Thrombocytopenia Evaluation

Brenda Shinar

1. A 35-year-old woman is evaluated following a recent diagnosis of iron deficiency anemia secondary to menorrhagia. She began an oral contraceptive to control the bleeding and oral iron sulfate 6 weeks ago. She has no other medical conditions and takes no additional medication.

On physical examination, vital signs are normal. The conjunctiva are pink. No petechiae or purpura is evident. The remainder of the examination is normal.

Laboratory studies show a hematocrit of 39%, leukocyte count of 5800/uL, and a platelet count of 35,000/uL.

Which of the following is the most appropriate next step in diagnosis?

A.Transfuse 1 unit single donor platelets
B.Order a peripheral smear
C.Order a bone marrow biopsy
D.Order a heparin induced thrombocytopenia (HIT) panel
E.Order a right upper quadrant ultrasound to evaluate for cirrhosis

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What is in your differential diagnosis?

Table 1. Etiologies of Thrombocytopenia

Decreased platelet production

Bone marrow failure (e.g., aplastic anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome)

Bone marrow suppression (e.g., from medication, chemotherapy, or irradiation)

Chronic alcohol abuse*

Congenital macrothrombocytopenias (e.g., Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudo–von Willebrand disease, Wiskott-Aldrich syndrome)

Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)

Myelodysplastic syndrome

Neoplastic marrow infiltration

Nutritional deficiencies (vitamin B_{12} and folate)

Increased platelet consumption

Alloimmune destruction (e.g., posttransfusion, neonatal, posttransplantation)

Autoimmune syndromes (e.g., antiphospholipid syndrome, systemic lupus erythematosus, sarcoidosis)

Disseminated intravascular coagulation*/severe sepsis*

Drug-induced thrombocytopenia

Increased platelet consumption *(continued)*

Heparin-induced thrombocytopenia

Immune thrombocytopenic purpura*

Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)

Mechanical destruction (e.g., aortic valve, mechanical valve, extracorporeal bypass)

Preeclampsia/HELLP syndrome

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Sequestration/other

Chronic alcohol abuse*

Dilutional thrombocytopenia (e.g., hemorrhage, excessive crystalloid infusion)

Gestational thrombocytopenia

Hypersplenism (e.g., distributional thrombocytopenia)

Liver disease (e.g., cirrhosis, fibrosis, portal hypertension)

Pseudothrombocytopenia

Pulmonary emboli

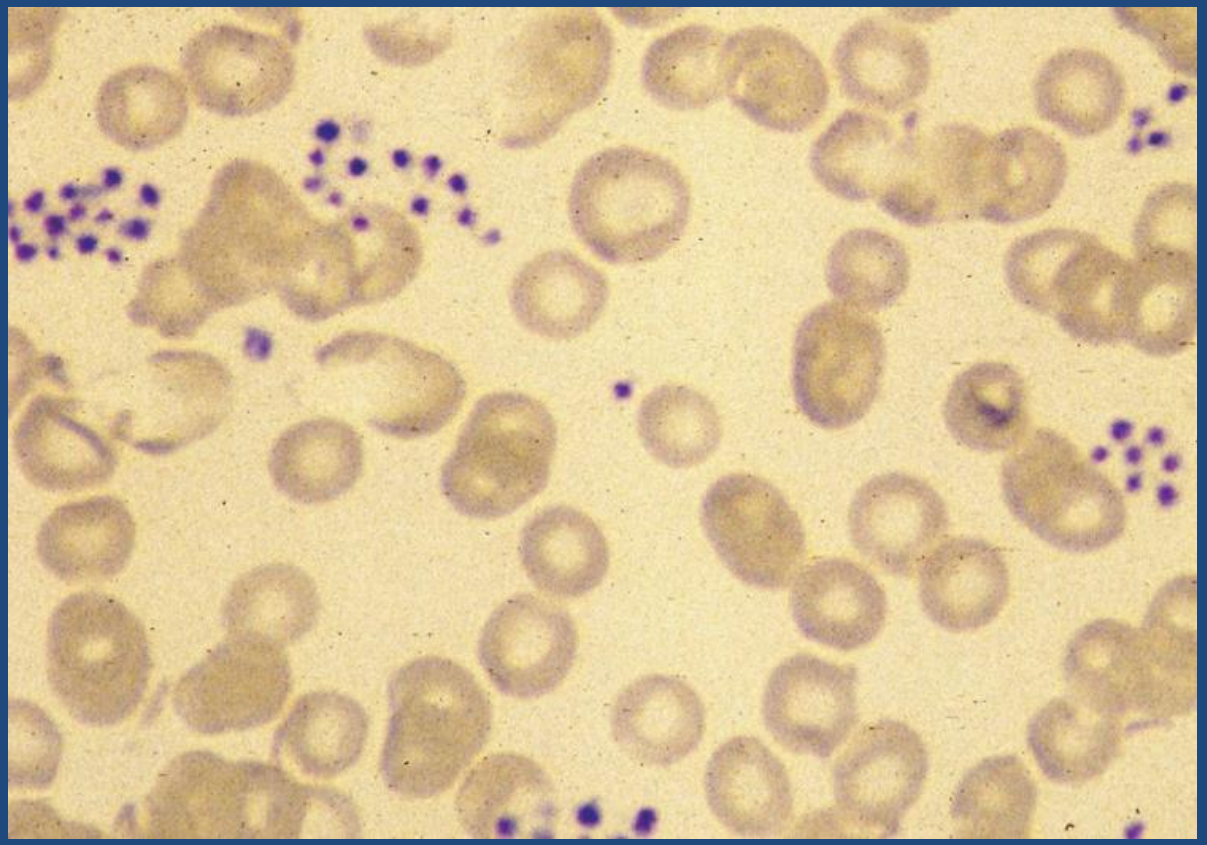
Pulmonary hypertension

HELLP = hemolysis, elevated liver enzymes, and low platelet count; HIV = human immunodeficiency virus.

**—More than one mechanism of action.*

†*—Thrombocytopenia with infection is usually caused by bone marrow suppression. In some cases, the thrombocytopenia is also immune-mediated.*

