Brigham and Women's Hospital
Founding Member, Mass General Brigham

Hematology Board Review

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- *Medical School:* Brown University
- *Medical Residency:* Brown University
- *Hematology-Oncology Fellowship:* Brown University
- *Clinical Focus:* Non-malignant hematology
- *Research Focus*: Novel anticoagulation therapies, acquired hypercoagulable disorders, adverse effects of anticoagulation in menstruating patients

Disclosures

No Disclosures

Objectives

Use case vignettes to:

- Review key hematology topics through board-style questions and answers.

Question 1

A 35-year-old woman comes to the emergency room with shortness of breath on exertion over the past several days. Her past medical history is unremarkable. She takes no medications and notes no additional symptoms. She is afebrile and her vital signs are stable. Physical examination is remarkable for a few small ecchymoses on the upper and lower extremities, mild scleral icterus, and a grade I/VI holosystolic murmur.

Question 1

Laboratory studies reveal:

White blood cell count	9,600/mm^3	(4,000-10,000)
Hematocrit	23%	(36-48)
Platelets	36,000/mm^3	(150,000-450,000)
PT	12 s	(11-13)
PTT	26 s	(22-34)
Fibrinogen	450 mg/dL	(200-400)
Creatinine	0.8 mg/dL	(0.7-1.3)
LDH	1535	(107-231)

Peripheral blood smear reveals decreased platelets and moderate schistocytes.

Question 1

Which of the following is the appropriate next step:

A. Send serum toxicology panel and stool studies for E. coli 0157:H7

B. Initiate therapeutic plasma exchange as soon as possible

C. Observation for now, initiate plasma exchange if the platelet count < 20,000/mm^3

D. Observation for now, initiate plasma exchange if the patient becomes febrile or the creatinine rises

Question 1

What are the key clinical data provided?

Thrombocytopenia, anemia, normal creatinine, and schistocytes

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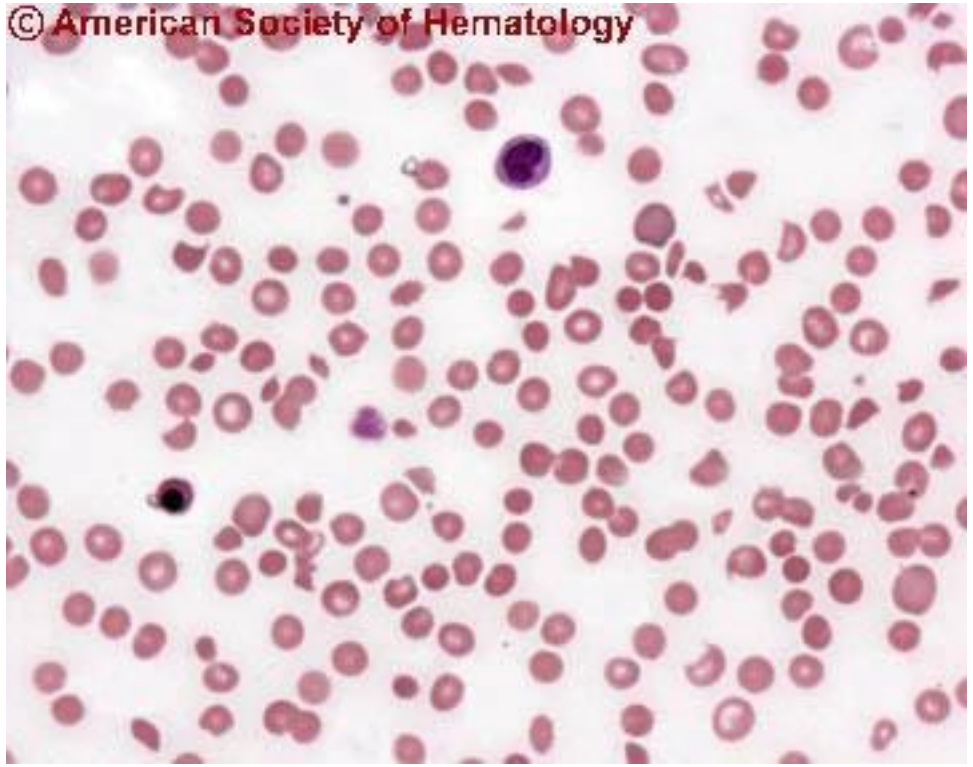
TTP Smear: Schistocytes



