

**Bon Secours Richmond
Pharmacy & Therapeutics Committees
Argatroban Dosing and Monitoring Protocol For Heparin Induced Thrombocytopenia
Marshall Pierce, PharmD.
2/2005**

Recommendation(s):

- The dosing and monitoring protocol is recommended for use when argatroban is used in the treatment of heparin-induced thrombocytopenia (HIT).
- A preprinted physician order form will be developed for the committee's approval.
- Pharmacy will send the infusion rates charts when dispensing argatroban.

Argatroban Protocol

Discontinue

All Heparin (including flushes and flush bags), Lovenox (enoxaparin), dalteparin (Fragmin)
Discontinue warfarin until platelets are back to baseline or > 100,000 (preferably when count is 150,000)
IM injections while on Argatroban, obtain physician order for alternative route
If warfarin has been started before HIT is recognized reverse it with 5-10 mg of vitamin K.

Baseline aPTT, PT/INR, Serum Creatinine, CMP, HCT, and platelet count

Platelet count every day while on argatroban

Guaiac all stools, Gastrocult all emesis, visually check for hematuria or other bleeding. Call physician for bleeding

Notify Physician immediately for any of the following: unexplained drop in blood pressure, development of hematoma, drop in hematocrit, significant bleed, flank pain, bright red urine, or bruising

aPTT monitoring

All aPTTs are to be run stat

Draw aPTT 2 hours and 6 hours after initiation of therapy and every 4 hours after any change in infusion rate until two consecutive PTT are therapeutic then draw aPTT every 24 Hours

If aPTT is greater than 100 seconds, stop argatroban, drawn aPTT every 2 hours until aPTT is within therapeutic range, and restart argatroban at new rate

Goal aPTT 40-83 seconds (1.5-3 times control) (round actual aPTT to closest whole number)

Starting Dose

2 mcg/kg/min

Renal Dysfunction (creatinine clearance less than 60 ml/min) consider starting at 1 mcg/kg/min

Liver Dysfunction: 0.5 mcg/kg/min (Hepatic Disease score greater than 6)

If Liver Function Test are greater than 3 times upper limit of normal do not use argatroban

Argatroban is contraindicated in overt major bleeding

Hepatic Disease Score and creatinine clearance calculators, infusion and rate change charts are available on the pharmacy web site

Argatroban Dosage adjustments

Infusion Rate Change Based on aPTT				
Please See Rate Change Chart for rate in ml/hr				
APTT (Seconds)				
33 or less	34-39	40-83	84-96	97 or higher
50% increase	25% increase	No change	25% decrease	50% decrease
Rate Change				
If aPTT is greater than 100 seconds stop argatroban, draw aPTT every 2 hours until aPTT is within therapeutic range, then restart argatroban at new rate				
Round the aPTT to the closest whole number				

Maximum dose 10 mcg/kg/min

Transition to Warfarin

Start warfarin when platelet count is greater than 100,000 (preferably when count is 150,000).

Do not use warfarin-starting doses greater than 5 mg

Overlap warfarin with argatroban for 5 days.

INR Monitoring

INR daily

If INR > 4 on combination therapy, stop argatroban, repeat INR in 4-6 hours, if INR is less than therapeutic restart argatroban at previous rate. Repeat the procedure daily. Discontinue argatroban when two consecutive daily INRs are therapeutic on warfarin alone after therapy has overlapped for at least 5 days.

Hepatic Disease Score for Argatroban Dosing			
	1 point	2 points	3 points
Bilirubin (mg/dl)	< 2 < 4 for patients with primary biliary cirrhosis	2-3 4-10 for patients with primary biliary cirrhosis	> 3 > 10 for patients with primary biliary cirrhosis
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
PT prolongation (INR)	< 4 seconds (INR < 1.7)	4-6 seconds (INR 1.7-2.3)	> 6 seconds (INR > 2.3)
Ascites	Absent	Slight	Moderate
Encephalopathy	Absent	Mild (1-2)	Severe (3-4)

To calculate the Hepatic Disease Score, determine the individual score (1,2,3) for each parameter. If the sum of all parameters is > 6 then the patient should be started on 0.5 mcg/kg/min of Argatroban.

