THROMBOCYTOPENIA

DIFFERENTIAL DIAGNOSIS

FALSELY LOW PLATELET COUNT
In vitro platelet clumping caused by EDTA–dependent agglutinins
Giant platelets

COMMON CAUSES OF THROMBOCYTOPENIA
Pregnancy (gestational thrombocytopenia, preeclampsia)
Drug–induced thrombocytopenia (i.e., heparin, quinidine, quinine, and sulfonamides)
Viral infections (i.e. HIV, rubella, infectious mononucleosis)
Hypersplenism due to chronic liver disease
Dilutional (massive transfusion)

OTHER CAUSES OF THROMBOCYTOPENIA
Myelodysplasia
Congenital thrombocytopenia
Thrombotic thrombocytopenic purpura (TTP) –hemolytic–uremic syndrome (HUS)
Chronic disseminated intravascular coagulation (DIC)
Autoimmune diseases, such as systemic lupus erythematosus–associated
lymphoproliferative disorders (CLL and NHL)
Sepsis
Idiopathic thrombocytopenic purpura (ITP)*

DIFFERENTIAL FOR THROMBOCYTOPENIA BASED ON CLINICAL SETTING

<table>
<thead>
<tr>
<th>CLINICAL SETTING</th>
<th>DIFFERENTIAL DIAGNOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgery</td>
<td>Cardiopulmonary bypass, HIT, dilutional thrombocytopenia, PTP</td>
</tr>
<tr>
<td>Interventional cardiac procedure</td>
<td>Abciximab or other IIb/IIIa blockers, HIT</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>DIC, ehrlichiosis, sepsis, hemophagocytosis syndrome, drug–induced, misdiagnosed TTP, mechanical ventilation, pulmonary artery catheters</td>
</tr>
<tr>
<td>Pulmonary failure</td>
<td>DIC, hantavirus pulmonary syndrome, mechanical ventilation, pulmonary artery catheters</td>
</tr>
<tr>
<td>Mental status changes/seizures</td>
<td>TTP, ehrlichiosis</td>
</tr>
<tr>
<td>Renal failure</td>
<td>TTP, Dengue, HIT, DIC, HUS</td>
</tr>
<tr>
<td>Continuous hemofiltration</td>
<td>HIT, consumption by filter and tubing</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>HIT, drug–induced, pulmonary artery catheter</td>
</tr>
<tr>
<td>Post–surgery</td>
<td>Dilutional, drug–induced, HIT, PTP</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Splenic sequestration, HIT, drug induced, DIC</td>
</tr>
</tbody>
</table>

Abbreviations: HIT = heparin–induced thrombocytopenia; DIC = disseminated intravascular coagulation; TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic–uremic syndrome; PTP = post–transfusion purpura

*NOTE: ITP is a diagnosis of exclusion.

IDIOPATHIC THROMBOCYTOPENIA PURPURA (ITP)

TREATMENT PHILOSOPHY

ITP is a diagnosis of exclusion without an absolute confirmatory test. Antiplatelet-antibodies are not thought to be sufficiently sensitive or specific to rule in or out ITP. The role of a bone marrow biopsy is to rule out other causes of thrombocytopenia or an underlying lymphoproliferative disorder. Treatment must be tailored to the individual patient and scenario. The main goal is to achieve hemostasis with the minimum amount of drug related side effects, not necessarily to attain a certain goal platelet count. ITP guidelines were published in 1996 by the American Society of Hematology and can be reviewed at [http://www.hematology.org/policy/guidelines/idiopathic.cfm](http://www.hematology.org/policy/guidelines/idiopathic.cfm).

SUGGESTED ITP TREATMENT ALGORITHM

NOTE: This is a listing of suggested treatment options, but physician and patient preference, comorbidities, and financial constraints need to be considered for each individual patient. Expert opinion may vary considerably in the absence of randomized clinical trial data.

