Bleeding and Platelet Disorders

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History of bleeding: ask patient about bleeding (particularly after surgery, including minor procedures) to determine hemorrhagic status; includes type of bleeding, age of onset, patient’s sex, family history, drugs taken (e.g., antiplatelet drugs), nutritional status (e.g., vitamin K), and comorbid conditions that increase risk of bleeding

Laboratory evaluation: begins with general screening (e.g., platelet count, peripheral blood smear, coagulation screen); if results abnormal, perform mixing study using 50% plasma from patient and 50% normal plasma (determines presence of inhibitor or deficiency of factor); interpretation of tests of platelet function difficult; results correlate with bleeding history; platelet function screen or test of platelet closure time replaces test of skin bleeding time; platelet aggregation test and flow cytometry used to diagnose qualitative platelet disorder; fibrinolytic tests assess defects that increase risk of bleeding; perform specific factor assays if results of coagulation screen abnormal

Idiopathic thrombocytopenic purpura (ITP): incidence higher in women than men; includes primary ITP (no underlying disease) and secondary ITP (other illness, medication, or infection present); normal or high levels of megakaryocytes found in bone marrow; diagnosis of exclusion; measuring platelet-associated IgG not useful because of passive absorption to platelets; resolves spontaneously in children and rarely without therapy in adults (<20%)

Thrombotic thrombocytopenic purpura (TTP): schistocytes present on peripheral blood smear; immune-mediated process involving ADAMTS13 metalloprotease inhibitor; ADAMTS13 — unable to cleave von Willebrand factor (VWF) and prevent its overactivity when antibody directed against it; cleavage sites on VWF present; VWF aggregates into multimers as it circulates; multimers adhere to damaged endothelium and bring in platelets to form initial plug; prevents VWF from exceeding its normal activity and causing increase in platelet activation (leading to thrombotic effects of TTP); management — plasma exchange

Antiphospholipid syndrome (APS): lupus anticoagulant (LAC) — antibodies that produce phospholipid-dependent prolongation of coagulation assays; phospholipid cofactors for binding antibodies to variety of antigens (e.g., β2-glycoprotein I); diagnosis — thrombotic event or fetal loss and laboratory evidence of antiphospholipid antibodies or LAC; guidelines recommend testing twice, with 12-wk interval (antibodies transient); catastrophic APS — multiorgan system failure; morbidity and mortality rate high; LAC (continued) — idiopathic or associated with other disorders (e.g., connective tissue disorders, lymphoproliferative diseases, drugs, infection); thrombotic condition in majority of cases; may be associated with deficiency in prothrombin or thrombocytopenia; management — study found increasing anticoagulation with warfarin does not increase efficacy and increases risk of bleeding; American College of Chest Physicians recommends 3-mo therapy for first episode of unprovoked thrombosis; role of aspirin unclear; dual therapy indicated (international normalized ratio in normal therapeutic range)

von Willebrand disease (VWD): type 2 defects qualitative (types 1 and 3 quantitative); qualitative differentiated from quantitative defects by levels of VWF antigen, factor VIII (FVII), and ristocetin cofactor; if decrease in all levels similar, diagnosis most likely type 1 VWD (≥70%); desmopressin (DDAVP) given to patients with type 1 VWD who undergo surgical procedures; DDAVP challenge test — levels of VWF antigen, FVII, and ristocetin cofactor increase after administration of DDAVP (release of VWF and FVIII from storage sites in endothelial cells stimulated)

Heparin-induced thrombocytopenia: typical develops 5 to 10 days after initiation of heparin therapy; decrease in platelet count ≥50%; return to normal platelet count 4 to 5 days after withdrawal of heparin; thrombosis can occur at any platelet count and with administration of any type of heparin (incidence with low-molecular-weight heparin [enoxaparin] lower and with fondaparinux, very low); diagnosis — pretest probability score based on degree of thrombocytopenia, timing, presence of thrombosis, and other causes; presence of antibodies demonstrated by heparin-platelet factor 4 enzyme-linked immunosorbent assay or Serotonin Release Assay; treatment — avoid delay if patient fits clinical criteria (do not rely on laboratory confirmation); discontinue heparin; administer direct thrombin inhibitor (DTI; eg, argatroban, bivalirudin); avoid warfarin until platelet count recovers; then overlap with DTI; avoid enoxaparin or dalteparin (cross-reactivity) and platelet transfusion (increases thrombotic potential)

Suggested Reading
Baquero-Salamanca M et al: Variability in the international normalised ratio (INR) in patients with antiphospholipid syndrome and positive lupus

Educational Objectives

The goal of this program is to improve the diagnosis and management of bleeding and platelet disorders, anemia, and Hodgkin and non-Hodgkin lymphomas. After hearing and assimilating this program, the clinician will be better able to:

1. Diagnose platelet and bleeding disorders using patient history and laboratory test results.
2. Manage common coagulation and platelet disorders.
3. Determine the cause of, and provide optimal treatment for, anemia.
5. Recognize the indications and contraindications for drugs used in the treatment of non-Hodgkin lymphoma.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing relevant to disclose.

