Approach to the Hospitalized Patient with Thrombocytopenia

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Disclosures

- None

Learning Objectives

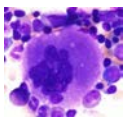
- Recognize common causes of thrombocytopenia in hospitalized patients
- Identify life threatening causes of thrombocytopenia that require urgent intervention
- Formulate a differential diagnosis for thrombocytopenia using key clinical and laboratory parameters

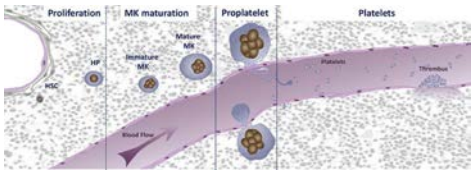
Thrombocytopenia

- Platelet count < 150,000
  - Platelets between 100,000-150,000 may be normal for some people
- Platelets > 50,000: minimal to no increase risk in bleeding
- Platelets 20-50K: minimal bleeding risk unless other hemostatic impairment or undergoing invasive procedure
- Platelets < 10,000: risk of spontaneous bleeding

Ali, N., & Auerbach, H. E. (2017). *Journal of Community Hospital Internal Medicine Perspectives*, *7*(3), 157–167. https://doi.org/10.1080/20009666.2017.1335156

Platelet Production





Strassel, C., Gachet, C., & Lanza, F. (2018). On the Way to in vitro Platelet Production. *Frontiers in Medicine*, *5*(AUG), 239. https://doi.org/10.3389/fmed.2018.00239

Thrombopoietin (TPO)

- Thrombopoietin secreted constitutively– at a constant rate regardless of physiological demand
- Platelets auto-regulate
- Results in platelet count remaining remarkably stable in an individual patient over time
- Platelet count is predominantly genetically determined
- Very little inter-individual variability

Buckley, M., James, J., Brown, D., Whyte, G., Dean, M., Chesterman, C., & Donald, J. (2000). A Novel Approach to the Assessment of Variations in the Human Platelet Count. *Thrombosis and Haemostasis*, *83*(03), 480–484. https://doi.org/10.1055/s-0037-1613840

Thrombocytopenia in Hospitalized Patients

- Very common-occurs in up to 50% of hospitalized patients
- Usually mild thrombocytopenia-platelets less than 10,000 highly unusual in hospitalized patient (except acute leukemia)
- Always a secondary cause
- Nearly always discovered incidentally
- Morbidity/mortality from thrombocytopenia VERY UNCOMMON
  - Usually results from underlying disorder
- Almost always due to increased platelet destruction
  - Sepsis
  - Drug induced
  - Immune
  - Post-op (low platelets often follow surgery)

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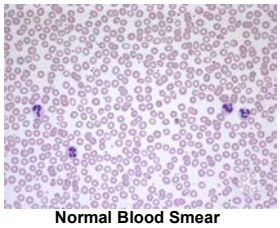
STEP 1: Thrombocytopenia should always be confirmed by examination of peripheral smear

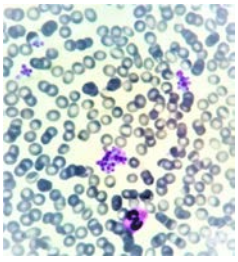


Normal Blood Smear

- Are the platelets clumped?
- RBC normal?
  - Fragmented plts=>DIC, TTP/HUS
- WBC- high or low
  - Infections, leukemia

Pseudothrombocytopenia

- 67 y/o man s/p cycle 1 FOLFOX admitted with neutropenic fevers
- Platelets < 20,000
- No petechiae, ecchymosis or bleeding from any site
- Physical exam normal
- Peripheral smear: platelets “clumped”
- CBC drawn with sodium citrate as anticoagulant, platelets = 210,000
- Occurs in 1:100-1:1000 collections



Multiple aggregates of platelets in CBCs done using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant (standard lavender top tube).

