Thrombocytopenia

November 21, 2016 by Josh Farkas

Thrombocytopenia

Thrombocytopenia is extremely common in the ICU. It is often a poor prognostic sign which is associated with systemic inflammation. Most cases will resolve in parallel with the patient's overall recovery.

when to initiate an evaluation?

Most ICU patients with mild thrombocytopenia don't require an exhaustive evaluation. Potential indications to evaluate further might include:
• Severe thrombocytopenia (e.g. below ~50,000).
• Features of HITT (abrupt drop in platelet count by >50%, skin necrosis at site of heparin injection).
• Clinical thrombosis.
• Underlying process is unclear, raising a possibility of an underlying hematologic disorder (e.g. thrombotic thrombocytopenic purpura or hemophagocytic lymphohistiocytosis).

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common causes of thrombocytopenia in the ICU

Thrombocytopenia in critical illness may be divided into roughly four classes:

**subacute/chronic thrombocytopenia:** often present before critical illness.

- Cirrhosis, alcoholism
- Bone marrow dysfunction (e.g. myelodysplastic syndrome)
- Bone marrow suppression (chemotherapy, alcoholism, some antiviral agents, linezolid, some penicillins/cephalosporins, NSAIDs, thiazides)
- HCV, HIV

**non-immune consumption:** often gradual decrease over several days, adequate response to platelet transfusion.

- Microangiopathic hemolytic anemia (TTP/HUS, HELLP, malignant hypertension)
- Disseminated intravascular coagulation (DIC)
- Catastrophic antiphospholipid antibody syndrome (CAPS)
- Sepsis: Can occur with any pathogen, but especially occurs with specific pathogens (ehrlichiosis, babesiosis, anaplasmosis, rocky mountain spotted fever, hantavirus, dengue)
- Surgery, trauma
- Hemophagocytic lymphohistiocytosis (HLH)
- Devices: intra-aortic balloon pump, hemodialysis, ECMO

**immune consumption:** often occurs several days after ICU admission, decrease is rapid (>50% fall in 24-48 hours), often with severe thrombocytopenia which is poorly responsive to platelet transfusion.

- HITT
- Drug-induced immune thrombocytopenia (D-ITP; see section below)
- Post-transfusional purpura
- Passive alloimmune thrombocytopenia
- Idiopathic thrombocytopenic purpura (ITP)

**other**

- Obvious causes
  - Massive transfusion
  - Hypothermia
- Pseudo-thrombocytopenia
  - Artificially low platelet count due to *in vitro* aggregation induced by EDTA in blood tubes.
  - Diagnosed by finding clumped platelets on blood smear and higher platelet count when measured in a citrated blood tube (blue top platelet tube).
  - Usually meaningless, but can be associated with lupus, vasculitis, or lymphoma.

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clinical clues & specific situations
The differential diagnosis of thrombocytopenia is broad. Below are some clues which may help point in the right direction. These shouldn't be used to narrow the differential diagnosis, but rather merely to highlight possibilities that deserve particular attention.

**thrombocytopenia with (paradoxical) clinical thrombosis**

- Heparin-Induced Thrombocytopenia and Thrombosis (HITT)
- Disseminated intravascular coagulation (DIC) of a pro-thrombotic type (e.g. associated with malignancy or sepsis)
  - Acute DIC/liver necrosis/limb necrosis syndrome: Shock liver causes depletion of protein C and anti-thrombin, with subsequent microvascular thrombosis of extremities.
- Catastrophic antiphospholipid antibody syndrome (CAPS)
- “Massive clot thrombocytopenia” – Venous thromboembolic disease itself may cause mild thrombocytopenia.
- Thrombotic thrombocytopenic purpura (TTP)
- Antiphospholipid antibody syndrome (APLS)
- Cirrhosis, in some patients
- Paroxysmal nocturnal hemoglobinuria (rare)

**severe thrombocytopenia (e.g., <20,000)**

- Immune-mediated thrombocytopenia of any cause:
  - Drug-induced immune thrombocytopenia (D-ITP)
  - Transfusion-related (post-transfusional purpura, passive alloimmune thrombocytopenia)
  - HITT causes severe thrombocytopenia in ~10% of cases (generally when HITT causes simultaneous DIC).
  - Idiopathic thrombocytic purpura (ITP)
  - Thrombotic thrombocytic purpura (TTP)
  - Hemophagocytic lymphohistiocytosis (HLH)
  - Severe marrow failure (e.g. chemotherapy or leukemia). Will usually see neutropenia here as well.
- (Usually not due solely to sepsis or DIC)

**thrombocytopenia in septic-appearing patient**

- Disseminated intravascular coagulation (DIC) due to the infection.
- Specific infections (ehrlichiosis, babesia, anaplasmosis, rocky mountain spotted fever, hantavirus, dengue).
- Hemophagocytic lymphohistiocytosis (HLH) – either mimicking sepsis or HLH secondary to infection.

