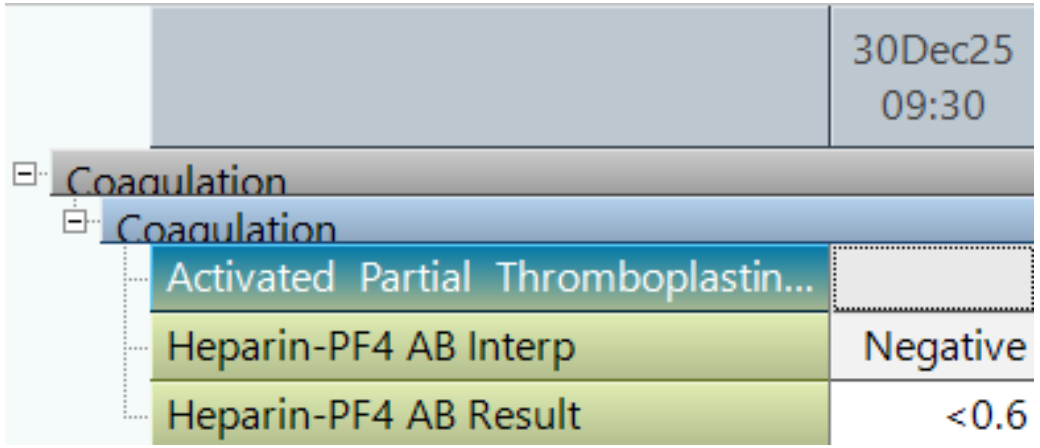
A) Follow up results of a Serotonin-Release Assay

