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107 - Don't get HIT: venous thromboembolism and heparin-induced thrombocytopenia

Chris Kyper, DNP, CPNP AC / PC

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Speaker Disclosure

I have no personal disclosures

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Learning Objectives

- Identify risk factors for venous thromboembolism
- Define Heparin-induced thrombocytopenia
- Describe treatment options for HIT
- Describe the use of direct oral anticoagulants in pediatrics

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Incidence venous thromboembolism (VTE)

- 0.14 to 0.21 per 10,000 children per year in the general population
- 0.2 to 1% in hospitalized patients
- Highest among children with underlying medical conditions, such as malignancy and cardiac disease
- Up to a third of all VTEs are CVC related

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Risk of VTE in children versus adults

- Substantially lower in children
- Less commonly develop diseases causing damage to the vascular endothelium
- Less exposure to acquired prothrombotic risk factors
- Lower plasma concentrations of all vitamin K dependent factors and almost all contact factors, as well as reduced capacity to generate thrombin

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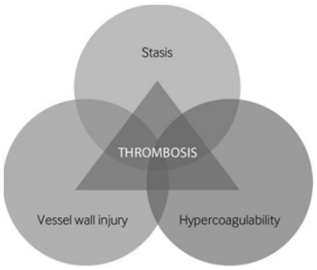
Virchow's Triad



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Provoked VTE

Develop due to identifiable underlying conditions and risk factors.

Criteria

- No prior history of VTE
- VTE is not severe or life threatening
- Provoking risk factor is transient
- Thrombus resolves or is nonocclusive within six weeks

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Unprovoked VTE

Not attributable to an underlying risk factor

- Rare in children
- Treatment consists of therapeutic anticoagulation for 6 - 12 months
- Recurrent unprovoked VTE are treated indefinitely
- Test for inherited thrombophilia

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VTE Risk factors

- Central venous catheters (CVC)
- Age
- Infection
- Malignancy
- Congenital heart disease
- Trauma
- Estrogen containing contraceptives
- Nephrotic syndrome
- Irritable bowel disease
- Systemic lupus erythematosus and antiphospholipid syndrome
- Vascular abnormalities
- Hospitalized patients

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Clinical Manifestations of VTE

- Central venous catheter (CVC)
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Renal vein thrombosis (RVT)
- Portal vein thrombosis (PVT)
- Central (sinus) venous thrombosis (CVT)

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Coagulation

- Gel plug
- Coagulation factors
- Calcium
- Phospholipids

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Coagulation can be initiated by either of two distinct pathways

Intrinsic pathway

Extrinsic pathway

Completion of the process follows a common pathway

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Coagulation factors and their common names

- Factor I - fibrinogen
- Factor II - prothrombin
- Factor III - tissue thromboplastin (tissue factor)
- Factor IV - ionized calcium (Ca++)
- Factor V - labile factor or proaccelerin
- Factor VI - unassigned
- Factor VII - stable factor or proconvertin
- Factor VIII - antihemophilic factor
- Factor IX - plasma thromboplastin component, Christmas factor
- Factor X - Stuart-Prower factor
- Factor XI - plasma thromboplastin antecedent
- Factor XII - Hageman factor
- Factor XIII - fibrin-stabilizing factor

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Phases of coagulation and fibrinolysis

- Platelet plug
- Fibrin deposition
- Termination
- Fibrinolysis
- Connections to the immune system

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Goals of treating VTE

- Prevent local extension and embolization of the thrombus
- Aid in resolving the existing thrombus
- Prevent VTE recurrence
- Minimize long-term complications

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Commonly used anticoagulant agents

- Unfractionated heparin (UFH, heparin)
- Low molecular weight heparin (LMWH, enoxaparin [Lovenox])
- Vitamin K antagonist (VKA, warfarin [Coumadin])
- Direct oral anticoagulants (DOAC)
- Thrombolytic therapy (eg, recombinant tissue plasminogen activator [tPA])

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Heparin Induced Thrombocytopenia (HIT)

Results from an autoantibody directed against endogenous platelet factor 4 (PF4) in complex with heparin

Untreated HIT has a mortality rate as high as 20% although with improved recognition and early intervention, mortality rates have been reported below 2%

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Distinguishing characteristics of type I versus type II heparin-induced thrombocytopenia

	Type I	Type II
Frequency	10 to 20%	1 to 3%
Timing of onset	1 to 4 days	5 to 10 days after start of heparin
Nadir platelet count	100,000/microL	usually >20,000/microL; median nadir 60,000/microL
Antibody mediated	No	Yes
Thromboembolic sequelae	None	30 to 80%
Hemorrhagic sequelae	None	Rare
Management	Observe	Cessation of heparin, alternative nonheparin anticoagulation to prevent thrombosis

Adapted from: Brieger DB, Mak KH, Kottke-Marchant K, Topol EJ. Heparin-induced thrombocytopenia. J Am Coll Cardiol 1998; 31:1449.

