PHARMACIST'S LETTER

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PHARMACIST'S LETTER / PRESCRIBER'S LETTER

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PRESCRIBER'S LETTER

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) can occur in up to 1% of medical and 5% of surgical patients receiving unfractionated heparin (UFH), and may have a mortality rate as high as 10%.[1] The chart below presents information to help clinicians prevent, recognize, and treat heparin-induced thrombocytopenia, in an FAQ format.

Abbreviations: aPTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; CrCl = creatinine clearance; ELISA = enzyme-linked immunosorbent assay; GTI = Genetics Testing Institute; HIPA = heparin-induced platelet activation; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; OD = optical density; PCI = percutaneous coronary intervention; PF4 = platelet factor 4; SRA = serotonin release assay; UFH =unfractionated heparin

Clinical Question	Pertinent Information
What is the mechanism of HIT?	• IgG is formed against the heparin/PF4 complex on platelets (i.e., anti-heparin antibody formation).[1] • When IgG binds to heparin/PF4 complex on platelets, the platelets become activated, triggering venous and arterial thrombi formation.[1]

What are the risk factors for HIT?	• Longer duration of heparin exposure[1]
	• Use of UFH as opposed to LMWH[1]
	  ◦ Higher risk with prophylactic or therapeutic dose heparin vs heparin flush[1]
	  ◦ Implementation of a program to use LMWH instead of heparin (with exceptions for dialysis, cardiovascular surgery, and some acute coronary syndrome patients), and saline instead of heparin flushes, reduced HIT by 79% at a 450-bed tertiary care, university hospital.[3] HIT complications (mostly deep venous thrombosis/pulmonary embolism) occurred in 43.4% of HIT cases before program implementation, and in 19.2% of HIT cases post-program implementation. After program implementation, LMWH use increased four-fold, but HIT-related costs decreased by over $250,000 (Canadian) per year.[3]
	• Post-op patients, particularly cardiac and orthopedic surgery patients[1]
	• Female patients[1]

More. . .

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How can HIT be prevented?	• Use LMWH instead of UHF when appropriate.[3] Exceptions might include dialysis, cardiovascular surgery, some acute coronary syndrome patients, and some patients with a CrCl <20 mL/min.[3,14] • Monitor platelets in higher risk patients (risk >1%, such as post-op patients receiving prophylactic- or therapeutic-dose UFH).[1] • Check platelets every two to four days from days four to 14, or until heparin is discontinued, whichever comes first.[1]

How is HIT identified?	• Be aware that 10% to 30% of patients receiving heparin will develop a mild, transient drop in platelets within the first two days of heparin therapy. This type of heparin-associated thrombocytopenia is not associated with thrombosis, and heparin can be continued.[13] This reaction should be differentiated from the antibody-mediated reaction described below because management is different. Consider other causes for platelet drop (e.g., sepsis, medications).[13]
	• Identification of HIT consists of clinical suspicion plus laboratory evidence.[1]
	  • Consider HIT in patients whose platelets drop significantly (e.g., to <150,000) five to ten days after heparin exposure. Thrombosis may occur before thrombocytopenia. HIT can occur up to three weeks after heparin discontinuation, or within 24 hours in patients with recent heparin exposure. Use tools such as the 4T score (see below) to help determine if thrombocytopenia is due to HIT.[1]
	  • The **4T score** should be used to identify patients that may have HIT,[4] assuming enough patient information is available to use the tool. 4T evaluates **T**hrombocytopenia degree and **T**iming, **T**hrombosis, and o**T**her causes. The 4T tool can be found at http://depts.washington.edu/anticoag/home/sites/default/files/Management%20of%20Suspected%20HIT.pdf. This document also includes an algorithm for management of suspected HIT. A low probability score (0 to 3) excludes HIT without the need for laboratory confirmation.[4]
	• **Lab tests for HIT** can be tricky to interpret. There are two general types: antigen assays that identify heparin antibodies, and functional assays (confirmatory tests) that identify platelet activation by antibodies in the presence of heparin.[1]
	  • Antigen assays (usually an ELISA; GTI-PF4 assay is an example) can exclude HIT, but a positive test does not confirm it. This is because not all anti-heparin antibodies the test detects can actually cause HIT (i.e., the test is sensitive, but not very specific). ELISAs that only detect IgG are more specific than those that also pick up IgA and IgM, because only IgG is likely to cause HIT.[1]
	  • The "strength" of the reaction on ELISA is associated with the probability of clinical HIT. The strength is measured in OD units. An OD value greater than 2 is strongly associated with HIT, while a value of <1 is not.[1] For example, a GTI-PF4 result of 0.4 to 1 OD in a patient with low or intermediate 4T score should be confirmed with a functional assay, when possible. Patients with an OD >1 with high or intermediate 4T score are more likely to have HIT, but a functional assay (SRA) should still be used for confirmation.[1]
	  • The confirmatory tests for HIT, the washed platelet SRA or HIPA, are only available at select labs,[1] so either will probably be a send-out.

