My patient has HITT: Now what?

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Objectives:

- **Understand the problems associated with managing patients with established HITT for cardiac surgery**
- **Explain the practical use, risks and benefits of the various pharmacological options during cardiac surgery**
- **Outline the use of these options both intraoperatively and postoperatively in the ICU**

Outline

1. Definition of HITT/Incidence of HITT
2. Review of coagulation cascade
3. American College of Chest Physicians (ACCP) recommendations/guidelines for patients with HITT.

1. Definition of HITT/Incidence of HITT

Heparin induced thrombocytopenia is an adverse reaction to heparin consisting of thrombocytopenia with or without thrombosis. Historically it has been classified as HIT I, HIT II and HITT. HIT I is a transient mild reduction in the platelet count (usually by less than $100X10^9$/L) in the first 1-2 days after heparin exposure. This form of HIT usually resolves without intervention and does not necessitate discontinuation of the drug [1]. HIT II is an immunologically mediated response that occurs approximately after 5-10 days of heparin exposure resulting in a drop in platelet count (usually > 50%), and (sometimes limb-/life-threatening) thrombosis (HITT – HIT II with thrombosis). Antibodies (IgG) form against the heparin-PF4 complex that then bind the Fc receptor on platelets thereby activating them and releasing procoagulant microparticles. This results in a paradoxical thrombosis [2,3]. For the purposes of this lecture, HITT and HIT II will be used interchangeably. Because the transient mild form of HIT I is not within the scope of this discussion, HITT will refer to only the immunologically mediated response with or without thrombosis.

The incidence of HITT varies depending on the population being evaluated (postsurgical > medical > OB/pregnant women), the type of heparin utilized (bovine unfractionated heparin [UFH] > Porcine UFH > low molecular weight heparin [LMWH]) and the length of exposure (longer exposure > shorter exposure) [4]. HITT can occur in about 1-3% of the general population, 5% in the orthopedic population or as high as 11% in patients awaiting cardiac transplantation [3]. In the adult cardiac surgical population, 27-50% of the patients develop antibodies to the Heparin-PF4 complex detectable by enzyme-linked

immunosorbent assay (ELISA) after cardiac surgery when UFH was used. Approximately 1-3% of cardiac surgical patients develop HITT [5].

HITT can be a devastating complication in the cardiac surgical patient population. Due to their already established/accelerated arteriosclerosis, these patients are at an especially higher risk of life/limb threatening thrombosis [6,7,8]. Although the diagnosis of HITT can be made using a combination of clinical and laboratory workup, this lecture will pertain to those patients in whom HITT is strongly suspected and/or confirmed as an acute process.

2. Review of Coagulation Cascade:

The coagulation cascade can be simplified into two major components: cellular (platelets) and protein (coagulation factors). This type of two-tier system is preserved in all mammals. The protein component results in the formation of fibrin via two pathways (extrinsic and intrinsic) which ultimately reinforces the plug that is formed by the cellular component (platelets). The extrinsic and intrinsic arms merge to a final common pathway consisting of thrombin (Factor IIa). Thrombin is generated from prothrombin by cofactor Xa. Antithrombin inhibits thrombin. Heparin increases antithrombin activity and thereby results in anticoagulation. In the absence of heparin, ultimately thrombin leads to the formation of fibrin. Simply by recognizing these keys steps one can begin to understand where and how research in nonheparin anticoagulants began – targeting Factor Xa and thrombin – Factor Xa and direct thrombin inhibitors.

3. ACCP Recommendations for patients with HITT who are undergoing Cardiac Surgery

In those patients with strongly suspected HITT or with acute confirmed HITT, the following (in descending order of preference) are recommended over the use of UFH for CPB: [4]

a. Wait if possible until HITT resolved and HIT antibody test negative or weakly positive. **(Grade 1B)**.
b. Use bilvalirudin - if techniques of cardiac surgery and anesthesiology have been adapted to the unique features of bivalirudin pharmacology. **(Grade 1B)**.
c. Perform off-pump coronary artery bypass grafting with bivalirudin. **(Grade 1B)**.
d. Use r-hirudin – only if ecarin clotting time (ECT) is available and renal function is normal and patient is at low risk for postoperative renal dysfunction. **(Grade 2C)**.
e. Use UFH and epoprostenol – if no ECT is available for intraoperative use or the patient has renal dysfunction. **(Grade 2C)**.
f. Use UFH and tirofiban **(Grade 2C)**.
g. Use Danaparoid for intraoperative coagulation for off-pump coronary artery bypass grafting **(Grade 2C)**.