ASH Image Bank. Image ID 62132. Authors: Shruti Mantri, DM;Govind Kendre, DM;Sunil Hilalpure, MD;Suraj Goyanka, MD;Leo Prince, MD;Murlidharan C, MD;Chandrakala S, DM;Farah Jijina, MD. **Pseudothrombocytopenia**

STEP 2: Initial Labs

- Electrolytes, LFTs, creatinine
- DIC screen: Fibrinogen, d-dimer, INR, PTT
- LDH
- Blood cultures, if appropriate

Bone marrow biopsy seldom useful

STEP 3: Rule Out Life Threatening Causes

- Sepsis=>blood cultures, lactate
- Heparin-induced thrombocytopenia (HIT)=>HIT EIA
- Disseminated Intravascular Coagulation (DIC)-DIC screen
- Thrombotic thrombocytopenia purpura/hemolytic uremic syndrome (TTP/HUS)=>fragmented RBC, increased LDH
- Drug-induced immune thrombocytopenia (DITP)
- Primary ITP with bleeding
- Acute leukemia
- Post transfusion purpura (PTP)

STEP 4: Determine Clinical Context

Most Common Causes of Thrombocytopenia in Hospitalized Patients

Medical Patients/ICU	Cardiac Patients
• Infections	• Heparin induced thrombocytopenia (HIT)
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	• Cardiac bypass
• Drug-induced thrombocytopenia (DITP)	• GPIIb/IIIa inhibitors
• Disseminated Intravascular Coagulation (DIC)	• Drug-induced thrombocytopenia (DITP)
• Liver disease	• Dilutional
• Heparin induced thrombocytopenia (HIT)	
• Macrophage activation syndrome	
• Bone marrow disorders	
• Chemotherapy-induced thrombocytopenia	

Ali, N., & Auerbach, H. E. (2017). *Journal of Community Hospital Internal Medicine Perspectives*, *7*(3), 157–167. https://doi.org/10.1080/20009666.2017.1335156

STEP 5: Assess Severity of Thrombocytopenia

	Platelet Count (x 10^9)	Diagnoses
Very Low	< 10	ITP DITP Very severe sepsis DIC
Low	10-20	ITP DITP Severe sepsis TTP
Moderate	20-100	TTP HIT Sepsis Cirrhosis

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STEP 6: Assess Timing In Relation to Exposures

- Within 24 hours: dilutional, postoperative
- Within 1-5 days: acute thrombosis thrombocytopenia, septic thrombocytopenia, DIC,TTP/HUS
- Between 5-10 days: classic HIT, DITP, PTP

Ali, N., & Auerbach, H. E. (2017). *Journal of Community Hospital Internal Medicine Perspectives*, 7(3), 157–167. https://doi.org/10.1080/20009666.2017.1335156

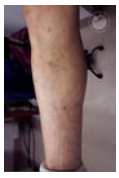
STEP 7: Assess for Bleeding or Thrombosis

Bleeding?
DITP, PTP, DIC

Absence of Bleeding or Thrombosis?
HIT, TTP, Sepsis, DIC

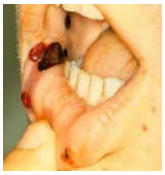
Ali, N., & Auerbach, H. E. (2017). *Journal of Community Hospital Internal Medicine Perspectives*, 7(3), 157–167. https://doi.org/10.1080/20009666.2017.1335156

Bleeding Manifestations in Thrombocytopenia



Petechiae

Ecchymoses (Dry Purpura)



Mucosal Bleeding (Wet Purpura)

Case

- 67 y/o man with metastatic colorectal cancer Day 10 s/p cycle 1 FOLFOX
- Presents with neutropenic fevers and treated with pipercillin/tazobactam
- Low molecular weight heparin SQ 40 mg/d started on admission date for DVT prophylaxis

Hospital Day	0	1	2	3	4	5	6	7
Platelets (x 10^9/L)	203	224	201	232	225	216	148	62
WBC (x 10^9/L)	0.8	0.8	0.9	1.2	2.5	4.1	5.7	5.7

Heparin Induced Thrombocytopenia (HIT)

- One of the most important and catastrophic complications of drug therapy
- Moderate thrombocytopenia that starts ≥ 5 days after heparin
  - Mean platelet count ~ 40K
  - Rarely less than 20K
- Bleeding is rare
- Thrombotic complications: SERIOUS

The paradoxical prothrombotic state makes early recognition of HIT critical.