**Anemia**

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**Diagnosis:** anemia symptom (not diagnosis); mean corpuscular volume diagnostic of some types of anemia; reticulocyte count reflects response of bone marrow (BM)

**Normocytic Anemia**

**Cause:** in majority of cases, abnormality in BM

**Aplastic anemia (AA):** majority of cases idiopathic; drug-induced AA—causative agents include nonsteroidal anti-inflammatory drugs; management includes transfusion of red blood cells and platelets, culturing, antibiotics, and discontinuation of offending agent; some drugs and toxins cause AA based on dose; others idiosyncratic (eg, chloramphenicol); other causes — viral infection; underlying disease (eg, paroxysmal nocturnal hemoglobinuria); management — discontinuing offending agent; if AA persists in patients aged >40 yr, administer antithymocyte globulin with cyclosporine and steroids; if patient aged <20 yr, BM transplantation recommended

**Anemia due to myelophthisic disorders:** causes include leukemia, lymphoma, myeloma, metastatic cancer, infections, and lysosomal storage diseases (eg, Gaucher disease)

**Pure red cell aplasia:** associated with thymoma, lymphoproliferative disorders, collagen vascular disorders, systemic lupus erythematosus, and parvovirus B19 infection

**Anemia of renal failure:** managed with erythropoietin; elevated hemoglobin levels due to excess administration can result in stroke, heart attack, and venous thromboembolic disease

**Anemia of endocrine disorders:** hypothyroidism, and hypopituitarism

**Anemia of chronic disease:** associated with low iron level, total iron-binding capacity, and percent saturation and normal or high ferritin level; occurs in inflammatory and neoplastic conditions and infections; manage underlying disease

**Macrocyclic Anemia**

**Vitamin B12 deficiency:** low levels of intrinsic factor (IF) can result in poor absorption of vitamin B12; administration of folate acid initially to vitamin B12-deficient individual can worsen neurologic state; deficiency occurs in absence of intact terminal ileum and stomach, strict ovo-lacto vegetarians, and individuals with pernicious anemia, gastrectomy or gastric bypass surgery, terminal ileal disease (eg, Crohn disease, carcinoid tumors, radiation enteritis, resection), and fish tapeworm infection; patient may develop immune reaction against parietal cells (antibodies against IF, antiparietal cell antibodies, and cell-mediated immunity); any disease or substance that reduces amount of stomach acid or production of IF can cause pernicious anemia; neurologic syndrome develops; dropout in dorsolateral column of spinal cord leads to ataxic gait, poor proprioception, and dementia; vitamin B12 stores thousand times daily requirement (deficiency develops over years)

**Folic acid deficiency:** causes include malabsorption (eg, celiac disease) and alcoholism; decreased intake causes deficiency state in weeks; folic acid absorbed in jejunum

Myelodysplasia: previous term preleukemia; often macrocytic; refractory anemia; refractory anemia with ringed sideroblasts; chronic myelomonocytic leukemia; refractory anemia poor risk (depends on chromosomal variant); incidence in older individuals increased

**Other causes of macrocytosis:** alcohol and drug use (eg, methotrexate, azathioprine)

**Microcytic Anemia**

**Causes:** iron deficiency; thalassemia; sideroblastic anemia

**Iron deficiency:** causes include blood loss in gastrointestinal tract, menstrual blood loss, pregnancy and lactation, and malabsorption

**Thalassemia:** chromosome 16 has 2 α-globin chains and chromosome 11, one β-globin chain; patients with β-globin chain abnormalities usually present early or have more symptoms; individuals who lose one α-globin chain can live normal lives (may be microcytic or anemic); sickle cell disease managed by increasing production of fetal hemoglobin; may cause life-long hypochromic microcytic anemia; major, intermediate, and minor categories based on disease severity; sickle cell anemia hemoglobinopathies (β-globin locus; substitution at 6-position)

**Hemolytic Anemia**

**Causes:** defects intrinsic to red blood cells (eg, enzymopathies, hemoglobinopathies) or membranes (eg, hereditary spherocytosis or elliptocytosis); cold agglutinin disease often precursor to lymphoproliferative disorders; living in warm climate helpful; warm autoimmune hemolytic anemias may be associated with drugs or underlying lymphoproliferative disorders or be idiopathic