DRUG	Dosing protocol	Comments
PREFERRED OPTIONS (based on ACCP guidelines – Level 1)		

Bivalirudin (direct thrombin inhibitor)	On CPB: 1 mg/kg bolus, 50 mg bolus to CPB prime, 2.5 mg/kg/h infusion, additional 0.1-0.5 mg boluses to maintain ACT > 2.5 X baseline ACT. Off-pump CABG: 0.75 mg/kg bolus then 1.75 mg/kg/h infusion to maintain ACT > 300s.	Not FDA approved for this use. Currently only FDA approved for treatment of HITT in patients undergoing PCI. Approved in Canada for patients with HITT or strongly suspected HITT undergoing cardiac surgery. t½ = 25 minutes, severe renal insufficiency ~1hour, HD patients ~ 4hours, 20% renally cleared, 80% non-organ proteolysis, not studied in severe renal failure patients undergoing cardiac surgery. No antidote Technical considerations: Issues with stagnant blood, avoiding use of patient blood for testing graft patency or for cardioplegia solution, special maneuvers and considerations exist for use of bivalirudin in cardiac surgery. **[9,10]**
Heparin plus Prostacyclin analogue (epoprostenol or iloprost)	Standard UFH dosing for CPB Epoprostenol: step-wise increments of 5ng/kg/min, beginning at 5 ng/kg/min, until target rate of 30ng/kg/min reached	Epoprostenol: t½ ~3 - 6 minutes, can result in severe arterial hypotension requiring vasopressors. Epoprostenol (not iloprost) is available in US, but is not FDA approved for use in HITT patients undergoing cardiac surgery. Only approved for primary pulmonary hypertension.
NONPREFERRED OPTIONS (based on ACCP guidelines – Level 2)		
r-Hirudin (direct thrombin inhibitor)		ECT monitoring recommended, t½ = 60-80 minutes, prolonged ½ life in renal insufficiency, no antidote, possible drug accumulation in setting of postoperative renal dysfunction. Target drug levels 3.5-4.0 μg/mL reported appropriate for CPB. Risk of anaphylaxis upon re-exposure **[11].**
Heparin plus	Standard UFH dosing for	***Manufacturer does not***

tirofiban	CPB; tirofiban: 10μg/kg bolus, then 0.15 μg/kg/min until 1 hour before anticipated discontinuation of CPB.	***recommend this approach as fatal bleeding has been reported.***
Danaparoid (Factor Xa inhibitor) withdrawn from market 4/02)	Protocols already published [9]	T½ life ~ 24 hours, does not affect INR, high bleeding risk, lower doses (1/3 – 1/2) may be required for off-pump cardiac surgery.
Argatroban (direct thrombin inhibitor)	Limited experience	T ½ life = 39-51 minutes, increased in moderate hepatic impairment, no antidote, unknown monitoring strategy. Not FDA approved for use in cardiac surgery. Interferes with INR, Limited experience/case reports.

CPB = cardiopulmonary bypass, PCI = percutaneous intervention, ECT = ecarin clotting time, ACT = activated clotting time. Information for this table has been adapted from various sources [4,9,10,11].

4. ACCP Recommendations for patients with HITT

Those patients who have HITT or are strongly suspected to have HITT, the following are recommended at the alternative nonheparin anticoagulant over the continuation of UFH or LMWH or the initiation or continuation of a Vitamin K antagonist [4]:

a. Danaproid **(Grade 1B)**
b. r-Hirudin **(Grade 1C)**
c. Argatroban **(Grade 1C)**
d. Fondaparinux **(Grade 2C)**
e. Bivalirudin **(Grade 2C)**

DRUG	**INITIAL RATE**	**BOLUS**	**MONITORING**
r-Hirudin **Off-label dosing**	If Cr : 90-140 μmol/L: 0.05 mg/kg/h 140-400 μmol/L: 0.01 mg/kg/h > 400 μmol/L: 0.005 mg/kg/h, initial rate not to exceed 0.10 mg/kg/h **Grade 1C**	Omit or give a decreased dose compared to package insert if life/limb threatening complications 0.2 mg/kg bolus **Grade 1C**	aPTT q4 hours until steady state reached (1.5-2x's patients baseline value or mean laboratory aPTT). **Grade 1C**
Argatroban **Off-label**	0.5-1.2 μg/kg/min (*use this over manufacturer recommended dose*		Adjust dose to target aPTT. No

dosing recommended IV route versus SC (**Grade 1B)**	*of 2.0 μg/kg/min due to concerns of impaired hepatic clearance in certain patient populations – heart failure, MOSF, severe anasarca, or after cardiac surgery*) **Grade 2C**		study to date that assesses target drug levels. **Grade 2C**
Danaparoid **Withdrawn from US market 4/02**	If weight: > 90kg: 3750 U 75-90 kg: 3000U 60-75 kg: 2250 U <60kg: 1500 U **Grade 1B**	400U/h for 4 hours, 300U/h for 4 hours, 200U/h (150U/h in severe renal failure thereafter) **Grade 1B**	After accelerated infusion, monitor anti-factor Xa levels (target 0.5-0.8 antiXa U/mL). If not therapeutic, bolus 750-1500U and or increase rate. Check anti-factor Xa levels Q24 hours and once a therapeutic level is reached and stable, change from IV to SC. 2250 U BID SC = 188 U/h IV and 1500 U BID SC = 125 U/h IV. *Note: if anti-factor Xa lab test is not available use is not contraindicated.* **Grade 1B**