Greinacher, A. (2015). *New England Journal of Medicine*, 373(3), 252–261. ; Warkentin, T. E. (2016). *Thrombosis and Haemostasis*, *116*(11), 813–822.

Non-Immune Heparin-Associated Thrombocytopenia (AKA Type I HIT)

- Not immune mediated: due to direct effect of heparin
- Heparin binds to platelets, which causes mild platelet activation and formation of tiny platelet aggregates which causes a moderate decrease in platelet count, typically soon after initiation of heparin.
- Fairly common: 10-20% prevalence
- Mild drop in platelets (but > 100k) within 2 days, and platelet count then recovers despite ongoing heparin use
- **NOT** clinically significant
- **NOT** associated with thrombosis

Many experts feel that this clinical scenario should no longer be referred to as HIT since the mechanism and clinical features are distinct from true autoimmune HIT

Greinacher, A. (2015). *New England Journal of Medicine*, *373*(3), 252–261. ; Warkentin, T. E. (2016). *Thrombosis and Haemostasis*, *116*(11), 813–822.

Heparin-Induced Thrombocytopenia Type II HIT - "True HIT"

- Clinically significant and potentially life-threatening syndrome due to autoantibodies to heparin/platelet factor 4 (PF4) complexed, referred to as "HIT antibodies" or "PF4/heparin antibodies"
- Sometimes referred to as HITT- **H**eparin-**I**nduced **T**hrombocytopenia and **T**hrombosis
- Main physiologic concern is activation of the clotting cascade
- Differs from classic drug-induced thrombocytopenia where every platelet is a target of the drug-induced antibody and usually results in a severe thrombocytopenia without thrombosis
- Due to IgG antibodies which take ~ 5 days to develop; unusual that they are transient and typically disappear
- If patient exposed to heparin in prior 1-3 months, circulating HIT Abs can still exist and cause HIT much earlier (within 1 day)

Greinacher, A. (2015). *New England Journal of Medicine*, *373*(3), 252–261.; Warkentin, T. E. (2016). *Thrombosis and Haemostasis*, *116*(11), 813–822.

Pretest Scoring System for HIT

4 Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% **AND** platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30%–50% **OR** platelet nadir 10–19 x 10^9/L	Platelet count fall < 30% **OR** platelet nadir < 10
Timing of platelet count fall Day 0= day heparin started Onset = day platelet count begins to decrease	Clear onset between Days 5–14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with Days 5–14 fall, but not clear (eg, missing platelet counts); onset after Day 14 or fall ≤ 1 day (prior heparin 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 IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes for Thrombocytopenia	None apparent	Possible	Definite

HIGH probability: 6-8 points
INTERMEDIATE probability: 4-5 points
LOW probability: ≤ 3 points (HIT Unlikely, negative predictive value: 97-99%)

Cuker, A., et al. (2012). Blood, 120(20), 4160–4167.; 2019 ASH Clinical Guideline

In the setting of progressive thrombocytopenia and heparin exposure, you are concerned about the possibility of HIT.
What is the clinical probability of HIT?

Our patient:
Platelets 62 which is > 50% drop = 2 points
Onset of drop on day 7 = 2 points
No thrombosis = 0 points
Other cause for thrombocytopenia possible = 1 point

HIGH probability: 6-8 points
INTERMEDIATE probability: 4-5 points
LOW probability: ≤ 3 points

Your patient's 4Ts score indicates intermediate clinical probability for HIT.

What diagnostic tests would you recommend at this point to confirm or exclude a diagnosis of HIT?