Stages of Hepatic Encephalopathy

Stage 1: Euphoria or depression, mild confusion, slurred speech, disordered sleep

Stage 2: Lethargy, moderate confusion

Stage 3: Marked confusion, incoherent speech, sleeping but arousable

Stage 4: Coma, initially responsive to noxious stimuli, but later unresponsive

Findings:

- HIT is an immune-mediated thrombocytopenia that results in serious arterial and venous thromboses, with devastating consequences of limb amputation or even death if not recognized and treated appropriately. Platelet counts typically begin to fall after 5 or more days of continuous heparin use, most often between days 7 and 14 of therapy
- HIT is a prothrombotic condition that is associated with increased in vivo thrombin generation and is considered an acquired hypercoagulability syndrome. HIT is transient, with recovery of platelets counts to normal levels within days or weeks, and disappearance of the pathogenic HIT antibodies within weeks or a few months.
- The hypercoagulability state is multifactorial and includes the following:
 - In vivo platelet activation, with formation of procoagulant, platelet derived micro particles caused by occupancy and cross-linking of platelet Fc receptors by in situ formation of PF4/heparin/IgG immune complexes
 - Expression of tissue factor on endothelial cells that have become activated because HIT antibodies recognize PF4 bound to endothelial heparan sulfate
 - Expression of tissue factor by monocytes activated by HIT antibodies
 - Marked in vivo thrombin generation
- Diagnosis is based on both clinical and serologic grounds. HIT antibody seroconversion without thrombocytopenia or other clinical sequelae is not considered HIT. HIT is seroconversion with unexplained platelet count fall, usually $\geq 50\%$, even if nadir remains $> 150 \times 10^9/\text{liter}$, or skin lesions at heparin injection sites or acute systemic reactions (fever, chills, cardiorespiratory distress: hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest) within 30 minutes of IV heparin bolus administration. Although heparin-induced antibody formation occurs in 10-20% of patients treated with heparin, the vast majority of these patients never develop HIT. Rapid onset HIT, platelet count falling within 24 hours of heparin, is strongly associated with recent heparin exposure within the past 100 days.
- Isolated HIT is defined as the initial recognition of HIT because of thrombocytopenia alone, rather than because of symptoms or signs of thrombosis.
- Approximately two thirds of HIT patients have typical-onset HIT, i.e., the platelet count begins to fall 5-10 days after starting heparin. One third of patients have rapid-onset HIT
- HIT antibody test in the absence of clinical indication of HIT (thrombocytopenia, thrombosis, heparin-induced skin lesions or sequelae of HIT) is not recommended.
- HIT antibodies resulting from UFH therapy usually cross react with LMWH
- Non immune mediated heparin-associated thrombocytopenia (HAT): as many as 25% of patients receiving heparin therapy develop a benign, mild reduction in platelet counts referred to as HAT, previously called HIT type I. Platelet counts rarely fall below 100,000 and the fall is early in the course of therapy, typically between day 2 and 4. It is not necessary to discontinue heparin therapy, as platelet counts generally rebound despite continued heparin therapy.
- Retrospective and prospective studies suggest that $> 90\%$ of patients with clinical HIT have a platelet count fall $> 50\%$ during heparin treatment.
- Frequency of HIT among patients exposed to heparin is highly variable, and is influenced by the heparin preparations (bovine UFH $>$ porcine UFH $>$ LMWH) and the exposed population (after surgery $>$ medical $>$ pregnancy).
- Onset is usually delayed, 5 days or more of heparin administration, unless previous exposure to heparin
- Treatment of isolated HIT, HIT/ HITTS
 - Prompt discontinuation of heparin and initiation of alternative anticoagulant, direct thrombin inhibitors are most commonly used. When managed by heparin cessation alone, 50% of HIT patients experience thrombosis within a month and 20%-30% die.

- Stop warfarin and do not restart until platelet count has substantially recovered (eg, to at least $100 \times 10^9/L$, and preferably $150 \times 10^9/L$). Overlap alternative anticoagulant with warfarin therapy for a minimum of 5 days. Do not use warfarin loading doses. If warfarin has been started before HIT is recognized reverse it with 5- 10 mg of vitamin K. Early initiation of warfarin and early discontinuation of direct thrombin inhibitor are associated with venous limb gangrene.
- Direct thrombin inhibitors (argatroban, lepirudin) provide a relative risk reduction of 44-66% of new thrombosis compared to historic controls
- HIT antibodies
 - No anamnestic immune response occurs in HIT.
 - In rapid-onset HIT, there is a strong association with recent (<100 days) heparin exposure
 - HIT antibodies are transient, with the median time to negative activation and antigen assays of 50 days and 80 days, respectively.
 - When heparin has been accidentally or deliberately re administered in situation when HIT antibodies were no longer present, recurrence of HIT antibodies usually did not occur. When antibodies were regenerated, they did not occur sooner or at stronger levels than in the previous seroconversion episode that had led to clinical HIT.

Table IV. Estimating the pretest probability of HIT: the 'four T's'.

	Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)		
	2	1	0
Thrombocytopenia	> 50% fall or platelet nadir 20–100 × 10 ⁹ /l	30–50% fall or platelet nadir 10–19 × 10 ⁹ /l	fall < 30% or platelet nadir < 10 × 10 ⁹ /l
Timing* of platelet count fall or other sequelae	Clear onset between d 5–10; or less than 1 d (if heparin exposure within past 100 d)	Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after d 10	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low

*First day of immunizing heparin exposure considered d 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 d more until an arbitrary threshold that defines thrombocytopenia is passed).

Reprinted from Warkentin, T.E. & Heddle, N.M. (2003) Laboratory diagnosis of immune heparin-induced thrombocytopenia. *Current Hematology Reports*. Copyright Current Medicine, used by permission.

Table V. Treatment paradoxes of HIT.

Paradox	Comment	References
Coumarins (e.g. warfarin) increase risk of microvascular thrombosis in acute HIT (venous limb gangrene; skin necrosis)	Coumarins are contraindicated in acute HIT; delay coumarin overlap with alternate anticoagulant pending substantial resolution of thrombocytopenia.	Warkentin <i>et al</i> (1997, 1999); Hirsh <i>et al</i> (2001); Smythe <i>et al</i> (2002)
LMWH is contraindicated to treat HIT despite its lower frequency of causing HIT	High risk (about 50%) of <i>in vivo</i> crossreactivity if LMWH is used to treat HIT caused by UFH	Ranze <i>et al</i> (2000); Greinacher & Warkentin (2001)
Prophylactic platelet transfusions are relatively contraindicated in HIT	Spontaneous bleeding is uncommon in HIT, and platelet transfusion theoretically may contribute to thrombotic risk	Greinacher & Warkentin (2001)
High risk of thrombosis persists even after heparin is stopped Therapeutic (rather than prophylactic) dose anticoagulation is appropriate even when treating isolated HIT	Treatment of 'isolated HIT' with alternative anticoagulant is recommended High treatment failure rate when (EU-approved) prophylactic-dose danaparoid regimen used to treat isolated HIT	Warkentin & Kelton (1996); Hirsh <i>et al</i> (2001); see also Table VIII Farner <i>et al</i> (2001); Lewis <i>et al</i> (2001); Warkentin (2001d)

gate outcome of HIT antibody formation, rather than clinical HIT, as their primary study endpoint. The biological basis for a difference in immunogenicity between animal sources of heparin could relate to the greater polysaccharide chain length and degree of sulfation in bovine lung heparin, which could facilitate immunogenicity by enhanced reactions with PF4.⁶

Recommendations

4.2.1. For the treatment of patients with thrombosis, we recommend **against** the use of bovine UFH, in comparison with porcine UFH or LMWH (**Grade 1A**).

4.2.2. For patients undergoing cardiac surgery, we recommend the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (**Grade 1B**).

SUMMARY OF RECOMMENDATIONS

1.0 Recognition of HIT

1.1 Platelet count monitoring for HIT

1.1. For patients receiving heparin in whom the risk of HIT is considered to be $> 0.1\%$, we recommend platelet count monitoring over no platelet count monitoring (**Grade 1C**).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

1.1.1 Platelet count monitoring of patients recently treated with heparin

1.1.1. For patients who are starting UFH or LMWH treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, we suggest obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin (**Grade 2C**).

1.1.2 Acute systemic reactions after IV UFH bolus

1.1.2. For patients who acquire acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 min following an IV UFH bolus, we recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, in comparison with not performing a platelet count measure (**Grade 1C**).

1.1.3 Platelet count monitoring in patients receiving therapeutic-dose UFH

1.1.3. For patients who are receiving therapeutic-dose UFH, we suggest at least every-other-day platelet count

monitoring until day 14, or until UFH is stopped, whichever occurs first (**Grade 2C**).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.4 Platelet count monitoring in postoperative patients receiving UFH antithrombotic prophylaxis

1.1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk $> 1\%$), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14, or until UFH is stopped, whichever occurs first (**Grade 2C**).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

1.1.5 Platelet count monitoring in patients in whom HIT is infrequent (0.1 to 1%)

1.1.5. For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH "flushes," or medical/obstetric patients receiving LMWH after first receiving UFH (HIT risk, 0.1 to 1%), we suggest platelet count monitoring every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical (**Grade 2C**).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

1.1.6 Platelet count monitoring when HIT is rare ($< 0.1\%$)

1.1.6. For medical/obstetric patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk $< 0.1\%$), we suggest clinicians do **not** use routine platelet count monitoring (**Grade 2C**).

Underlying values and preferences. This recommendation places a lower value on the rare diagnosis and early treatment of HIT to prevent sequelae, and a higher value on the burden and cost of monitoring platelet counts.