**thrombocytopenia in the cardiac patient**

- Heparin-Induced Thrombocytopenia and Thrombosis (HITT)
- Cardiopulmonary bypass, ECMO, intra-aortic balloon pump (IABP)
- GPIIb/IIIa inhibitors
- Thrombotic thrombocytic purpura (TTP) related to clopidogrel

**thrombocytopenia in pregnant patient**

- Pre-eclampsia and/or HELLP syndrome (Hemolysis, Elevated LFTs and Low Platelets)
- Acute fatty liver of pregnancy
- Thrombotic microangiopathy (including TTP, pregnancy-induced atypical HUS)
- Disseminated intravascular coagulation (may result from various obstetric catastrophes)
- Idiopathic thrombocytic purpura (ITP)
- Gestational thrombocytopenia

**drug-induced immune thrombocytopenia (D-ITP)**

- Typically begins 1-3 weeks after starting new medication (can occur within a day if previously sensitized to medication).
Immune consumption often causes severe thrombocytopenia (e.g. <10,000-20,000) with bleeding. Often causes systemic symptoms including fever and chills.4

commonly implicated medications

- **Cardiac**: Abciximab, Amiodarone, Amlodipine, Captopril, Digoxin, Diltiazem, Eptifibatide, Hydralazine, Procainamide, Quinidine, Simvastatin, Tirofiban.
- **Heme/onc**: Bleomycin, Fludarabine, Gemcitabine, Checkpoint inhibitors? (Ipilimumab), Oxaliplatin, Rituximab, Trastuzumab.
- **Infectious disease**: Amphotericin B, Beta-lactams (esp. ampicillin, ceftriaxone, penicillin, piperacillin), Clarithromycin, Fluconazole, Fluoroquinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin), Indinavir, Interferon-alpha, Linezolid, Rifampin.
- **Trimethoprim/Sulfamethoxazole, Vancomycin**
- **Nephrology**: Acetazolamide, Chlorothiazide, Desmopressin, Hydrochlorothiazide.
- **Neuro/Psych**: Carbamazepine, Clozapine, Diazepam, Fluoxetine, Haloperidol, Lamotrigine, Levetiracetam, Olanzapine, Ondansetron, Phenytoin, Quetiapine, Valproic acid.
- **Rheum**: Allopurinol, Cyclosporin, Methotrexate, Tacrolimus, TNF-inhibitors (Adalimumab, Etanercept, Infliximab).
- **General/Misc**: Acetaminophen, Aspirin, Danazol, H2 blockers (Famotidine, Ranitidine), NSAIDs (esp. Diclofenac, Ibuprofen, Indomethacin, Naproxen), Pantoprazole, Quinine (found in tonic water, mixed drinks).

More information including more detailed up-to-date lists [here](https://ouhsc.edu/platelets/ditp.html). Bolded drugs seem to be more common causes of D-ITP.

treatment

- Discontinuation of drug.
- May require platelet transfusion (however, ongoing consumption can be refractory to platelet transfusion).
- IVIG may be used in severe cases (e.g. 1 gram/kg on two consecutive days).

transfusion related thrombocytopenias

**post-transfusion purpura (PTP)**

- Mechanism
  - Patient was previously sensitized to platelet antigens (especially HPA-1a).
  - Transfusion leads to antibody against HPA-1a, which ends up destroying patient’s own platelets as well.
- Epidemiology
  - At-risk host: Usually mothers (previously sensitized at pregnancy) or patients with history of transfusion or transplantation
- Clinical presentation
  - Occurs ~5-10 days after transfusion of platelets or packed RBCs
  - Abrupt fall in platelets to <20,000 which can cause life-threatening bleeding.
  - May be refractory to platelet transfusion
- Investigation
  - Diagnosis supported by anti-HLA allo-antibodies in patient’s serum.
- Treatment
  - IV immunoglobulin and/or steroids should be considered early.
  - Avoid un-matched platelets; ideally, transfusion of platelets from compatible donor.