A. None; patient is intermediate probability and diagnosis is confirmed
B. Immunoassay only (ex. HIT PF4/heparin ELISA)
C. Functional test only (ex. serotonin release assay)
D. Immunoassay, and if positive then perform functional test

Laboratory Diagnostic Testing for HIT

HIT Immunoassay *Detect the presence of anti-PF4/heparin antibodies*	Functional HIT Assays *Assays that detect antibodies capable of binding and activating platelets*
ELISA: Anti–PF4–heparin enzyme immunoassay (detect IgG): • Excellent negative predictive value (98-99%) • Low positive predictive value (detects clinically insignificant anti–PF4–heparin antibodies) • Should NOT be used as a screening test	Heparin-induced platelet aggregation: • Highly specific (>90%) but not as sensitive as immunoassay Serotonin Release Assay: • Gold standard, (sensitivity >95%, specificity >95%). Measures radiolabeled serotonin release on donor platelets in response to heparin and patient plasma.

Greinacher, A. (2015). NEJM. 373(3), 252–261. https://doi.org/10.1056/NEJMcp1411910;
Greinacher, A., et al. (2019). In A. D. B. T-P. (Fourth E. Michelson (Ed.), Platelets (4th ed., pp. 741–767). https://doi.org/https://doi.org/10.1016/B978-0-12-813456-6.00041-2; Cuker, A., et al.. (2018). Blood Advances, 2(22), 3360–3392. https://doi.org/10.1182/bloodadvances.2018024489

Your patient's 4Ts score indicates intermediate probability for HIT and HIT ELISA test pending. Currently, your patient is receiving subcutaneous enoxaparin 40 mg/d. What management strategy would you recommend while awaiting the HIT ELISA test results?

A. Continue heparin as the diagnosis of HIT is not confirmed
B. Stop heparin, wait for ELISA result
C. Stop heparin, start non-heparin anticoagulant at prophylactic intensity
D. Stop heparin, start non-heparin anticoagulant at therapeutic intensity
E. Stop heparin, transfuse platelets

Initial Recommendations

For suspected HIT with HIGH or INTERMEDIATE PROBABILITY 4Ts score:
Discontinue heparin and start a non-heparin anticoagulant at **therapeutic** dosing

For suspected HIT with INTERMEDIATE PROBABILITY 4Ts score AND High Bleeding Risk:
Discontinue heparin and start a non-heparin anticoagulant at **prophylactic** dosing

- **Order an immunoassay:**
  - If negative, HIT unlikely
  - If positive, order functional testing to rule out false positive.
  - If high probability 4Ts score and very strongly positive immunoassay (ELISA value of > 2.0 OD units), functional assay probably not necessary

Cuker, A., et al.. (2018). Blood Advances, 2(22), 3360–3392.
https://doi.org/10.1182/bloodadvances.2018024489

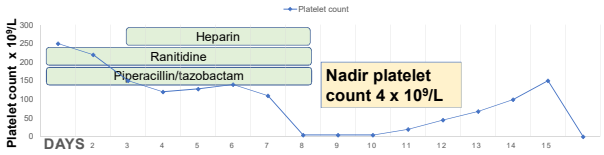
Treatment of HIT

- **Stop** heparin-including LMWH
- Start alternative anticoagulant **even** if patient does not have thrombotic complications:
  - Critically ill, increased bleeding risk, or possible urgent procedures:
    - Parenteral Direct thrombin inhibitor: Argatroban or Bivalirudin (Angiomax) in CV surgery & ECMO
  - Clinically stable patients at average bleeding risk
    - Fondaparinux
    - DOACs: Rivaroxaban, apixaban, dabigatran
- Platelet count should respond within days
- Severe refractory HIT-Consider high dose IVIG (1g/kg/day x 2 days)
- Extended anticoagulation (1+ month) generally recommended (even in absence of thrombosis)
  - The risk of thrombosis with HIT is ~50% at 1 month
- Prognosis: antibodies to heparin-PF4 typically disappear within 3 months, and at this point, if heparin is absolutely necessary (e.g. CABG), can potentially re-challenge

Warkentin TE et al. *Blood* 2017
Sanfilippo F et al. *J Intensive Care Med* 2017
Padmanabhan A, et al. *Chest* 2017

Case

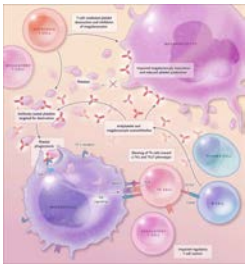
- 67 y/o man with metastatic colorectal cancer s/p cycle 1 FOLFOX
- Presents with neutropenic fevers, and treated with pipercillin/tazobactam

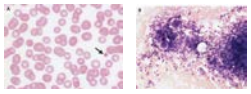


What is the most likely cause of thrombocytopenia in this patient?