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HIT Variants / autoimmune HIT

- Delayed-onset HIT
- Refractory (persistent) HIT
- Spontaneous HIT (SpHIT)
- Vaccine-induced immune thrombotic thrombocytopenia (VITT)
- Heparin-induced antibodies (HIA)

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Five phases of heparin-induced thrombocytopenia (HIT)

Suspected HIT
- Platelet count – Low
- Heparin-PF4 assays – Not yet available

Acute HIT (confirmed diagnosis)
- Platelet count – Low
- Heparin-PF4 assays – Positive (functional assays and/or immunoassays)

Subacute HIT A (platelet count recovered but persistent HIT antibodies)
- Platelet count – Recovered to normal or patient's baseline
- Heparin-PF4 assays – Positive (functional assays and immunoassays)

Subacute HIT B (persistent HIT antibodies but functional assay no longer positive)
- Platelet count – Recovered to normal or patient's baseline
- Heparin-PF4 assays – Functional assay has become negative (after previously being positive); immunoassay remains positive

Remote HIT (HIT resolved, but patient remains at risk for developing acute HIT)
- Platelet count – Normal or patient's baseline
- Heparin-PF4 assays – Negative (after previously being positive)

Heparin-PF4 assays include functional and immunoassays; refer to UpToDate for the use of this testing and interpretation of the results. Refer to UpToDate and the source articles for guideline recommendations that relate to these phases of HIT.

HIT: heparin-induced thrombocytopenia; PF4: platelet factor 4.

Adapted from:
1. Cuker A. Management of the multiple phases of heparin-induced thrombocytopenia. Thromb Haemost 2016; 116:805.
2. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv 2018; 2:3360.

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Pathophysiology

- Formation of HIT antibodies
  - Unusual immunobiology
  - IgG antibodies form rapidly
  - No IgM response
  - Immune memory does not always persist
- Platelet factor 4 (PF4)
  - PF4 forms a tetramer that binds to and neutralizes heparin
  - Once HIT antibodies bind to PF4 on platelet surface, their Fc region is captured by Fc receptors on the surface of the same or adjacent platelets
  - A positive feedback loop is formed which furthers platelet activation
  - This leads to more PF4 release which creates more antigenic substrate for HIT antibodies
- Mechanism of thrombocytopenia
  - Includes removal of IgG-coated platelets by macrophages of the reticuloendothelial system (spleen, liver, bone marrow) via binding to FcγRIIA
  - Consumption of platelets at sites of thrombus and platelet destruction due to development of consumptive coagulopathy

Clinical Manifestations

- Thrombocytopenia
- Bleeding
- Timing
- Delayed-onset HIT following withdrawal of heparin
- Thrombosis

Thrombotic sequelae

- Skin necrosis
- Limb gangrene
- Organ ischemia or infarction
- Anaphylaxis

Evaluation

Suspecting HIT

- New onset thrombocytopenia
- Decrease in platelet count by 50% or more
- Venous or arterial thrombosis
- Necrotic skin lesions at heparin injection site
- Acute systemic reactions

Do Not wait for thrombus to develop, thrombocytopenia often precedes thrombosis with HIT

Early intervention has the potential to prevent thrombus wich is major cause of morbidity and mortality in HIT

Approach to evaluation

- Consider clinical AND laboratory evidence in evaluating for HIT
- Definitive laboratory data may not be available or take days to result
- 4Ts scoring system
- Treatment is initiated based on scoring and diagnosis is either confirmed or refuted based on lab results

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4 Ts score for estimating the pretest probability of heparin-induced thrombocytopenia (HIT)

4 Ts score parameters:	
Thrombocytopenia:	
• PLT decrease >50% **AND** nadir ≥20,000/mcmL **AND** no surgery within preceding 3 days	2 points
• PLT decrease >50% **BUT** surgery within preceding 3 days **OR** any combination of PLT fall and nadir that does not fit criteria for 2 or 0 points (eg, 30 to 50% fall or nadir 10,000 to 19,000/mcmL)	1 point
• PLT decrease <30% **OR** nadir <10,000/mcmL	0 points
Timing of onset after heparin exposure:	
• 5 to 10 days **OR** ≤ 1 day if exposure within past 5 to 30 days	2 points
• Probable 5 to 10 days (eg, missing PLT counts) **OR** >10 days **OR** ≤1 day if exposure within past 31 to 100 days	1 point
• ≥4 days without exposure within past 100 days	0 points
Thrombosis or other clinical sequelae:	
• Confirmed new thrombosis, skin necrosis, anaphylactoid reaction, or adrenal hemorrhage	2 points
• Suspected, progressive, or recurrent thrombosis, skin erythema	1 point
• None	0 points
Other cause for thrombocytopenia:	
• None	2 points
• Possible (eg, sepsis)	1 point
• Probable (eg, DIC, medication, within 72 hours of surgery)	0 points
Interpretation:	
6 to 8 points – High probability (approximately 50%)	
4 to 5 points – Intermediate probability (approximately 10%)	
0 to 3 points – Low probability (<1%)	

HIT is a clinical and laboratory diagnosis, and this score is not intended to take the place of clinical judgment by a clinician with experience in diagnosing and managing HIT. Refer to UpToDate for details of the evaluation.

