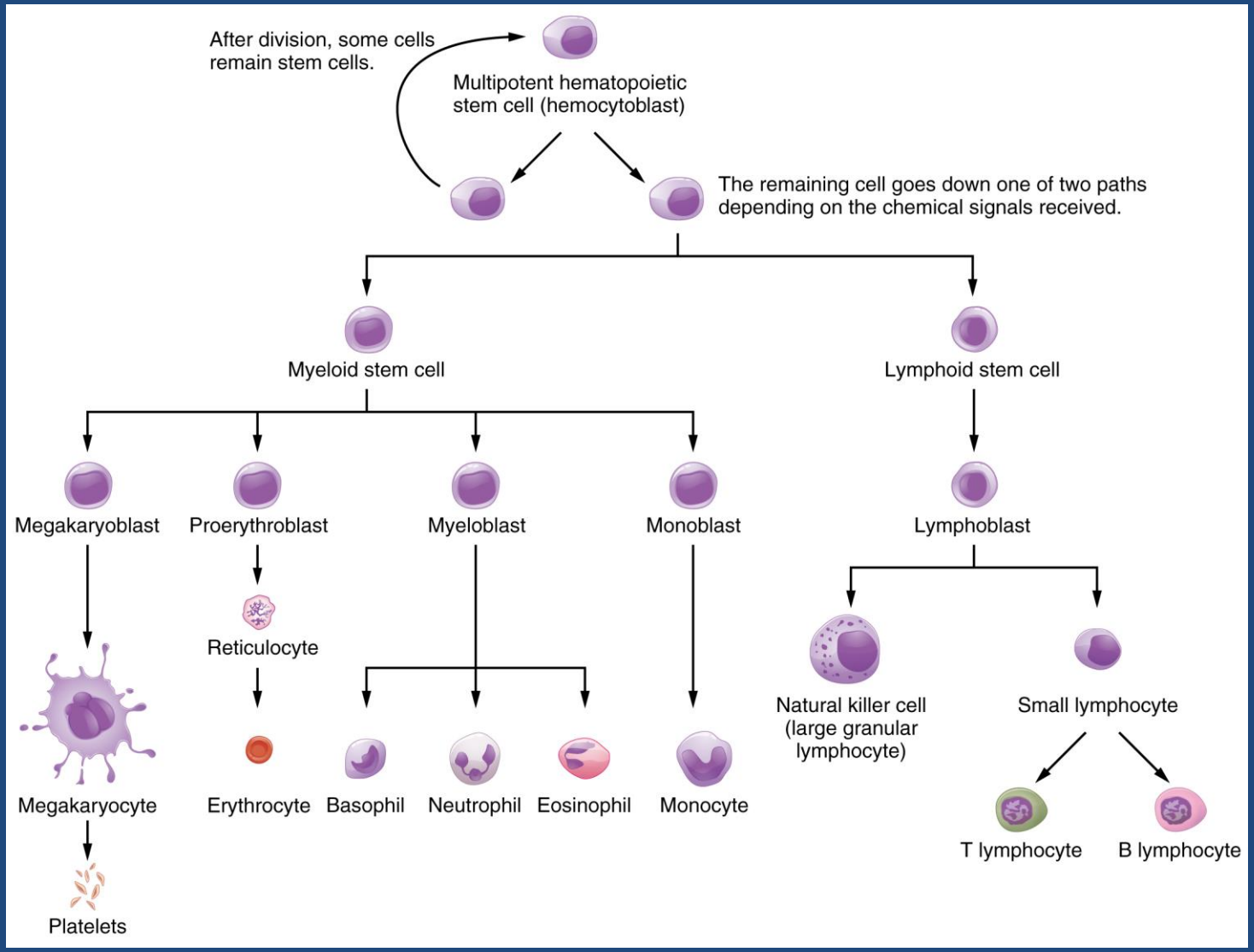
Thrombocytopenia Evaluation

Brenda Shinar, MD, FACP

September 20, 2022


After division, some cells remain stem cells.
Multipotent hematopoietic stem cell (hemocytoblast)
The remaining cell goes down one of two paths depending on the chemical signals received.
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Proerythroblast
Myeloblast
Monoblast
Lymphoblast
Reticulocyte
Natural killer cell (large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Erythrocyte
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Platelets

What is in your differential diagnosis?

- Decreased Production
  - Bone marrow failure
  - Bone marrow suppression
  - Chronic alcohol use*
  - Congenital macrothrombocytopenia
  - Infection
  - Myelodysplastic syndrome
  - Neoplastic marrow infiltration
  - Nutritional deficiencies
- Sequestration
  - Hypersplenism/Portal hypertension
- Increased consumption
  - Alloimmune destruction
  - Autoimmune syndromes
  - DIC/severe sepsis
  - Drug induced thrombocytopenia
  - HIT(T)
  - ITP
  - Infection/Sepsis
  - Mechanical destruction
  - Preeclampsia/HELLP
  - TTP/HUS

Case 1

A 28-year-old female internal medicine resident presents to labor and delivery at full term with spontaneous rupture of membranes. She is started on Pitocin for inadequate contractions and 3 hours later she asks for an epidural.

A CBC is performed and reveals a platelet count of 68,000/uL. (Two months ago, her prenatal labs showed platelets of 158,000.)

The remainder of the cbc and chemistries are normal.

What is the most appropriate management at this time?

A. Advise the patient that the epidural is contraindicated
B. Transfuse a single donor platelet unit and perform the epidural
C. Perform the epidural with the current platelet count and signed consent
D. Transfuse 2 single-donor platelet units and perform the epidural

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Platelet Counts for Safe Procedures

- Neurosurgery, epidural, or lumbar puncture

  > 100K
- Surgery (C-section, solid organ biopsy)

  >50K
- Spontaneous vaginal delivery

  > 30K
- Central venous catheter

  >20K
- Spontaneous bleeding

  < 10K

- *1 unit single donor platelet should increase count by 30K*
- 1 single donor platelet is equivalent to platelets present in 6 units of whole blood
- Platelets are stored at room temperature in the blood bank and most likely of all blood products to be contaminated with bacteria; they are only allowed to be stored for 5 days in US blood banks

Thrombocytopenia in Pregnancy

- Gestational thrombocytopenia (>50K) 70-80% of cases
  - First diagnosis of thrombocytopenia during pregnancy
  - Negative maternal-platelet associated IgG, Normal coagulation studies
  - Recovery within 12 weeks of delivery
- Idiopathic thrombocytopenia (ITP) (3-4% of cases)
  - 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***
- Pre-eclampsia (+ HELLP = 20% cases)
  - Hypertension >140/90 with any one of the following:
  - Proteinuria > 300 mg/24 hours
  - 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 severe pre-eclampsia)
  - 10-20% of women with severe pre-eclampsia develop HELLP
  - 85% of HELLP patients have preeclampsia
  - Microangiopathic anemia (schistocytes)
  - ***Immediate delivery is the treatment!***

Ciobanu AM, Colibaba S, Cimpoca B, Peltecu G, Panaitescu AM. Thrombocytopenia in Pregnancy. Maedica (Bucur). 2016 Mar;11(1):55-60. PMID: 28465752; PMCID: PMC5394486.

Case 2

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:
Hemoglobin 13 g/dL
Hematocrit of 39%
Leukocyte count of 5800/uL
Platelet count of 35,000/uL.

