

Heparin-Induced Thrombocytopenia Type II: Criteria for Diagnosis and Options for Treatment

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Heparin-induced thrombocytopenia (HIT) has two distinct presentations. The first is a nonimmune-mediated process with a relatively benign progression. The second (HIT Type II) is an immune-mediated process associated with mortality estimated at 20–30%.^{1,2} The characteristics differentiating the two types of HIT were discussed in the Oct-Nov 2000 issue of this newsletter (http://depts.washington.edu/druginfo/DTT/2000_Vol29_Files/V29N10-11.pdf). The focus of this article is the diagnosis and treatment of the immune-mediated process referred to as HIT Type II. In addition, a brief explanation of available laboratory assays and their interpretation is included.

The incidence of HIT Type II in patients who receive at least two weeks of unfractionated heparin therapy is 2-5% and for low molecular weight heparin is 1-2%.^{1,3} The diagnosis of HIT Type II is based on clinical, as well as serologic, evidence. A high index of suspicion for HIT Type II should be clinically established, and other potential causes of thrombocytopenia should be considered, before ordering serologic tests. Criteria for meeting the clinical definition of HIT Type II include the following combination of factors: heparin exposure with the occurrence of thrombocytopenia in the appropriate time frame, with or without a new thrombotic complication following initiation of heparin therapy.⁴

Thrombocytopenia is quantitatively defined in HIT patients as a drop in the platelet count of >50% from baseline or an absolute platelet count of <100,000/mm³.^{1,5} The time between first heparin exposure until the onset of HIT Type II characteristically distinguishes itself from other potential causes of thrombocytopenia. HIT Type II typically develops between 5 and 10 days after heparin initiation; however, it may develop earlier, 1–3 days after initiation of therapy, in patients who have received heparin previously.^{1,4} HIT Type II rarely develops later than 14 days after initiation of therapy.⁴

HIT Type II is caused by heparin and platelet factor 4 (PF4) complex-induced antibody activation of platelets. Procoagulable products are subsequently released resulting in platelet aggregation and thrombosis.^{1,2} A retrospective review found that 75% of 127 patients with HIT Type II developed venous and arterial thromboses.³ Despite the discontinuation of heparin following the development of HIT Type II, 38% of patients will still develop thromboembolic complications, making obvious the paradoxical need for anticoagulation in these thrombocytopenic patients.⁶

In addition, HIT Type II, and alternative anticoagulation, should be considered in recently hospitalized patients exposed to heparin who have returned to the hospital with thromboembolism. Rice, et al., have identified and termed this phenomenon delayed onset HIT which they observed in 14 out of 260 HIT Type II patients with a median onset of 14 days (range 9 to 40 days). Anticoagulation with either lepirudin or argatroban can reduce the mortality associated with HIT Type II from >30% to <10%.⁷

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**Table Ia:
Some Drugs Associated
with Thrombocytopenia**

Drugs
Allopurinol
Aspirin
Carbamazepine
Ganciclovir
Gold Salts
Interferons
MMR vaccine
NSAIDs
Penicillins
Quinine
Quinidine
Sulfonamides
Trimethoprim
Valproic acid

**Table Ib:
Some Conditions Associated
with Thrombocytopenia**

Conditions
Aplastic anemia
Chemotherapy
Disseminated intravascular coagulation (DIC)
Hemolytic uremic syndrome
HIV
Post-transfusion
Post-transplantation
Pregnancy
Radiation
Sepsis
Vascular Prostheses
Viral infections
Vitamin deficiencies (B12, folate)

Other potential causes of thrombocytopenia should be considered before a diagnosis of HIT Type II is made.

Other Potential Causes of Thrombocytopenia

Patients who develop thrombocytopenia while on heparin therapy should be evaluated for other potential causes of thrombocytopenia. HIT Type II patients typically do not develop mucosal or cutaneous bleeding or petechiae which is characteristically seen with other types of thrombocytopenia.^{1,9} Thrombocytopenia can occur through two mechanisms: decreased platelet production or increased platelet destruction. The first mechanism, decreased platelet production, may be caused by viral infections, chemotherapy, radiation, hematologic disease, alcohol toxicity, and vitamin B12 or folate deficiencies. Some potential contributors to platelet destruction include transfusions, other drugs (see Table I), infections, cardiopulmonary bypass, and sepsis.⁹ These other potential causes of thrombocytopenia should be considered before a diagnosis of HIT Type II is made.