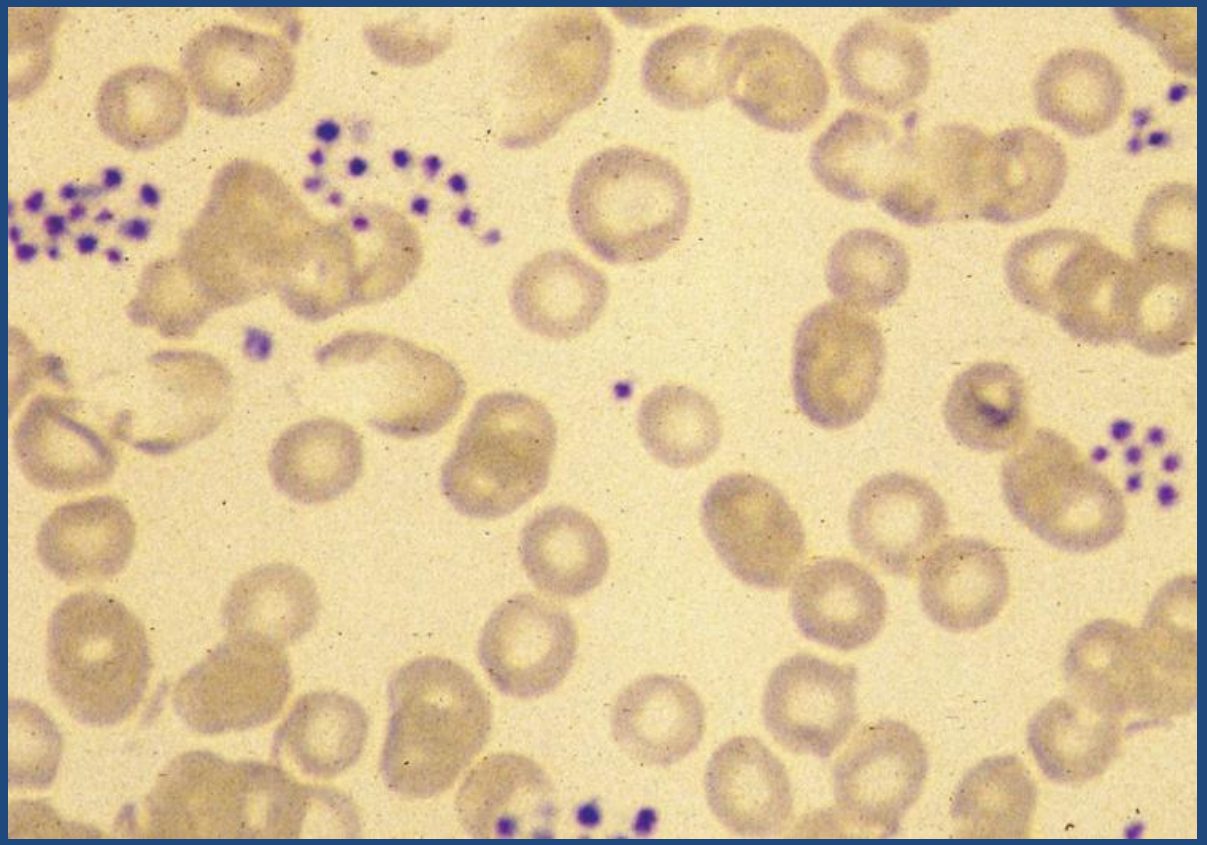
Information from references 3 through 6.



This is your patient's peripheral smear.

Which of the following is the most appropriate management?

A.Antinuclear antibody and HIV test
B.Plasma exchange
C.Prednisone
D.Repeat platelet count in EDTA free tube



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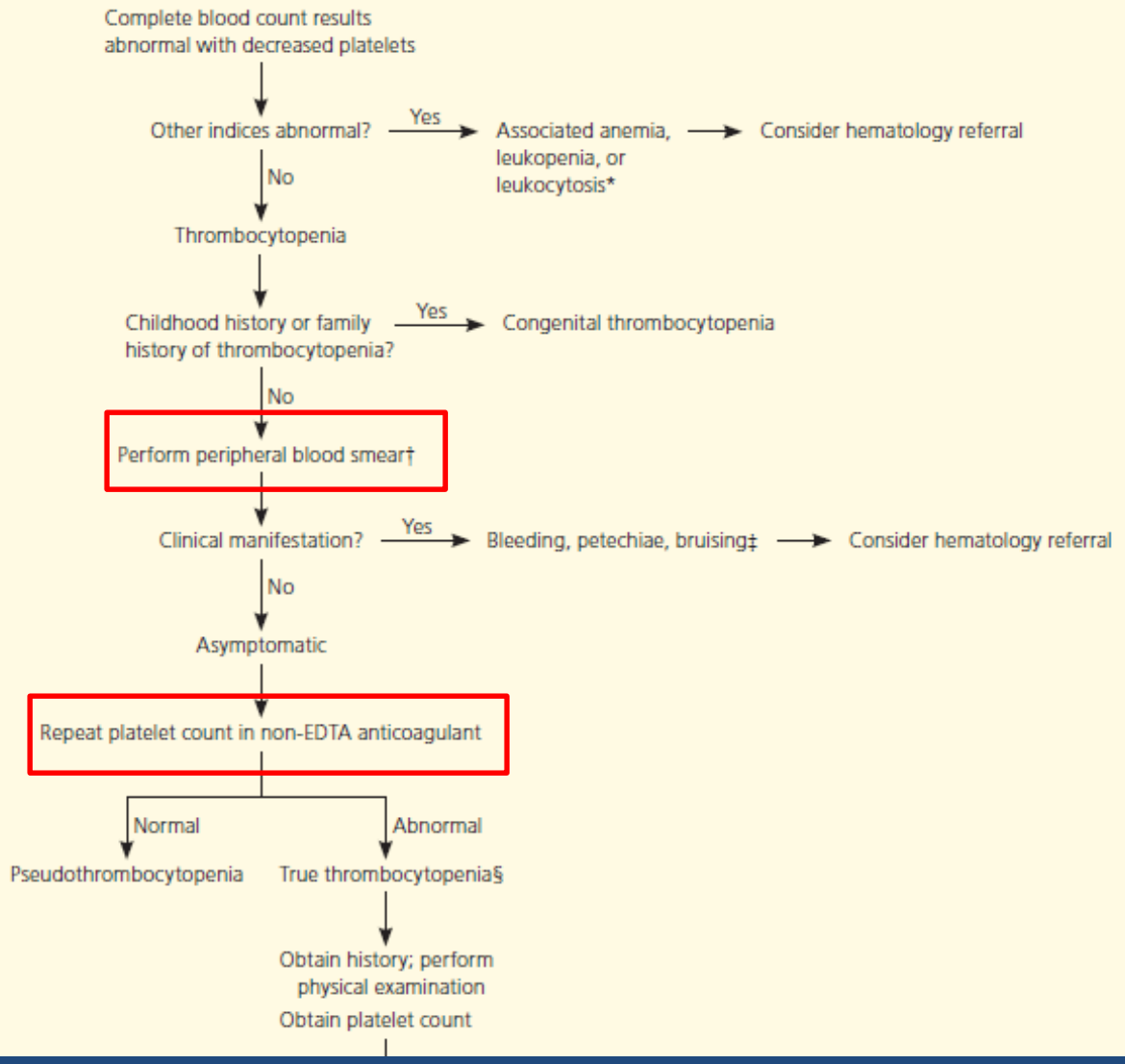
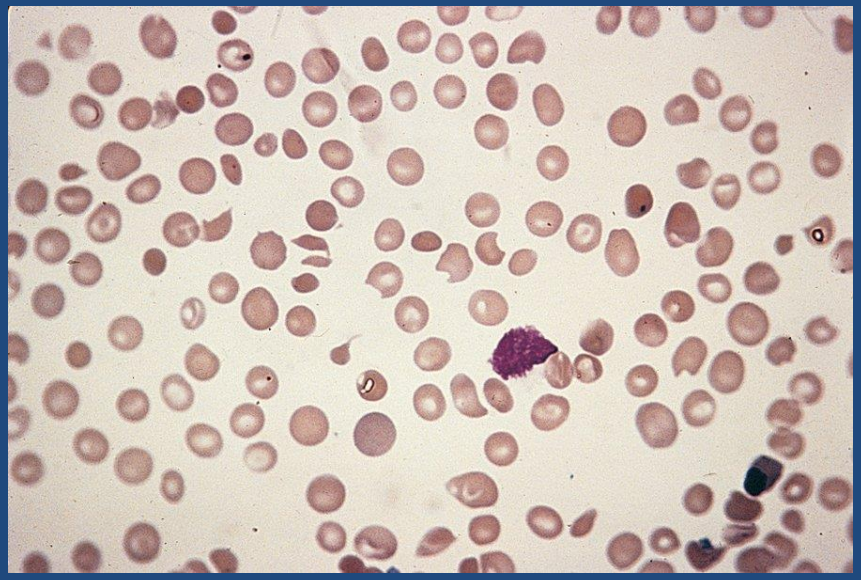
Management of Thrombocytopenia



2. A 35-year-old woman is evaluated for worsening thrombocytopenia; she is pregnant at 36 weeks' gestation. Medical history is significant for immune thrombocytopenic purpura. Previous platelet counts during this pregnancy have been 80,000-100,000/uL. Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 C (98.6 F), blood pressure is 165/110 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. Abdominal examination reveals mild right upper quadrant discomfort on palpation. Reflexes are normal, no clonus is observed. She has lower extremity edema to the level of the knees bilaterally.