1.1.7 Screening for subclinical HIT antibody seroconversion

1.1.7. In patients who receive heparin, we recommend **against** routine HIT antibody testing in the absence of

thrombocytopenia, thrombosis, heparin-induced skin lesions, or other sequelae of HIT (Grade 1C).

1.1.8 When should HIT be suspected?

1.1.8. For patients receiving heparin, or who have received heparin within the previous 2 weeks, we recommend excluding a diagnosis of HIT if the platelet count falls by $\geq 50\%$, and/or a thrombotic event occurs, between days 4 to 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia have occurred (Grade 1C).

1.1.9 Special situation: anticoagulant prophylaxis and platelet count monitoring after cardiac surgery

1.1.9. For postoperative cardiac surgery patients, we recommend excluding a diagnosis of HIT if the platelet count falls by $\geq 50\%$ (and/or a thrombotic event occurs) between postoperative days 4 to day 14 (day of cardiac surgery = day zero) (Grade 1C).

2.0 Treatment of HIT

2.1 Nonheparin anticoagulants for HIT

2.1.1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter).

2.1.2. For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb DVT, we recommend routine ultrasonography of the lower-limb veins for investigation of DVT, over not performing routine ultrasonography (Grade 1C).

2.2 VKAs

2.2.1 Management of DTI-VKA overlap

2.2.1. For patients with strongly suspected or confirmed HIT, we recommend against the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (eg, to at least $100 \times 10^9/L$, and preferably, $150 \times 10^9/L$); that the VKA be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low, maintenance doses (maximum, 5 mg warfarin; 6 mg phenprocoumon); that the alternative anticoagulant not be stopped until the platelet count has reached a stable

plateau, and with at least the last 2 days the INR within the target therapeutic range (all Grade 1C).

2.2.2 Reversal of VKA anticoagulation

2.2.2. For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (Grade 2C).

2.3 LMWH for HIT

2.3. For patients with strongly suspected HIT, whether or not complicated by thrombosis, we recommend against use of LMWH (Grade 1C+).

2.4 Prophylactic platelet transfusions for HIT

2.4. For patients with strongly-suspected or confirmed HIT who do not have active bleeding, we suggest that prophylactic platelet transfusions not be administered (Grade 2C).

3.0 Special Patient Populations

3.1 Patients with previous HIT undergoing cardiac or vascular surgery

3.1.1. For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, we recommend the use of UFH over a nonheparin anticoagulant (Grade 1C).

Remark: Preoperative and postoperative anticoagulation, if indicated, should be administered with a nonheparin anticoagulant.

3.2 Patients with acute or subacute HIT undergoing cardiac surgery

3.2.1. For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, we recommend one of the following alternative anticoagulant approaches (in descending order of preference): delaying surgery (if possible) until HIT antibodies are negative (see recommendation 3.1.1.) [Grade 1C]; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if ecarin clotting time [ECT] available) [Grade 1C] or during off-pump cardiac surgery (Grade 1C+); using lepirudin for intraoperative anticoagulation (if ecarin clotting time available and patient has normal renal function) [Grade 1C]; using UFH plus the antiplatelet agent, epoprostenol (if ECT monitoring not available or renal insufficiency precludes lepirudin use) [Grade 2C]; using UFH plus the antiplatelet agent, tirofiban (Grade 2C); or using danaparoid for intraoperative anticoagulation (if anti-factor Xa levels are available) [Grade 2C].

3.2.2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody-positive), we rec-

ommend delaying surgery (if possible) until HIT antibodies are negative, then using heparin (see recommendation 3.1.1.) [Grade 1C]. Alternatively, we suggest the use of a nonheparin anticoagulant (see recommendation 3.2.1.) [Grade 2C].

3.3 PCIs

3.3. For patients with acute or previous HIT who require cardiac catheterization or PCI, we recommend use of an alternative anticoagulant, such as argatroban (Grade 1C), bivalirudin (Grade 1C), lepirudin (Grade 1C), or danaparoid (Grade 2C), over the use of heparin.

4.0 Prevention of HIT

4.1 Reducing HIT antibody formation and clinical HIT

4.1.1 UFH vs LMWH

4.1.1. For postoperative orthopedic surgery patients, we recommend the use of LMWH over UFH (Grade 1A).

4.2 Bovine vs porcine UFH

4.2.1. For the treatment of patients with thrombosis, we recommend **against** the use of bovine UFH, in comparison with porcine UFH or LMWH (Grade 1A).

4.2.2. For patients undergoing cardiac surgery, we recommend the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (Grade 1B).