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 (ie. 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

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

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.

Reference: Adapted from American Society of Hematology Education Book, 1999.

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

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.

CLINICAL SETTING	TREATMENT OPTIONS OUTSIDE A CLINICAL TRIAL
Emergency Treatment	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
Initial Treatment: Platelets <25-30,000/uL	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 5days
Failure of Initial Therapy or Relapse with Tapering Therapy: Platelets <25-30,000/uL	Splenectomy Rituximab 375 mg/m^2 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 5days Eltrombopag Romiplistin
Failure of Second Line Therapy with Clinical Bleeding, High Bleeding Risk or Platelets <10-20,000/uL	Low dose prednisone Danazol Azathioprine Cyclophosphamide Mycophenolate motefil Cyclosporine Colchicine Dapsone Eltrombopag Romiplistin
Failure of Third Line Therapy with Clinical Bleeding or Platelets <10,000/uL	High dose cyclophosphamide Combination chemotherapy Stem-cell transplantation Eltrombopag Romiplistin

Reference: Adapted from Cines DB and McMillan R. *Annu Rev Med* 2005;56:425 - 42.

Last Updated on June 3, 2009

SELECTED ITP THERAPIES

STEROIDS

Prednisone	1 – 2 mg/kg	PO	Daily

References: Pizzuto J and Ambriz R. *Blood* 1984;64:1179 – 83; George JN, et al. *Blood* 1996:88:3 – 40.

Methylprednisolone	5 – 30 mg/kg	IV	Daily
	OR		
	1 – 2 gm	IV	Daily

References: Cines DB and Bussel JB. *Blood* 2005;106:2244 – 51; George JN, et al. *Blood* 1996:88:3 – 40; Ozsoylu S, et al. *Pediatr Hematol Oncol* 1993;10:317 – 21.

Dexamethasone	40 mg	PO	Days 1 – 4

References: Mazzucconi MG, et al. *Blood* 2007;109:1401 – 7; Andersen JC. *N Engl J Med* 1994;330:1560 – 4; Cheng Y, et al. *N Engl J Med* 2003;349;831 – 6.

IMMUNOGLOBULINS

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

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

References: Godeau B, et al. *Blood* 1993:82:1415 – 212; Bussel JB, et al. *Blood* 1983;62:480 – 6.

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: Cooper N, et al. *Blood* 2002:99:1922 – 7; Newman GC, et al. *S Br J Haematol* 2001;112:1076 – 8; Tarantino MD, et al. *J Pediatr* 2006;148:489 – 94.

BIOLOGICS

Rituximab	375 mg/m^2	IV	Weekly x 4

References: Arnold DM, et al. *Ann Int Med* 2007;146:25 – 33; Cooper N, et al. *Br J Haematol* 2004;125:232 – 9; Zaja F, et al. *Haematoligica* 2003;88:538 – 46.

Romiplistin	1 mcg/kg initial dose	SQ	Weekly

Reference: Kuter DJ, et al. *Lancet* 2008;371:394 – 403.

Eltrombopag	50–75 mg initial dose	PO	Daily

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

Reference: Bussel JB, et al. *N Engl J Med* 2007;357:2237 – 47.

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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

References: Ahn YS, et al. *Ann Intern Med* 1989;111:723 – 9; Maloisel F, et al. *Am J Med* 2004;116:590 –4.

Azathioprine	1 – 2 mg/kg	PO	Daily

NOTE: Typically titrated to 150-200 mg

References: Quiquandon I, et al. *Br J Haematol* 1990;74:223 – 8; Pizzuto J and Ambriz R. *Blood* 1984;64:1179 – 83.

Cyclophosphamide	1 – 2 mg/kg	PO	Daily
	OR		
	1 – 1.5 grams/m^2	IV	Every 3 – 4 weeks

NOTE: 150 mg dose often used.

References: Verlin M, et al. *Am J Hematol* 1976;1:97 – 104; Reiner A, et al. *Blood* 1995;85:351 – 8; Pizzuto J and Ambriz R. *Blood* 1984;64:1179 – 83.

Cyclosporine	1.25 – 2.5 mg/kg	PO	BID

References: Emilia G, et al. *Blood* 2002;99;1482 – 5; Kappers-Klunne MC, et al. *Br J Haematol* 2001;114:121 – 5.

Mycophenolate	250 – 500 mg	PO	BID

References: Provan D, et al. *Am J Hematology* 2006;81:19 – 25; Howard J, et al. *Br J Haematol* 2002;117:712 – 5; Hou M, et al. *Eur J Haematol* 2003;70;353 – 7.

Vincristine	1 – 2 mg	IV	Weekly

References: Ahn YS, et al. *N Engl J Med* 1974;291:376 – 80; Manoharan A. *Am J Hematol* 1986;21:135 – 8; Pizzuto J and Ambriz R. *Blood* 1984;64:1179 – 83.

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Vinblastine	0.1 mg/kg	IV	Weekly

NOTE: Most often 5 – 10 mg.

References: Simon M, et al. *Eur J Hematol* 1987;39:193 – 6; Facon T,et al. *Br J Hematol* 1994;86:678 –80.

Colchicine	0.5 – 0.6 mg	PO	BID to TID

References: Strother SV, et al. *Arch Intern Med* 1984;144:2198 – 200; Baker RI, et al. *Aust N Z J Med* 1989;19:412 – 3.

Dapsone	1 – 2 mg/kg	PO	Dailiy

NOTE: Most often 75 – 100mg.

References: Damodar S, et al. *Eur J Haematol* 2005;75:328 – 31; Godeau B, et al. *Br J Haematol* 1997;97:336 – 9.