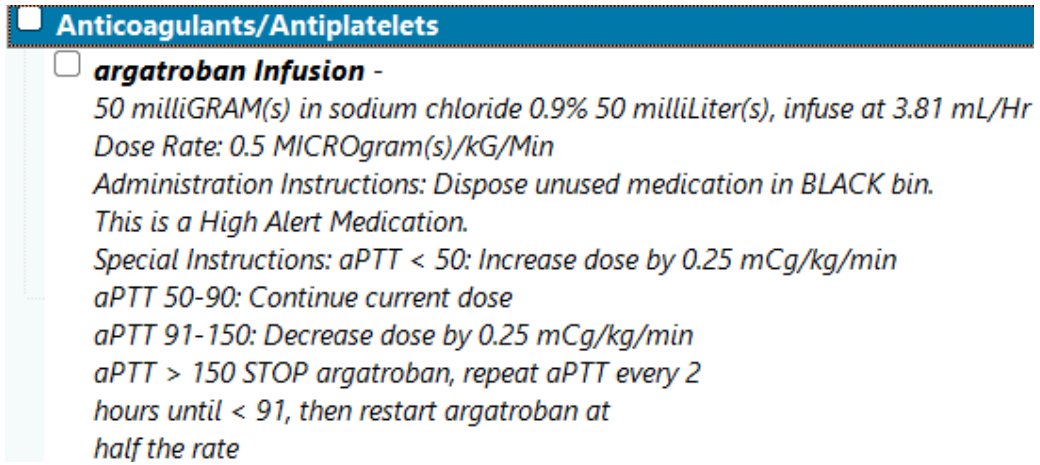
B) Switch argatroban to a DOAC

C) Continue with argatroban infusion and titrate according to aPTT value

D) Discontinue argatroban infusion and switch back to heparin infusion

KNOWLEDGE CHECK





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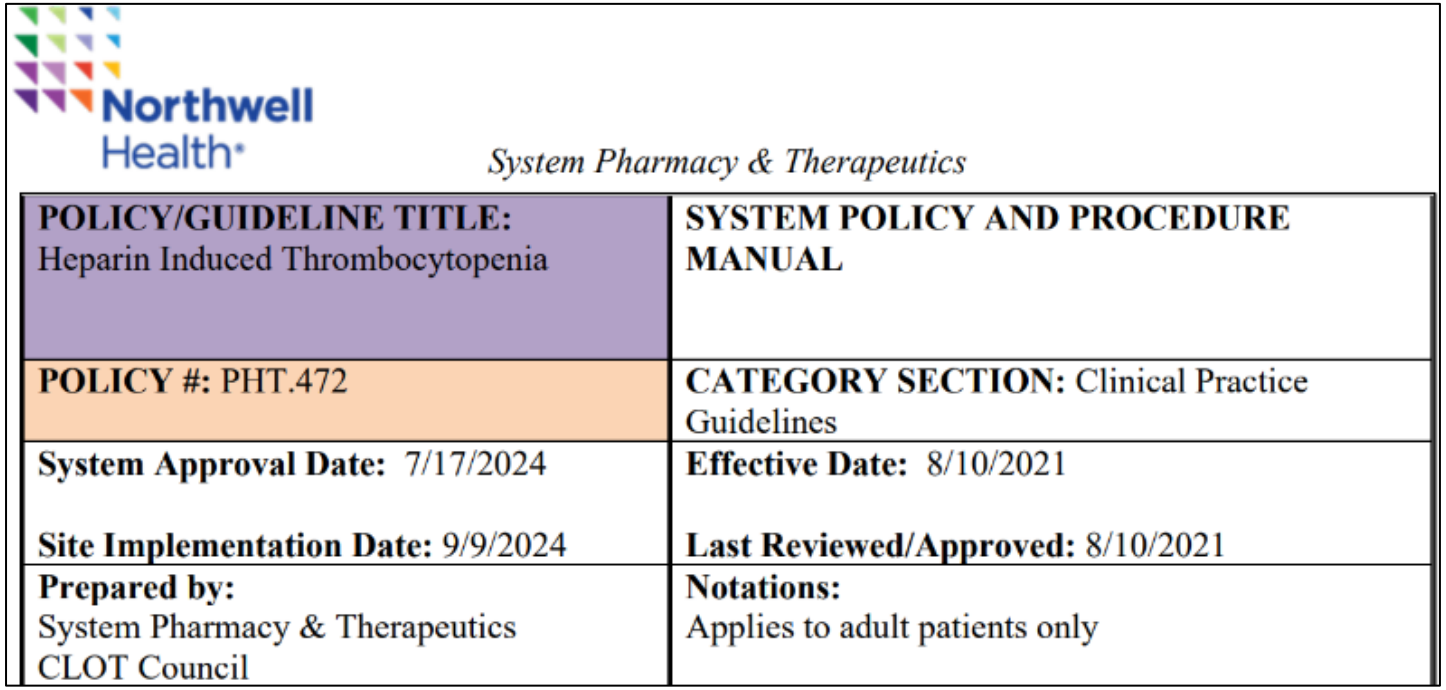
PLAINVIEW HOSPITAL PRACTICAL TIPS

HEALTH SYSTEM POLICY



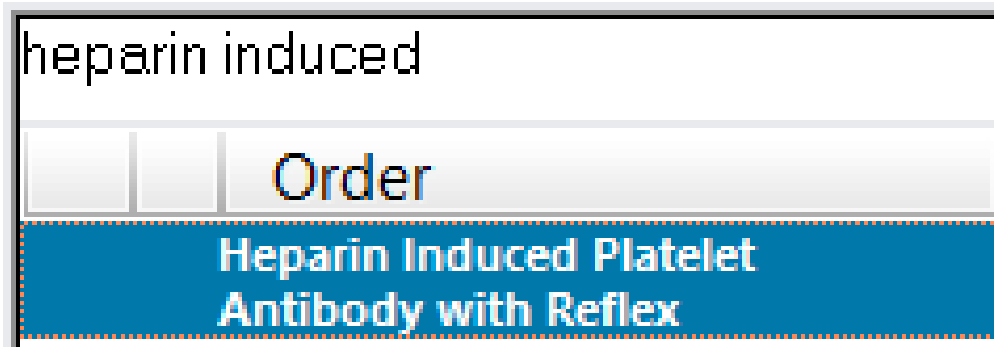
Northwell Health

System Pharmacy & Therapeutics

POLICY/GUIDELINE TITLE: Heparin Induced Thrombocytopenia	**SYSTEM POLICY AND PROCEDURE MANUAL**
POLICY #: PHT.472	**CATEGORY SECTION:** Clinical Practice Guidelines
System Approval Date: 7/17/2024 **Site Implementation Date:** 9/9/2024	**Effective Date:** 8/10/2021 **Last Reviewed/Approved:** 8/10/2021
Prepared by: System Pharmacy & Therapeutics CLOT Council	**Notations:** Applies to adult patients only