Laboratory studies:
Hemoglobin: 10.5 g/dL
Platelet count: 21,000/uL
Alanine aminotransferase: 480 U/L
Aspartate aminotransferase: 600 U/L
Creatinine: 1.2 mg/dL
Urinalysis: 3+ protein



A peripheral smear is shown:

Which of the following is the most appropriate management of this patient's thrombocytopenia?

A.Emergent delivery
B.Intravenous immune globulin
C.Plasma exchange
D.Prednisone

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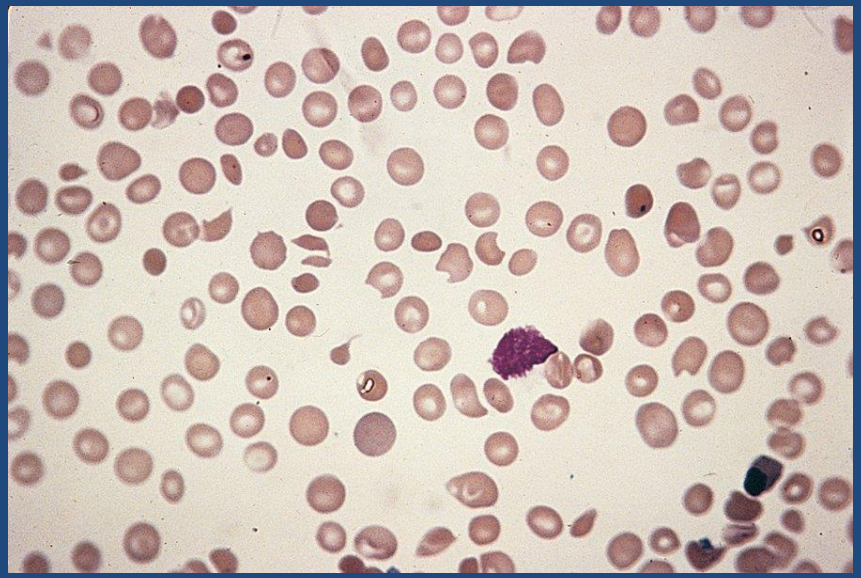

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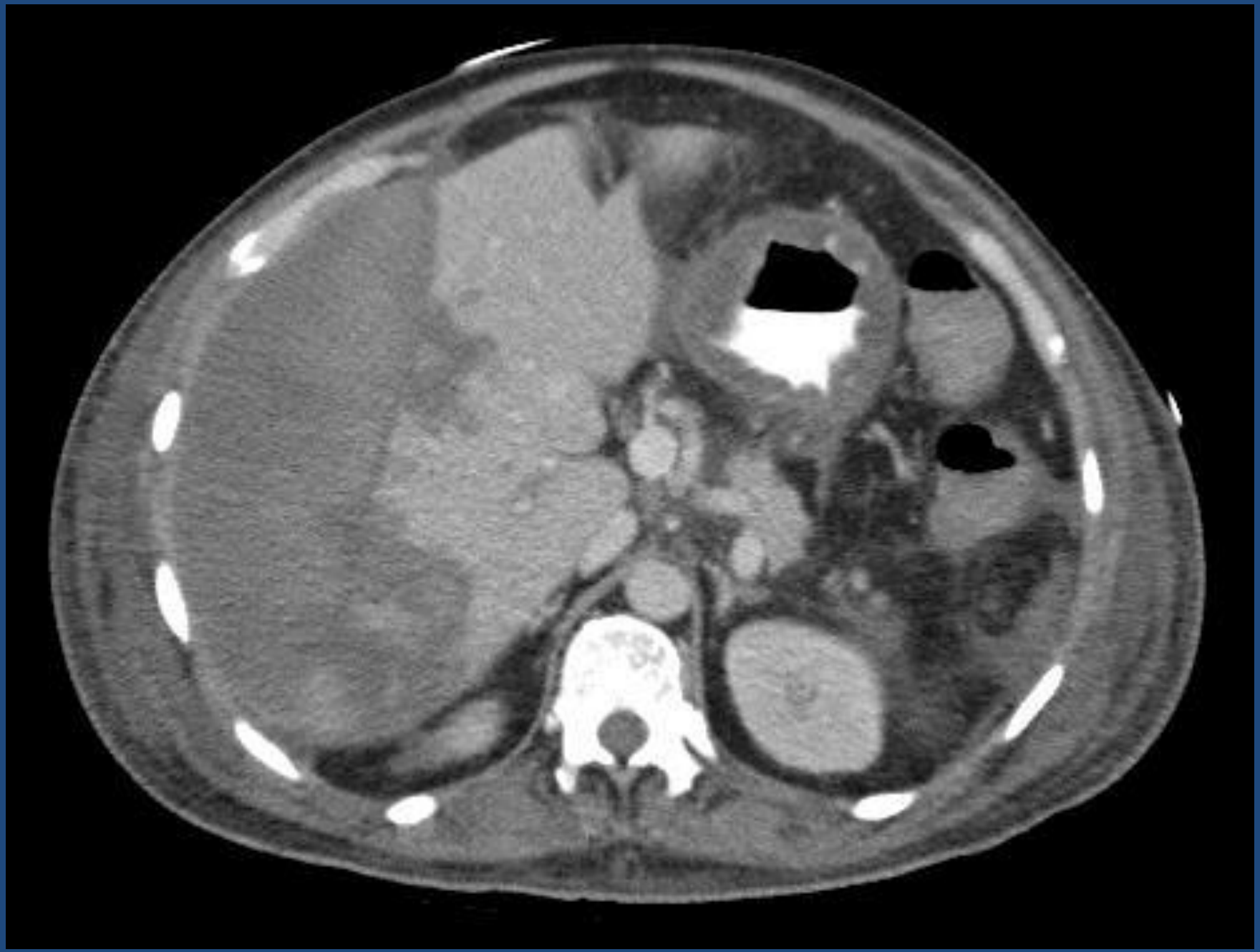
Thrombocytopenia in Pregnancy