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

A. Transfuse one-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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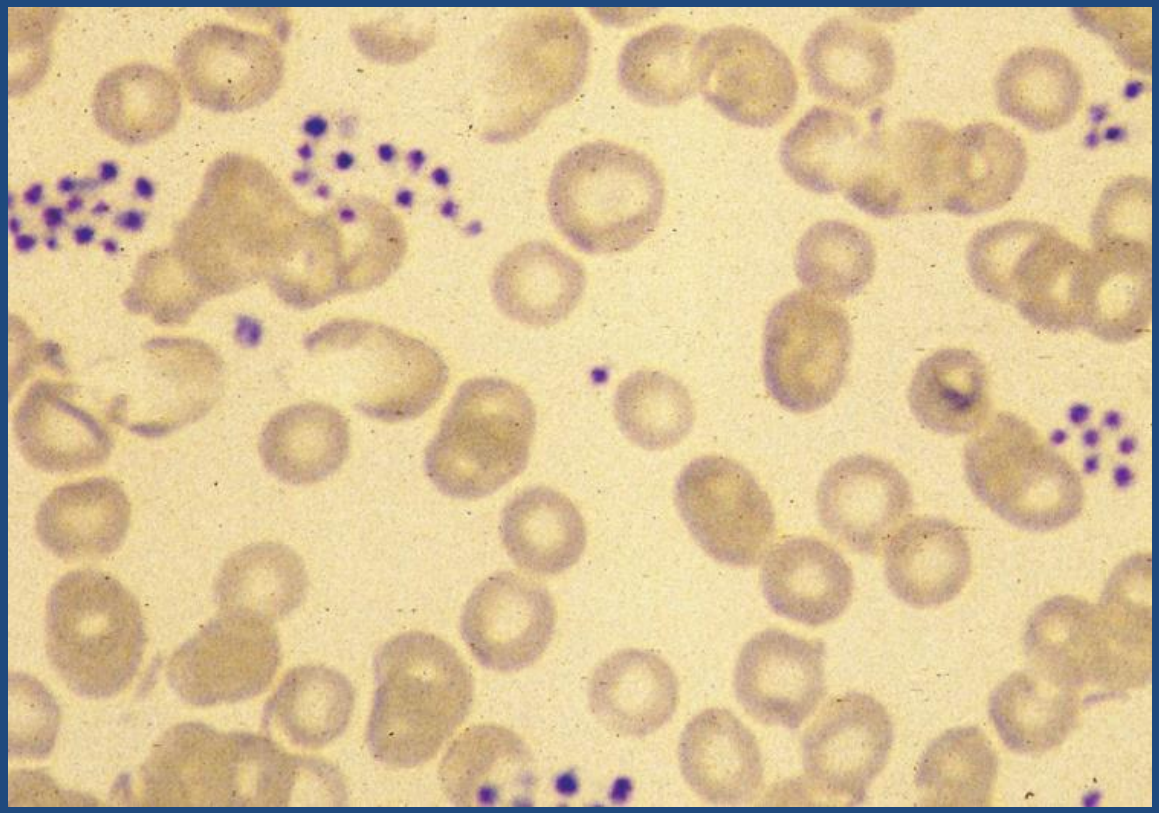
(continued)



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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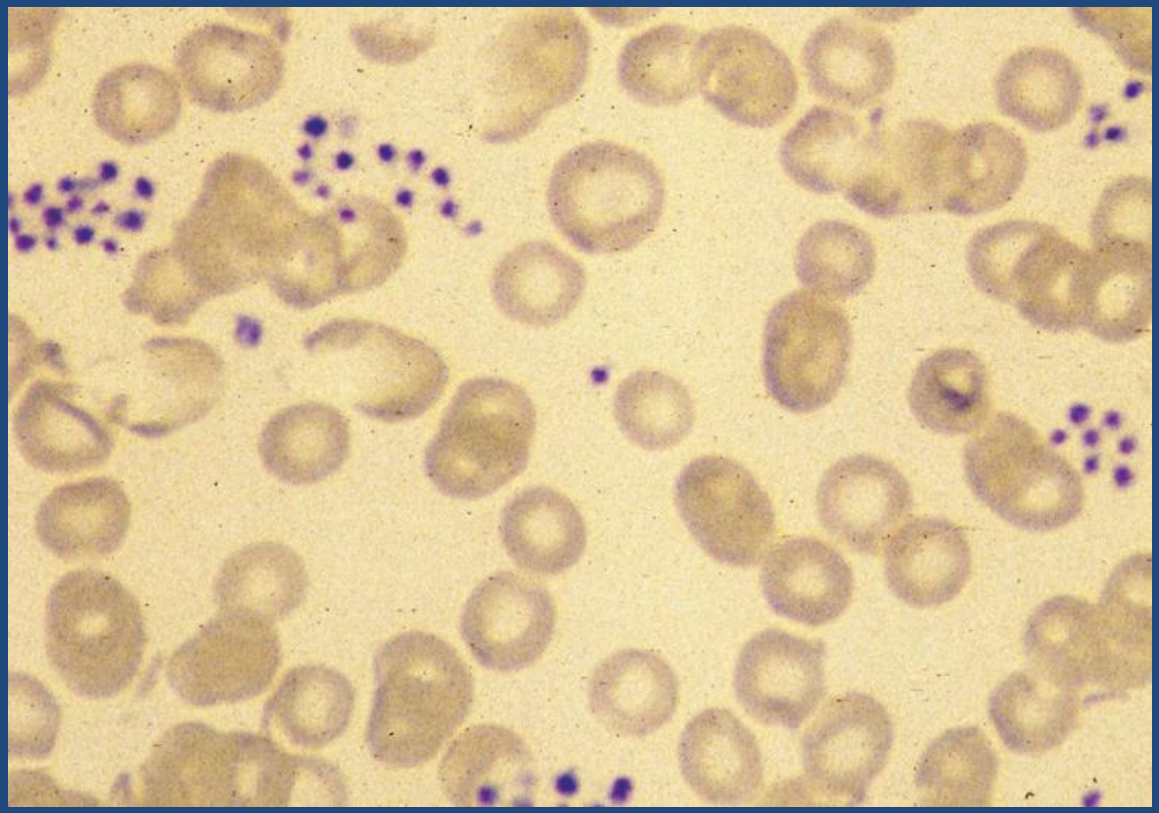