Diagnosis of TTP

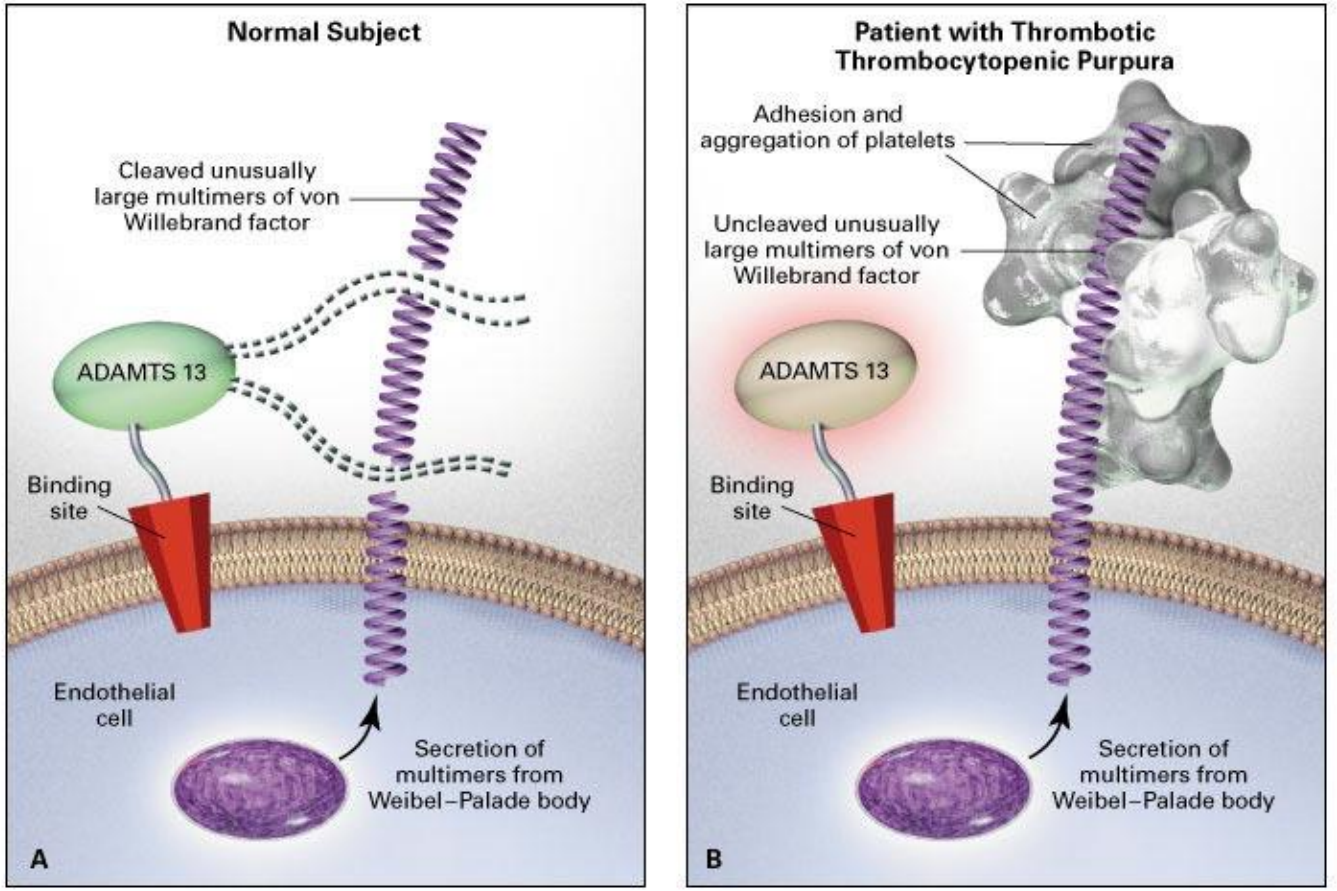
Two major characteristics of the classic pentad are enough to diagnose TTP:

- Microangiopathic hemolytic anemia
- Thrombocytopenia

Other manifestations may or not be present:

- Fever
- Neurologic symptoms
- Renal Insufficiency/Failure

Pathophysiology of TTP



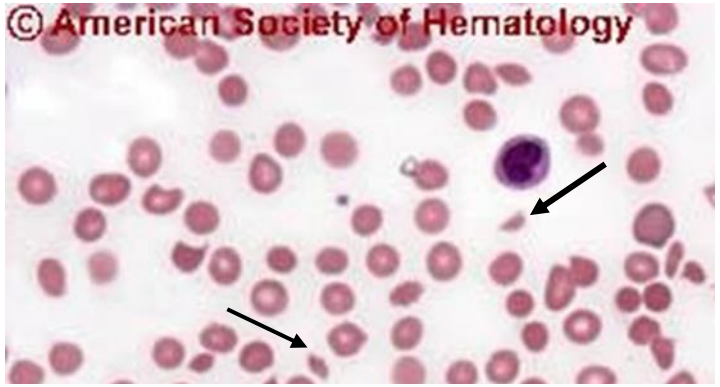
Moake, J. L. N Engl J Med 2002;347:589-600

Course of TTP

- About 90% of cases of TTP improve with plasma exchange.
- However, given that 30% of patients after plasma exchange, rituximab is now commonly used along with plasma exchange as first line therapy.
- Additional therapies to consider include cytotoxic agents, caplacizumab (blocks VWF-PLT binding)

TTP - BRIEF TAKE AWAY NOTES

- *Pathophysiology*: ADAMTS13 deficiency
- *Smear*



- *Diagnosis*:
  - Two major characteristics of the classic pentad are enough to diagnose TTP:
    - Microangiopathic hemolytic anemia
    - Thrombocytopenia

- *Treatment*:
  - Plasma exchange – initiate as soon as possible
  - Rituximab

Question 2

A 54-year-old man of Greek ancestry is seen for follow-up 3 days after completing a course of trimethoprim/sulfamethoxazole for an upper respiratory tract infection. While his cough has improved, he now feels more shortness of breath with exertion and fatigue. In addition, he notes that his eyes have become yellow.

Laboratory studies reveal:

- White blood cell count 5,860/mm^3 (4,000-10,000)
- Hematocrit 28% (36-48)
- Reticulocyte count 11% (1-1.5%)
- MCV 101 fL (80-95)
- Platelets 175,000/mm^3 (150,00-450,000)

Question 2

The most appropriate course of action at this time is:

A. Obtain folate and vitamin B12 levels

B. Observation, return visit in a few weeks for further laboratory studies

C. Test for glucose-6-phosphate dehydrogenase deficiency

D. Bone marrow aspirate and biopsy

Question 2

What are the key clinical data provided?

Anemia with an elevated reticulocyte count, recent course of antibiotics, Greek ancestry

Question 2

The most appropriate course of action at this time is:

A. Obtain folate and vitamin B12 levels

B. Observation, return visit in a few weeks for further laboratory studies

C. Test for glucose-6-phosphate dehydrogenase deficiency

D. Bone marrow aspirate and biopsy

G6PD Deficiency

Two Isoforms:

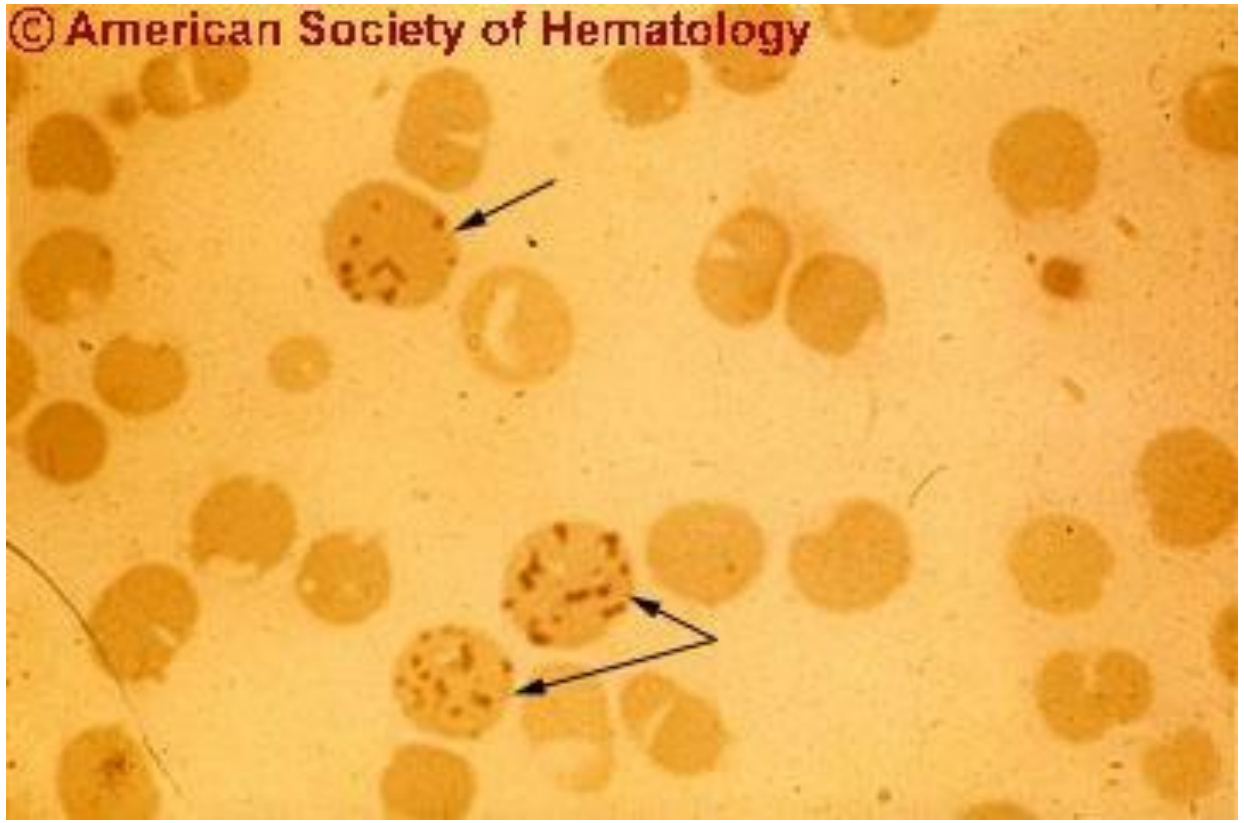
A- isoform

- G6PD activity declines due to enzyme instability during the red cell lifespan
- Present in 10% of African-American males
- G6PD levels in reticulocytes are normal
- May require Heinz Body identification to diagnose during acute hemolytic episode

Mediterranean Isoform

- Essentially no G6PD activity in RBC = more severe
- Present in 5% of Mediterranean people
- Can always be diagnosed (even during hemolysis)

Heinz Body Prep



Heinz bodies: oxidized, denatured precipitates of hemoglobin

Oxidant Stressors in G6PD Deficiency

Antibacterials

- Dapsone
- Nalidixic acid
- Nitrofurantoin
- Sulfamethoxasole
- Sulfapyridine

Antimalarials

- Primaquine
- Pamaquine

Miscellaneous

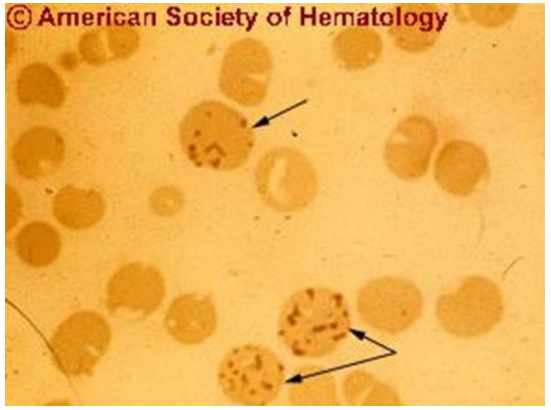
- Doxorubicin
- Methylene blue
- Phenazopyridine (PYRIDIUM)
- Phenylhydrazine
- Probenacid

Environmental/Food

- Fava beans
- Naphthalene (moth balls)
- Toluene blue

G6PD - BRIEF TAKE AWAY NOTES

- *Presentation*: acute hemolytic anemia after initiating a new medication
- *Smear:*



- *Diagnosis*:
  - Test for glucose-6-phosphate dehydrogenase deficiency

- *Key Classes of Oxidant Stressors*:
  - Antibiotics
  - Antimalarials
  - Other Medications (ex: doxorubicin)
  - Environmental/Food (ex: fava beans)

Question 3

A 35-year-old woman originally from the Dominican Republic presents to clinic for her first visit. She has no significant medical problems and has had two children. After the birth of her second child who is now 3 years old, she was told to take iron tablets twice daily. Aside from an oral contraceptive, iron is her only medication.

Laboratory studies reveal:

White blood cell count	4,600/mm^3	(4,000-10,000)
Hematocrit	35%	(36-48)
MCV	66 fL	(80-95)
Platelets	256,000/mm^3	(150,000-450,000)
Fe	150 μg/dL	(40-159)
TIBC	275 μg/dL	(250-400)

Question 3

The most appropriate next step is:

A. Therapeutic phlebotomy for hereditary hemochromatosis

B. Continue current iron therapy and send an ESR and CRP

C. Switch from oral iron sulfate to intravenous ferric gluconate

D. Discontinue iron therapy. Send ferritin and hemoglobin electrophoresis

Question 3

What are the key clinical data provided?