Information from ACCP guidelines [4].
Cr = creatinine; IV = intravenous; SC = subcutaneous; MOSF = multi-organ system failure

Other points to consider:

1. Lower extremity ultrasound? Use of LMWH?
   According to the ACCP guidelines, ultrasound of the lower limbs is recommended inpatients strongly suspected for HIT **(Grade 1C)** [4]. Furthermore, similarly in this same patient population, it recommended against the use of LMWH whether or not thrombus was present) **(Grade 1B)** [4].

2. Use of platelets?
   Hopkins et al report a somewhat unsubstantiated risk of thrombotic events associated with platelet transfusions in patients diagnosed with HITT and did not find an increased risk of this dreadful complication in their study - although this may be attributable to the small study size and it being retrospective in nature [2]. Further studies need to be done in order to identify the true risk of adding insult to injury as they point out[2]. According to the ACCP, in patients who are actively bleeding or at risk thereof, where the clinical diagnosis of HITT is not apparent, platelet transfusions in the setting of HITT or probable HITT may be appropriate. Prophylactic platelet transfusions should not be given in patients without active bleeding with strongly suspected or confirmed HITT **(Grade 2C)** [4].

References:

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2. Hopkins CK, Goldfinger D. Platelet transfusions in heparin-induced thrombocytopenia: a report of four cases and review of the literature. Transfusion 2008;48:2128-2132.
3. Hourigan LA, Walters DL, Keck SA, et al. Heparin-induced Thrombocytopenia: A common complication in cardiac transplant recipients. J Heart Lung Transplant 2002;21:1283-1289.
4. **Warkentin TE, Greinacher A, Koster A, et al. Treatment and Prevention of Heparin-Induced Thrombocytopenia: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th Edition) Chest 2008;133:340-380.**
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6. Kerendi F, Thourani VH, Puskas JD, et al. Impact of Heparin-Induced Thrombocytopenia on Postoperative Outcomes after Cardiac Surgery. Ann Thorac Surg 2007;84:1548-55.
7. **Koster A, Dyke CM, Aldea G, et al. Bivalirudin During Cardiopulmonary Bypass in Patients with Previous or Acute Heparin-Induced Thrombocytopenia and Heparin Antibodies: Results of the CHOOSE-ON Trial. Ann Thorac Surg 2007;83:572-7.**
8. Gray A, Wallis DE, Husting MJ, et al. Argatroban Therapy for Heparin-Induced Thrombocytopenia in Acutely Ill Patients. Clin Appl Thromb Hemost 2007;13:353.
9. **Poetzsch B, Madlener K. Management of cardiopulmonary bypass anticoagulation in patients with heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. Heparin-Induced Thrombocytopenia. 2nd Edition. New York: Marchel Dekker, 2001:429-44**
10. Mann JM, Tseng E, Ratcliffe M, et al. Use of Bivalirudin, a Direct Thrombin Inhibitor, and Its Reversal wit Modified Ultrafiltration During Heart

Transplantation in a Patient with Heparin-Induced Thrombocytopenia. J Heart Lung Transplant 2005;24:222-5.

11. **Czosnowski QA, Finks SW, Rogers KC. Bivalirudin for Patients with Heparin-Induced Thrombocytopenia Undergoing Cardiovascular Surgery. Ann Pharmacother 2008;42:1304-9.**

Recommended Readings:
(In addition to those bolded above)

1. Merry AF, Raudkivi PJ, Middleton NG, et al. Bivalirudin Versus Heparin and Protamine in Off-Pump Coronary Artery Bypass Surgery. Ann Thorac Surg 2004;77:925-31.
2. Koster A, Spiess B, Jurmann M, et al. Bivalirudin Provides Rapid, Effective, and Reliable Anticoagulation During Off-Pump Coronary Revascularization: Results of the "EVOLUTION OFF" Trial. Anesth Analg 2006;103:540-4.
3. Dyke CM, Aldea G, Koster A, et al. Off-Pump Coronary Artery Bypass with Bivalirudin for Patients with Heparin-Induced Thrombocytopenia or Antiplatelet Factor Four/Heparin Antibodies. Ann Thorac Surg 2007;84:836-40.
4. Dyke CM, Smedira NG, Koster A, et al. A comparison of Bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: The EVOLUTION-ON Study. J Thorac Cardiovasc Surg 2006;131:533-9.
5. Greinacher A, Levy JH. HIT Happens: Diagnosing and Evaluating the Patient with Heparin-Induced Thrombocytopenia. Anesth Analg 2008;107:356-358.