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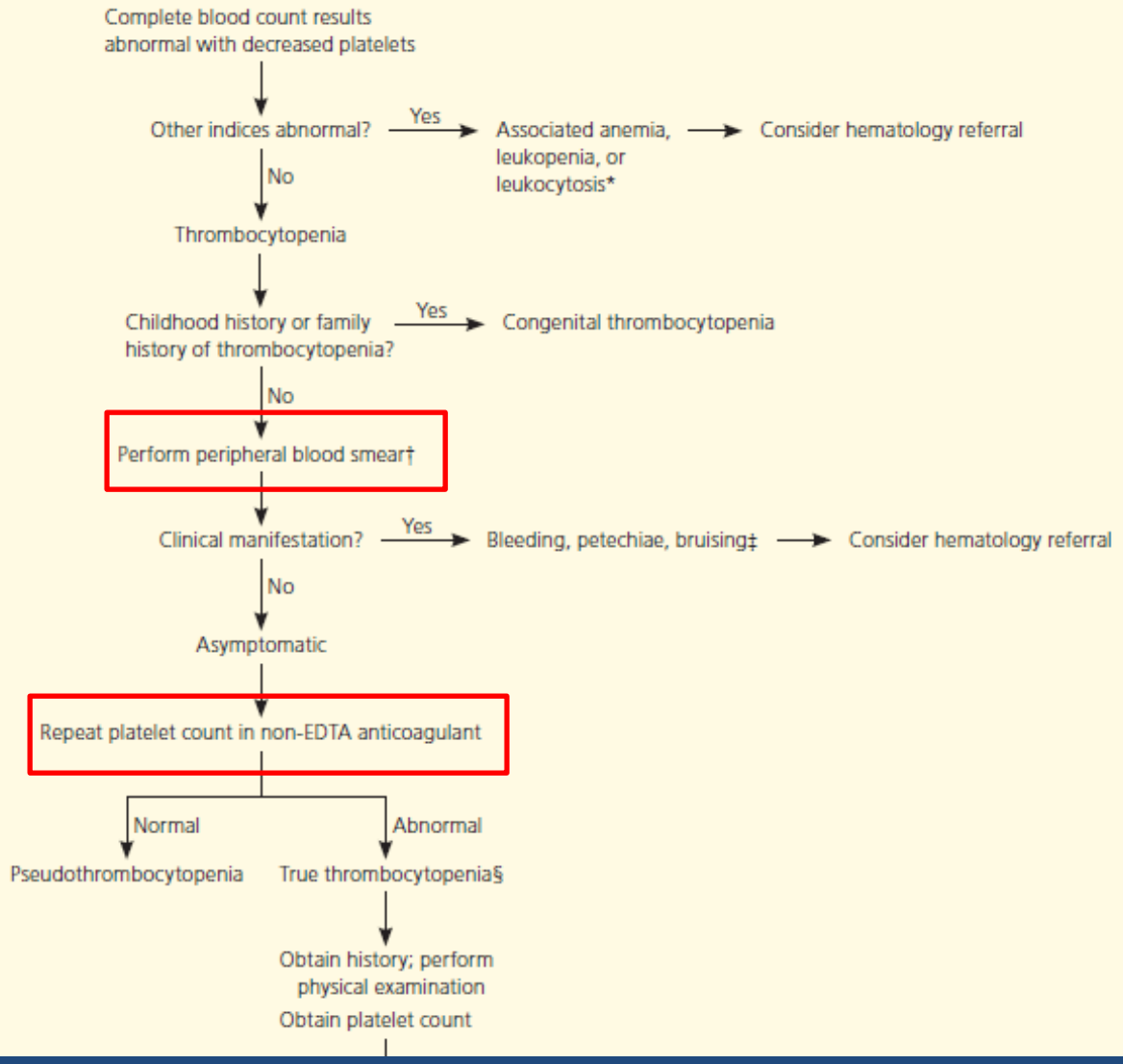
Management of Thrombocytopenia



Case 3

A 35-year-old woman is evaluated for thrombocytopenia; she is pregnant at 36 weeks' gestation. Previous platelet counts during this pregnancy have been 150,000/uL. Her only medication is a prenatal vitamin.

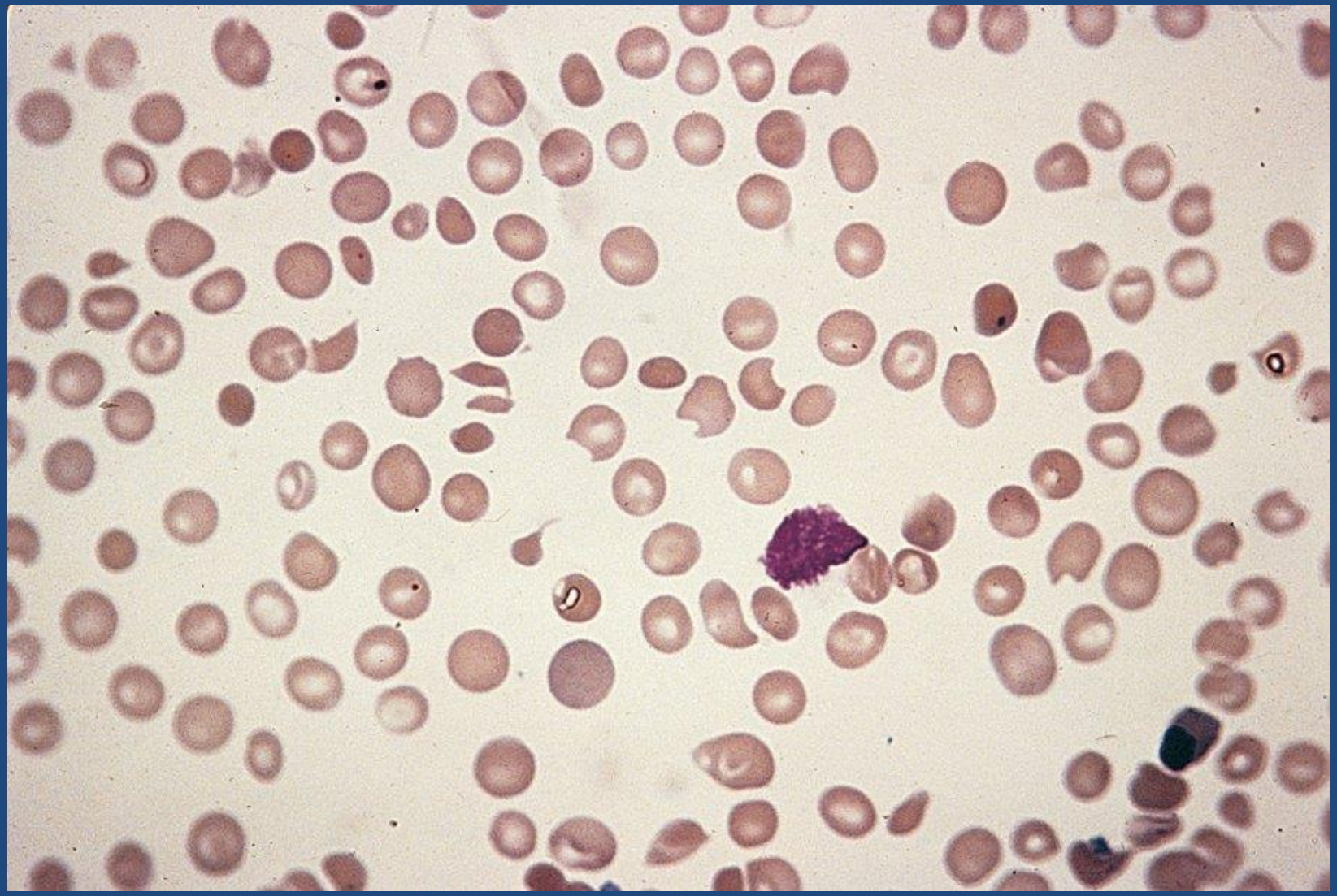
On physical examination, temperature is 37.0 C (98.6 F), blood pressure is 165/110 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. Abdominal examination reveals mild right upper quadrant discomfort on palpation. Reflexes are normal, no clonus is observed. She has lower extremity edema to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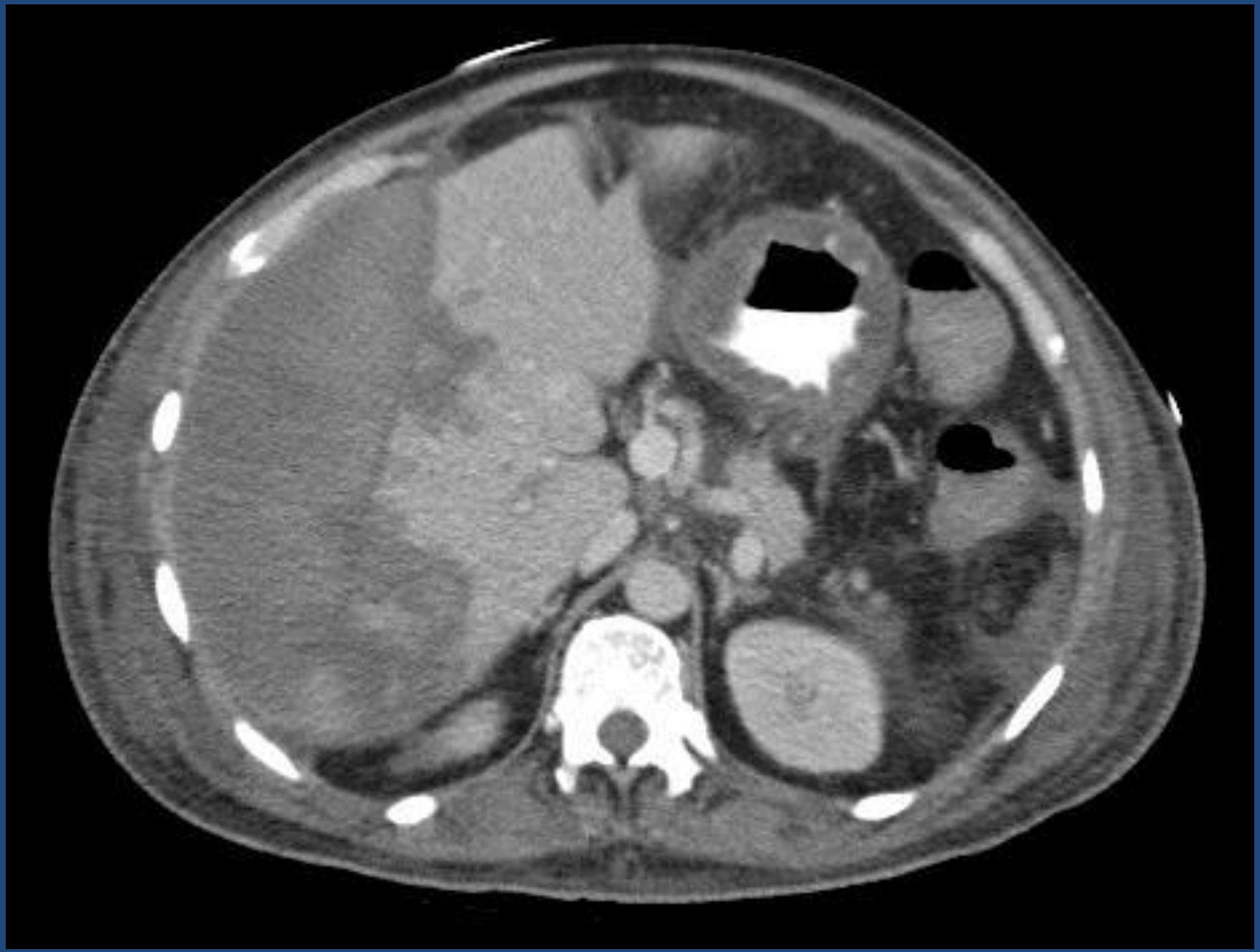