HIT Assays

Two different strategies exist for evaluating heparin-induced thrombocytopenia in the laboratory: functional tests and antibody tests. Functional tests, such as platelet aggregation studies in the presence of heparin and the platelet C-serotonin release assay (SRA), assess platelet aggregation or the quantity of intracellular products that are released after antibody binding. Antibody tests, such as ELISA, detect IgA, IgG, and IgM antibodies that bind to the immunogenic heparin-PF4 (H-PF4) complex.⁵

Platelet receptors are thought to be more reactive to IgG immunocomplexes as opposed to IgA or IgM varieties.^{5,11} Since the ELISA does not distinguish between these antibodies, lower specificity rates are reported with this test compared to the SRA assay which assesses only IgG binding.^{5,12} The disadvantage of ELISA tests are that results may be positive in ~20% of cases without expression of thrombocytopenia or subsequent thrombosis.¹² Therefore, it is essential to interpret a positive ELISA in the context of a high pre-test probability for HIT. The Puget Sound Blood Center runs H-PF4 antibody assays using ELISA Monday through Friday with a turnaround time of <24hours.

Table II: Comparative Predictive Values of Heparin Antibody Assays¹¹⁻¹³

Diagnostic Assays	Sensitivity	Specificity
SRA	88%	100%
H-PF4 ELISA	60-97%	77-93%

Table II indicates that the SRA and H-PF4 ELISA assays have similar sensi-

tivities; however, the SRA assay has a higher specificity resulting in a greater positive predictive value and better utility. Ideally SRA tests would be preferred for patients in whom HIT Type II is suspected since it is the gold standard test with the most reliable positive predictive value.⁵ However, SRA is a labor-intensive and expensive test which is generally reserved for follow-up confirmation or for cardiopulmonary bypass (CPB) patients for whom ELISA assays are difficult to interpret. Of note, neither assay has a sensitivity of 100%; hence, negative laboratory results do not exclude HIT Type II in patients with a high pre-test probability but positive assays may confirm this diagnosis.

Heparin-Induced Antibody Development In Specific Patient Populations

Certain patients undergoing surgery and treated with heparin are more likely to develop heparin-induced antibodies. Fifty vascular surgery patients who received >5 days of heparin therapy were followed for clinical and laboratory signs of HIT Type II. At the end of heparin therapy, 54% of patients had one positive test, either ELISA or aggregation, yet only 8% actually developed thrombocytopenia or thrombosis indicating there was not a definitive correlation between a positive assay and HIT Type II in these patients.¹⁵ In cardiopulmonary bypass (CPB) patients, studies suggest that ~27% will develop heparin-induced antibodies detected by ELISA but that the test is not absolutely predictive of

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Assay Expenses:

ELISA \$200

SRA \$250

Although the ELISA is done at the Puget Sound Blood Center, the SRA is done at McMaster labs in Canada.

ELISA test results may be positive in ~20% of cases without expression of thrombocytopenia or subsequent thrombosis.

adverse sequelae evidenced by a 0–3.8% occurrence of thrombocytopenia, with or without thrombosis.^{16,17} In both vascular surgery and CPB patients it was observed that higher IgG-specific H-PF4 antibodies correlated with an increased risk for developing HIT-II upon continued therapy.^{15–17} Therefore, although assays are not positively predictive of HIT Type II in these patients, high IgG titers may provide insight into a patient’s level of risk for HIT Type II development. To make an accurate diagnosis of HIT Type II in vascular surgery and CPB patients, strong clinical criteria for HIT Type II must be identified before ordering serologies since they are difficult to interpret. Once assays return positive, there is a clinical obligation to stop heparin therapy and anticoagulate patients with an alternative therapy, such as lepirudin or argatroban.

Alternative Therapy for Heparin-Induced Thrombocytopenia

Patients who develop HIT Type II require heparin cessation and alternative anticoagulation to prevent subsequent thromboses and the resultant mortality. Currently two direct thrombin inhibitors are indicated for use in patients with HIT Type II: lepirudin (Refludan^R) and argatroban (Novastan^R). Both agents are available on the UWMC/HMC Drug Formulary; lepirudin was added in March 1999, recently followed by argatroban in January 2002.