Minimal anemia with significant microcytosis and normal iron studies

Question 3

The most appropriate next step is:

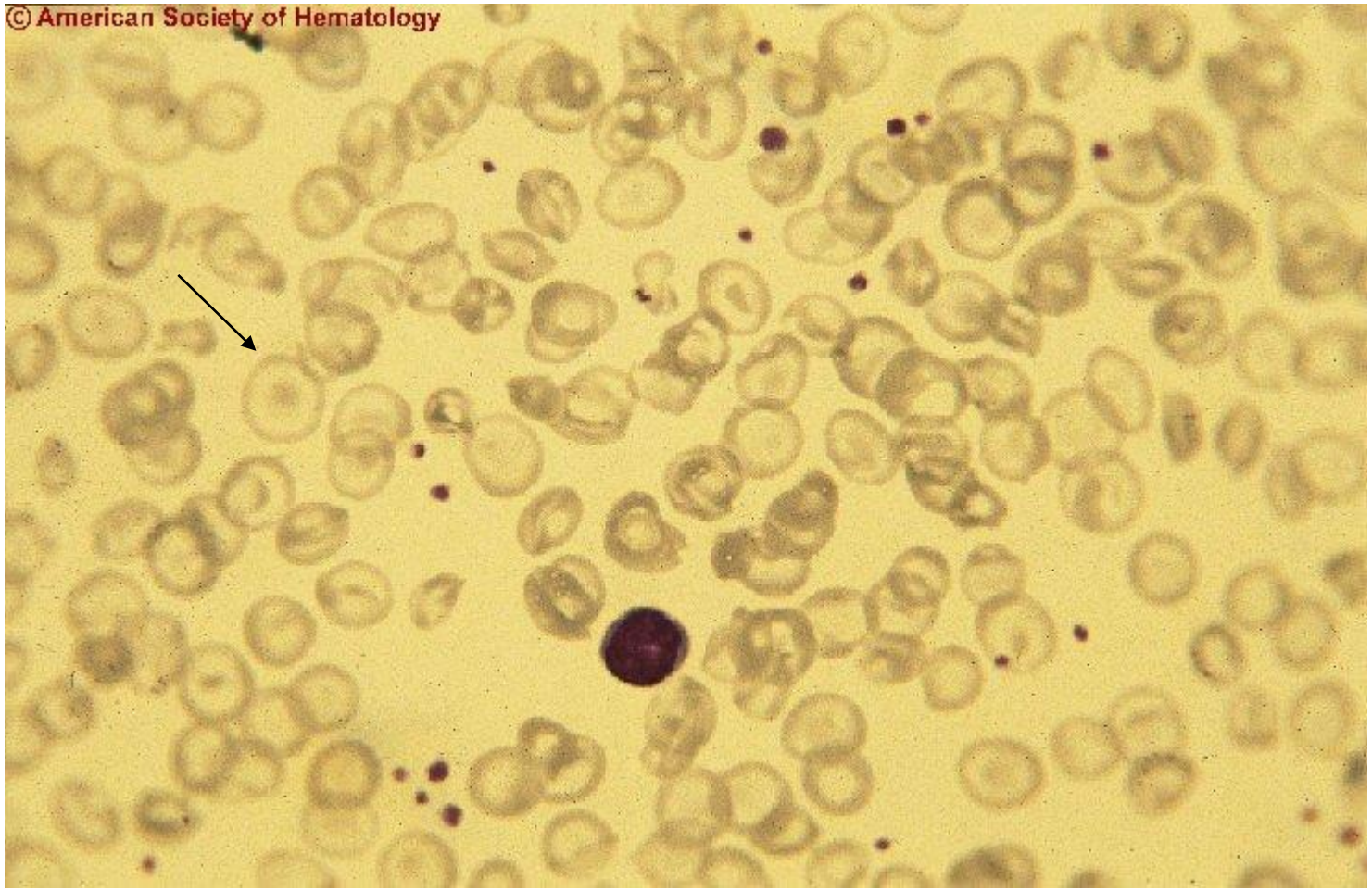
A. Therapeutic phlebotomy for hereditary hemochromatosis

B. Continue current iron therapy and send an ESR and CRP

C. Switch from oral iron sulfate to intravenous ferric gluconate

D. Discontinue iron therapy. Send ferritin and hemoglobin electrophoresis

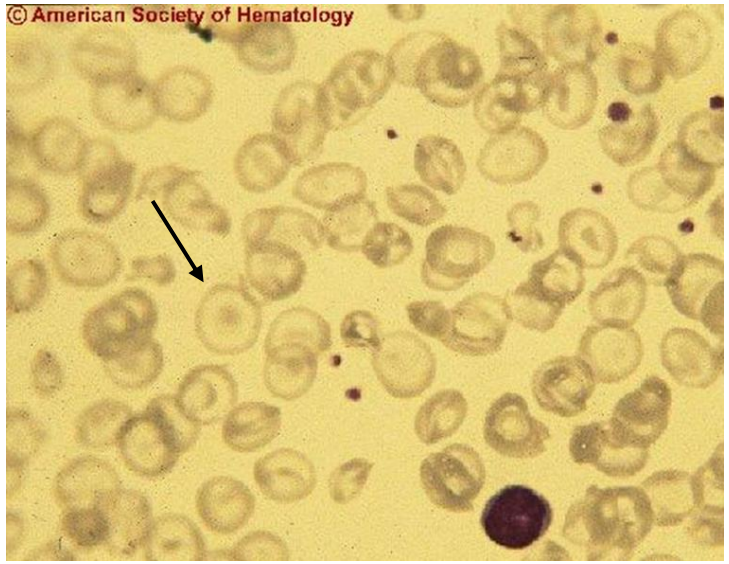
Smear: Thalassemia



Hypochromia, microcytosis, target cells (see arrow)

THALASSEMIA - BRIEF TAKE AWAY NOTES

- *Presentation*: Chronic, microcytic anemia with normal iron studies
- Smear:



- *Diagnosis*: Hemoglobin electrophoresis

Question 4

A 74-year-old man with diabetes mellitus, hypertension, and benign prostatic hypertrophy presents for routine follow-up. On review of his records, you note that his hematocrit has been gradually declining over the past three years. On his visit today laboratories reveal:

Hematocrit	28%	(36-48)
MCV	84 fL	(80-95)
Platelets	340,000/mm^3	(150,000-450,000)
BUN	35 mg/dL	(9-25)
Creatinine	2.3 mg/dL	(0.7-1.3)
LDH	230	(107-231)

Question 4

The most likely etiology of his anemia is:

A. Combined iron and B12 deficiency

B. Medication effect from the ACE inhibitor

C. Erythropoietin deficiency

D. Anemia due to marrow replacement by metastatic prostate cancer

Question 4

What are the key clinical data provided?

