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 100x10⁹/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 bivalirudin - 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).

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| **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 HIT in patients undergoing PCI. Approved in Canada for patients with HIT or strongly suspected HIT 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.  
[9,10] |
| **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.  
Manufacturer does not |
| Heparin plus | Standard UFH dosing for |
tirofiban  | CPB; tirofiban: 10\(\mu\)g/kg bolus, then 0.15 \(\mu\)g/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.  

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)

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| r-Hirudin Off-label dosing | If Cr :  
90-140 \(\mu\)mol/L: 0.05 mg/kg/h  
140-400 \(\mu\)mol/L: 0.01 mg/kg/h  
> 400 \(\mu\)mol/L: 0.005 mg/kg/h, initial rate not to exceed 0.10 mg/kg/h | Omit or give a decreased dose compared to package insert if life/limb threatening complications  
0.2 mg/kg bolus | aPTT q4 hours until steady state reached (1.5-2x’s patients baseline value or mean laboratory aPTT). **Grade 1C** |
<p>| Argatroban Off-label | 0.5-1.2 (\mu)g/kg/min (<em>use this over manufacturer recommended dose</em>) | | Adjust dose to target aPTT. No |</p>
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<th><strong>dosing</strong></th>
<th><strong>recommended IV route versus SC (Grade 1B)</strong></th>
<th><strong>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</strong></th>
<th><strong>study to date that assesses target drug levels. Grade 2C</strong></th>
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| **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 HIT 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 HIT is not apparent, platelet transfusions in the setting of HIT or probable HIT may be appropriate. Prophylactic platelet transfusions should not be given in patients without active bleeding with strongly suspected or confirmed HIT (Grade 2C) [4].

References:

10. Mann JM, Tseng E, Ratcliffe M, et al. Use of Bivalirudin, a Direct Thrombin Inhibitor, and Its Reversal wit Modified Ultrafiltration During Heart


Recommended Readings:
(In addition to those bolded above)