<table>
<thead>
<tr>
<th>CLINICAL SETTING</th>
<th>TREATMENT OPTIONS OUTSIDE A CLINICAL TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Treatment</td>
<td>IVIG 1 gram/kg/day for 2 days AND Methylprednisolone 1 gram/day for 3 days or Dexamethasone 40mg daily for 4 days +/- platelet transfusion +/- Factor VIIa if life threatening bleeding</td>
</tr>
<tr>
<td>Initial Treatment: Platelets &lt;25–30,000/uL</td>
<td>Prednisone 1 mg/kg oral daily or Dexamethasone 40 mg oral daily for 4 days or Periodic Anti-D 50–75 mcg/kg IV or Periodic IVIG 1 gram/kg/day for 2 days or 0.4 gram/kg/day for 5 days</td>
</tr>
<tr>
<td>Failure of Initial Therapy or Relapse with Tapering Therapy: Platelets &lt;25–30,000/uL</td>
<td>Splenectomy Rituximab 375 mg/m² IV weekly for 4–8 weeks Periodic Anti-D 50–75 mcg/kg IV or Periodic IVIG 1 gram/kg/day for 2 days or 0.4 gram/kg/day for 5 days Eltrombopag Romiplistin</td>
</tr>
<tr>
<td>Failure of Second Line Therapy with Clinical Bleeding, High Bleeding Risk or Platelets &lt;10–20,000/uL</td>
<td>Low dose prednisone Danazol Azathioprine Cyclophosphamide Mycophenolate motefil Cyclosporine Colchicine Dapsone Eltrombopag Romiplistin</td>
</tr>
<tr>
<td>Failure of Third Line Therapy with Clinical Bleeding or Platelets &lt;10,000/uL</td>
<td>High dose cyclophosphamide Combination chemotherapy Stem–cell transplantation Eltrombopag Romiplistin</td>
</tr>
</tbody>
</table>

### SELECTED ITP THERAPIES

#### STEROIDS

**Prednisone**  
1 – 2 mg/kg  
PO  
Daily  

References:  

**Methylprednisolone**  
5 – 30 mg/kg  
IV  
Daily  

OR  
1 – 2 gm  
IV  
Daily  

References:  

**Dexamethasone**  
40 mg  
PO  
Days 1 – 4  

References:  

#### IMMUNOGLOBULINS

**IVIG**  
1 – 2 gm/kg  
IV  
Days 1 – 5 then PRN  

NOTE: Duration of therapy is typically 2 to 5 days.

References:  

**Anti–Rh(D)**  
50 – 75 mg/kg  
IV  
Day 1 then PRN  

NOTE: Only use if blood type Rh+ and patient has a functional spleen.

References:  

#### BIOLOGICS

**Rituximab**  
375 mg/m²  
IV  
Weekly x 4  

References:  

**Romiplistin**  
1 mcg/kg initial dose  
SQ  
Weekly  

Reference:  

**Eltrombopag**  
50–75 mg initial dose  
PO  
Daily  

NOTE: If patient is of Asian descent, start initial dose at 25 mg  

Reference:  

CONTINUED ON NEXT PAGE...

Last Updated on June 3, 2009
SELECTED ITP THERAPIES – CONTINUED

OTHER
Please note that much of the available literature on these medications are based on small case series and phase II data. Most have not been studied in randomized clinical trials. Response rates are generally less than 30% and each drug has its own unique toxicity profile which needs to be considered. These drugs are often reserved for those patients who have failed standard therapy, and who have failed or are not candidates for splenectomy. Due to side effects and poor response rates, these therapies are usually reserved for those patients with symptomatic ITP or severe thrombocytopenia (less than 10–30,000/uL) or those at high risk of bleeding due to other comorbidities. It may take several months to see a response to these agents and therapy should therefore not be discontinued prior to a proper trial. If no response is seen within 3–4 months the drug should be discontinued. Proper monitoring for drug–related side effects is essential.