Case 4

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.

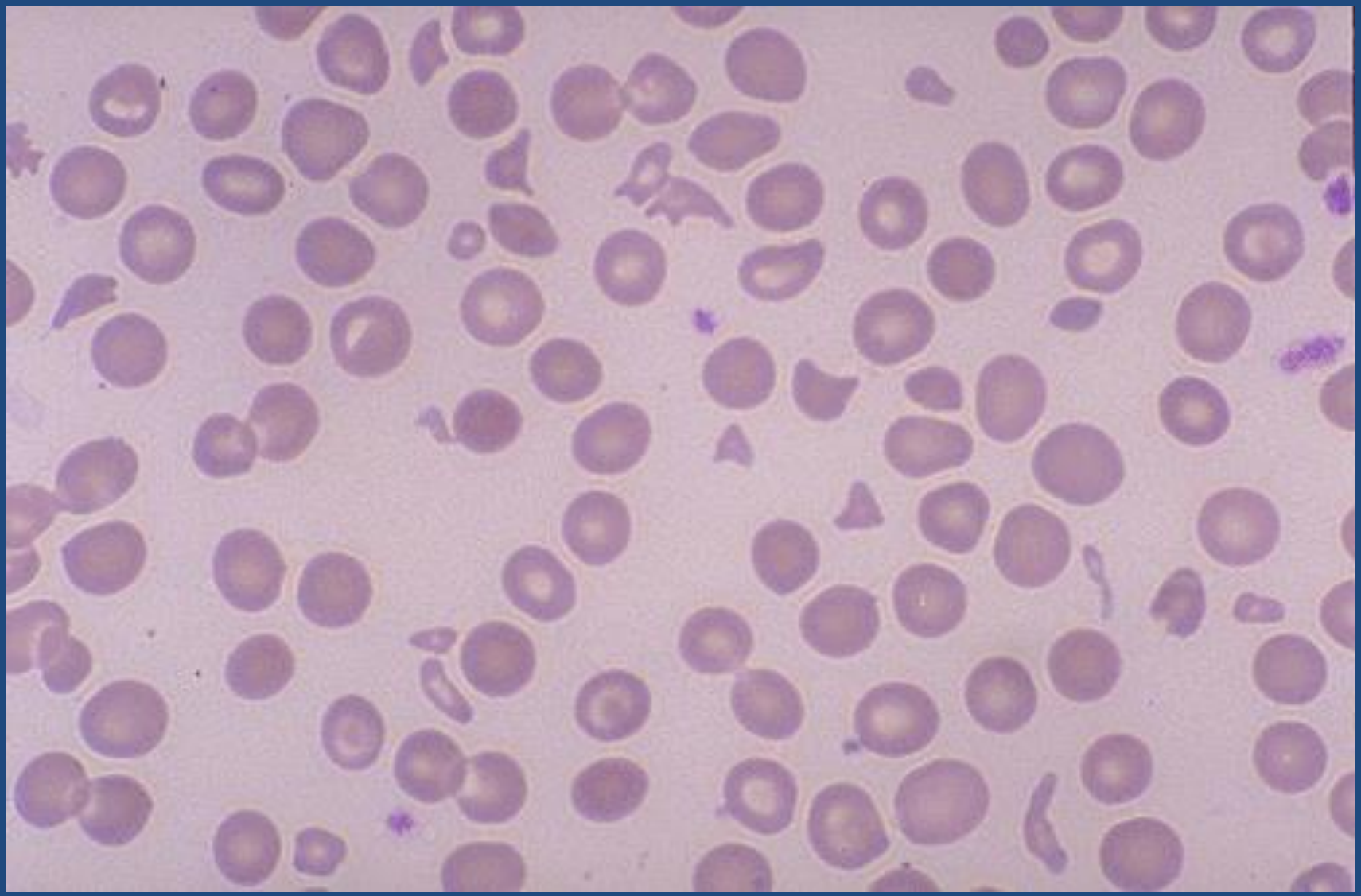
Laboratory studies:
Hematocrit: 26%
Leukocyte count: 10,300/uL
Platelet count: 24,000/uL
Reticulocyte count: 8.3% of erythrocytes
Bilirubin, Total: 2.3 mg/dL

Creatinine: 3.2 mg/dL
Lactate dehydrogenase: 1500 U/L

A peripheral blood smear is shown:

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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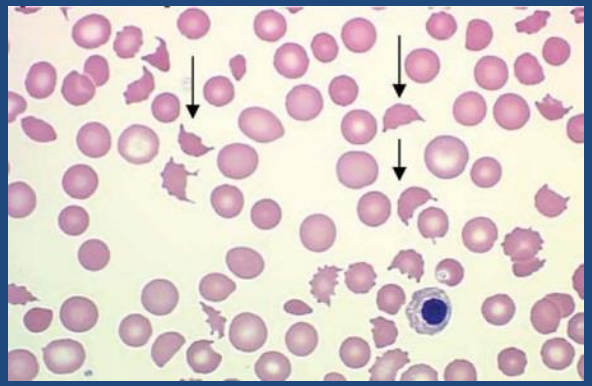
Diagnose a patient with thrombotic thrombocytopenic purpura

Definition of TTP:

- Initiation of intravascular platelet aggregation and coagulation/fibrin strands within the microcirculation
- Deficiency of ADAMTS 13 (< 5% normal activity)
- Cannot break down von Willebrand multimers



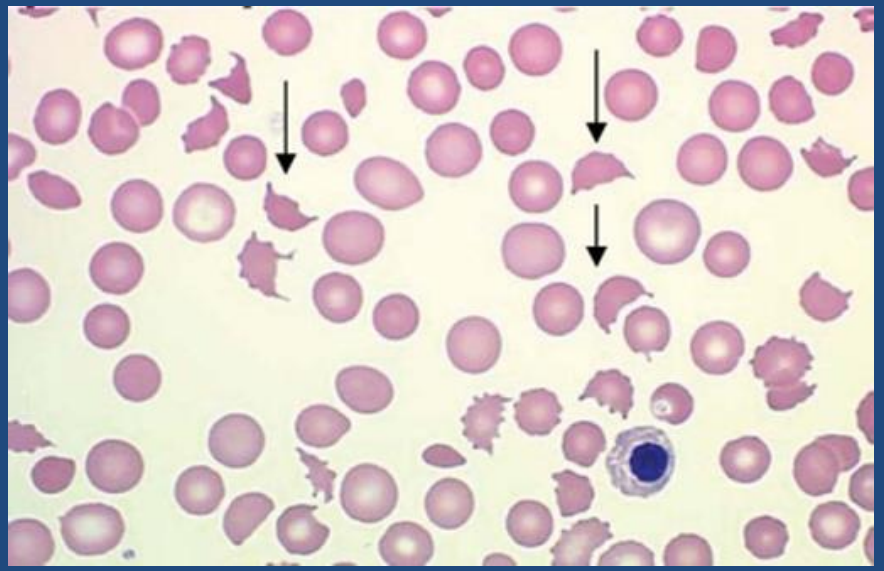
Clinical Diagnosis: Pentad of TTP:

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



Case 5

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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Who is at risk for HIT(T)?
(PRE-TEST *clinical* probability)

High-risk populations: (>1.0%)

- surgical and trauma patients receiving postoperative UFH*

Intermediate-risk patients: (0.1%-1.0%)

- medical and obstetrical patients receiving UFH
- patients receiving LMWH after major surgery or major trauma.

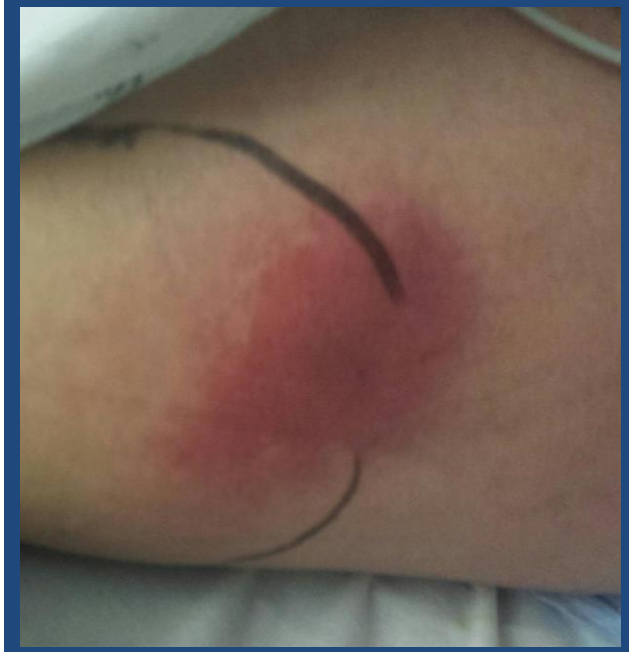
Low-risk patients: (<0.1%)

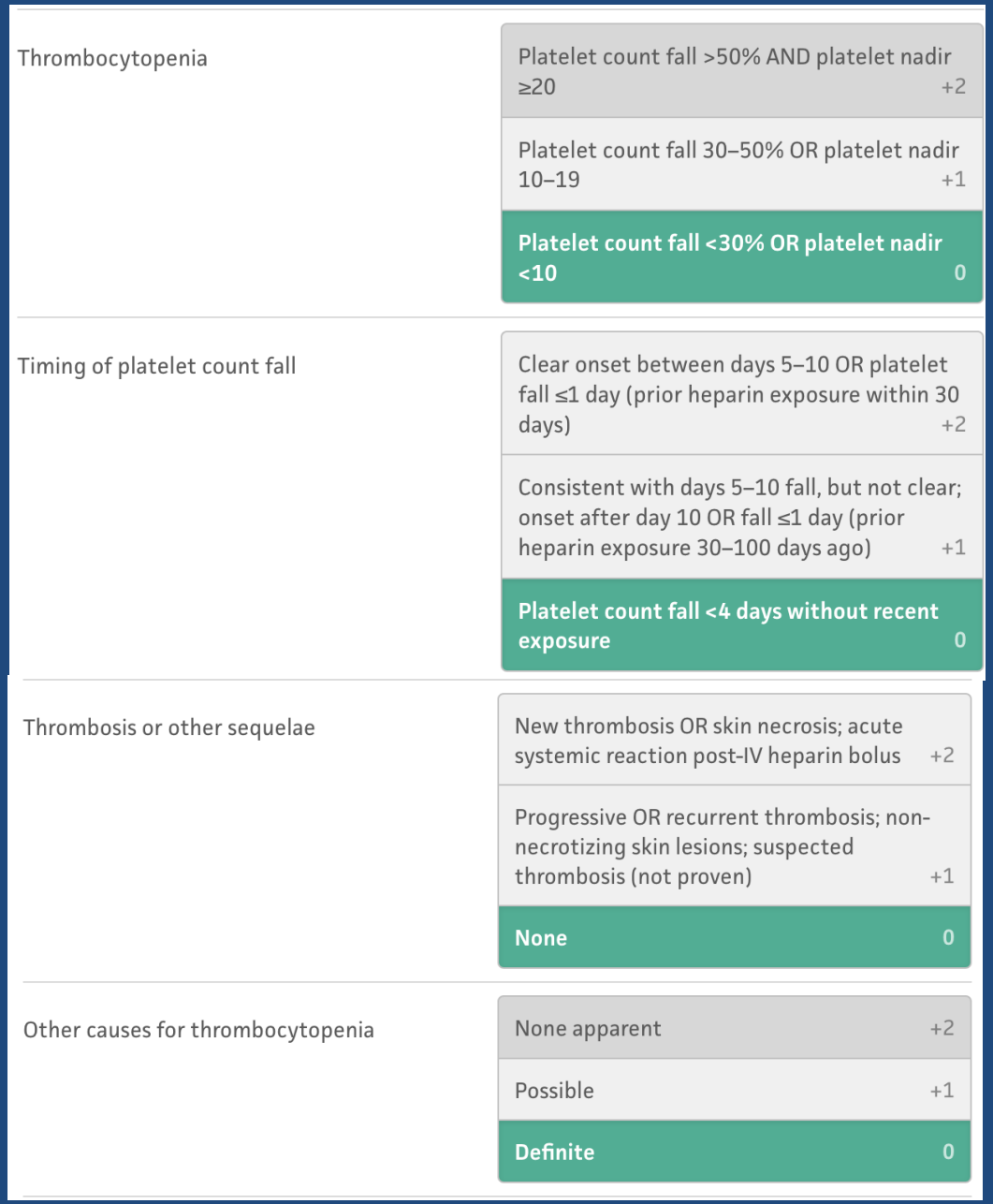
- medical and obstetrical patients receiving LMWH
- patients receiving LMWH after minor surgery or minor trauma
- any patients receiving fondaparinux.