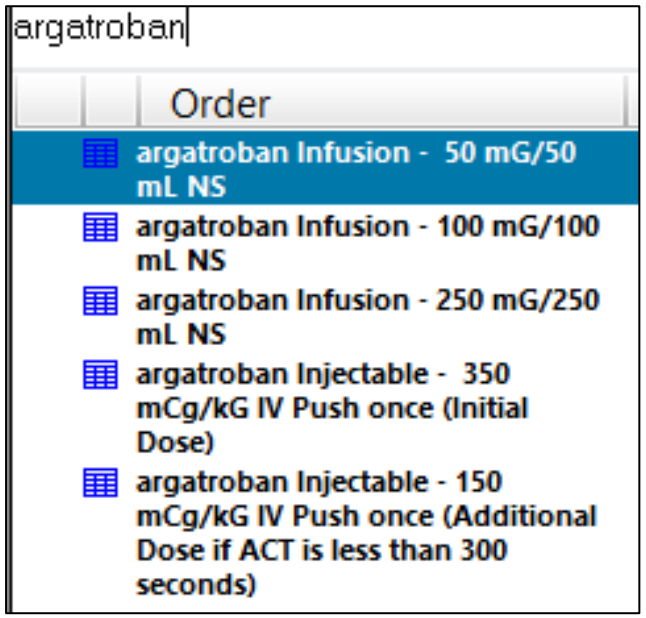
Provides information and guidance regarding HIT including diagnosis, management and monitoring

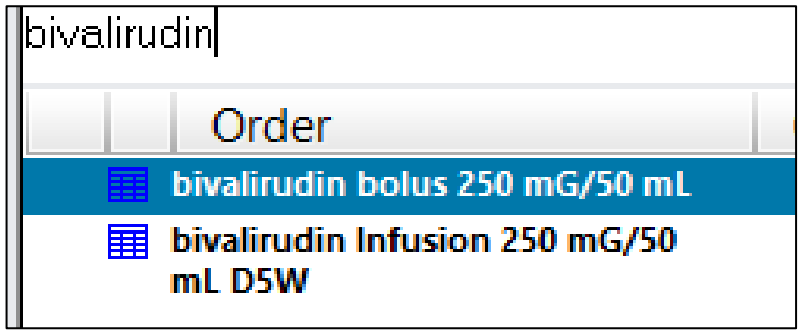
ORDERABLE DIAGNOSTICS- HIPAX

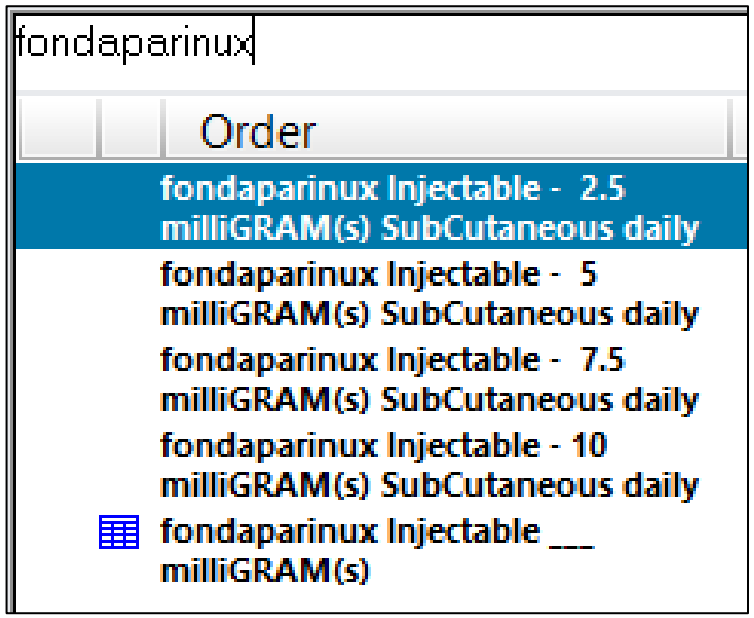


- This test is used as the initial screening test which reflexes to the confirmatory Serotonin Release Assay based on the screening result
- If the HIPAX test result is negative but there is clinically high suspicion for HIT
  - Contact the lab to request SRA