A. Drug-induced thrombocytopenia
B. Heparin-Induced thrombocytopenia
C. Sepsis-induced thrombocytopenia
D. Chemotherapy-induced thrombocytopenia
E. TTP/HUS

Immune Thrombocytopenia





- Production of antiplatelet autoantibodies that target platelets for destruction by macrophages in the spleen, liver, or both through activation of Fcγ receptors.
- May be idiopathic, drug-induced or secondary to an underlying inflammatory condition
- Antiplatelet autoantibodies not detected in up to 50% of patients, thus there may be alternate mechanism such as T cells
- The peripheral smear (Panel A) will reveal thrombocytopenia, while the bone marrow (Panel B) will reveal increased numbers of megakaryocytes in a response to produce additional platelets

Cooper, N., & Ghanima, W. (2019). NEJM, 381(10), 945–955.

Characteristics of Drug-Induced Immune Thrombocytopenia (DITP)

- Platelets < 20, often bleeding
- Onset 5-10 d after exposure
  - Abciximab-within hours
- Diagnosis and Treatment: Stop Drug
- Consider serology, but really hard to prove with serology
- Consider platelet transfusions

Arnold DM Kukaswadia S Kelton J Thromb Haemost 2013 Jan

HIT versus DITP

- Patients with typical DITP usually bleed when symptomatic
- In contrast to heparin-induced thrombocytopenia (HIT), where most patients usually have thrombotic complications without bleeding

Arnold DM Kukaswadia S Kelton J Thromb Haemost 2013 Jan

DITP: Common Culprits

- Quinine
- Quinidine
- Trimethoprim/sulfamethoxazole
- Vancomycin
- Penicillin
- Rifampin
- Carbamazepine
- Ceftriaxone
- Ibuprofen
- Mirtazapine
- Oxaliplatin
- Suramin
- Abciximab
- Tirofiban
- Eptifibatide
- Heparin

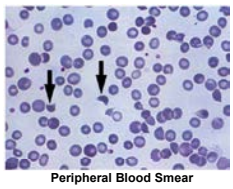
DITP = Drug-induced immune thrombocytopenia

Database of reports of drug induced thrombocytopenia: "Platelets on the Web" https://www.ouhsc.edu/platelets/ditp.html

Case

- 67 y/o man with metastatic colorectal cancer s/p cycle 1 FOLFOX
- Presents with neutropenic fevers and treated with pipercillin/tazobactam

CBC	
WBC	0.8
ANC	300 mcL
Hb	7.8 g/dL
Platelets	12 x 10^9/L



Peripheral Blood Smear

- Fragments
- Schistocytes
- Decreased platelets

ISTH Scoring System for DIC

Points	3	2	1	0
Platelet count (10^9/L)		< 50	< 100	> 100
Elevated fibrin marker (e.g. D-dimer, fibrin degradation products)	Strong increase	Moderate increase	--	No increase
Prolonged PT (sec)	--	> 6	> 3 but <6	< 3
Fibrinogen (g/dL)	--	--	< 100	> 100
≥5 compatible with overt DIC: repeat score daily <5 suggestive for non-overt DIC: repeat next 1–2 d				

This algorithm not recommended if patient does not have an underlying disorder known to be associated with overt DIC

Levi, M. et al. British Journal of Haematology, 2009, 145, 24–33

Disseminated Intravascular Coagulation (DIC)