**passive allo-immune thrombocytopenia**

- Rare, results from passive transfer of anti-HPA-1a antibodies.
- Immediate, severe thrombocytopenia occurs within hours of transfusion.
- Treatment unclear, but IV immunoglobulin has been used.

heparin induced thrombocytopenia and thrombosis (HITT)
introduction

- Rare, yet important to recognize early. HITT is challenging to diagnose, because the vast majority of patients with DVT or thrombocytopenia won't have HITT.
- In ~10% of cases, HITT leads to overt DIC. These cases are distinguished by unusually low platelet counts (e.g. <20,000), lab derangements of DIC (e.g. elevated INR and low fibrinogen), and often microvascular thrombosis. This combination of HITT and DIC can be difficult to diagnose, because the unusually low platelet count will confound diagnostic algorithms for HITT.

epidemiology of HITT

- Rare, with incidence varying, depending on the type of unit:
  - Surgical ICU (especially cardiothoracic surgery) has highest rate, up to ~2%.
  - Cardiac ICU: Intermediate rate, may approach 1%.
  - Medical ICU: Lowest rate, <<1%.
- Risk varies depending on drugs and dosages:
  - Unfractionated heparin is higher risk than low molecular-weight heparin
  - Heparin infusion is higher risk than DVT prophylactic doses of heparin
- Additional risk factors: Female sex, older age, obesity, hemodialysis.
- Overall, HITT causes at most ~1% of thrombocytopenia which is seen in an ICU (so the vast majority of thrombocytopenia isn't HITT).6

when to evaluate for HITT
- Consider HIT in a patient recently treated with heparin and with:
  - New-onset thrombocytopenia or a platelet count that suddenly drops by 50%.
  - Skin necrosis at sites of heparin injection.
  - Anaphylactoid response to systemic heparin infusion.
  - Venous and/or arterial thromboses.
- Evaluation begins with risk-stratification using the 4T score.²

### 4T score to risk-stratify for heparin-induced thrombocytopenia (HITT)

<table>
<thead>
<tr>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Pattern most suggestive of HITT: &gt;50% drop AND Nadir &gt;30,000</td>
<td>Patterns less suggestive of HITT: 30-50% drop OR Nadir 10,000-19,000</td>
</tr>
<tr>
<td>Timing</td>
<td>Fall 5-10 days after starting heparin OR Fall 1 day after starting heparin in patient exposed within prior month</td>
<td>Platelet fall after &gt;10 days OR Fall 1 day after starting heparin &amp; exposure to heparin in past 30-100 days OR Fall possibly 5-10 days after starting heparin, but incomplete data</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>New thrombosis (arterial or venous) OR Skin necrosis at site of heparin injection OR Anaphylactoid reaction to IV heparin bolus OR Adrenal hemorrhage</td>
<td>Recurrent or progressive venous thrombosis OR Suspended thrombosis awaiting imaging OR Erythematous skin lesion at site of heparin injection</td>
</tr>
<tr>
<td>Other explanation?</td>
<td>None</td>
<td>Possible</td>
</tr>
</tbody>
</table>

**Add up total score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>&lt;1% probability of HITT</td>
<td>10-15% probability of HITT</td>
<td>50-60% probability of HITT</td>
</tr>
<tr>
<td>4-5</td>
<td>10-15% probability of HITT</td>
<td>20-35% probability of HITT</td>
<td>50-60% probability of HITT</td>
</tr>
<tr>
<td>6-7</td>
<td>High risk</td>
<td>Very high risk</td>
<td>Extreme risk</td>
</tr>
</tbody>
</table>

**Interpretation of the 4T score:**

- 0-3 points: Low probability (<1%)
  - No further workup of HIT is indicated (avoid checking heparin-PF4 antibodies).
- 4-5 points: Intermediate probability (~10%)
  - Stop heparin & check anti-PF4 antibody titer
  - Consider therapeutic anticoagulation with non-heparin agent (more on this below).
- 6-8 points: High probability (50%)
  - Stop heparin & check anti-PF4 antibody titer
  - Initiate therapeutic anticoagulation with a non-heparin agent
PF4 antibody titer (ELISA for Heparin-PF4 antibody complex)