COMBINATION AGENTS

Many different combination chemotherapy regiments exist and none have been compared with others in the treatment of ITP (References: Figueroa M, et al. *N Engl J Med* 1993;328:1226 – 9 and Boruchov DM, et al. *Blood* 2007;110:3526 – 31). High dose chemotherapy with bone marrow transplantation has also been used in highly refractory symptomatic patients (Reference: Huhn RD, et al. *Blood* 2003;101:71 – 7).

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.

References: Emillia G, et al. *Blood* 2007;110:3833 – 41; Stasi R, et al. *Am J Med* 2005;118:414 – 9.

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

Thrombopoeitin (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/mm^3. Do not exceed maximum weekly dose of 10 mcg/kg weekly.
B) If the platelet count increases to >200,000/mm^3 for 2 weeks, reduce the dose by 1 mcg/kg/wk. If the platelet count is >400,000mm^3 temporarily stop the drug and restart when platelet count is <200,000mm^3. 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, romiplistin 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 thrombopoeitin (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 $>50 \times 10^9/L$.
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 $\geq$ 3x upper limit of normal AND are:
C) progressive, or persistent for $\geq$ 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.

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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.

Rh_0 [D] IMMUNE GLOBULIN
(WIN Rh_0 SDF®)

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 Rh_0 [D] immune globulin products and treatment for prevention of isoimmunization in Rh_0 [D]-negative women exposed to Rh_0 [D]-positive blood are not covered in this monograph. The use of this product should be limited to Rh_0 [D]-positive patients who have not undergone splenectomy.

I. MECHANISM OF ACTION

The actions of Rh_0 [D] immune globulin in idiopathic thrombocytopenic purpura (ITP) are not well understood. Intravenous infusion of Rh_0 [D] immune globulin into an Rh_0 [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 Rh_0 [D] immune globulin appears to occur via immunologic blockade of Fc-receptors within the RES. Other immunomodulatory mechanisms may also play a role in Rh_0 [D] immune globulin efficacy in ITP. After administration, Rh_0 [D] immune globulin produces a 2—3 day delay in increasing the platelet count. The mean duration of response is about 30 days. Repeated Rh_0 [D] immune globulin infusions do not cure the disease but are used to maintain platelet counts at levels sufficient enough to provide adequate hemostasis. Rh_0 [D] immune globulin is not effective in splenectomized or Rh_0 [D]-negative patients with ITP.

II. PHARMACOKINETICS

A) Peak plasma concentrations occur within 30 minutes of IV administration.
B) The half-life of Rh_0 [D] immune globulin is approximately 24 days after IV administration and approximately 30 days after IM administration.
C) Passively acquired anti-Rh_0 [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 Rh_0 [D]-negative women exposed to Rh_0 [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 Rh_0 [D] immune globulin are mild and transient. Increased destruction of Rh_0 [D]-positive red cells with attendant decreased serum hemoglobin concentrations and associated clinical symptoms occurs after Rh_0 [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 Rh_0 [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 Rh_0 [D] immune globulin administration. Rh_0 [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 Rh_0 [D] immune globulin. Rh_0 [D] immune globulin contains antibodies that can interact with certain live virus vaccines. Rh_0 [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

Reference: George JN. *N Engl J Med* 2006;354:1927 – 35.

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 emperic intravenous thrombin inhibition or Fondaparinux 2.5-7.5 mg SQ QD based on above variables
- Send serum ELISA testing as above

LABORATORY TESING 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)

Suspicion of HIT based upon the "4 T's"	Score	Pre-test Probability Score Criteria 2	1	0
Thrombocytopenia	☐	nadir 20-100, or >50% platelet fall	nadir 10-19, or 30-50% platelet fall	nadir <10, or <30% platelet fall
Timing of onset of platelet fall	☐	day 5-10, or ≤day 1 with recent heparin*	>day 10 or timing unclear (but fits with HIT)	≤day 1 (no recent heparin)
Thrombosis or other sequelae	☐	proven thrombosis, skin necrosis, or ASR†	progressive, recurrent, or silent thrombosis; erythematous skin lesions	none
OTher cause of platelet fall	☐	none evident	possible	definite
Total Pre-test Probability Score	☐	periodic reassessment as new information can change pre-test probability (e.g., positive blood cultures)		

Total Pre-test Probability Score

High			Moderate		Low				
8	7	6	5	4	3	2	1	0

Stop heparin‡, give alternative non-heparin anticoagulant argatroban¶ or lepirudin# or danaparoid** (or bivalirudin†† or fondaparinux‡‡)

Physician judgment

Continue (LMW) heparin

HIT Test

Positive test for HIT antibodies
Continue non-heparin anticoagulant until platelet count recovery

Negative test for HIT antibodies
Consider continuing or switching back to (LMW) heparin ##

Imaging studies for lower-limb DVT †††

Thrombosis***
If HIT, continue non-heparin anticoagulant until platelet count recovery, then **cautious coumarin overlap ¶¶**

No Thrombosis
If HIT, consider anticoagulating until platelet count recovery, even if no thrombosis apparent (± coumarin ¶¶)

* recent heparin indicates exposure within the past 30 days (2 points) or past 30-100 days (1 point)
† ASR, 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 1.5-3.0*X* patient's baseline aPTT or the mean of the laboratory normal range); reduce dose for hepatobiliary compromise; 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 1.5-2.5*X* 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 as *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/h for 4 h, then 200 U/h, 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 enzyme-immunoassay and/or 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)

Reference: Warkentin T, Aird W, and Rand J. *Hematology Education Book* 2003;497 - 519.

Last Updated on June 3, 2009