Progressive anemia, normal MCV, and elevated creatinine

Question 4

The most likely etiology of his anemia is:

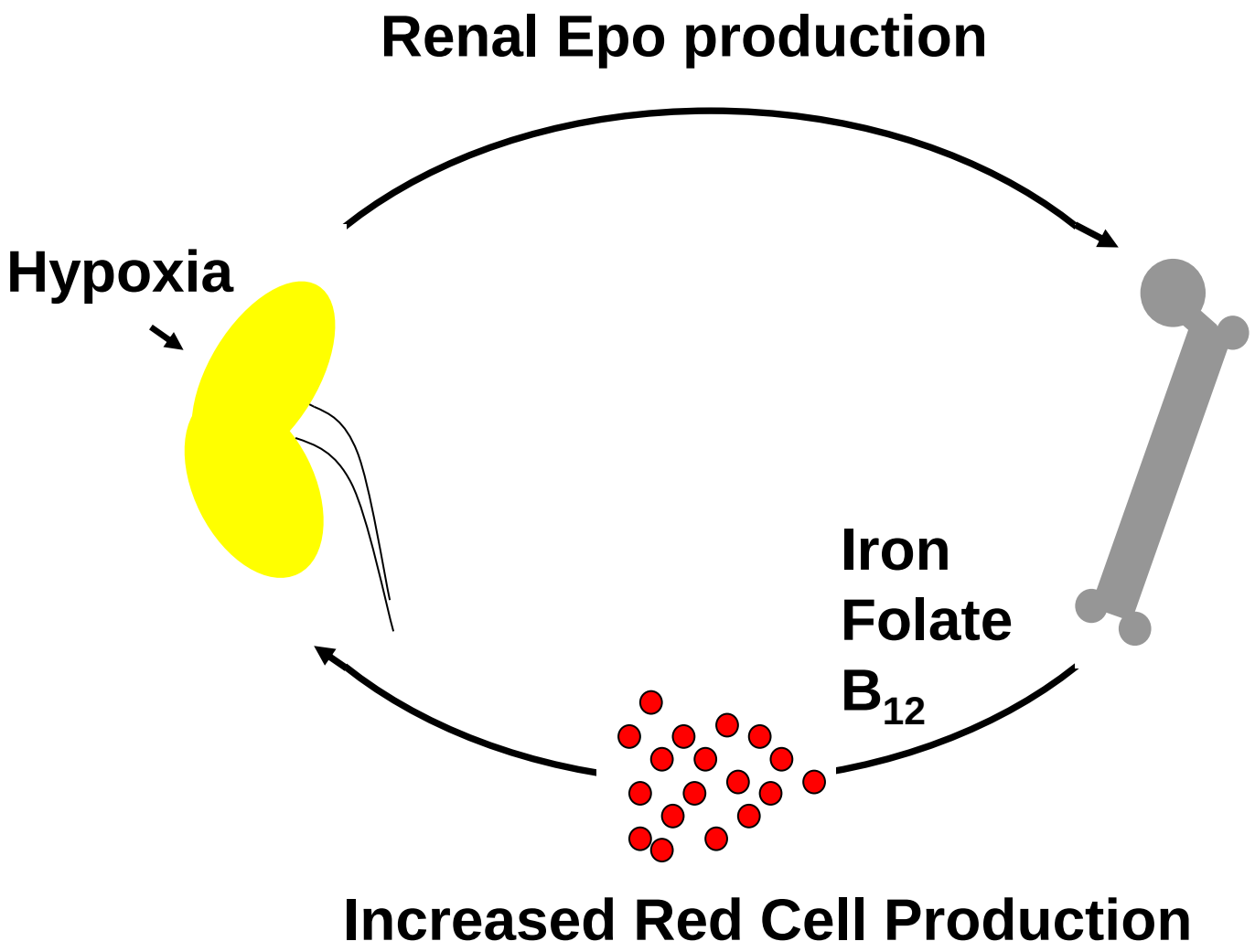
A. Combined iron and B12 deficiency

B. Medication effect from the ACE inhibitor

C. Erythropoietin deficiency

D. Anemia due to marrow replacement by metastatic prostate cancer

Regulation of Erythropoietin



ANEMIA OF CHRONIC KIDNEY DISEASE – BRIEF TAKE AWAY NOTES

- Decline in renal function is associated with decreased erythropoietin production
- Anemic patients with diabetes mellitus and even modestly abnormal renal function are often erythropoietin deficient
- ***The normal range for erythropoietin values is for patients who are not anemic***
- Anemia of any significant degree should lead to a rise in the erythropoietin level above the normal range

Question 5

A 23-year-old man with a history of sickle cell anemia is admitted to the hospital for fever. He has a two-day history of a dry, non-productive cough, and fever to 101°F. A chest X-ray in the emergency department was found to have a right lower lobe infiltrate. On admission to the medicine service, his oxygen saturation was 94% on room air, and he did not feel short of breath. He was placed on levofloxacin and given 1L of IV fluids.

Question 5

CBC on admission:

• White blood cell count	18,000/mm^3	(4,000-10,000)
• Hematocrit	21%	(36-48)
• Platelets	247,000/mm^3	(150,000-450,000)

One day following admission, the patient develops increasing shortness of breath and is found to have an oxygen saturation of 86% on room air. Chest radiograph reveals bilateral lower lobe opacities.