No head-to-head trials have compared the safety and efficacy of lepirudin to argatroban. Both agents are similarly efficacious in reducing composite endpoints of new thromboembolic complications, limb amputation, and death in HIT Type II patients, with and without thrombosis, compared to historical controls. Lepirudin demonstrated a reduction of composite endpoints in HIT Type II patients from 42% to 29% while argatroban showed a reduction from 43% to 34%, both of which were statistically significant.^{18,19}

Table III: New Guidelines for Lepirudin Dosing Adjustments Based on aPTT Measurement

APTT (in seconds)	Dosing Adjustment
<60	Increase infusion rate by 20%
60-80	NONE
>80	Hold infusion for 2 hours, then restart at 50% lower rate

****Recheck aPTT 4 hours after any change in lepirudin dose.****

Both lepirudin and argatroban are monitored, and dose adjusted, via aPTT. Recently new UWMC/HMC guidelines suggest a goal aPTT of 60–80 seconds (rather than the previous goals of 1.5-2.5 times normal aPTT). The new guidelines are outlined in Table III. Although no specific recommendations exist for dose adjusting argatroban, it would be appropriate to follow the same guidelines as lepirudin. However, aPTT should be checked 2 hours after any argatroban dose change due to its shorter half-life. Each agent is discussed in more detail below.

Patients who develop HIT Type II require heparin cessation and alternative anticoagulation to prevent subsequent thromboses and the resultant mortality.

Lepirudin

Lepirudin (Refludan^R), a recombinant product of hirudin, irreversibly inhibits free and clot-bound thrombin.¹⁸ It is primarily renally excreted and has a half-life of 48–120 minutes.¹⁸ Adverse effects associated with lepirudin include hemorrhage as well as antihirudin antibody production. Bleeding is the most important complication following lepirudin therapy. Overall bleeding rates were significantly greater in the lepirudin group compared to historical controls, 33–45% vs. 27%.²⁰ In spite of higher overall bleeding rates, major bleeding events requiring transfusion occurred at a rate of 10–13% in lepirudin treated patients which is similar to the rate in historical controls.^{18,20} Ironically, Eichler, et al., found that of 198 HIT patients treated with lepirudin for ≥5 days, 44.4% developed antibodies specific to lepirudin. These antihirudin antibodies were not associated with any adverse consequences but did necessitate lepirudin dosage reductions in 45% of affected patients.²¹ Although hypersensitivity reactions did occur in <1% of patients, these reactions were not correlated to antihirudin antibody production.²²

Lepirudin has been used successfully during coronary artery bypass grafting. During surgery the ecarin clotting time can be used to monitor lepirudin.

Disadvantages of lepirudin therapy include the necessity of dose alterations in cases of renal insufficiency (see Table IV) and antihirudin antibody induction. Dosage

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Heparin-Induced Thrombocytopenia Type II (continued)

Table IV: Lepirudin Dosing Based on Renal Function

Clcr (mL/minute)	Serum Creatinine (mg/dL)	Bolus Dose (mg/kg)	Adjusted infusion rate	
			% of standard initial infusion rate	mg/kg/hour
>60	<1.6	0.4	100%	0.15
45-60	1.6-2	0.2	50%	0.075
30-44	2.1-3	0.2	30%	0.045
15-29	3.1-6	0.2	15%	0.0225
<15	>6	0.1	Avoid infusion. Rebolus with 0.05mg/kg PRN aPTT <60 to maintain aPTT 60-80	

Danaparoid, a low molecular weight heparin, has been used for anticoagulation in HIT Type II patients, but has been associated with a 10-40% *in vitro* cross-reactivity rate. A discussion of danaparoid is not included in this article.

Table V:
Comparison
of Lepirudin and
Argatroban
Characteristics

Argatroban

Argatroban (Novastan[®]), a synthetic *l*-arginine-derived thrombin inhibitor, competitively and reversibly binds to the catalytic component of both free and fibrin-bound thrombin.²³ It is metabolized in the liver to predominantly inactive metabolites and 65% is excreted in the feces via biliary secretion.²⁴ Overall bleeding rates are greater in argatroban patients compared to historical controls (47.3% vs. 27%);¹⁹ whereas major bleeding with argatroban has not been significantly different from historical controls with rates reported at 4.9%.²³

An advantage of argatroban over lepirudin is its shorter half-life, 39–51 minutes,²⁴ which may allow for a more rapid resolution of anticoagulation in the event of bleeding. There is limited excretion in the urine; hence, no dosing adjustments are necessary for patients with renal impairment. However, argatroban undergoes extensive liver metabolism, which leads to the necessity of dose reductions in patients with hepatic disease.^{23,24}

