Shanna and Sierra
March 2020

Heparin-Induced Thrombocytopenia (HIT) II

Pathophysiology[1]: HIT II is an immune mediated pathway that forms antibodies and activates Platelet-Factor 4 (PF4). The antibodies lead to an increase in platelets and therefore an increased risk for thrombosis. The PF4 complexes with the heparin-platelet combination and triggers an immunologic response, causing macrophages to eliminate the complexes. This leads to thrombocytopenia.

Evaluation[1]:
4Ts: **T**hrombocytopenia, **T**iming of platelet count fall, **T**hrombosis or other sequelae, Other causes for **T**hrombocytopenia. If ≤3 points then low probability (≤5%), 4-5 points intermediate probability (14%), and 6-8 points is high probability (64%). If low score, no immediate assumption of HIT unless clinical judgment suggests otherwise. If score is intermediate or high, treat as HIT and perform testing to confirm.
Signs/Tests: Platelet count $\leq$ $150x10^9$/uL, antibody formation (ELISA testing), platelet activation (Serotonin-Release Assay)

Treatment Course[2]**:** Stop inciting heparin agent. Choose a non-heparin anticoagulant based on patient specific characteristics. Serial monitoring for bleeding and thrombotic complications and platelet counts should continue until episode has resolved. Anticoagulation is recommended post HIT for at least 4 weeks if there was no thrombus and for at least 3 months if a thrombotic event occurred.

Drug	Mechanism[3]	Dose and Route[3]	Therapeutic Monitoring[3]	Clinical Trial Evidence	Other considerations
Argatroban Acova	Direct thrombin inhibitor Activate coag factors V,VIII, XIII	2 mcg/kg/min Max: 10 mcg/kg/min IV	Dose to an aPTT 1.5 to 3 times baseline	Tardy-Poncet B, *et al*.[4] n=20 Argatroban (initial dose range mean 0.77 $\pm$ 0.45 ug/kg/min); 10 patients had thrombosis within 30 days, five had thrombosis after 30 days, four had bleeding events, and 0 had amputations	Dose based on ABW and adjustment is unnecessary for BMI up to 51 kg/m[3] Dose adjustments[3]: Child Pugh class C Warfarin Bridging[3]: Reduce argatroban dose to 2 mcg/kg/min or less and initiate daily warfarin dose D/C argatroban when INR>4 Repeat INR in 4-6 hours, if below therapeutic level- re-initiate argatroban and repeat daily until desired INR on warfarin alone is achieved
Bivalirudin Angiomax	Direct thrombin inhibitor Activate coag factors V,VIII, XIII	0.15-0.2 mg/kg/hour IV	Dose to an aPTT 1.5 to 2.5 times baseline	Joseph L, *et al*.[5] n=461 Retrospective data analysis Platelet recovery in 58.3% Median treatment time of 9 days	Dose adjustments[3]: When CrCl<60 ml/min and for hemodialysis Bridge for 5 days when initiating warfarin[3]
Fondaparinux Arixtra	Factor Xa inhibitor	<50 kg: 5 mg QD 50-100 kg: 7.5 mg QD >100 kg: 10 mg QD SQ	PT and aPTT times not recommended May monitor anti-Xa assay if necessary	Warkentin TE.[6] n=84 Patients with suspected HIT were treated with fondaparinux; 0 developed thrombosis and 3 had a bleeding event	Dose reduction by 50% in CrCl 30-50 ml/min[3] Contraindications[3]: CrCl<30 ml/min and hemodialysis Case reports (three) of cross-reactivity between HIT antibodies and fondaparinux. Fondaparinux further increased platelet activation and treatment failure[6] Warfarin bridge: Overlap until therapeutic INR achieved[3]