<table>
<thead>
<tr>
<th>Assay result* (measured in optical density)</th>
<th>Clinical interpretation &amp; significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.6</td>
<td>Negative (largely excludes HITT)</td>
</tr>
<tr>
<td>0.6-1.5</td>
<td>Indeterminant (likelihood ratio for having HITT is ~1.2). This result provides no reliable information about the risk of HITT. Commonly misconstrued as &quot;positive&quot; for HITT - but it's actually not.</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Positive (likelihood ratio for having HITT is ~7)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>Strongly positive (likelihood ratio for having HITT is ~70)</td>
</tr>
</tbody>
</table>

*Assay cut-off values may vary somewhat between different assays, but these general ranges appear fairly generalizable across the threshold.

- This test detects any antibodies that bind the heparin-PF4 complex. However, most antibodies that bind this complex don't cause clinical HITT.
- Overall heparin-PF4 has high sensitivity but poor specificity (it's positive in ~15% of ICU patients). Therefore, a negative result largely excludes HITT, but a positive result doesn't prove the diagnosis of HITT. Care should be taken to avoid ordering this test indiscriminately, because that will increase the generation of false-positive results.
- PF4 is often treated as a binary test (positive/negative) but this is a gross over-simplification. In reality, the risk of HITT increases with increasing antibody titer as shown above.
- The best way to interpret the PF4 level is in combination with the 4T score, using Bayesian analysis.
Bayesian combination of 4T score with Heparin-PF4 antibody titer to obtain the post-test probability of HITT

<table>
<thead>
<tr>
<th>Pre-Test Probability</th>
<th>Low-risk 4T score (0-3)</th>
<th>Indeterminate 4T score (4-5)</th>
<th>High-risk 4T score (6-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Anti-PF4 (&lt;0.6)</td>
<td>&lt;1% pre-test prob of HITT</td>
<td>&lt;10% pre-test prob of HITT</td>
<td>&lt;50% pre-test prob of HITT</td>
</tr>
<tr>
<td>Likelihood ratio of 0.04</td>
<td>7% probability HITT is excluded</td>
<td>12% probability of HITT</td>
<td>55% probability of HITT</td>
</tr>
<tr>
<td>Indeterminate Anti-PF4 (0.6-1.5)</td>
<td>&lt;2% probability of HITT unlikely</td>
<td>&lt;10% pre-test prob of HITT</td>
<td>&lt;50% pre-test prob of HITT</td>
</tr>
<tr>
<td>Likelihood ratio of 1.2</td>
<td>9% probability of HITT</td>
<td>12% probability of HITT</td>
<td>55% probability of HITT</td>
</tr>
<tr>
<td>Positive Anti-PF4 (1.5-2)</td>
<td>&lt;7% probability HITT unlikely</td>
<td>&lt;10% pre-test prob of HITT</td>
<td>&lt;50% pre-test prob of HITT</td>
</tr>
<tr>
<td>Likelihood ratio of 1.7</td>
<td>9% probability of HITT</td>
<td>12% probability of HITT</td>
<td>55% probability of HITT</td>
</tr>
<tr>
<td>Strongly positive Anti-PF4 (&gt;2)</td>
<td>&lt;42% probability HITT unlikely</td>
<td>&lt;10% pre-test prob of HITT</td>
<td>&lt;50% pre-test prob of HITT</td>
</tr>
<tr>
<td>Likelihood ratio of 7.0</td>
<td>91% probability of HITT</td>
<td>99% probability of HITT</td>
<td></td>
</tr>
</tbody>
</table>

*Anti-PF4 levels shouldn’t generally be ordered in patients with a 4T score of 0-3.*

Based on Lusher A 2013 PRID 2496231 and Raschke BA et al. 2017 PRID 2862243.

Serotonin Release Assay (SRA)

- This is the gold-standard diagnostic test with excellent sensitivity and specificity.
- Unfortunately, this test is expensive and usually takes several days to return. In some cases, empiric therapy for HITT is indicated while waiting for the serotonin release assay to result.

usual approach to HITT evaluation

4T score

4T score 4-8

Initial HITT evaluation

- Heparin-PF4 antibody
- D-dimer & fibrinogen
- Ultrasound to evaluate for DVT** (Other tests to evaluate alternative causes of thrombocytopenia)

4T score 0-3

PF4 antibody negative

Serotonin release assay

Positive

HITT diagnosis confirmed

HITT diagnosis excluded.