ORDERABLES AT PLAINVIEW HOSPITAL







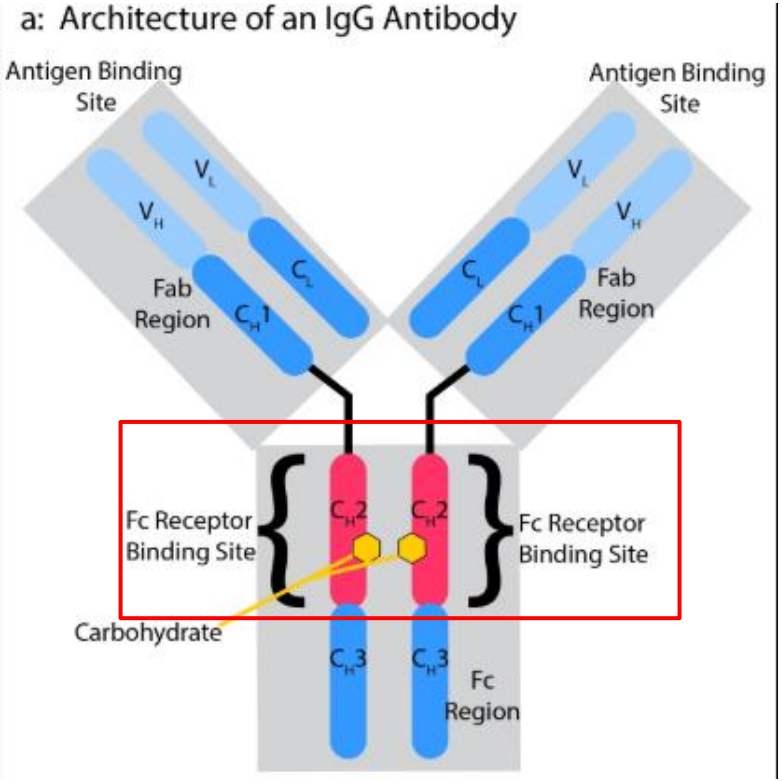
FUTURE DIRECTION

MONOCLONAL ANTIBODIES IN THE PATHOGENESIS OF HIT

Study Design	Patient Population	Results	Clinical Findings/ Outcome
Antibodies against PF4–heparin were affinity-purified with the use of PF4–heparin beads from serum samples Clonality was assessed by means of immunofixation electrophoresis and mass spectrometry Antibody binding to PF4 was evaluated by an enzyme immunoassay Functional platelet activation was evaluated with the use of a P-selectin expression assay	Nine patients with clinically and serologically confirmed HIT	All the serum samples from these **patients tested positive in the anti–PF4–heparin enzyme immunoassay** **6/9 samples (67%) had a monoclonal antibody detectable by immunofixation electrophoresis** **After affinity purification, antibody-depleted serum samples lost binding activity in the enzyme immunoassay**	The pathogenic antibodies in all nine patients with HIT were **found to be monoclonal** This finding provides insight into the pathogenesis of HIT and has **implications for improved diagnostics and targeted therapeutics**

Treverton J. et al. *N Engl J Med*. 2025

HIGH DOSE IV IMMUNE GLOBULIN G



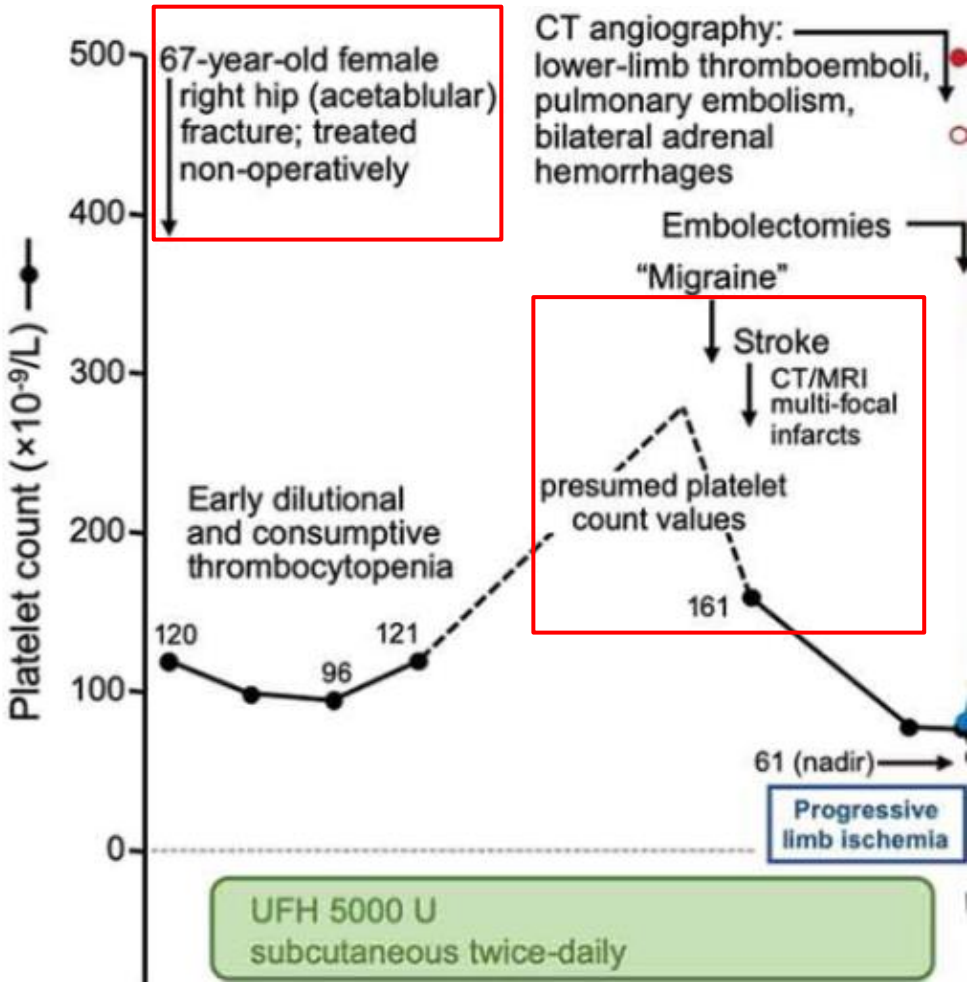
- IVIG inhibits HIT antibody-mediated platelet activation due to the presence of the Fc receptor domain