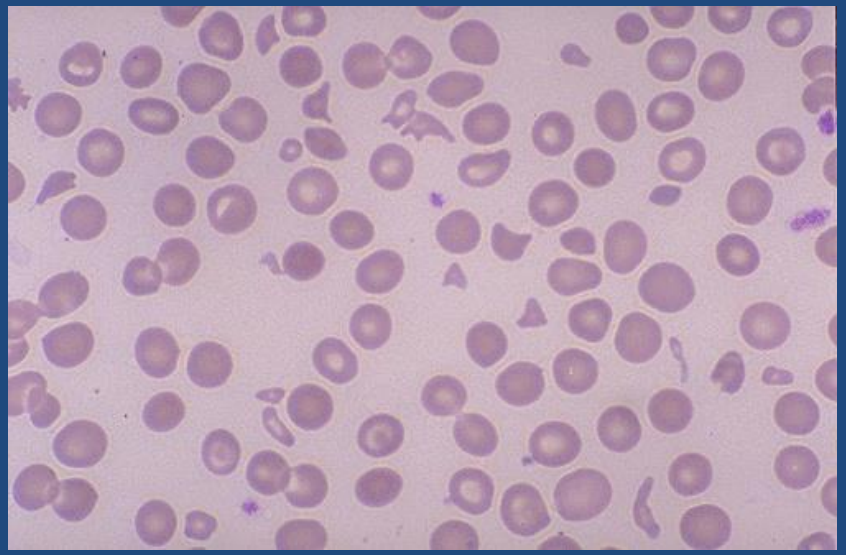
- Pregnancy-associated thrombocytopenia (PAT)
  - First diagnosis of thrombocytopenia during pregnancy
  - Negative maternal-platelet associated IgG, Normal coagulation studies
  - Recovery within 12 weeks of delivery
- Idiopathic thrombocytopenia (ITP)
  - ITP diagnosed before pregnancy
  - ITP associated with pregnancy
- Pregnancy-induced hypertension (PIH)
  - New onset hypertension ≥ 140/90
  - Proteinuria/ 24 hours ≥ 300 mg
  - Occurs after 20 weeks gestation
- Pregancy-induced hypertension/Pre-eclampsia
  - Hypertension with or without proteinuria and any one of the following:
  - Platelet < 100,000/uL
  - Creatinine > 1.1 mg/dL or doubling
  - Liver enzymes 2X ULN
  - Pulmonary edema
  - Cerebral or visual symptoms (headache, scotoma, flashing lights)
- Hemolysis with Elevated Liver Enzymes and Low Platelets (HELLP)
  - 10-20% of women with severe pre-eclampsia develop HELLP
  - 85% of HELLP patients have preeclampsia
  - Microangiopathic anemia (schistocytes)
  - ***Immediate delivery is the treatment!***



3. A 45-year-old woman is evaluated in the ED for a 1-day history of abdominal pain and fever. She also reports unexpected heavy menstrual bleeding of 1 day's duration and easy bruising of 2 days' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, the patient is oriented to person and place, but not time. Temperature is 38.1 C (100.6 F), blood pressure is 170/98 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Other than confusion, neurologic examination is normal. Subconjunctival hemorrhages are present. Cardiopulmonary examination is normal. Abdominal examination reveals tenderness to palpation without guarding or rebound. Pelvic examination shows blood in the vaginal vault with no cervical motion tenderness or adnexal masses.

Laboratory studies:
Hematocrit: 26%
Leukocyte count: 10,300/uL
Platelet count: 24,000/uL
Reticulocyte count: 8.3% of erythrocytes
Bilirubin, Total: 2.3 mg/dL
Creatinine: 3.2 mg/dL
Lactate dehydrogenase: 1500 U/L



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Which of the following is the most appropriate next step in the management of this patient?

A. Order an ADAMTS-13 level
B. Start plasma exchange
C. Order stool for E. coli 0157:H7
D. Type and cross and transfuse 1 unit single donor platelets

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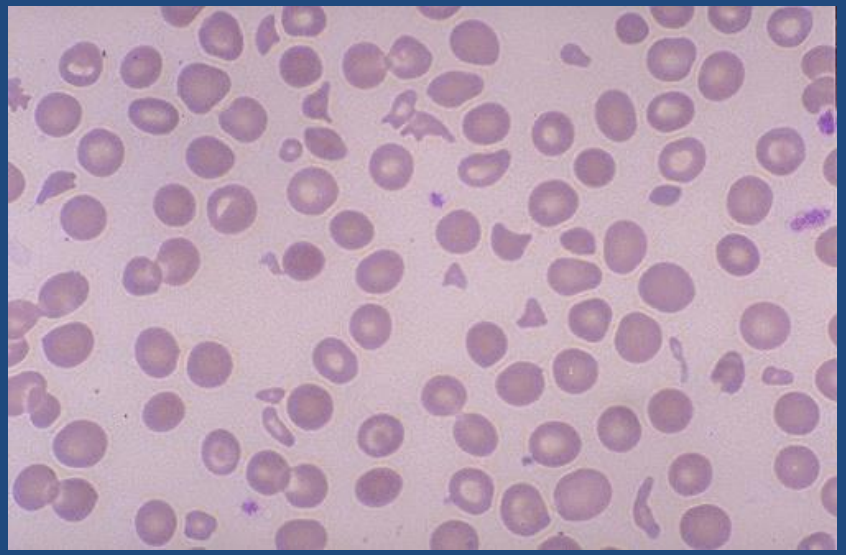

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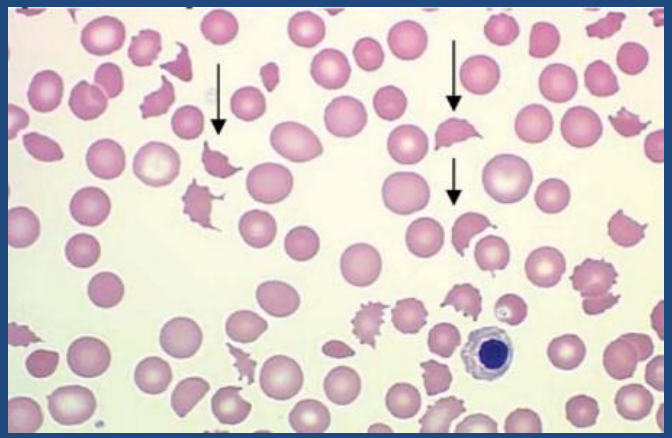
Diagnose a patient with thrombotic thrombocytopenic purpura

Definition of TTP:

- Initiation of intravascular platelet aggregation and coagulation/fibrin strands within the microcirculation
- Deficiency of ADAMTS 13
- Cannot break down von Willebrand multimers



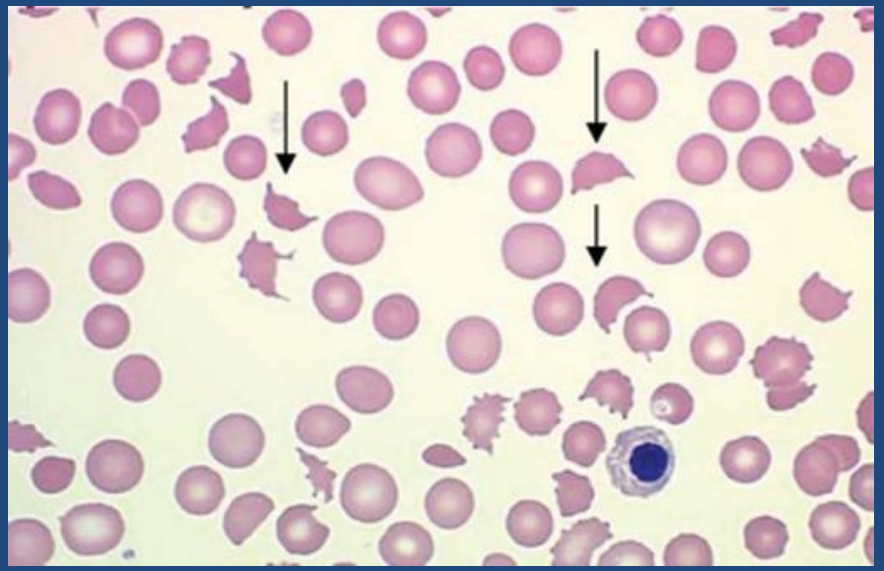
Clinical Diagnosis: Pentad of TTP:

1. *Thrombocytopenia
2. *Microangiopathic hemolytic anemia (schistocytes)
3. Neurologic Deficits
4. Kidney Impairment
5. Fever

(Diagnosis needs only these 2 major criteria without another clinically apparent cause to initiate therapy)

Diagnose a patient with thrombotic thrombocytopenic purpura

- Associated Conditions:
  - Drug-induced
    - Quinine, clopidogrel, chemotherapy, immunosuppressive agents
  - Pregnancy related
  - Following bloody diarrhea (shiga toxin producing E.coli)
  - Idiopathic (ADAMTS13)
  - Autoimmune (lupus)
  - Hereditary



4. A 65 year-old woman is evaluated in the Emergency Department for a 1-day history of pain and swelling in her left leg. Medical history is significant for coronary artery bypass graft surgery 9 days ago with vein harvesting from the right leg. She also has hypertension and hyperlipidemia. Medications are atorvastatin, atenolol, clopidogrel, and aspirin.

On physical examination, temperature is 37.0 C (98.6 F), blood pressure is 115/68 mm Hg, pulse rate is 65/min, Oxygen saturation breathing ambient air is 96%. Her sternotomy incision is healing well. The cardiopulmonary examination is normal. The left leg is swollen to the mid-thigh.

Laboratory studies reveal a hematocrit of 33%, leukocyte count of 12,000/ul, and platelet count of 55,000/uL. Her platelets before surgery were 250,000/uL.

Duplex ultrasonography of the left leg shows acute thrombus in the common femoral vein.

Which of the following is the most appropriate next step in management?

A.Await platelet factor 4 immunoassay before initiating anticoagulation
B.Await serotonin release assay before initiating anticoagulation
C.Initiate argatroban
D.Initiate heparin
E.Initiate warfarin

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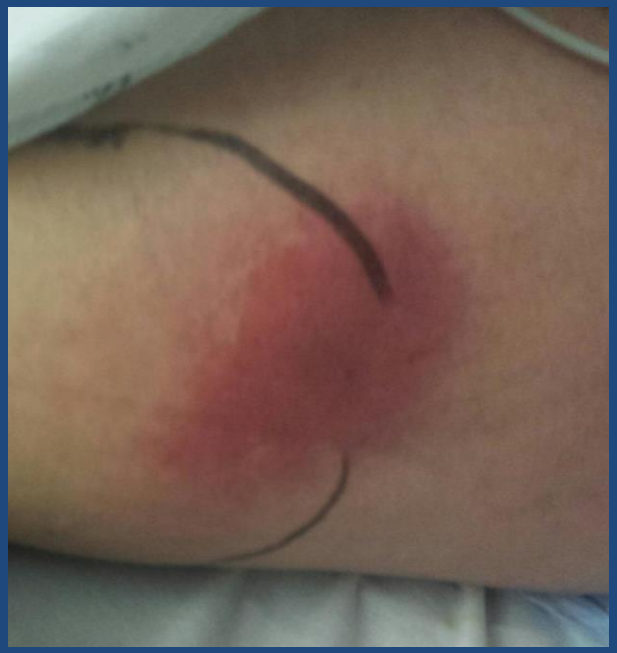
A. Features of the history and physical examination that support a diagnosis of HIT

Feature	Comments
Fall in platelet count ≥ 50%	From highest platelet count after heparin exposure; platelet count fall is 30–50% in 10% of cases
Fall in platelet count begins 5–14 days after immunizing heparin exposure	Heparin administered during or soon after surgery is more likely to be immunizing
Fall in platelet count begins within 24 hours after heparin exposure	May occur in patients with previous heparin exposure within last 100 days
Nadir platelet count ≥ 20×10^9/L	Nadir may exceed lower limit of normal range (i.e. 150×10^9/L) in patients with high baseline platelet counts. May be < 20×10^9/L in cases associated with DIC
Venous or arterial thrombosis	Occurring ≥ 5 days after heparin exposure and up to 30 days after heparin cessation
Skin necrosis	At subcutaneous heparin injection sites
Anaphylactoid reaction	Within 30 minutes after intravenous heparin bolus or subcutaneous injection
Absence of alternative causes of thrombocytopenia	Such as infection, other medications known to cause thrombocytopenia, cardiopulmonary bypass within previous 96 hours, intra-aortic balloon pump, extracorporeal membrane oxygenation, etc.
Absence of petechiae and other mucocutaneous bleeding	Adrenal hemorrhage secondary to adrenal vein thrombosis may occur in association with HIT



“4 T’s”

	2 points	1 point
Thrombocytopenia	>50% drop nadir > 20K	30-50% drop nadir 10-19K
Timing	5-10 days < 1d + prior hep < 30ds	? 5-10 d >10 d <1d + prior hep 30-100d)
Thrombosis	New Clot anaphylaxis, skin necrosis	Suspected progressive or recurrent clot
alTernative dx	none	possible

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Original Article

Clinical effectiveness of a Bayesian algorithm for the diagnosis and management of heparin-induced thrombocytopenia

R. A. Raschke ✉, T. Gallo, S. C. Curry, T. Whiting, A. Padilla-Jones, T. E. Warkentin, A. Puri

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Final decision: F. R. Rosendaal, 5 June 2017

Abstract

Essentials

- We previously published a diagnostic algorithm for heparin-induced thrombocytopenia (HIT).
- In this study, we validated the algorithm in an independent large healthcare system.
- The accuracy was 98%, sensitivity 82% and specificity 99%.
- The algorithm has potential to improve accuracy and efficiency in the diagnosis of HIT.

Pretest Probability of HIT by 4T score*	ELISA test result (OD)	Reasonable clinical action:
Low (0-3 points) *<1% chance patient has HIT*	>2.00	Order SRA**
	1.50 - 1.99	
	0.60 - 1.49	HIT ruled out***
	< 0.6	
Intermediate (4-5 points) *~10% chance patient has HIT*	>2.00	Treat HIT
	1.50 - 1.99	Order SRA**
	0.60 - 1.49	
	< 0.6	HIT ruled out***
High (6-8 points) *~50% chance patient has HIT*	>2.00	Treat HIT
	1.50 - 1.99	
	0.60 - 1.49	Order SRA**
	< 0.60	

IV. Treatment

A. Non-heparin anticoagulants: selection, dosing, and monitoring

Agent	Initial dosing	Monitoring
Argatroban	**Bolus:** None **Continuous infusion:** Normal organ function→2 mcg/kg/min[1] Liver dysfunction (total serum bilirubin >1.5 mg/dL), heart failure, post-cardiac surgery, anasarca→0.5–1.2 mcg/kg/min[2]	Adjust dose to APTT of 1.5–3.0 times patient baseline. Monitor APTT every 4 hours during dose titration.
Danaparoid[3]	**Bolus:** Weight <60 kg→1500 U Weight 60–75 kg→2250 U Weight 75-90 kg→3000 U Weight >90 kg→3750 U **Accelerated initial infusion:** 400 U/hr x 4 hrs, then 300 U/hr x 4 hrs **Maintenance infusion:** Cr < 2.5 mg/dL→200 U/hr Cr ≥ 2.5 mg/dL→150 U/hr	Adjust dose to danaparoid-specific anti-Xa level of 0.5–0.8 U/ml (if assay is available).
Bivalirudin[4]	**Bolus:** None **Continuous infusion:** Normal organ function→0.15 mg/kg/hr Renal or hepatic insufficiency→dose reduction may be necessary	Adjust dose to APTT of 1.5–2.5 times patient baseline.
Fondaparinux[5]	<50 kg→5 mg SC daily 50-100 kg→7.5 mg SC daily >100 kg→10 mg SC daily Cl_{Cr} 30–50 ml/min→use caution Cl_{Cr} <30 ml/min→contraindicated	Some experts recommend adjusting dose to a peak anti-Xa activity of 1.5 fondaparinux-specific U/ml. Others do not recommend routine monitoring.
NOACs[6]	At the time of writing, none of the NOACs (e.g. rivaroxaban, dabigatran, apixaban) had been assessed for treatment of patients with suspected or proven HIT and none had FDA approval for this indication. Until supporting data are available, their use cannot be endorsed.	