Drug	Mechanism[3]	Dose and Route[3]	Therapeutic Monitoring[3]	Clinical Trial Evidence	Other considerations
Apixaban Eliquis	Factor Xa inhibitor	10 mg BID x 7 days then 5 mg BID PO	May monitor anti-Xa assay if necessary	Warkentin TE, *et al.*[7,8] n=12 Patients were given apixaban (dose 5 mg BID for 6 months) for HIT; 0 thrombus or bleeding event	Contraindications[3]: Child Pugh class C No bridging required
Dabigatran Pradaxa	Reversible, direct thrombin inhibitor V, VIII, XI, XIII	150 mg BID PO	No routine coagulation testing	Warkentin TE, *et al.*[7,8] n=11 Patients were treated with dabigatran (dose range 110-150 mg BID ≥10 days); 1 developed thrombosis and 0 had bleeding events	Has not been studied in CrCl <30 ml/min[3] Avoid in patients >120 kg[3] Transitioning from parenteral anticoagulation: Initiate within 2 hours of next scheduled LMWH dose OR start when heparin drip is turned off[3]
Edoxaban Savaysa	Reversible, selective Xa inhibitor	>60 kg: 60 mg QD ≤60 kg: 30 mg QD PO	May monitor anti-Xa assay if necessary	Fallon JM, *et al.*[8] No studies for HIT therapy	Not recommended when CrCl > 95 ml/min or <15 ml/min OR in Child Pugh class B or C[3] Must bridge for 5 days with parenteral anticoagulant[3]
Rivaroxaban Xarelto	Reversible, selective Xa inhibitor	15 mg BID for 21 days or until platelet recovery, whichever is longer, then 20 mg daily PO	May monitor anti-Xa assay if necessary	Warkentin TE, *et al.*[7,8] n=46 Patients were given rivaroxaban (dosage range 10-30 mg daily ≥30 days) for HIT; 1 developed thrombosis and 0 had bleeding events	Avoid in CrCl <30 ml/min OR in Child Pugh class B or C[3] No bridging required[3]
Warfarin Coumadin	Vitamin K antagonist via VKOR subunit 1 inhibition	Initial: 5 mg daily; check INR and adjust PO	Target INR of 2-3	There are case reports of limb ischemia and necrosis if warfarin is initiated in acute HIT II due to the initial depletion of protein C and S[9]	If a patient was on warfarin when HIT occurred, stop warfarin and give vitamin K to reverse. Use intravenous anticoagulant and only reinstate warfarin when platelet count is > $150x10^9/L$[3]

References:
1. UpToDate.com.libnet.swosu.edu. Clinical presentation and diagnosis of heparin-induced thrombocytopenia. SWOSU Libraries: Library Login. 2020. Accessed March 15, 2020.
2. UpToDate.com.libnet.swosu.edu. Management of heparin induced thrombocytopenia. SWOSU Libraries: Library Login. 2020. Accessed March 21, 2020.
3. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.
4. Tardy-Poncet B, Nguyen P, Thiranos JC, Morange PE, Biron-Andréani C, Gruel, Y., Maistre ED. Argatroban in the management of heparin-induced thrombocytopenia: a multicenter clinical trial. *Critical Care* 2015;19:396.
5. Joseph L, Casanegra AI, Dhariwal M, Smith MA, Raju MG, Militello MA, Gomes MP, Gornik HL, Bartholomew JR. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost 2014; 12: 1044–53.
6. Warkentin Theodore E. Fondaparinux for Treatment of Heparin-Induced Thrombocytopenia. *Journal of the American College of Cardiology* 2017;70:2649-2651.
7. Warkentin TE, Pai M, Linkins L. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood* 2017;103:1104-1113.
8. Fallon JM, Palkimas S, Kunk PR, Maitland HS. The Growing Potential of Direct Oral Anticoagulants in Hypercoagulable States. J Basic Clin Pharma 2017;8:S49-S55.
9. Fawaz B, Candelario NM, Rochet N, Tran C, Brau C. Warfarin-induced skin necrosis following heparin-induced thrombocytopenia. *Proc (Bayl Univ Med Cent)*. 2016;29(1):60–61.