PLT: platelet; DIC: disseminated intravascular coagulation.

Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 Ts) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006; 4:759.

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Caveats to Evaluation

- Diagnosis
- Presumptive diagnosis
- Immediate discontinuation of heparin
- Confirmatory testing
- Non-heparin anticoagulant

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HIT antibody testing

- Immunoassays (ELISA)
- Functional assays
- Serotonin release assay (SRA)
- Heparin-induced platelet activation (HIPA)
- Pediatrics

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Management of HIT

Two major goals:

Halt platelet activation as rapidly as possible

Provide therapeutic-dose anticoagulation with a non-heparin anticoagulant until thrombus risk has returned to baseline

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Considerations for anticoagulation

- Urgency of anticoagulation
- Possible need for urgent reversal
- Chronic kidney or liver disease
- Other considerations

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Anticoagulants

Warfarin (VKA) - use in children is well established

Direct Thrombin Inhibitors (DTIs)

- Argatroban - no pediatric indications
- Bivalirudin - phase I trials in pediatrics
- Dabigatran (Prodaxa) - Pediatric approval in 2021 for 3 months and up

Direct Factor Xa Inhibitors

- Fondaparinux (Arixta) - Approved for pediatrics over 1 year
- Rivaroxaban (Xarelto) - Approved for gestational age >37 weeks

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DOACs

- Includes both thrombin and factor Xa inhibitors
- Given orally
- Rivaroxaban (Xarelto) and Dabigatran (Prodaxa) most commonly used in pediatrics
- Consideration of initiation
- Most common interactions are with medications that induce or inhibit cytochrome P450
- Common drugs in pediatrics that use this pathway include rifampin, carbamazepine, phenytoin, phenobarbital, clarithromycin, amiodarone, fluconazole, and cyclosporine
- Management around procedures has not been studied in children

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Long-term sequelae

Life-long avoidance of heparin

Sources of heparin:

- All forms of heparin and LMWH
- Heparin flushes (arterial lines, CVC, PIV)
- Heparin bonded catheters
- Heparin-containing medications such as prothrombin complex concentrate (Kcentra)
- Apheresis-derived peripheral blood stem cells
- Some TPN products

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Summary

- As the number of children with chronic diseases increases the incidence of thrombus will rise
- HIT is a dangerous diagnosis to miss but also problematic if made in error
- The introduction of alternative anticoagulants available in pediatrics will make long-term treatment of thrombus easier

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Thank you!!!

Chris Kyper, DNP, CPNP AC/PC
Alaska Native Medical Center
Anchorage, AK
cmbkyper@anthc.org

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References

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; American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv* 2018; 2 (22): 3360–3392. doi: https://doi.org/10.1182/bloodadvances.2018024489

Dabbous, M. K., Sakr, F. R., & Malaeb, D. N. (2014). Anticoagulant therapy in pediatrics. *Journal of basic and clinical pharmacy*, *5*(2), 27–33.https://doi.org/10.4103/0976-0105.134947

Heestermans, M., Poenou, G., Hamzeh-Cognasse, H., Cognasse, F., & Bertoletti, L. (2022). Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. *Cells*, *11*(20), 3214. https://doi.org/10.3390/cells11203214

Franchini, M., Liumbruno, G. M., Bonfanti, C., & Lippi, G. (2016). The evolution of anticoagulant therapy. *Blood transfusion = Trasfusione del sangue*, *14*(2), 175–184.

Linkins, L. A., Dans, A. L., Moores, L. K., Bona, R., Davidson, B. L., Schulman, S., & Crowther, M. (2012). Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141*(2 Suppl), e495S–e530S.

May, J., Westbrook, B., & Cuker, A. (2023). Heparin-induced thrombocytopenia: An illustrated review. *Research and practice in thrombosis and haemostasis*, *7*(5), 100283.

O'Brien, S. H., Stanek, J. R., Wittmer, C. M., & Raffini, L. (2022). The Continued Rise of Venous Thromboembolism Across US Children's Hospitals. *Pediatrics*, *149*(3), e2021054649.

Patel, N., Petersen, T. L., Simpson, P. M., Feng, M., & Hanson, S. J. (2020). Rates of Venous Thromboembolism and Central Line-Associated Bloodstream Infections Among Types of Central Venous Access Devices in Critically Ill Children. *Critical care medicine*, *48*(9), 1340–1348.

Smythe, M. A., Priziola, J., Dobesh, P. P., Wirth, D., Cuker, A., & Wittkowsky, A. K. (2016). Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *Journal of thrombosis and thrombolysis*, *41*(1), 165–186. https://doi.org/10.1007/s11239-015-1315-2

Warkentin, T. E., Sheppard, J. I., Moore, J. C., Sigouin, C. S., & Kelton, J. G. (2008). Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. *Journal of thrombosis and haemostasis : JTH*, *6*(8), 1304–1312.

Whitworth, H., & Raffini, L. (2022). Practical Considerations for Use of Direct Oral Anticoagulants in Children. *Frontiers in pediatrics*, *10*, 860369.

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