SINGLE AGENTS
Danazol 200 mg PO BID to QID


Azathioprine 1 – 2 mg/kg PO Daily

NOTE: Typically titrated to 150–200 mg


Cyclophosphamide 1 – 2 mg/kg PO Daily

OR
1 – 1.5 grams/m² IV Every 3 – 4 weeks

NOTE: 150 mg dose often used.


Cyclosporine 1.25 – 2.5 mg/kg PO BID


Mycophenolate 250 – 500 mg PO BID


Vincristine 1 – 2 mg IV Weekly


CONTINUED ON NEXT PAGE...
Vinblastine 0.1 mg/kg IV Weekly

NOTE: Most often 5 – 10 mg.


Colchicine 0.5 – 0.6 mg PO BID to TID


Dapsone 1 – 2 mg/kg PO Daily

NOTE: Most often 75 – 100mg.


**COMBINATION AGENTS**

**H. PYLORI ERADICATION**
Many different *H. pylori* eradication regimens exist and none have been compared to others in the treatment of ITP. One acceptable option is listed below.

Amoxicillin 1000 mg PO BID
Clarithromycin 250 – 500 mg PO BID to TID
Protonix 20 mg PO Daily to BID

Treatment continues for 7 days. If eradication was unsuccessful after the first course of therapy, treatment was repeated with the addition of metronizadole.

ROMIPLISTIN
(Nplate®)

FDA approved in August 2008 for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplistin is available only through the Nplate NEXUS Program. Prescribers and patients must register with the program. It is not FDA approved in patients with thrombocytopenia due to MDS or any other cause.

I. MECHANISM OF ACTION
Thrombopoietin (TPO) receptor agonist produced by recombinant DNA technology in Escherichia coli.
A) Shares no sequence homology to endogenous TPO and therefore not expected to cause cross–reactive antibodies that cause thrombocytopenia, a problem that has occurred with previously studied recombinant TPO.

II. PHARMACOKINETICS
A) Weekly as a subcutaneous injection.
B) Peak serum concentration approximately 7–50 (median 14) hours after administration.
C) Dose dependent increases in platelet counts. Platelet counts generally peak within 2–3 weeks after initiation.
D) Half–life ranges from 1–34 (median 3.5) days.

III. DOSAGE AND ADMINISTRATION
A) Initial dose is 1 mcg/kg SC once weekly (actual body weight). Increase the weekly dose in increments of 1 mcg/kg SC until the patient achieves a platelet count > 50,000/mm³. Do not exceed maximum weekly dose of 10 mcg/kg weekly.
B) If the platelet count increases to >200,000/mm³ for 2 weeks, reduce the dose by 1 mcg/kg/wk. If the platelet count is >400,000/mm³ temporarily stop the drug and restart when platelet count is <200,000/mm³. Reduce the previous dose by 1 mcg/kg/wk.
C) Romiplistin may be administered concomitantly with other medical ITP therapies.
D) Discontinue if the platelet count does not increase to a sufficient point within 4 weeks of maximal dose 10 mcg/kg.
E) Dose adjustments in hepatic and renal impairment are not needed.
Safe and effective use or dose has not been established in children.

IV. TOXICITY
A) Most common (>5%) but less severe side effects: headache (35%), arthralgia (26%), dizziness (17%), insomnia (16%), myalgia (14%), pain in extremity (13%), abdominal pain (11%), shoulder pain (8%), dyspepsia (7%), and paresthesias (6%).
B) Increased megakaryocyte production may lead to bone marrow reticulin deposition, which may lead to marrow fibrosis. It is recommended to check peripheral blood smear before initiation, weekly during dose escalation, and monthly thereafter.
C) Absolute contraindications: mannitol hypersensitivity
D) If platelet count increases to above normal range a potential for thrombosis exists.
E) Precautions include use with anticoagulant therapy, bleeding, bone marrow suppression, breast–feeding, children, neoplastic disease, and pregnancy (category C).
F) No pharmacokinetic drug interactions involving romiplistin have been reported.