- Evaluate for other causes of thrombocytopenia
- Continue to monitor the patient. If the 4T score increases to 4-8, then re-consider the diagnosis.

**Additional tests (other than PF4) don’t directly drive the diagnostic strategy, but they may affect the therapeutic plan.

The Internet Book of Critical Care by @PedsCrit


- **(1)** For patients with clinical thrombosis (e.g. DVT/PT) on therapeutic heparin anticoagulation, heparin should be switched to a non-heparin agent such as argatroban (more on this below).
- **(2)** For patients without clinical thrombosis who have a high likelihood of HITT (e.g. ~50%), empiric anticoagulation with a non-heparin agent should generally be started empirically before the diagnosis is confirmed. Delaying therapy for HITT carries a significant risk of thrombosis, so anticoagulation is generally rational in high-likelihood patients.8
- **(3)** For patients without clinical thrombosis who have an intermediate likelihood of HITT (e.g. ~10-15%), management is controversial.9 If the patient is thrombocytopenic due to another cause, then anticoagulation could compound thrombocytopenia to cause major bleeding.10 Thromboelastography might theoretically be helpful here, because HITT seems to associate with a hyper-coagulable pattern whereas hypo-coagulability would argue against HITT and potentially signal harm from anticoagulation.11,12 A sensible compromise might be to use a DVT-prophylactic dose of fondaparinux in this situation (2.5 mg sq. daily).3 Ultrascanography should be performed to exclude DVT if this hasn’t already been done. Ongoing evaluation for HITT should be expedited, with further management depending on the results of additional testing.

non-heparin anticoagulants for HITT

https://emcrit.org/ibcc/thrombocytopenia/
Argatroban is the most commonly used agent. It is a small molecule which directly inhibits thrombin (figure above). It is cleared by the liver with an approximate 45-minute half-life. Coagulation will normalize two hours after holding the infusion, if hepatic function is normal. It is monitored with aPTT level, targeting aPTT 1.5-3 times baseline. Make sure to obtain a baseline aPTT before starting the argatroban infusion. If the PTT is elevated at baseline and this is unrecognized, it may lead to subtherapeutic argatroban dosing (“PTT confounding”).

Starting dose is a 2 ug/kg/min infusion, possibly lower in multi-organ failure (1 ug/kg/min) or hepatic dysfunction (0.5 ug/kg/min). Medscape monograph on argatroban.

Fondaparinux is another option. Full-dose fondaparinux is often avoided in the ICU, because in case of bleeding it is impossible to reverse and it has a relatively long half-life (~20 hours). The DVT prophylactic dose of fondaparinux may be reasonable for patients with possible HITT and with no evidence of thrombosis, as explored above (2.5 mg sq daily). Fondaparinux is cleared by the kidneys, so this cannot be used in patients with significant renal dysfunction.

Medscape monograph on fondaparinux.

**investigation of thrombocytopenia**

**chart review**

- Chronicity of thrombocytopenia? (Obtaining baseline CBC from prior admissions or from other hospitals may be extremely helpful.)
- Medication review? (Many drugs can cause thrombocytopenia, not all of which are listed above.)
- Calculate the 4T score for HITT (see above)
- Recent events known to cause thrombocytopenia (e.g. massive transfusion, surgery, hemodialysis, intra-aortic balloon pump, ECMO, transfusion)?

**thrombocytopenia tests to consider:**

- Core investigations
  - Platelet count in citrated tube to exclude pseudothrombocytopenia (blue top tube)
  - Blood smear
  - Coagulation studies (INR, PTT)
  - DIC labs (fibrinogen, D-dimer)
- Additional studies to consider

https://emcrit.org/ibcc/thrombocytopenia/
- Heparin-PF4 antibody to evaluate for HIT if the 4T score is 4-8
- Ferritin, if concern for hemophagocytic lymphohistiocytosis (HLH)
- Ultrasonography to evaluate for DVT (if HIT or other thrombogenic forms of thrombocytopenia are possible)
- Liver function tests, if concern for cirrhosis
- Thromboelastography (TEG) may be considered in selected cases.  