- Platelets have a class of Fc receptors known as **FcγR** which are **low affinity receptors**
- **FcγRI and FcγRIIIa are found on macrophages/monocytes** which have **higher affinity** constraints
  - Circulating immune complexes are more likely to be bound to macrophages rather than platelets
- **IgG antibodies can bind to platelet FcγRIIa** if their target antigens bind to platelet surface -> **as seen in HIT**

Warkentin TE. Et al. *Expert Review of Hematology*. 2019

IgG Antibodies and Fcγ Receptors in Immunotherapy

CASE REPORT



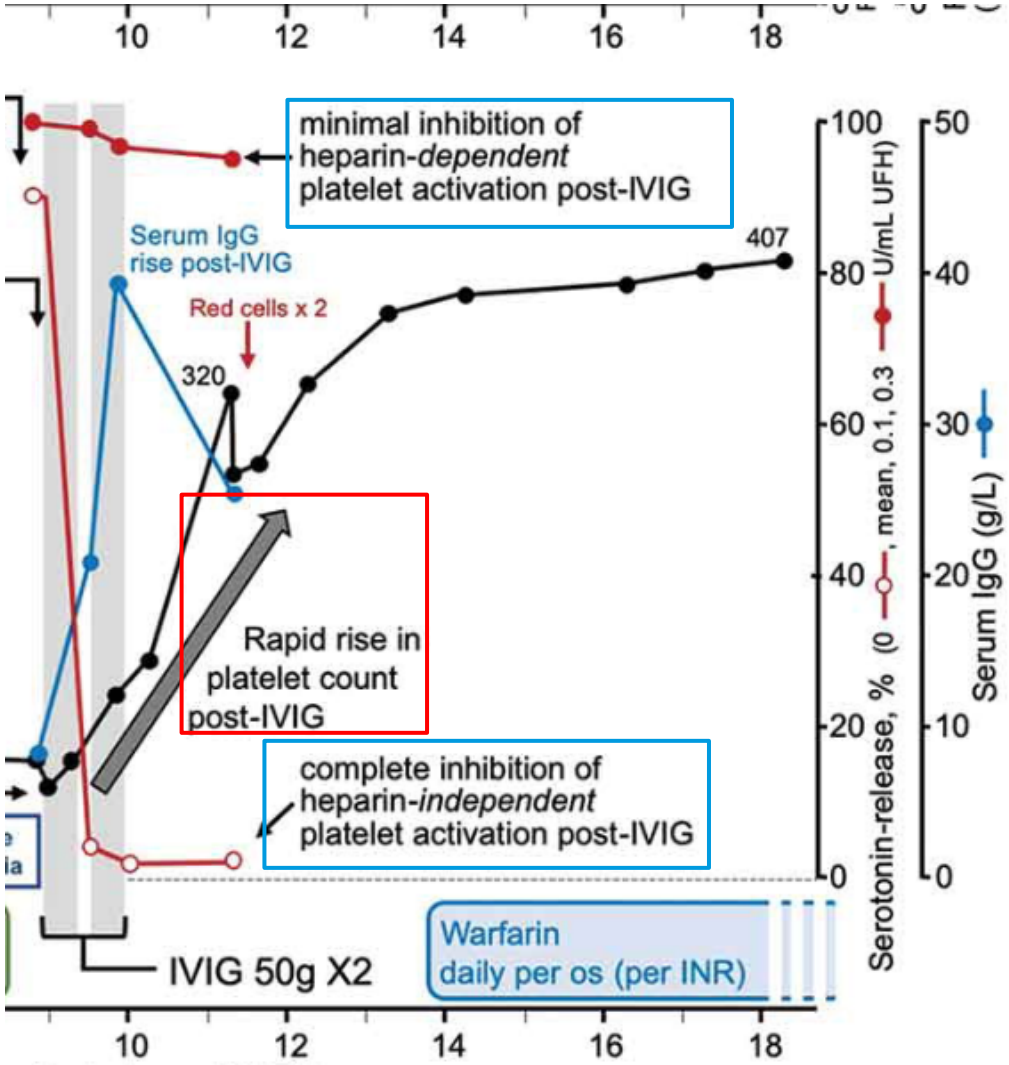
- 67 y/o woman receiving prophylactic UFH following admission for right hip fracture
- Platelet count 78 $*10^9$ /L and hx of recent arterial thrombotic stroke and acute limb artery thrombosis
- CT angiography documented numerous occlusive and non-occlusive thrombi
- Recent stroke began on day 6 of UFH thromboprophylaxis