Question 5

In addition to starting supplemental oxygen, the most appropriate next step is to:

A. Obtain a V/Q scan

B. Administer furosemide

C. Transfuse RBCs

D. Add coverage for atypical organisms and perform exchange transfusion

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ACUTE CHEST SYNDROME - BRIEF TAKE AWAY NOTES

- *Presentation*: Clinical syndrome of fever, hypoxia, and pulmonary infiltrates in a patient with sickle cell disease
  - Often associated with infection with atypical organisms such as Chlamydia or Mycoplasma

- *Treatment*: Blood transfusion (simple or exchange) may be life-saving
  - Exchange transfusion:
    - Demonstrated to improve outcome in acute chest syndrome in adult
    - Indications for exchange: Stroke, acute chest syndrome, priapism

Question 6

A 76-year-old woman on warfarin for chronic atrial fibrillation (INR goal: 2-3) is found to have an INR of 5.8 on routine testing. She is otherwise asymptomatic. The most appropriate next step is:

A. Decrease dose of warfarin by 50%
B. Hold warfarin, administer 1 mg vitamin K subcutaneously
C. Hold warfarin, administer 2.5 mg vitamin K orally
D. Hold warfarin, recheck INR in 1 to 2 days prior to restarting therapy
E. Hold warfarin for one day, restart at 50% of previous dose the next day

Question 6

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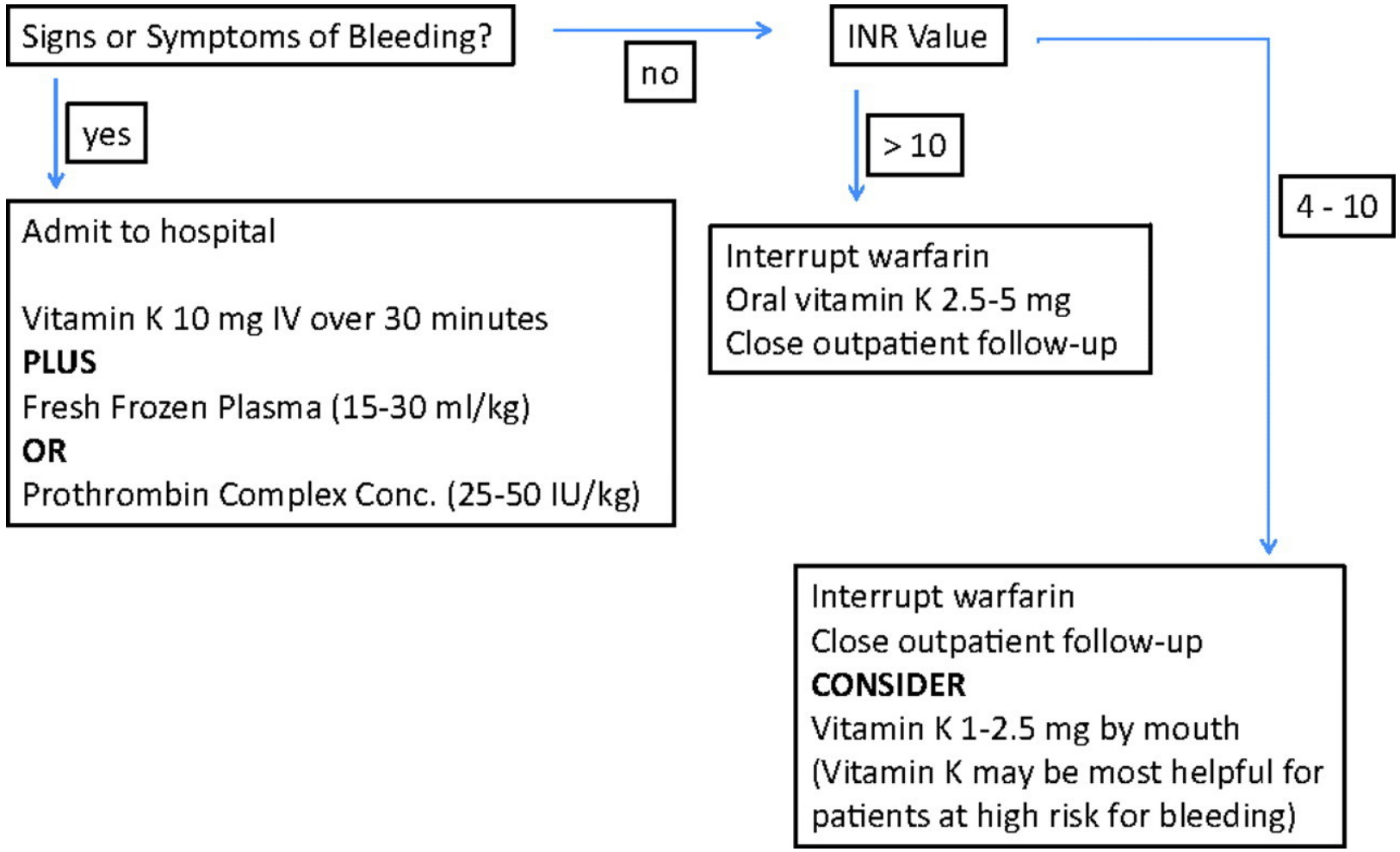
Warfarin (Coumadin)

- Inhibits Vitamin K dependent gamma-carboxylation of coagulation Factors II, VII, IX, and X
- Half life is 40 hours (highly variable)
- Duration of effect is 2-5 days

Warfarin Reversal



David A. Garcia. Circulation. Reversal of Warfarin, Volume: 125, Issue: 23, Pages: 2944-2947

Direct Oral Anticoagulant Reversal

- FFP: No benefit
- PCCs Possible benefit
- Factor VIIa Possible benefit
- Idarucizumab (PRAXBIND) Effective against dabigatran
- Andexanet alfa (ANDEXXA) Effective against direct Xa inhibitors (apixaban, rivaroxaban …)

Question 7

A 24-year-old female whose family is of European ancestry is found to have a right popliteal deep venous thrombosis while taking oral contraceptives. Of the following heritable conditions, which is most likely to be found on diagnostic evaluation:

A. Antithrombin III deficiency
B. Protein C deficiency
C. Homocysteinemia
D. Factor V Leiden
E. Prothrombin gene mutation (G20210A)

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Common Inherited Thrombophilias

Factor V Leiden

- G1691A mutation (arg to glu amino acid 506)
- Prevents inactivation of factor V
- Present in 4-6% of individuals of European ancestry and only 0.05% of individuals of Asian and African ancestry.

Prothrombin Gene Mutation

- G20210A mutation
- Leads to elevated levels of prothrombin
- Present in 2-3% of individuals of European ancestry and is rarely seen in individuals of Asian and African ancestry.

Common Inherited Thrombophilias

Rare (<1% of population combined)

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency

Very Rare

- Dysfibrinogenemia
- Homozygous homocystinuria

Common Inherited Thrombophilias

How common are the inherited thrombophilias?