Consult pharmacy for help with direct thrombin inhibitors!

- HIT patients are at risk of venous limb gangrene and skin necrosis during initiation of warfarin
- Warfarin should not be initiated until platelet count is ≥ 150K
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target

What is the recommended duration of anticoagulation for HIT ***without*** thrombosis versus HITT ***with*** thrombosis…

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography may be considered in patients with HIT, whether or not there is clinical evidence of lower-limb DVT, because silent DVT is common and its presence may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulate for a defined course (typically 3 months) as with other provoked thromboses.
- For patients with HIT without thrombosis (i.e. isolated HIT), the optimal duration of anticoagulation is unknown. Because there is an elevated risk of thrombosis extending 2 to 4 weeks after heparin is stopped, anticoagulation for up to 4 weeks should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

5. A 30 year-old previously healthy veteran man presented to his primary care doctor 4 weeks before admission to the hospital for fever to 104 and diffuse throat pain. He had cervical lymphadenopathy and was treated empirically for streptococcal pharyngitis with amoxicillin, but after 2 days, his symptoms did not remit, and he went to urgent care where he was given clindamycin and decadron and again discharged to home.

Despite the change in treatment, he continued to have high fever to 103 and diffuse myalgias. He was admitted to the hospital for a possible sepsis, with hypotention, high fever, and diffuse lymphadenopathy. He had a diffuse pink rash on his back and chest at the time of admission.He was started on empiric broad spectrum antibiotics after cultures were obtained. He was fluid resuscitated and started on pressors for refractory hypotension. CT of the chest, abdomen, and pelvis revealed diffuse lymphadenopathy and moderate splenomegaly.

Laboratory evaluation revealed the following:
White blood count: 15,000/uL with normal differential
Hemoglobin 7.8 g/dL
Hematocrit 22%
Platelet count: 55,000/uL
AST: 780 U/L
ALT: 1200 U/L
Total bilirubin: 2.5 mg/dL
INR 2.1
Blood cultures: no growth after 72 hours
Urine analysis and culture: negative
Ferritin: 10,000 ng/mL

Which of the following is the most appropriate next step in management?
A.Order fasting triglycerides and fibrinogen levels
B.Order excisional lymph node biopsy
C.Order bone marrow biopsy
D.Order liver biopsy

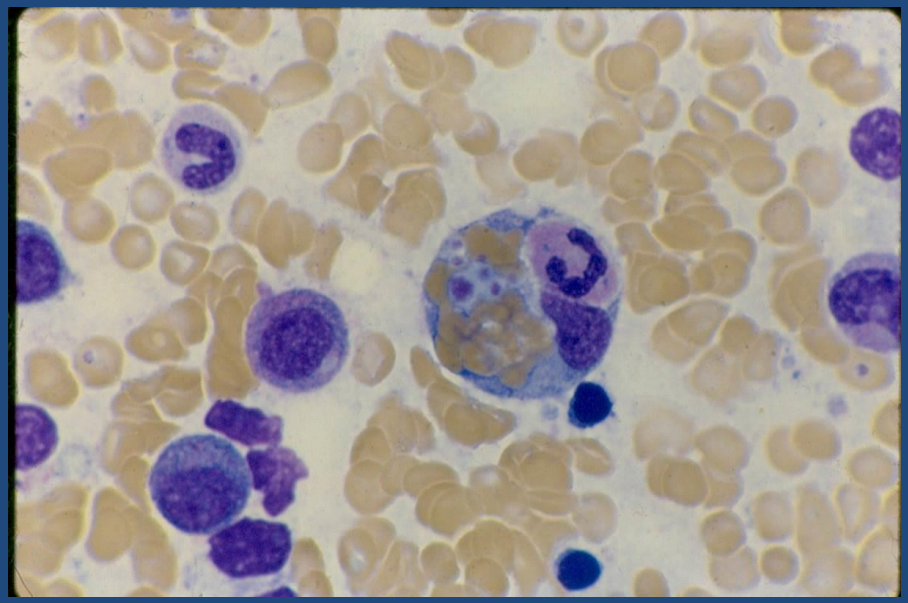
Hemophagocytic Lymphohistocytosis (HLH)

- Life-threatening disorder of excessive immune activation resulting in organ and tissue destruction due to lack of normal downregulation of activated macrophages and lymphocytes
- Genetic predisposition, infectious or autoimmune trigger
- Unremitting septic shock w/ MSOF
- Pancytopenia →Hyperferritinemia →bone marrow
- 29 cases diagnosed at B-UMCP
- Diagnostic Criteria = 5 of the following 8
  - Fever ≥ 38.5
  - Splenomegaly
  - Peripheral blood cytopenias
  - Ferritin > 3000 ng/mL
  - Hypertriglyceridemia and or hypofibrinogenemia
  - Hemophagocytosis in bone marrow, lymph node, liver or spleen
  - Low or absent NK cell activity
  - Elevated IL-2 receptor alpha

Hemophagocytic Lymphohistiocytosis (HLH)

Clinical syndromes

- Fever of unknown origin
  - > 102 F, prolonged
- Liver disease and coagulopathy
  - Hepatitis, lymphocytic infiltration
- Bone marrow failure
  - >80% anemia and thrombocytopenia
  - HLH in BM not sensitive or specific!
- Skin manifestations
  - 6-65% all types of rashes
- Pulmonary dysfunction
  - Ominous sign, 88% mortality
- Neurologic manifestations
  - 33% seizures, decreased LOC, meningitis, cranial neuropathies

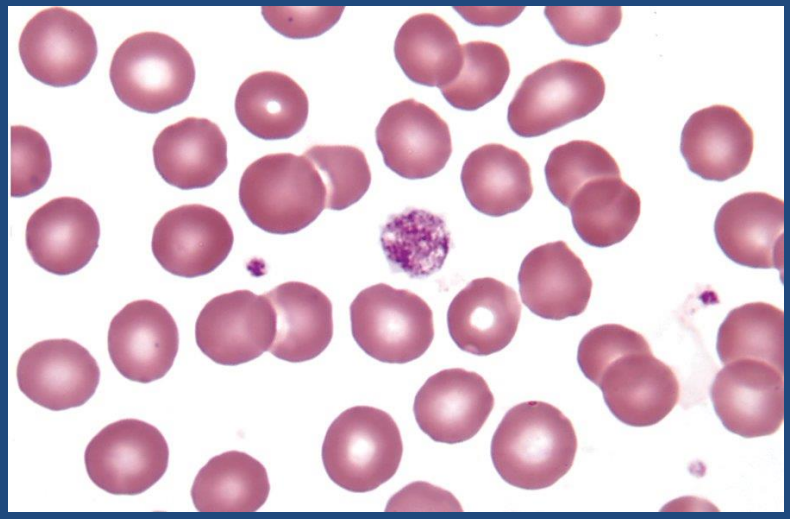


6. A 35 year-old woman is evaluated for the recent onset of a rash on her legs. She has no other symptoms. She does not drink alcohol. Medications are an oral contraceptive and a multivitamin.