Warkentin TE. Et al. *Expert Review of Hematology*. 2019

CASE REPORT CONTINUED

- Intra and postoperative anticoagulation was given with therapeutic dose danaparoid
- **Patient received 1 g/kg IVIG on two consecutive days, i.e. a total dose of 100 g (50 g × 2)**
  - Platelet count increase from 61 to 320 × 10^9/L (>58 h)
  - Concomitant ex vivo inhibition of heparin-independent serotonin-release (from ~90% to <5%)
  - Recovery from thrombotic events (no ischemic limb loss; no neurological deficits; no dyspnea)

Suggestive of IVIG as adjunctive therapy to non-heparin anticoagulation



Warkentin TE. Et al. *Expert Review of Hematology*. 2019

RECHALLENGING IN THE SETTING OF HIT

RELEVANT LITERATURE CONTINUED

CLINICAL TRIALS AND OBSERVATIONS

Serological investigation of patients with a previous history of heparin-induced thrombocytopenia who are reexposed to heparin

Theodore E. Warkentin[1,2] and Jo-Ann I. Sheppard[1]

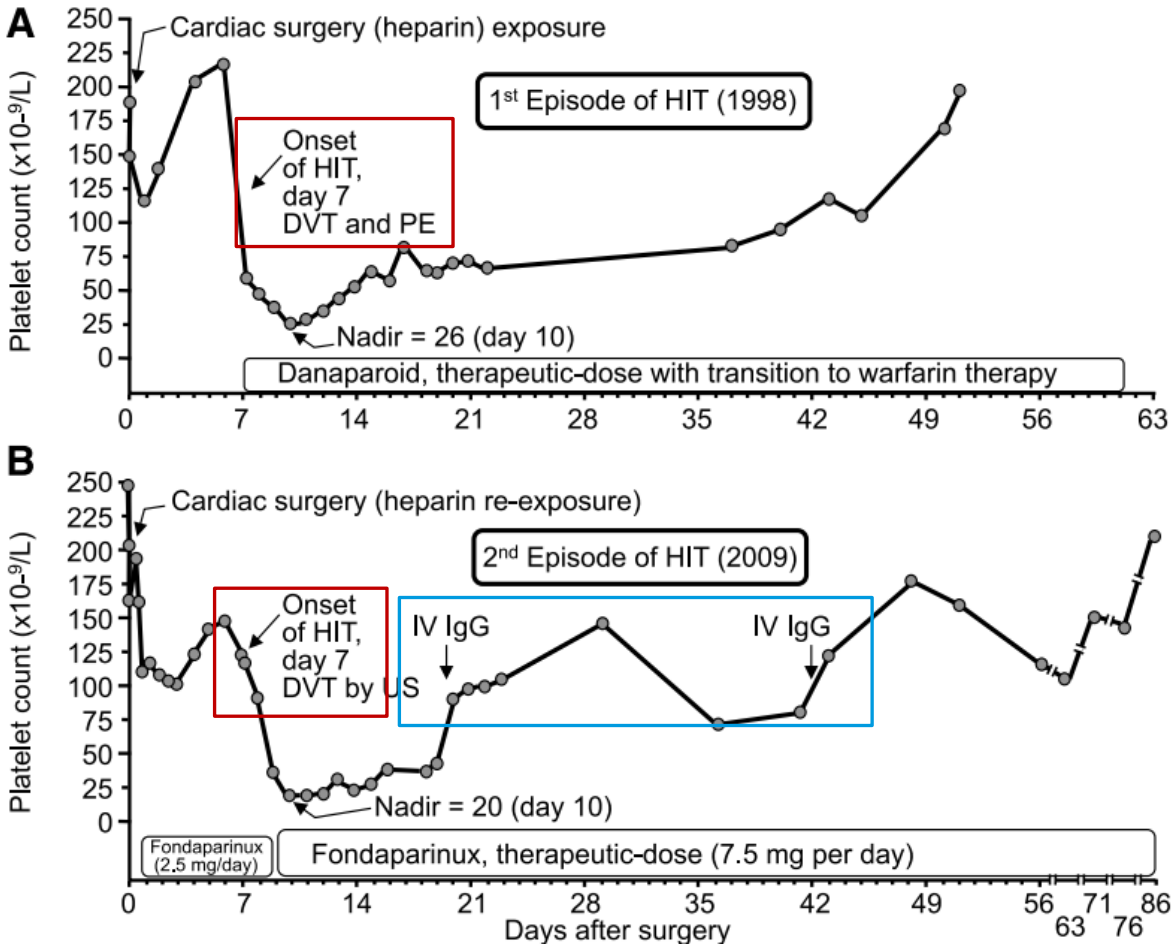
[1]Department of Pathology and Molecular Medicine and [2]Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

SEROLOGICAL INVESTIGATION OF PATIENTS WITH A PREVIOUS HISTORY OF HIT WHO ARE RE-EXPOSED TO HEPARIN

Study Design	Objectives	Results
A retrospective chart review assessing serological conversion in patients with well-documented previous HIT who underwent re-exposure to heparin Previous episode of HIT categorized by 4T's score >4, positive SRA	• **Primary:** Determine frequency, timing and isotype profile of antibody formation • **Secondary:** Determine whether heparin-re-exposed patients develop recurrent HIT	20 patients with previous HIT who underwent repeat re-exposure to heparin occurring 4.4 years post-HIT diagnosis 8 of 17 patients re-exposed to heparin because of cardiac or vascular surgery developed seroconversion to a positive SRA despite none of the 17 receiving LMWH postoperatively Anti-PF4/heparin IgG became detectable at day 7