In patients with VTE who are:

- less than 50 years of age
- have a family history of thrombosis
- have a history of recurrent events
- no acquired risk factors except for pregnancy or oral contraceptive:

Factor V Leiden	40%
Prothrombin Gene Mutation	16%
Protein C, S, or Antithrombin	13%

INHERITED THROMBOPHILIAS – BRIEF TAKE AWAY NOTES

- *Rate of Inherited Thrombophilias*:
  - Most Common: Factor V Leiden
  - Second Most Common: Prothrombin G20210A Gene Mutation
  - Both more common in patients of European ancestry

- *When to Suspect Inherited Thrombophilia in First Episode VTE*:
  - Less than 50 years of age
  - Family history of VTE
  - No risk factors except for pregnancy or oral contraceptive

Question 8

Which of the following statements is true regarding oral replacement of Vitamin B12?

A. Oral B12 is only effective in patients who possess intrinsic factor

B. Since oral B12 costs more than parenteral replacement, it should not be used

C. It is generally effective, though requires monitoring for compliance

D. Methylmalonate and homocysteine levels cannot be used for monitoring of therapy

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Cobalamin (Vitamin B_{12}) Deficiency

Diagnosis:

- Levels of less than 200 pg/mL are diagnostic of B12 deficiency.
- Levels of 200-400 pg/mL are indeterminate. If clinical concern for B12 deficiency, homocysteine and methylmalonate levels can be helpful (both increase in B_{12} deficiency)

Clinical Features:

- Hematopoiesis: Pancytopenia with an increase in the MCV
- Neurological: Peripheral neuropathy, subacute combined degeneration of posterior column → dementia

Cobalamin (Vitamin B_{12}) Deficiency

Reasons for B12 deficiency:

- Malabsorption
- Intrinsic factor deficiency: Pernicious anemia, gastric bypass
- Resection of distal ileum; celiac disease, ileitis
- Competition from parasites: Blind loop, intestinal diverticulum
- Dietary deficiency (though this is less common)

Treatment

- Parenteral: 1000 mcg/month IM after loading
- Oral: 1000mcg daily, absorbed by mass action

Question 9

An asymptomatic 35-year-old woman is seen as a new patient in primary care. A routine CBC shows:

White blood cell count	6,200/mm^3	(4,000-10,000)
Hematocrit	36%	(36-48)
Platelets	758,000/mm^3	(150,000-450,000)

Which of the following statements is true:

A. Therapy with hydroxyurea is indicated
B. Warfarin therapy is indicated to prevent thrombotic complications
C. The possibility of iron deficiency, an inflammatory state or a myeloproliferative neoplasm should be investigated
D. The patient has a very high risk of thrombosis or hemorrhage during the next five years

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Thrombocytosis

Thrombocytosis can be reactive or can be due to a bone marrow disorder.

Reactive causes:

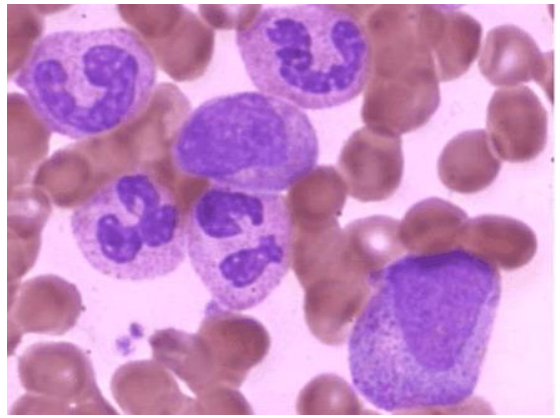
- Infection
- Inflammation
- Iron Deficiency

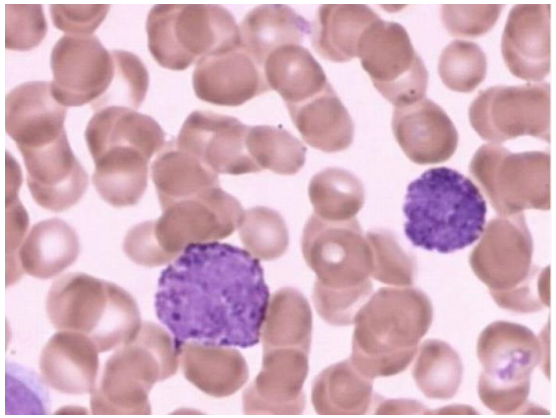
Malignant Causes:

- Myeloproliferative disorders
- Myelodysplasia (5q- syndrome)

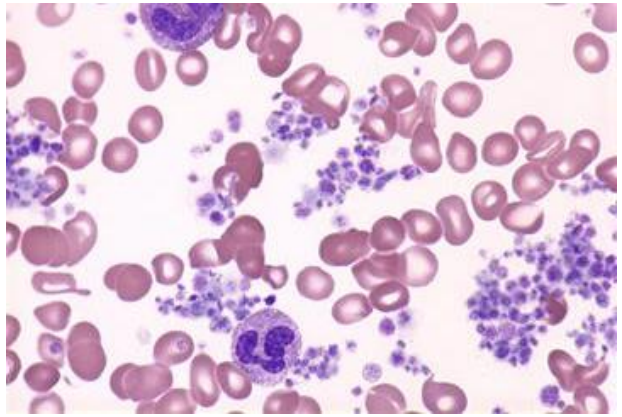
Smear: Myeloproliferative disorders

CML: Neutrophilia, myeloid precursors





CML: Increased basophils



Essential thrombocythemia

Essential thrombocytosis

- No platelet lowering agents needed in asymptomatic individuals without history of thrombosis, age < 60, with platelet counts of < 1,500,000/mm^3
- Increased risk of arterial or venous thrombosis
- Pathogenesis: JAK2, CALR, MPL mutations
- Low-dose aspirin (81 mg daily) is generally recommended
- Patients with bleeding or platelet counts > 1,000,000/mm^3 should be evaluated for acquired Von Willebrand Disease

THROMBOCYTOSIS – BRIEF TAKE AWAY NOTES

- *Causes*:
  - Primary
    - Myeloproliferative disorders
    - Myelodysplasia (5q- syndrome)
  - Secondary/Reactive
    - Infection
    - Inflammation
    - Iron Deficiency

- *Diagnosis*:
  - Rule out iron deficiency
  - Essential Thrombocytosis (ET): JAK2, CALR, MPL mutations

- *Treatment of ET*:
  - Aspirin 81mg (all)
  - Hydroxyurea (age > 60, history of thrombosis)

Question 10

A 67-year-old man with a history of unstable angina is admitted to the coronary care unit for management of chest pain. His CBC is normal on admission, and he is started on unfractionated heparin. On hospital day 7, his platelet count is noted have drifted down to 80,000/mm3. There are no other clear reasons for his thrombocytopenia. An ELISA assay for antibodies to the heparin-PF4 complex is sent.