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V. CLINICAL MONITORING
A) Monitor CBC, peripheral blood smears prior to initiation and then weekly during dose escalation then monthly thereafter.
B) In clinical studies of non-splenectomized and splenectomized patients with chronic ITP, romiplostim produced response rates of 79–88% and increased platelet count in a dose-dependent fashion.
C) After drug discontinuation, platelet count can drop lower then before drug initiation. This typically resolves within 14 days after drug discontinuation.
D) CBC for at least 2 weeks after drug discontinuation.
ELTROMBOPAG  
(PROMACTA®) 

FDA approved in November 2008 for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is available only through the PROMACTA CARES program. Prescribers and patients must register with the program. It is not indicated for thrombocytopenia due to MDS or other cause other than chronic ITP.

I. MECHANISM OF ACTION
Orally bioavailable, small–molecule thrombopoietin (TPO) receptor agonist

II. PHARMACOKINETICS
A) Peak concentration between 2–6 hours of oral dose.
B) Eltrombopag is highly bound to human plasma proteins (>99%).
C) Absorbed eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation, and conjugation with glucoronic acid, glutathione, or cysteine.
D) The predominant route of eltrombopag excretion is via feces (59%) and 31% is found unchanged in the urine.
E) The plasma elimination half-life is approximately 21–32 hours in healthy subjects and 26–35 hours in ITP patients.

III. DOSAGE AND ADMINISTRATION
A) Starting dose is 50 mg PO daily.
B) East Asian ancestry or patients with moderate to severe hepatic insufficiency should start at 25 mg PO daily.
C) Should be taken on an empty stomach.
D) Adjust the daily dose to achieve and maintain a platelet count >50 x 10⁹/L.
E) Do not exceed 75 mg PO daily.
F) Discontinue Eltrombopag if the platelet count does not increase after 4 weeks at the maximum dose. Also discontinue if liver abnormalities or thrombocytosis develop.

IV. TOXICITY
A) Most common side effects (>5%): nausea, vomiting, menorrhagia, myalgias, paresthesias, dyspepsia, ecchymosis, conjunctival bleeding.
B) Black box warning: Hepatotoxicity, LFT monitoring prior to initiation, every 2 weeks during dose adjustment, and monthly once stable dose achieved. Discontinue drug if ALT levels increase to >3 x upper limit of normal AND are:
C) progressive, or persistent for ≥4 weeks, accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence of hepatic decompensation.
D) Bone marrow reticulin formation and risk for bone marrow fibrosis.
E) Worsened thrombocytopenia after cessation of drug.
F) Thrombotic/thromboembolic complications from excessive increases in platelet count.
G) Increased risk of hematologic malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplasia.
H) New or worsened cataracts.

CONTINUED ON NEXT PAGE...
V. CLINICAL MONITORING
A) LFTs prior to initiation, every 2 weeks during dose escalation, and monthly after stable dose achieved.
B) Examine peripheral blood smear prior to initiation, weekly during dose adjustment phase, then monthly after stable dose achieved.
C) CBC with differential prior to initiation, weekly during dose adjustment phase, then monthly after stable dose achieved. Follow CBCs weekly for at least 4 weeks after discontinuation of drug.
D) Ocular exam at baseline and during therapy.
This immune globulin product, when given intravenously, is indicated for acute and chronic idiopathic thrombocytopenic purpura (ITP) in certain patients. Patients and clinicians need to be alert for the potential development of intravascular hemolysis. Also, administration of the liquid WinRho® SDF product may cause falsely elevated serum glucose concentrations. Other Rh0 [D] immune globulin products and treatment for prevention of isoimmunization in Rh0 [D]–negative women exposed to Rh0 [D]–positive blood are not covered in this monograph. The use of this product should be limited to Rh0 [D]–positive patients who have not undergone splenectomy.