**Immediate management steps to consider (while awaiting labs)**

- Discontinue heparin if there is concern for HIT.
- Discontinue other potentially causative drugs if possible.
- Review all anti-coagulating medications and consider holding them, if there is concern for possible hemorrhage (especially anti-platelet drugs).
- Consider platelet transfusion (next section).

### Platelet Transfusion

**Indications & contraindications to platelet transfusion**

- **Relative contraindications** to platelet transfusion:
  - HIT
  - TTP/HUS
  - DIC with clinical thrombosis
- **Conventional transfusion targets**:
  - Target >100 if active intracranial hemorrhage or pre-operative before neurosurgery/ophthalmic surgery.
  - Target >50 if active bleeding or pre-operative (non-neurologic surgery).
  - Target >20 possibly in patients with other coagulopathies (e.g. DIC, severe renal dysfunction).  
- Target >10 in most patients.

**Response to platelet transfusion**

- Platelets may be given in one of the forms listed below, which are functionally equivalent. Either one should increase platelet count by roughly 30,000-60,000.
  - 4-6 pack of pooled platelets from multiple donors.
- If the patient doesn't respond appropriately to platelet transfusion, this may be investigated by checking a platelet level one hour after the next platelet transfusion.
  - If the 1-hour platelet level fails to increase appropriately, this implies *immune* platelet consumption. In addition to the causes of immune platelet consumption listed above, this can also be due to alloimmunization (antibodies against donor platelet antigens). Alloimmunization may be managed by obtaining HLA-matched platelets (with the help of the blood bank).
  - If the 1-hour platelet level increases appropriately and then platelet count falls over the following day, this indicates *non-immune* platelet consumption (causes listed above).

**Approach to thrombocytopenia**
Approach to HITT

**4T score to risk-stratify for heparin-induced thrombocytopenia (HITT)**

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<td>Fall 5-10 days after starting heparin exposure OR Fall 1 day after starting heparin in patient exposed within past month</td>
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**Other explanation?** None Possible Definite

**Add up total score**

- Score 0-3 Low risk <1% probability of HITT
- Score 4-5 Intermediate risk 10-15% probability of HITT
- Score 6-7 High risk 50-60% probability of HITT

**Bayesian combination of 4T score with Heparin-PF4 antibody titer to obtain the post-test probability of HITT**

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<tr>
<td><strong>Negative Anti-PF4 (&lt;0.6)</strong></td>
<td>96% probability HITT* HITT is excluded</td>
<td>96% probability of HITT HITT is excluded</td>
<td>~10% probability of HITT Check serotonin release assay Stop heparin Empiric tx for HITT (see text)</td>
</tr>
<tr>
<td>Likelihood ratio of ~0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indeterminate Anti-PF4 (0.6-1.5)</strong></td>
<td>&lt;2% probability of HITT* HITT unlikely. Consider serotonin release assay.</td>
<td>~1.2% probability of HITT Stop serotonin release assay Stop heparin Empiric tx for HITT (see text)</td>
<td>~53% probability of HITT Check serotonin release assay Stop heparin Empiric tx for HITT</td>
</tr>
<tr>
<td>Likelihood ratio of ~1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive Anti-PF4 (1.5-2)</strong></td>
<td>~7% probability HITT* Check serotonin release assay Stop heparin Empiric tx for HITT (see text)</td>
<td>~50% probability of HITT Check serotonin release assay Stop heparin Empiric tx for HITT</td>
<td>~90% probability of HITT HITT largely ruled in. Stop heparin Empiric tx for HITT</td>
</tr>
<tr>
<td>Likelihood ratio of ~7</td>
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<td></td>
</tr>
<tr>
<td><strong>Strongly positive Anti-PF4 (&gt;2)</strong></td>
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<td>99% probability of HITT HITT is ruled in. Stop heparin Empiric tx for HITT</td>
</tr>
<tr>
<td>Likelihood ratio of ~70</td>
<td></td>
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</table>

*Anti-PF4 levels should not generally be ordered in patients with a 4T score of 0-3.

Based on: Luken A 2013 PMID 24363239 and Raschke RA et al. 2017 PMID 28624435
Avoid checking HITT labs if the 4T score is 0-3 points. These patients are at very low risk for HIT, so if the heparin-PF4 test is positive it is probably a false-positive.

Avoid platelet transfusions unless truly indicated. Platelet transfusion has a significant side-effect profile, and transfused platelets often don’t last long anyway.