Some patients may receive a combination of UFH and LMWH or UFH and fondaparinux; these patients should be considered to belong to the UFH group.

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

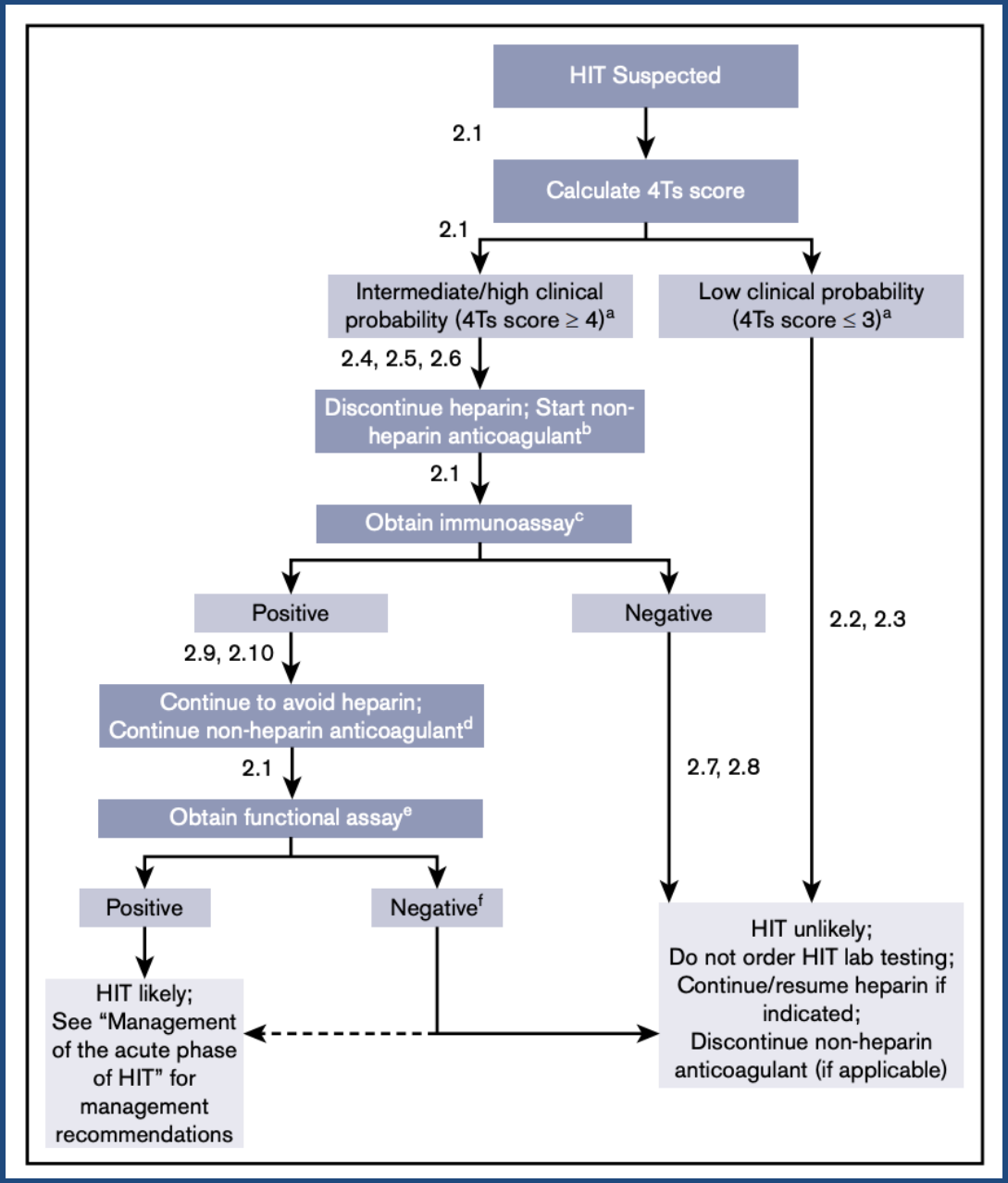
Feature	Comments
Fall in platelet count ≥ 50%	From highest platelet count after heparin exposure; platelet count fall is 30–50% in 10% of cases
Fall in platelet count begins 5–14 days after immunizing heparin exposure	Heparin administered during or soon after surgery is more likely to be immunizing
Fall 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





Calculate the 4-T Score:

- *LOW* ≤ 3 points
  - ≤ 5% in original study
  - < 1% in meta – analysis
- MEDIUM 4-5 points
  - ~ 14% probability of HIT
- HIGH 6-8 points
  - ~ 64% probability of HIT



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6258919/pdf/advances024489CG.pdf

IV. Treatment

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

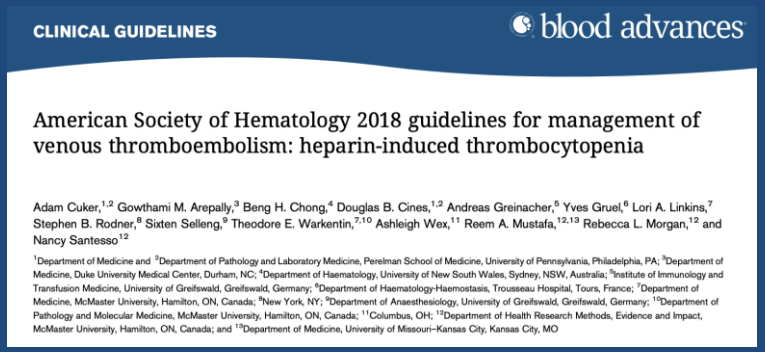
Agent	Initial dosing	Monitoring
Argatroban	**Bolus:** None **Continuous infusion:** Normal organ function→2 mcg/kg/min[1] Liver dysfunction (total serum bilirubin >1.5 mg/dL), heart failure, post-cardiac surgery, anasarca→0.5–1.2 mcg/kg/min[2]	Adjust dose to APTT of 1.5–3.0 times patient baseline. Monitor 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

HIT(T) Management

- Patients *with HIT* without obvious clot should have bilateral LE doppler u/s to evaluate for DVT and doppler u/s in upper limb with CVC only *to screen for DVT*


CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

Adam Cuker,[1,2] Gowthami M. Arepally,[3] Beng H. Chong,[4] Douglas B. Cines,[1,2] Andreas Greinacher,[5] Yves Gruel,[6] Lori A. Linkins,[7] Stephen B. Rodner,[8] Sixten Selleng,[9] Theodore E. Warkentin,[7,10] Ashleigh Wex,[11] Reem A. Mustafa,[12,13] Rebecca L. Morgan,[12] and Nancy Santesso[12]

[1]Department of Medicine and [2]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [3]Department of Medicine, Duke University Medical Center, Durham, NC; [4]Department of Haematology, University of New South Wales, Sydney, NSW, Australia; [5]Institute of Immunology and Transfusion Medicine, University of Greifswald, Greifswald, Germany; [6]Department of Haematology-Haemostasis, Trousseau Hospital, Tours, France; [7]Department of Medicine, McMaster University, Hamilton, ON, Canada; [8]New York, NY; [9]Department of Anaesthesiology, University of Greifswald, Greifswald, Germany; [10]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; [11]Columbus, OH; [12]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; and [13]Department of Medicine, University of Missouri–Kansas City, Kansas City, MO

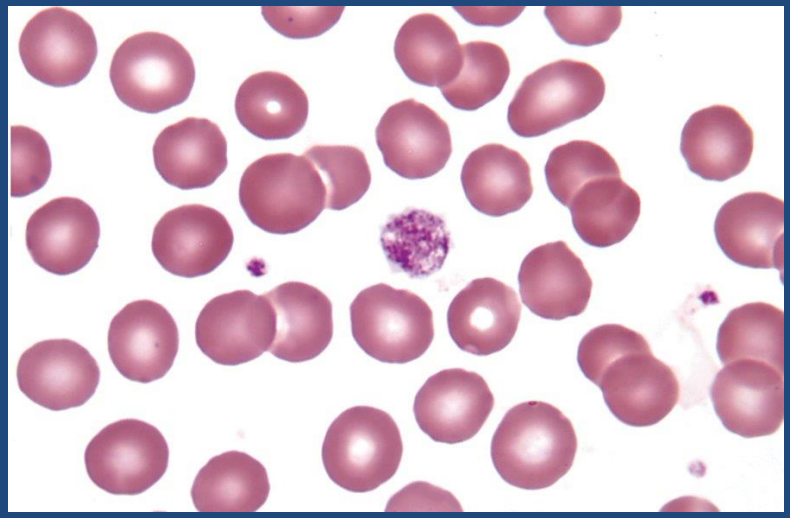
- Warfarin or DOAC (rivaroxaban) for full dose anticoagulation for 3 months if clot is present and *at least* 1 month if clot is not found

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.

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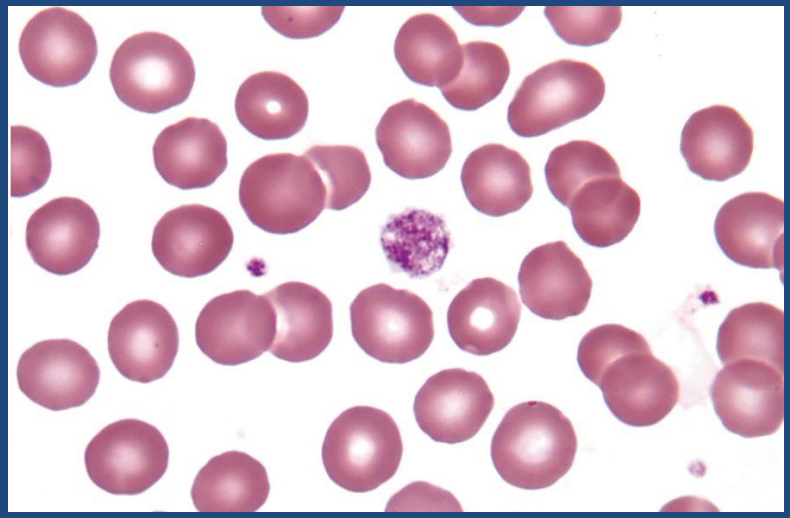

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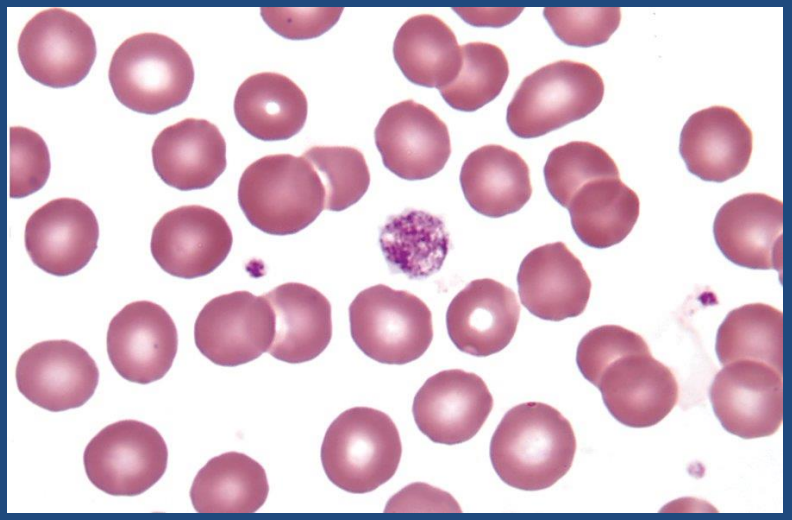
Immune Thrombocytopenic Purpura (ITP)

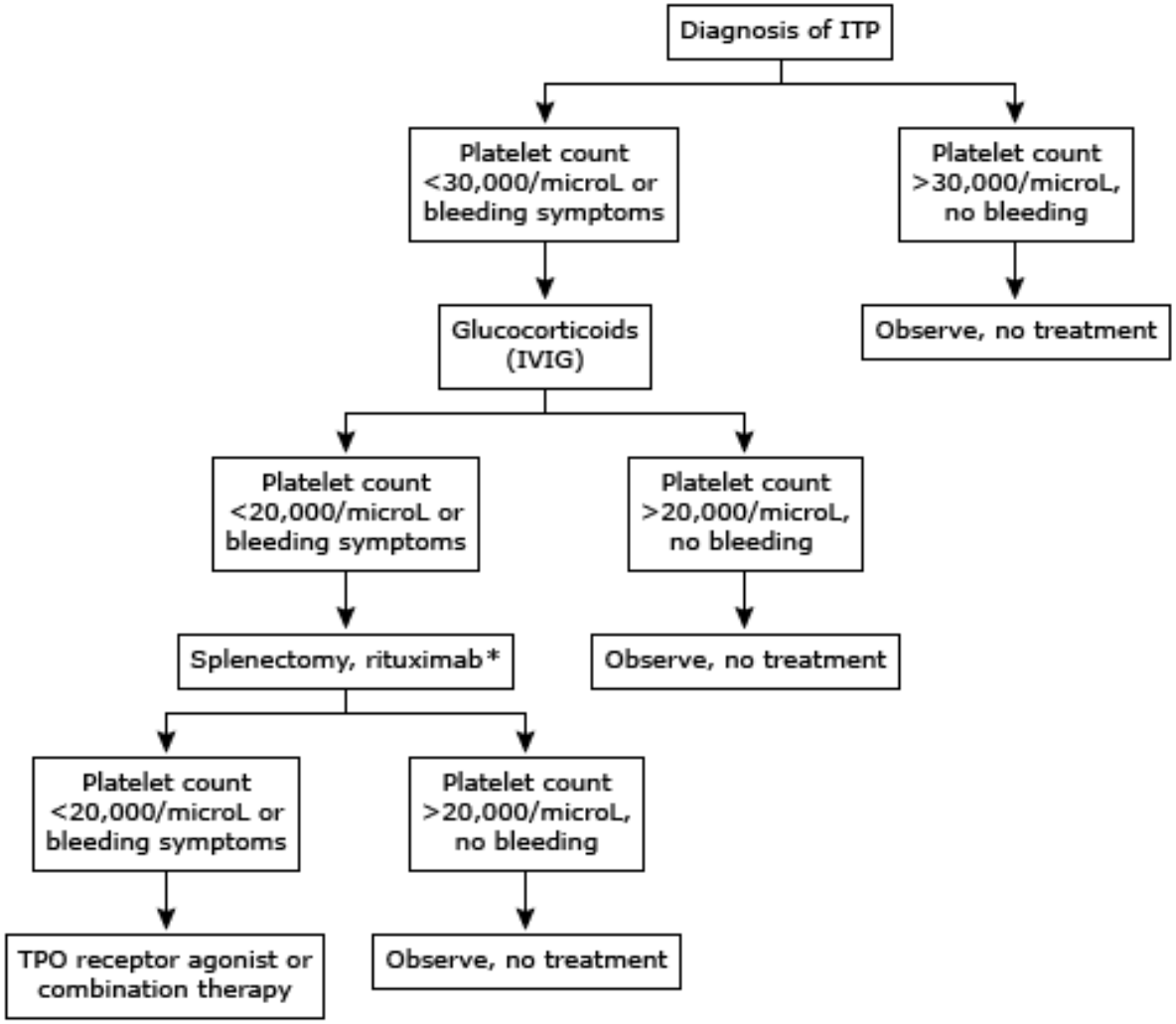
- Diagnosis of exclusion
- No splenomegaly
- No other cytopenias
- No coagulopathies