I. MECHANISM OF ACTION
The actions of Rh0 [D] immune globulin in idiopathic thrombocytopenic purpura (ITP) are not well understood. Intravenous infusion of Rh0 [D] immune globulin into an Rh0 [D]–positive patient leads to antibody coating of circulating erythrocytes. These coated red cells are cleared primarily by the spleen. The immune–mediated clearance of these sensitized erythrocytes occupies the reticuloendothelial system (RES) and allows for the survival of antibody coated platelets. The primary mechanism of action of Rh0 [D] immune globulin appears to occur via immunologic blockade of Fc–receptors within the RES. Other immunomodulatory mechanisms may also play a role in Rh0 [D] immune globulin efficacy in ITP. After administration, Rh0 [D] immune globulin produces a 2—3 day delay in increasing the platelet count. The mean duration of response is about 30 days. Repeated Rh0 [D] immune globulin infusions do not cure the disease but are used to maintain platelet counts at levels sufficient enough to provide adequate hemostasis. Rh0 [D] immune globulin is not effective in splenectomized or Rh0 [D]–negative patients with ITP.

II. PHARMACOKINETICS
A) Peak plasma concentrations occur within 30 minutes of IV administration.
B) The half–life of Rh0 [D] immune globulin is approximately 24 days after IV administration and approximately 30 days after IM administration.
C) Passively acquired anti–Rh0 [D] antibodies are not detectable 6 months after administration.

III. DOSAGE AND ADMINISTRATION
A) In the treatment of ITP doses of 50–75 mcg/kg have been used. In a small trial of adults and children, a dose of 75 mcg/kg IV as a single dose resulted in higher median day 1 platelet counts and a longer duration of response as compared to the standard 50 mcg/kg IV dose, respectively.
B) Dosing for other indications including for prevention of isoimmunization in Rh0 [D]–negative women exposed to Rh0 [D]–positive blood can be found in the package insert.
C) FDA pregnancy risk category C.
D) No obvious dose reduction for renal or hepatic impairment.
E) The drug should be used with caution in patients with a baseline moderate anemia (hb <10 g/dL) and is discouraged with severe (hb <8 g/dL) anemia due to the risk of hemolysis and worsening of the anemia.

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IV. TOXICITY
Most adverse reactions associated with Rh₀[D] immune globulin are mild and transient. Increased destruction of Rh₀[D]-positive red cells with attendant decreased serum hemoglobin concentrations and associated clinical symptoms occurs after Rh₀[D] immune globulin administration. As expected, mild extravascular hemolysis, manifested as an increase in bilirubin, a decrease in hemoglobin, or a decrease in haptoglobin can be observed. To reduce the risk of increasing the anemia severity, a reduced WinRho® SDF dose is recommended for patients with a hemoglobin concentration of less than 10 g/dL. Extreme caution is recommended in patients with a hemoglobin concentration of less than 8 g/dL. While most of the red cell destruction will occur in the spleen, there have been rare reports of acute hemoglobinuria consistent with intravascular hemolysis that have occurred during Rh₀[D] immune globulin administration. Hemolysis and hematuria may be accompanied by reversible acute renal impairment. Cases of acute DIC have also been reported to the FDA soon after WinRho administration. Anaphylactic shock is rare but has occurred after Rh₀[D] immune globulin administration. Rh₀[D] immune globulin is derived from human plasma donors and carries the possibility of causing iatrogenic infection via blood borne pathogens. The risk is considered to be low due to the careful screening of plasma donors.

The most commonly reported side effects include:
A.) Headache
B.) Cough
C.) Chills/Fever
D.) GI symptoms
E.) Abdominal pain
F.) Arthralgias
G.) Pruritis
H.) Diaphoresis

V. CLINICAL MONITORING
A) Platelet count
B) Hemoglobin/Hematocrit
C) Reticulocyte count, LDH, bilirubin if hemolysis is suspected
D) Rh serology
E) Clinical signs of bleeding or anemia

VI. DRUG INTERACTIONS
Do not vaccinate patients with most live virus vaccines for at least 3 months after administration of intravenous immune globulin Rh₀[D] immune globulin. Rh₀[D] immune globulin contains antibodies that can interact with certain live virus vaccines. Rh₀[D] immune globulin should not be administered concomitantly with measles/mumps/rubella vaccines, MMR, rotavirus vaccine; or varicella virus vaccine live. Consult specific CDC guidelines for the most current clinical recommendations in accordance with the individual patient circumstances and the vaccine in question.
THROMBOTIC THROMBOCYTOPENIA PURPURA (TTP)