To keep this page small and fast, questions & discussion about this post can be found on another page here.
- Warfarin is contraindicated in the acute (thrombocytopenic) phase of HIT. Initiation of warfarin in this context may cause depletion of endogenous anticoagulants (proteins C and S), leading to ischemic limb necrosis.
- Avoid the use of unfractionated heparin for DVT prophylaxis if possible, given that unfractionated heparin causes a substantially higher risk of HIT as compared to low molecular weight heparin (e.g. enoxaparin) or fondaparinux.  
- Don’t assume that a “positive” anti-PF4 antibody proves a diagnosis of HIT. The significance of a positive result depends on the antibody titer. A validated Bayesian algorithm incorporating the 4T score and anti-PF4 antibody titer is probably the best way to approach this. 

### References

1. By definition, ITP is a diagnosis of exclusion. Therefore, be extremely careful about using this diagnosis to explain new-onset thrombocytopenia in the ICU. The acute onset of an idiopathic illness during an ICU stay would be extremely unlikely – it’s more likely that thrombocytopenia is related to the underlying disease or ongoing treatments (especially drugs).

### Going further:
- Thrombocytopenia
  - [Thrombocytopenia](https://lifeinthefastlane.com/ccc/thrombocytopenia/) (Chris Nickson, LitFL)
  - [Thrombocytopenia](https://wikem.org/wiki/Thrombocytopenia) (WikEM)
- HIT
  - [Heparin Induced Thrombotic Thrombocytopenia](https://lifeinthefastlane.com/ccc/heparin-induced-thrombotic-thrombocytopenia-syndrome-hits/) (Chris Nickson, LitFL)
  - [HIT overview](https://pubmedcentral.gov/review-articles/heparin-induced-thrombocytopenia-hit-review/) (PulmCCM)

## Bayesian combination of 4T score with Heparin-PF4 antibody titer to obtain the post-test probability of HIT

<table>
<thead>
<tr>
<th>Pre-Test Probability</th>
<th>Low-risk 4T score (0-3)</th>
<th>Indeterminate 4T score (4-5)</th>
<th>High-risk 4T score (6-8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1% pre-test prob of HIT</td>
<td>~10% pre-test prob of HIT</td>
<td>~50% pre-test prob of HIT</td>
</tr>
<tr>
<td><strong>Post-test probability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative Anti-PF4</strong></td>
<td>(~0.6)</td>
<td>0% probability of HIT = excluded</td>
<td>0% probability of HIT is excluded</td>
</tr>
<tr>
<td>Likelihood ratio of ~0.04</td>
<td></td>
<td>~10% probability of HIT is excluded</td>
<td>~10% probability of HIT is excluded</td>
</tr>
<tr>
<td><strong>Indeterminate Anti-PF4</strong></td>
<td>(~0.6-1.5)</td>
<td>~12% probability of HIT is excluded</td>
<td>~12% probability of HIT is excluded</td>
</tr>
<tr>
<td>Likelihood ratio of ~1.2</td>
<td></td>
<td>~50% probability of HIT is excluded</td>
<td>~50% probability of HIT is excluded</td>
</tr>
<tr>
<td><strong>Positive Anti-PF4</strong></td>
<td>(~1.5-2)</td>
<td>~12% probability of HIT is excluded</td>
<td>~12% probability of HIT is excluded</td>
</tr>
<tr>
<td>Likelihood ratio of ~&gt;3</td>
<td></td>
<td>~50% probability of HIT is excluded</td>
<td>~50% probability of HIT is excluded</td>
</tr>
<tr>
<td><strong>Strongly positive Anti-PF4</strong></td>
<td>(&gt;2)</td>
<td>91% probability of HIT is excluded</td>
<td>91% probability of HIT is excluded</td>
</tr>
<tr>
<td>Likelihood ratio of ~76</td>
<td></td>
<td>99% probability of HIT is excluded</td>
<td>99% probability of HIT is excluded</td>
</tr>
</tbody>
</table>

*Anti-PF4 levels should not generally be ordered in patients with a 4T score of 0-3.*

13. Lepirudin was traditionally used but no longer available in the US. Fondaparinux is another option, but it has a long half-life (~16 hours) which makes its use in the ICU unwieldy (e.g. if the patient starts bleeding or requires an unexpected procedure).