Characteristics	Lepirudin	Argatroban
Half-life	48-120 minutes	39-51 minutes
Renal failure	Adjustments necessary for CLcr <60mL/minute	No adjustment necessary
Hepatic failure	No adjustment necessary	Initiate at 0.05mcg/kg/minute
Dosing	0.4mg/kg bolus followed by a continuous infusion of 0.15mg/kg/hour, titrate to goal aPTT	No bolus dose Continuous infusion of 2mcg/kg/minute, titrate to a maximum of 10mcg/kg/minute
Monitoring	aPTT	aPTT
Therapeutic Range	UWMC/HMC: 60-80 seconds Others: 1.5-2.5 times normal aPTT	UWMC/HMC: 60-80 seconds Others: 1.5-3 times normal aPTT
Influence on INR	Elevates	Elevates
Antidote	None available	None available
Bleeding rates	Major 10-13% Minor 33-45%	Major 4.9% Minor 47.3%
Cost (70kg patient x 5 days)	\$3,606	\$3,044

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Conversion From Argatroban or Lepirudin to Oral Anticoagulation

Patients with thrombotic complications associated with HIT Type II require 3–6 months of anticoagulation to prevent secondary events. Oral anticoagulation is preferred in these patients; however, oral therapy is not appropriate in acute HIT Type II because of the slow onset of action, and because of the association with venous limb gangrene.²⁵ Direct thrombin inhibitors, lepirudin and argatroban, provide a bridge to therapeutic anticoagulation with warfarin.

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Due to their effects on the prothrombin time (PT) and the INR, converting patients from intravenous lepirudin or argatroban to warfarin can be challenging and requires careful monitoring to avoid over- or under-anticoagulation.

Diagnosis of HIT Type II is based on the observation of clinical criteria followed by laboratory confirmation.

Due to their effects on the prothrombin time (PT) and the INR, converting patients from intravenous lepirudin or argatroban to warfarin can be challenging and requires careful monitoring to avoid over- or under-anticoagulation. Recommendations for conversion from lepirudin to warfarin include aiming for a goal aPTT of 60 rather than 80 seconds and discontinuing lepirudin once an INR of 2.0 is reached.¹⁸ Available recommendations for argatroban currently suggest momentarily decreasing the dose of argatroban to 2mcg/kg/minute for patients receiving >2mcg/kg/minute before conversion to warfarin.²³ For patients receiving doses of argatroban ≤2mcg/kg/minute, an INR of 4 is estimated to be equivalent to an INR of 2–3 for warfarin alone. Hence, it is recommended that argatroban be stopped once an INR of 4 is achieved with a recheck of the INR 4–6 hours after the argatroban infusion is stopped.

Conclusion

In conclusion, diagnosis of HIT Type II is based on the observation of clinical criteria followed by laboratory confirmation. In the absence of laboratory confirmation, clinical suspicion should guide therapy. Once HIT Type II is established, it is essential to provide alternative anticoagulation in order to reduce the likelihood of significant adverse consequences such as thrombosis, amputation, or death. Currently two direct thrombin inhibitors are available for alternative anticoagulation, lepirudin and argatroban. Lepirudin may be preferred for patients with hepatic disease while argatroban may be preferred in renally impaired patients. Advantages for argatroban include its shorter half-life, which may result in quicker resolution of bleeding events, and reversible binding, which may influence safety.

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Drotrecogin alfa (Xigris)	Injection: 5mg vial-\$207.04, 20mg vial-\$828.16	Recombinant human activated protein C	Severe sepsis, Septic shock	24mcg/kg/hour
Ramipril (Altace)	Capsule: 1.25mg-\$0.51, 2.5mg-\$0.54, 5mg-\$0.64, 10mg-\$0.75	ACE inhibitor	Risk reduction from cardiovascular causes	Individualized
Formulary Deletions	Dosage Form(s), Strength(s)	Therapeutic Classification	Use	Comment
Benazepril (Lotensin)	All dosage forms and strengths	ACE inhibitor	Hypertension	Replaced by captopril, enalapril, lisinopril
Dolasetron (Anzemet)	All dosage forms and strengths	5HT3 antagonist	Nausea and vomiting	Replaced by ondansetron
Granisetron (Kytrel)	All dosage forms and strengths	5HT3 antagonist	Nausea and vomiting	Replace by ondansetron

* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

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