The diagnosis of TTP should be suspected in a patient who presents with otherwise unexplained microangiopathic hemolytic anemia and thrombocytopenia. The presence of renal failure, fever, and mental status changes further support the diagnosis, but are not always present or obvious in early stages. Plasma exchange should be begun promptly once the diagnosis is suspected, and can be discontinued should another diagnosis become more likely. If plasma exchange is not immediately available, FFP should be infused while plans are being made to initiate plasma exchange. All other treatments should be considered ancillary to plasma exchange and there is significant institutional variance on their use (i.e., steroids, vincristine, rituximab).

SUGGESTED TTP TREATMENT ALGORITHM

DAILY PLASMA EXCHANGES OF 1.3 – 1.5 X PLASMA VOLUME
   Fresh-frozen plasma
   Cryoprecipitate-poor plasma

POSSIBLE MECHANISMS OF EFFICACY
   Supply vWF metalloproteinase (ADAMTS-13)
   Removal of ultra-large vWF multimers or autoantibodies against ADAMTS-13
   Deficiency of plasma ADAMTS-13 in chronic relapsing TTP

SUGGESTED TREATMENT OF THROMBOTIC THROMBOCYTOPENIA PURPURA
   Infuse fresh frozen plasma (FFP) at 30 mL/kg until plasma exchange is available
   Plasma exchange ASAP, especially if acute organ dysfunction
   Steroids (uncertain efficacy) – Prednisone 1 mg/kg PO daily
   Continue plasma exchange for 1 to 3 days after obtaining complete remission based on hematocrit/platelet count and LDH. There is significant institutional variation on whether to taper plasma exchange procedures.
   Taper steroids

POOR RESPONSE
   Substitute cryosupernatant for FFP (Cryopoor FFP).

OTHER ANCILLARY TREATMENTS
   Rituximab
   ECASA
   Vincristine
   Splenectomy
   Other immunosuppressive agents
   Protein-A column immunoadsorption

HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

The diagnosis of HIT should be based on a clinical probability model and confirmed with laboratory testing. Treatment should not be delayed while awaiting laboratory confirmation. ELISA testing for heparin–PF4 antibodies is very sensitive, but not specific. The level of positivity does seem to correlate with positivity on the more specific serotonin release assay (SRA) and clinical events.

SUGGESTED HIT TREATMENT ALGORITHM

IMMEDIATE CLINICAL INTERVENTION
- Consider doppler studies of the 4 extremities
- Determine bleeding risk with empiric alternative anticoagulant therapy
- Consider empiric intravenous thrombin inhibition or Fondaparinux 2.5–7.5 mg SQ QD based on above variables
- Send serum ELISA testing as above

LABORATORY TESTING RESULTS
- ELISA <4: Patient unlikely to have HIT. If high clinical suspicion send SRA and consider empiric treatment as above.
- ELISA 4–10: Result is positive, but nonspecific. Send SRA. Consider above empiric therapy
- ELISA >10: Result is positive, and specificity increases. Consider sending SRA. Lower threshold for above empiric therapy

NON-HEPARIN TREATMENT OPTIONS
- Argatroban
- Lepirudin
- Bivalirudin
- Fondaparinux

Please see specific drug monographs and package inserts for dosing and dose reduction. Drugs should be chosen based on their mechanism of clearance and underlying organ dysfunction of the patient. No randomized trials comparing these drugs in the treatment of HIT are available. Length of therapy in the absence of VTE or arterial thrombosis is controversial. Coumadin should not be started until the platelet count has normalized and patient is therapeutic on alternative antiocoagulation. Platelet transfusion should be avoided.
**CLINICAL PROBABILITY OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)**