Clinical Question	Pertinent Information

How is HIT treated?	• Stop UFH (including flushes), LMWH, and warfarin if HIT is suspected.[1]
	  • Give vitamin K to reverse warfarin.[1]
	• Use a non-heparin anticoagulant (argatroban, bivalirudin, or fondaparinux) to prevent thrombosis (see discussion, below).[1]
	  • Although direct-acting oral anticoagulants (e.g., rivaroxaban) have been used in the treatment of HIT, there is not enough information to recommend their use for acute treatment of HIT at this time.[1,11]
	• Due to concern that platelet transfusion could cause thrombosis, it is suggested that platelet transfusion be reserved for patients who are bleeding, or are undergoing a procedure with a high risk of bleeding.[1]

How do you choose among the parenteral anticoagulant options for HIT patients?	When choosing an agent, consider cost, availability, and monitoring.[1] (NOTE: Guidelines do not give a recommendation for desirudin [*Iprivask*] use in HIT. Data is extremely limited.[1]) <u>Argatroban continuous infusion</u> • Argatroban is the only FDA-approved HIT treatment.[1] Approval was based on prospective studies with historical controls.[7] • Argatroban is suggested for most patients; however, guidelines suggest bivalirudin over argatroban for cardiac surgery.[1] • May increase INR, complicating the transition to warfarin.[5] • Argatroban is suggested for <u>renal failure patients</u>, as it is not renally cleared.[1,5] • Reduced dosing (initial dose 0.5 mcg/kg/min) is recommended in moderate to severe hepatic impairment, and titration to a therapeutic aPTT may take longer in these patients.[13] • Guidelines suggest dosing that is slightly modified from the product labeling, to reduce bleeding risk.[1] A modified dosing protocol is available at http://depts.washington.edu/anticoag/home/sites/default/files/argatroban.pdf. <u>Bivalirudin (*Angiomax*) continuous infusion</u> • Compared to argatroban, bivalirudin has a shorter half-life, so it is easier to titrate, reaches therapeutic aPTT faster, and has a quick offset.[6,13] It causes less of a bump in INR than argatroban, and might be less expensive.[6] • Preliminary evidence suggests bivalirudin is an effective and safe argatroban alternative [Evidence level B; retrospective cohort studies].[6-8] • Consider bivalirudin for patients who require PCI or urgent cardiac surgery due to evidence in these populations.[1] • Be aware that dosing for HIT is different than dosing for PCI, and that special protocols exist for bypass patients.[13] • Requires reduced starting dose in renal dysfunction.[13] • A dosing protocol is available at http://depts.washington.edu/anticoag/home/content/bivalirudin-initial-dosing.

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Clinical Question	Pertinent Information
How do you choose among the parenteral anticoagulant options for HIT patients, continued	<u>Fondaparinux (*Arixtra*) subcutaneous injection</u> • Unlike argatroban and bivalirudin, fondaparinux does not require aPTT monitoring and dose titration.[13] • Preliminary evidence suggests fondaparinux is an effective and safe argatroban alternative [Evidence level B; retrospective cohort studies].[9,10] • Consider fondaparinux for stable patients with HIT or suspected HIT, but no acute thrombosis, not at high bleeding risk, CrCl >30 mL/min., and no planned invasive procedures, and pregnant patients.[1,2,5,10] • For treatment of HIT, guidelines suggest daily doses of 5 mg for patients <50 kg, 7.5 mg for patients 50 to 100 kg, and 10 mg for those >100 kg.[1] • Do not use in PCI.[1] • Some experts will use fondaparinux as an intermediate step between argatroban to warfarin, once platelets exceed 150,000/mm^3.[1]
For how long should you anticoagulate HIT patients?	• Anticoagulate for four weeks in isolated HIT, or three months after thrombosis secondary to HIT (as for other reversible causes of thrombosis).[1] • Switch to warfarin once platelets reach 150,000/mm^3. Overlap for at least five days and until INR is therapeutic. Start with no more than 5 mg once daily.[1]
Can patients with a history of HIT ever receive heparin again?	• Avoid heparin for at least three months in HIT patients.[1] • Heparin-induced antibodies are detectable for only 50 to 100 days, and re-exposure to heparin for less than four days does not usually cause HIT So after three months, heparin could be justified short-term in CABG patients, after confirming that HIT antibodies are negative.[1] • If a patient with HIT needs a PCI, use bivalirudin or argatroban.[1] • Avoid use of heparin or LMWH for thromboprophylaxis.[1] Options include fondaparinux, direct-acting oral anticoagulants (e.g., apixaban, etc), or warfarin.[1] • If a patient with a history of HIT requires treatment for acute thrombosis, and has normal renal function, fondaparinux is suggested, followed by warfarin.[1] Direct-acting oral anticoagulants (e.g., apixaban, etc) could be used.[12]

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

Project Leader in preparation of this professional resource: *Melanie Cupp, Pharm.D., BCPS*

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