On physical examination, vital signs are normal. Non-pruritic, non-blanching red macules are noted on the lower extremities. Abdominal examination reveals no splenomegaly.

Laboratory studies show a hematocrit of 38%, a leukocyte count of 7000/uL, and a platelet count of 31,000/uL.

The peripheral blood smear is shown.



Which of the following is the most likely diagnosis?

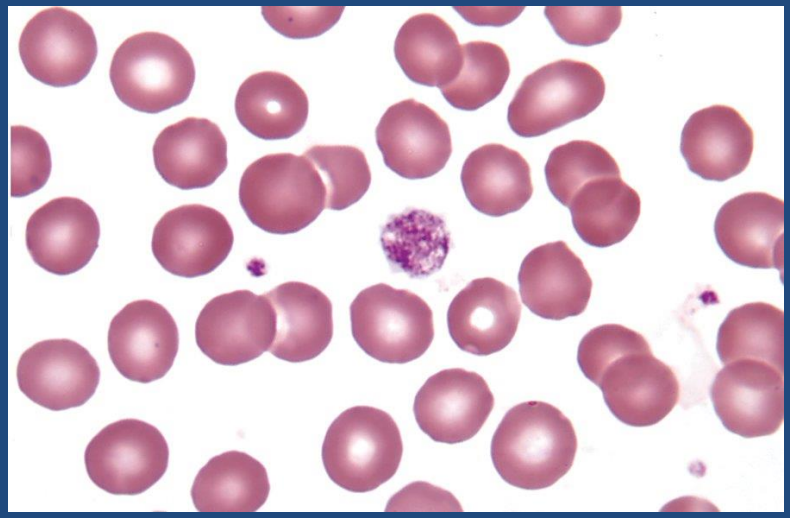
A. Thrombotic thrombocytopenia purpura
B. Henoch Schonlein purpura
C. Leukocytoclastic vasculitis
D. Immune thrombocytopenic purpura
E. Systemic lupus erythematosis

6. A 35 year-old woman is evaluated for the recent onset of a rash on her legs. She has no other symptoms. She does not drink alcohol. Medications are an oral contraceptive and a multivitamin.

On physical examination, vital signs are normal. Non-pruritic, non-blanching red macules are noted on the lower extremities. Abdominal examination reveals no splenomegaly.

Laboratory studies show a hematocrit of 38%, a leukocyte count of 7000/uL, and a platelet count of 31,000/uL.

The peripheral blood smear is shown.

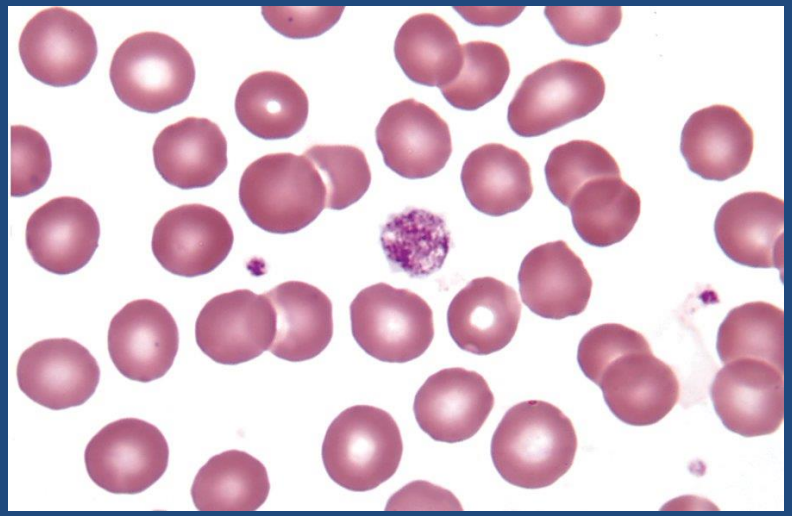


Which of the following is the most likely diagnosis?

A. Thrombotic thrombocytopenia purpura
B. Henoch Schonlein purpura
C. Leukocytoclastic vasculitis
D. Immune thrombocytopenic purpura
E. Systemic lupus erythematosis

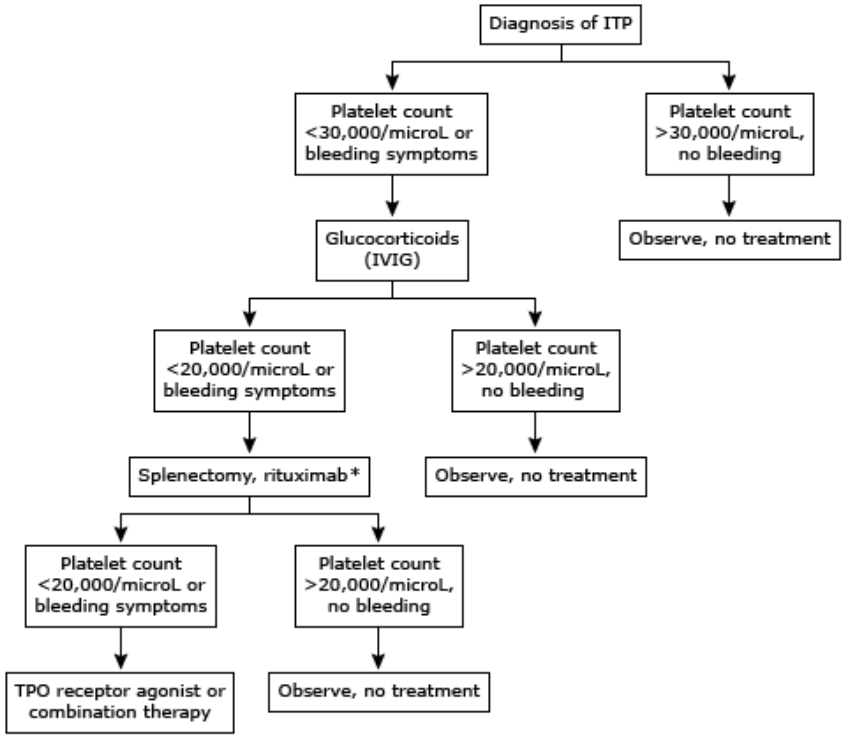
Immune Thrombocytopenic Purpura (ITP)

- Diagnosis of exclusion
- No splenomegaly
- No other cytopenias
- No coagulopathies



- Drugs
  - Quinine
- Infections
  - HIV
- Alcohol
  - With or without liver disease
- Nutritional deficiencies
  - B12, folate, copper
- Rheumatologic disease
  - Systemic lupus erythematosus
  - Antiphospholipid antibody syndrome

Treatment approach in immune thrombocytopenia (ITP) in adults



This algorithm represents a **simplified** approach to the treatment of patients with ITP. Threshold platelet counts are presented, but clinical symptoms and patients' concerns must be weighed. The treatment of serious bleeding requires additional therapy including platelet transfusions.