<table>
<thead>
<tr>
<th>Suspicion of HIT based upon the &quot;4 T's&quot;</th>
<th>Pre-test Probability Score Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>nadir 20-100, or &gt;50% platelet fall</td>
</tr>
<tr>
<td>Timing of onset of platelet fall</td>
<td>nadir 10-19, or 30-50% platelet fall</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>&gt;day 10 or timing unclear (but fits with HIT)</td>
</tr>
<tr>
<td>Other cause of platelet fall</td>
<td>&lt;day 1 (no recent heparin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Pre-test Probability Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>periodic reassessment as new information can change pre-test probability (e.g., positive blood cultures)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Pre-test Probability Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>Stop heparin; give alternative non-heparin anticoagulant</td>
</tr>
</tbody>
</table>
| argatroban† or lepirudin‡ or danaparoid**  
(or bivalirudin†† or fondaparinux‡‡) |

<table>
<thead>
<tr>
<th>Positive test for HIT antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue non-heparin anticoagulant</td>
</tr>
<tr>
<td>until platelet count recovery</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging studies for lower-limb DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Thrombosis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HIT Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative test for HIT antibodies</td>
</tr>
<tr>
<td>Consider continuing or switching back to (LMW) heparin ##</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombosis***</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HIT, continue non-heparin anticoagulant</td>
</tr>
<tr>
<td>until platelet count recovery, then cautionous coumarin overlap ¶¶</td>
</tr>
</tbody>
</table>

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* recent heparin indicates exposure within the past 30 days (2 points); or past 30-100 days (1 point)
† STOP, acute systemic reaction following i.v. heparin bolus (see Table 4)
‡ stop all heparin, including catheter “flushes” and, possibly, heparin-coated catheters
† argatroban: approved (U.S., Canada) for isolated HIT and HIT complicated by thrombosis (2 µg/kg/min i.v., adjusted to 1.5-3.0X patient’s baseline aPTT or the mean of the laboratory normal range); reduce dose for heparin-induced thrombocytopenia; may increase INR more than the other direct thrombin inhibitors, thus requiring care in managing coumarin overlap (see ¶¶ below)
‡ lepirudin: approved (U.S., Canada, E.U., elsewhere) for treatment of thrombosis complicating HIT (± 0.4 mg/kg i.v. bolus, then 0.15 mg/kg/h adjusted to 1.5-2.5X patient’s baseline aPTT or mean of the laboratory normal range); used (off-label) also to treat isolated HIT (0.1 mg/kg/h, adjusted by aPTT); to avoid overdosing and anaphylaxis, it may be preferable to omit the bolus, and begin at i.v. infusion (except when facing life-or-limb-threatening thrombosis); reduce dose for renal insufficiency
** danaparoid: usual i.v. bolus, 2,250 U (body weight 60-75 kg) followed by infusion (400 U/hr for 4 h, then 300 U/hr for 4 h, then 200 U/hr, adjusted by anti-factor Xa levels); this therapeutic-dose regimen is appropriate both for isolated HIT and for HIT complicated by thrombosis (though higher than approved dose in some jurisdictions); withdrawn from U.S. market (2002)
†† bivalirudin: no bolus, i.v. infusion 0.15 mg/kg/h adjusted by aPTT; limited experience (off-label)
‡‡ fondaparinux: dosing for HIT not established; limited experience (off-label)
¶¶ delay coumarin pending substantial platelet count recovery (at least >100, preferably >150); begin coumarin in low doses, with at least 4-5 day overlap, stopping alternative anticoagulant when INR therapeutic for 2 days and platelets recovered
## depending on physician confidence in the laboratory’s ability to rule out HIT antibodies (usually, negative PF4-dependent enzymes-immunocassay and washed platelet activation assay performed by an experienced laboratory)
*** some thrombi may require special treatment, e.g., thrombectomy for large limb artery thrombosis
††† routine ultrasound of lower-limb veins recommended; since many HIT patients have subclinical deep-vein thrombosis (DVT)


Last Updated on June 3, 2009