Warkentin TE, et al. 2014. *Blood*.

RESULTS CONTINUED



One patient experienced recurrent HIT after re-exposure to UFH for cardiac surgery

- Onset of HIT occurred by day 7 for both episodes
- The patient's platelet count rose transiently on 2 occasions after administration of high dose IV IgG
- Both the EIA-IgG and SRA became positive on day 6

- Heparin rechallenge despite prior HIT induces anti-PF4/heparin antibodies but no faster than seen with typical HIT
- Risk of HIT recurring after heparin rechallenge is low but possible if IgG with heparin-independent platelet activating properties are made

Warkentin TE, et al. 2014. *Blood*. 70

KEY TAKEAWAYS

HIT is a prothrombotic, immune-mediated complication of heparin

The 4T's score, immunoassay and functional assay are tools used to guide testing and management in the setting of HIT

When suspicion is intermediate/high, stop heparin products and promptly initiate a non-heparin anticoagulant

Early detection and optimization of therapy is crucial in the management of HIT

New advancements in pathogenicity of HIT antibodies allow for potential changes for detection and optimization of therapy

ACKNOWLEDGEMENTS

The collaborative contributions from the following individuals have been greatly appreciated:

Co-Preceptors:

- Jonathan Anson, PharmD, BCPS
- Jansher Khan PharmD, BCPS, BCEMP

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THE CLOT THICKENS: UNDERSTANDING HEPARIN INDUCED THROMBOCYTOPENIA

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