NOTE: Only some of the possible treatments for ITP are described in this algorithm. As an example, for first-line therapy, IVIG may be used together with or instead of glucocorticoids when a more rapid increase in platelet count is required; IVIG or anti-D (in appropriate patients) may also be used as first-line or rescue treatment if glucocorticoids are contraindicated or cannot be tolerated. Refer to UpToDate topics on management of ITP for further details regarding management of bleeding, indications for ITP treatment, and choices among available therapies.

Platelet Pearls

- Neurosurg, epidural
  > 100K
- Surgery
  >50K
- CVC
  >20K
- Spont bleeding usually
  < 10K

- *1 unit single donor platelet increases count by 30K*
- Equivalent to platelets present in 6 units of whole blood 6:6:1

7. A 42 year-old woman is evaluated for thrombocytopenia. She was admitted to the hospital one week ago for newly diagnosed acute myeloid leukemia. She has been receiving leukoreduced, irradiated erythrocyte and platelet transfusions since admission. Yesterday, her platelet count was 8000/uL. A platelet count checked 30 minutes after a random, donor-pooled platelet transfusion was 11,000/uL. This morning her platelet count was 6000/uL. Thirty minutes after a random donor-pooled platelet transfusion, the platelet count is 9000/uL. She has had four uncomplicated pregnancies and deliveries. Medications are daunorubicin, cytarabine, cefepime, posaconazole, valacyclovir, and ondansetron.

On physical examination, vital signs are normal. No splenomegaly is present. Ecchymoses are seen at previous venipuncture sites. She has scattered petechiae over the lower extremities. The remainder of the examination is normal.

Peripheral blood smear reveals no schistocytes or platelet clumps.

Which of the following is the most appropriate management?

A.Transfuse ABO-matched platelets
B.Transfuse HLA-matched platelets
C.Transfuse washed platelets
D.Observation

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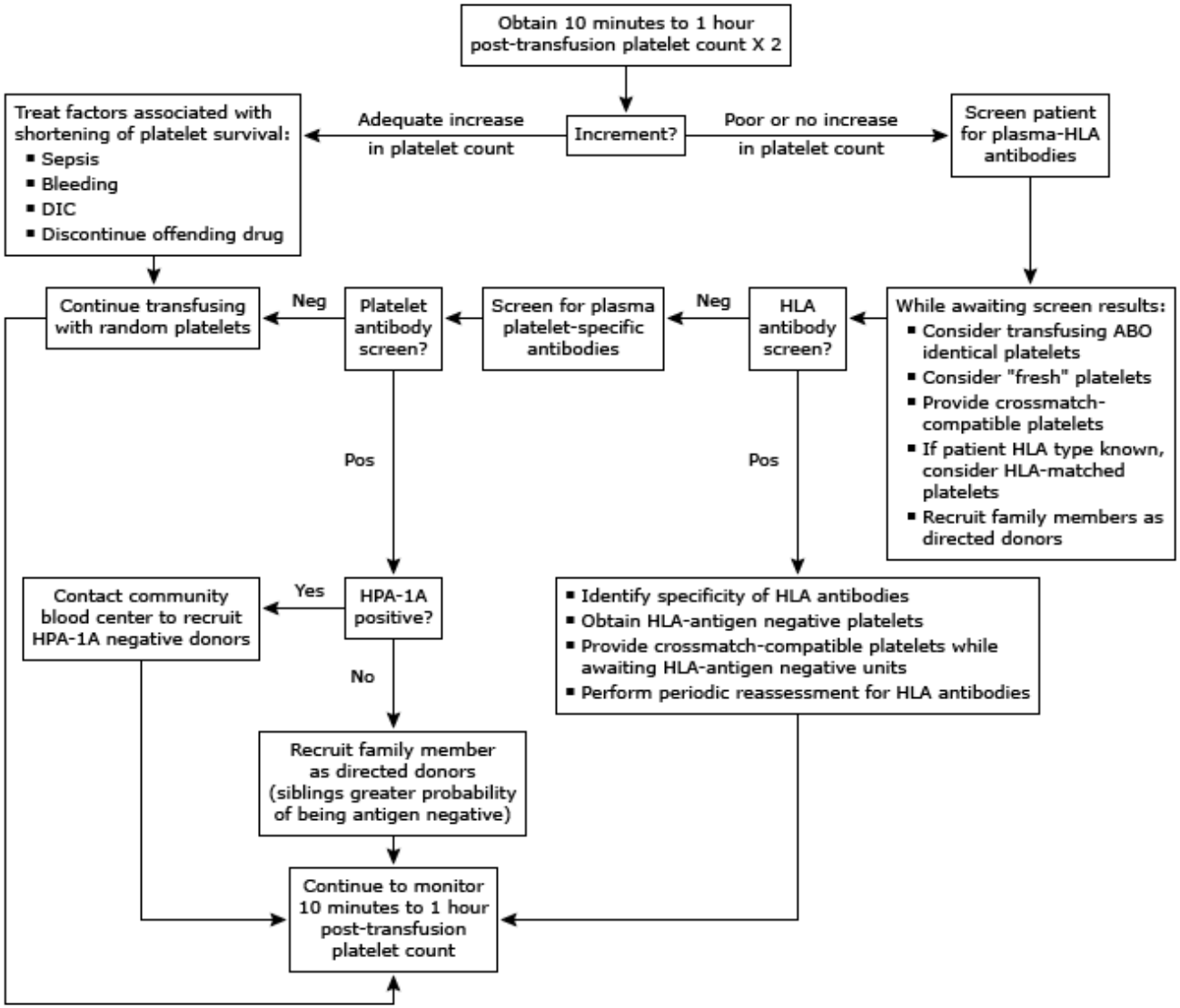
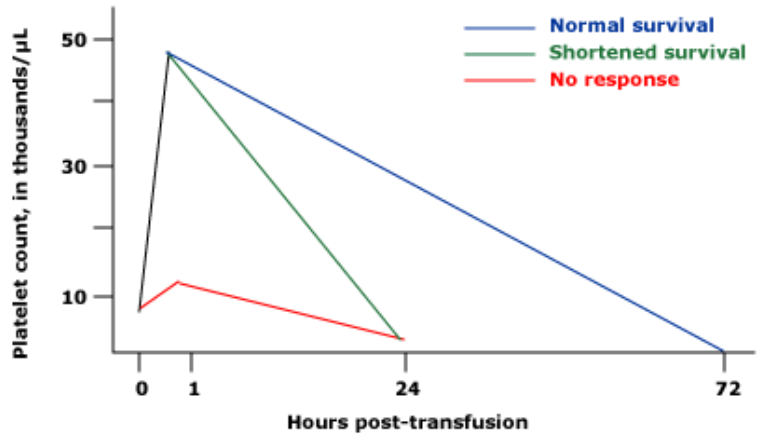
Diagnosis and management of platelet refractoriness



Patterns of response to platelet transfusion



Two patterns can be seen in refractory patients. A normal increment at one hour following transfusion with return to the baseline count within 24 hours (green curve) is typical of the shortening of platelet survival seen with sepsis, hematopoietic cell transplantation, disseminated intravascular coagulation, and possibly in bleeding patients and those taking medications that interfere with platelet survival. The second pattern consists of little or no increment in platelet count, even within one hour of transfusion (red curve); this pattern is seen with alloimmunization.

Graphic 82283 Version 2.0

Two ways to prevent alloimmunization of platelets:

1. Transfuse only leukoreduced blood products
2. Transfuse only ABO compatible platelets