Most common acquired hypercoagulable state in hospitalized patients

- Characterized by the systemic activation of the coagulation system followed by activation of fibrinolytic system
  - thrombosis
  - bleeding
- DIC is not a disease itself, but is a manifestation of a serious underlying disorder; usually due to:
  - Trauma = tissue factor release from tissues as a result of the trauma
  - Malignancy = increased malignant cell expression of tissue factor. Since there is no acute release of tissue factor, the DIC of malignancy is often chronic
  - Sepsis = increased expression of tissue factor by monocytes and endothelial cells via inflammatory mediators

Toh, C. H., & Alhamdi, Y. (2013). *Hematology. American Society of Hematology. Education Program*, *2013*(1), 286–291

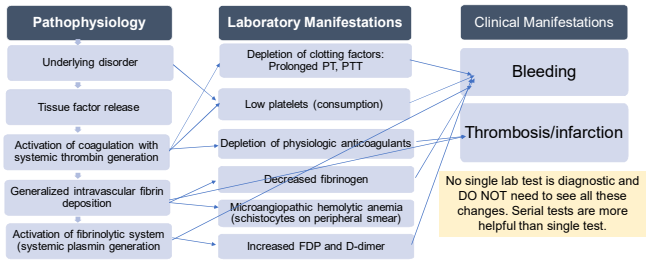
Clinical Conditions Most Frequently Associated with DIC

Condition	Examples	Impact of precipitating condition
Severe infectious diseases	Gram-positive or -negative organisms, malaria, hemorrhagic fevers	Thrombosis may contribute to organ failure (eg acute kidney failure)
Malignancy	Solid tumors (eg, adenocarcinomas)	Primarily thrombotic consequences/VTE
	Acute promyelocytic leukemia or monocytic leukemia	Severe thrombocytopenia and factor deficiency may lead to bleeding
Trauma	Multitrauma	Primary feature is acute bleeding, followed by thrombosis
	Brain injury	
	Burns	
Obstetrical complications	Abruptio placentae	Profuse bleeding in combination with thrombotic complications
	Amniotic fluid embolism	
Vascular malformations	Kasabach-Merrit syndrome	Bleeding primarily with severe thrombocytopenia and hypofibrinogenaemia
	Giant hemangiomas	
	Other vascular malformations	
	Large aortic aneurysms	
Severe immunologic reactions	Transfusion reaction	
Heat stroke		Thrombotic features more common than bleeding
Post–CPR		Thrombosis is a greater risk than bleeding

CPR = cardiopulmonary resuscitation; VTE = venous thromboembolism

Levi, M., & Scully, M. (2018). *Blood, 131*(8), 845–854.

Laboratory and Clinical Manifestations of DIC



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Diagnostic and Therapeutic Management of DIC

- Clinical Suspicion of DIC: Underlying condition known to be associated with DIC AND low/decreasing platelet count and/or prolonged clotting assays
- Use DIC scoring algorithm
  - If score < 5=> no DIC, consider repeating after 1-2 days
  - If score ≥ 5=> c/w DIC; treat the underlying condition and supportive care as below:

Active Bleeding or Need to undergo Invasive Procedure

- Platelet transfusion to keep plts > 30-50 x 109/L
- Plasma and/or factor concentrate to keep PT < 3 sec prolonged and fibrinogen > 1.5 g/L
- Vitamin K suppletion if suspected/known deficiency
- Antifibrinolytic treatment if indicated for severe hyperfibrinolysis

No Major Bleeding or Thrombosis

- Prophylactic anticoagulant (e.g. LMW heparin)

Overt Thromboembolism an/or Organ failure due to clot formation

- Therapeutic anticoagulant (e.g. unfractionated heparin)

LMW = low molecular weight

Levi, M., & Scully, M. (2018). *Blood, 131*(8), 845–854.

Summary

- Thrombocytopenia common finding in hospitalized patients
- Always review peripheral smear
- Rule out life threatening causes
- Determine clinic context
- Assess timing and severity of thrombocytopenia
- Thrombosis is generally more common and serious sequela than bleeding for the patient with thrombocytopenia