WORK-UP/DIFF DX

- 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



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 leuko-reduced, 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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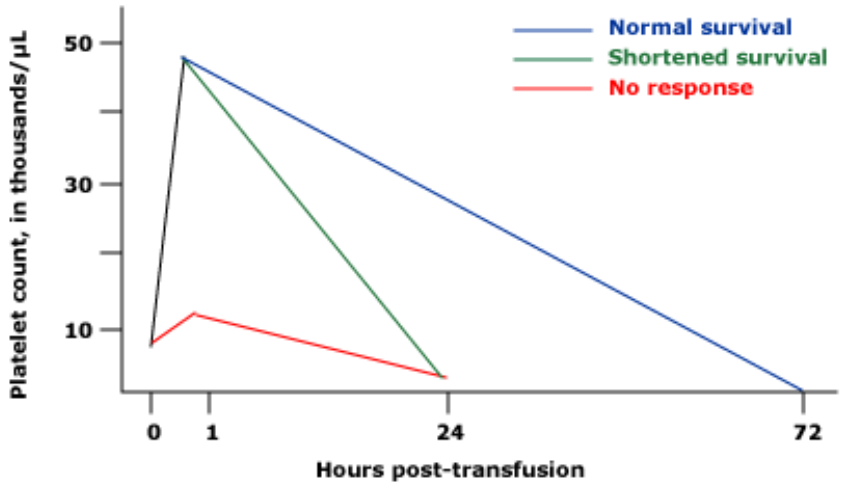
Patterns of response to platelet transfusion



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.

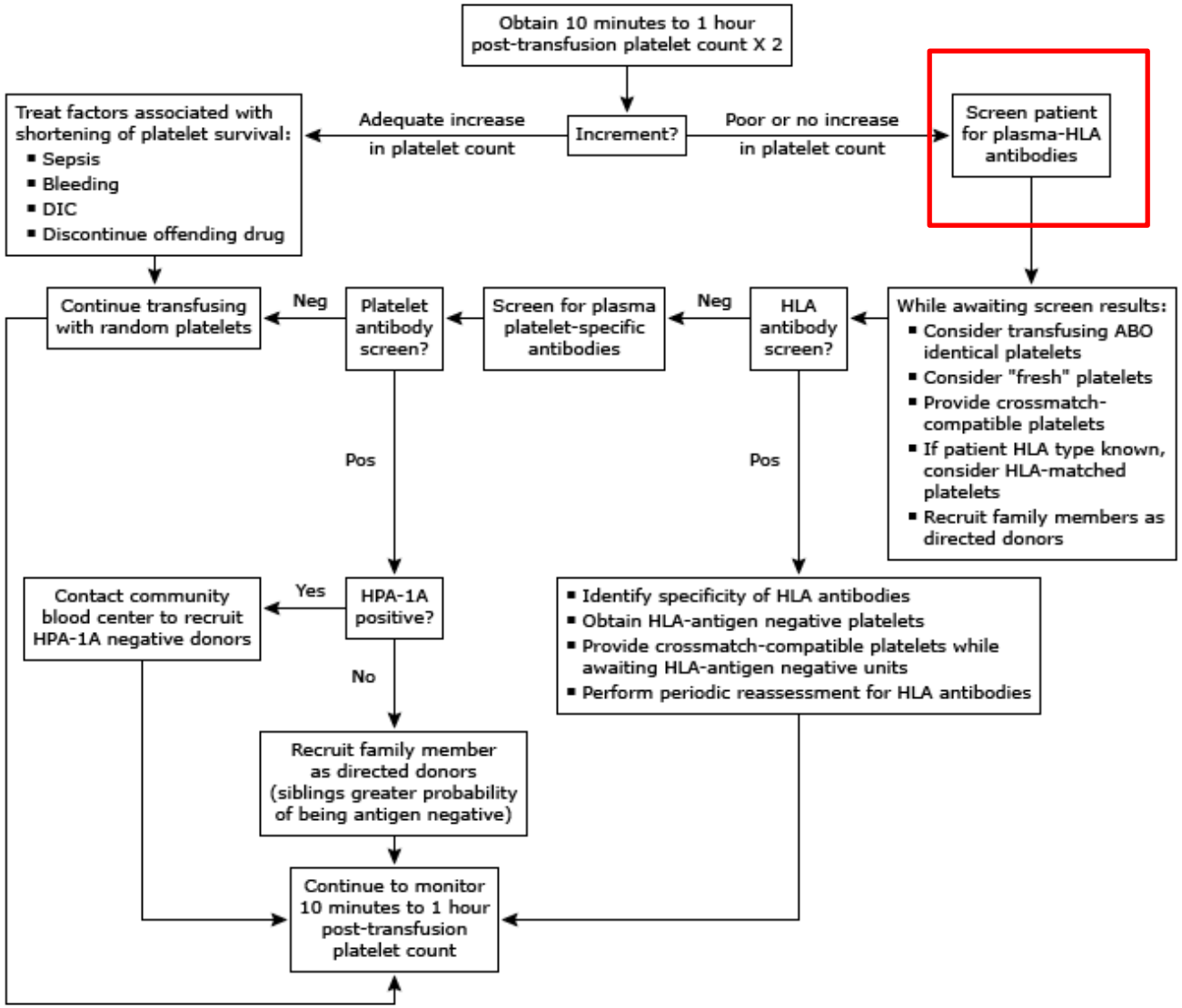
Graphic 82283 Version 2.0

2 types of platelet refractoriness:

1. **Non-immune:** normal response at 1 hour but back down in 24 hours

2. **Immune:** little to no increase in plt count even 1 hour after transfusion

Diagnosis and management of platelet refractoriness



What did you learn?

Write it down!
Teach it to your med student!