What is the appropriate next step:

A. Continue unfractionated heparin pending the ELISA results
B. Switch to a low molecular weight heparin pending the ELISA results
C. Discontinue unfractionated heparin and begin anticoagulation with a direct thrombin inhibitor pending ELISA results
D. Discontinue unfractionated heparin and begin warfarin to target an INR 2-3 pending the ELISA results

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Heparin-Induced Thrombocytopenia

- Fall in the platelet count that is typically greater than 50% of the peak platelet count
- Rarely occurs within the first five days of heparin unless there has been a *recent* pre-exposure to heparin
- Less common with LMWH, but once a patient has HIT, antibodies may be cross-reactive
- There is no absolute platelet number that is diagnostic of HIT and it is always important to consider in the appropriate clinical setting

Heparin-Induced Thrombocytopenia

If heparin-induced thrombocytopenia is suspected, STOP all heparin products and start a direct thrombin inhibitor.

Question 11

A 28-year-old female is seen in clinic for preconception counseling. Her past medical history is notable for significant bleeding after extraction of her wisdom teeth. She takes no medications. Her mother required 2 blood transfusions after the birth of each of her two children. Her sister also had major bleeding several days after the birth of her child.

An appropriate evaluation at this time would include:

A. Thrombin and reptilase times

B. Von Willebrand antigen level, ristocetin cofactor levels, and factor VIII activity level

C. Factor XIII screen

D. PT/INR

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B. Von Willebrand antigen level, ristocetin cofactor levels, and factor VIII activity level

C. Factor XIII screen

D. PT/INR

Von Willebrand Disease Screening Panel

Includes:

- Factor VIII activity
- Von Willebrand Antigen
- Von Willebrand ristocetin cofactor activity level

Note: Those with blood type O have a VW:Ag level ~25% lower

Von Willebrand Factor

- A 270 kD monomer that assembles into multimers ranging from 600 kD to 20,000 kD in size
- VWF binds to subendothelial collagen and to platelets via GPIb and GPIIb/IIIa receptors
- Facilitates platelet-platelet interactions
- Acts as a carrier for Factor VIII, protecting it and prolonging its half life
- The VWF:Ristocetin co-factor assay measures the functional activity of VWF

Von Willebrand Disease Types

Type 1: Quantitative (partial) VWF deficiency

Type 2: Qualitative defects in VWF

- 2A: Decreased platelet dependent function
- 2B: Increased affinity of VWF for platelets
- 2M: Decreased affinity of VWF for platelets
- 2N: Defective factor VIII binding site

Type 3: Complete VWF deficiency

VON WILLEBRAND DISEASE – BRIEF TAKE AWAY NOTES

- *Presentation*: Abnormal bleeding in a patient with a family history of bleeding issues

- *Diagnosis*: Von Willebrand Panel
  - Factor VIII activity
  - Von Willebrand Antigen
  - Von Willebrand ristocetin cofactor activity level

- *Types of Von Willebrand Disease*:
  - Type 1: Quantitative (partial) VWF deficiency
  - Type 2: Qualitative defects in VWF
  - Type 3: Complete VWF deficiency

Question 12

A 67-year-old man with a history of hypertension is seen for an annual physical. He appears flushed and exam is notable for a grade II/VI systolic flow murmur. CBC shows:

White blood cell count	9,800/mm^3	(4,000-10,000)
Hematocrit	58%	(36-48)
Platelets	430,000/mm^3	(150,000-450,000)

The serum erythropoietin level is low. Which of the following is the most appropriate next step in evaluation:

A. Serum iron panel with HFE gene mutation analysis
B. JAK2 V617F mutation analysis
C. Polysomnography (sleep study)
D. Hemoglobin electrophoresis with p50 dissociation curve

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Erythrocytosis

Like thrombocytosis, erythrocytosis can be reactive or due to a malignancy.

Reactive causes:

- Sleep apnea
- Renal disease
- Chronic hypoxia

Malignant Causes:

- Polycythemia Vera (95% of cases have a JAK2 V617F mutation)
- EPO producing tumors

Question 13

A 28-year-old man with no significant past medical history presents with several weeks of worsening fatigue and dark urine. On exam, he is tachycardic (130 beats/min), tachypneic (24/minute), and jaundiced. His CBC shows:

White blood cell count	9,800/mm^3	(4,000-10,000)
Hematocrit	12%	(36-48)
Platelets	430,000/mm^3	(150,000-450,000)
MCV	106 fL	(80-100)

The peripheral blood smear shows numerous spherocytes and his Direct Coombs (DAT) is positive for IgG. His antibody screen is reactive to all cells tested. The blood bank says that it may be 4-6 hours before a fully compatible cross-match unit is available.

Question 13

In addition to supportive care with folic acid and initiation of corticosteroids, which of the following is the next appropriate step in management:

A. Transfusion of emergency release AB-negative red cell units until fully crossmatched compatible red cell units are available

B. Transfusion with the least incompatible type-specific red cell units

C. Observation until fully compatible type-specific red cells units are available

D. Red cell exchange transfusion with concurrent plasmapheresis

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AUTOIMMUNE HEMOLYTIC ANEMIA – BRIEF TAKE AWAY NOTES

- Due to antibody-mediated destruction of red cells leading to shortened RBC survival
- Compensation by the bone marrow (elevated retic count)
- Treatments include:
  - Corticosteroids
  - Rituximab
  - Supportive Care: Folic Acid, Transfusion support

TAKE HOME MESSAGES

- Hematology encompasses a lot of disorders and thank you for your time.
- Have a wonderful dinner and evening!

References

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