**Suggested Reading**


**Lymphomas**

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**Hodgkin Lymphoma (HL)**

**Diagnosis:** diagnostic yield increased using excisional biopsy of lymph node; fine-needle aspiration inadequate

**Pathophysiology:** Reed-Sternberg cells (RSCs; derived from precursor B cells) classic finding; CD30 present on Hodgkin cells and in anaplastic large T cell lymphoma (anti-CD30 antibody given every 3 wk on outpatient basis); lymphocytes around Hodgkin cell combination of B and T cells and express programmed cell death 1 (PD-1); nivolumab (Opdivo) approved to treat relapse (reawakens immune system to attack RSCs); brentuximab and PD-1 inhibitors active in HL

**Clinical presentation:** any age; some survive 40+ yrs; stage I, few higher; patients asymptomatic; pruritus not considered B symptom (prognosis unchanged; relationship to HL clear); incidence of B symptoms low (eg, fever, night sweats, unexplained weight loss)

**Staging:** determined by positron emission tomography and biopsy of bone marrow (BM); lesions on spleen affect stage and prognosis; stage affects management and prognosis (management of stages I and II and stages III and IV similar); in stage I, one lymph node group involved; stage II, ≥1 (all above or all below diaphragm); stage III, ≥1 (all below and above
diaphragm), but no extranodal sites; stage IV, extranodal sites (incidence highest in BM; low in liver)

Treatment: majority of patients cured; in patients with stage I or II HL, goal to minimize treatment; standard course for advanced-stage disease 6 cycles of chemotherapy with doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (DTIC; ABVD); early stages — patient may receive only 2 cycles with radiation therapy (RT) to small areas or 4 cycles without RT; stages III and IV — relapse rates significant; management 6 cycles of ABVD; long-term adverse effects of ABVD — delayed cardiomyopathy (doxorubicin); pneumonitis (bleomycin, especially if patient underwent radiation therapy); peripheral neuropathy (vinblastine); alkylating agents (eg, DTIC); can cause acute myeloid leukemia within first 7 yr; effects of RT — can occur ≤20 yr after therapy; hypothyroidism, second cancer (eg, breast cancer in patients aged <30 yr when irradiated), cardiomyopathy, and pneumonitis

Prognosis: cure rate in early stage ≥90%; in advanced stage ≥60%; in relapse after stem cell transplantation ≥50%; age, performance status, and extent of disease predict prognosis

Complications: infection (possible years after treatment); incidence of shingles high, but patients should not receive herpes zoster vaccine because of immunosuppression; premature menopause and infertility; secondary malignancies; patients monitored primarily in first 3 yr

Non-Hodgkin Lymphoma (NHL)

Characteristics: growth slow; CD19, CD20, and immunoglobulins expressed; CD3 (T cell marker) not expressed; incidence increases with age

Clinical presentation: majority of cases asymptomatic; liver, BM, and stomach most common extranodal sites; cytopenia (involvement of BM); for low-grade lymphoma, length of survival long (average 10 yr), but condition not curable; in patients with aggressive lymphoma, early progression followed by plateau; goal to cure (cure rate >50%)

Indolent NHL: ≥50% of NHL; incidence of follicular lymphoma highest; origin B cells; transformation to more aggressive lymphoma possible; incurable; median length of survival 10 to 20 yr; rituximab plus chemotherapy prolongs length of survival; goals of treatment — alleviate symptoms; improve cytopenia; prevent complications; prolong length of survival; for non-cytopenic and asymptomatic patients with low-grade NHL, expectant observation recommended; by 10 yr, ≥20% have not had treatment; rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), and prednisolone (R-CHOP) — previously used to manage all NHL; can cure aggressive NHL, but not indolent NHL; has numerous adverse effects; rituximab and bendamustine — replaced R-CHOP as standard treatment; toxicity lower; efficacy higher

Aggressive NHL: ≥50% of NHL; goal of treatment cure (without cure, death occurs in 1-2 yr); majority cases advanced stage at diagnosis; treatment — R-CHOP standard; stem cell transplantation indicated in young healthy patient with relapse; performance status important in prognosis

New drugs: B cell receptor signaling inhibitors (eg, ibritumide, idealsisib) and apoptosis promoter (venetoclax) recently approved (oral drugs); ibritumide — antiplatelet agent; contraindicated in patients who take warfarin (and possibly other anticoagulants); can induce atrial fibrillation; interacts with azoles; administered for years (until disease progression or toxicity occurs); idealsisib — blocks PI3-kinase δ (specific to lymphocytes); adverse effects include transient hepatitis and pneumonitis (at >6 mo); venetoclax — blocks BCL2; causes tumor lysis within first month; effective; deaths found in early studies; administered for years

Suggested Reading


Acknowledgments

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Estimated time to complete the educational process:

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
1. Which of the following features is diagnostic of idiopathic thrombocytopenic purpura?
   (A) Increase in number of megakaryocytes in the bone marrow
   (B) Absence of splenomegaly
   (C) Positive findings on testing for platelet-associated IgG
   (D) None of the above

2. Which of the following is the treatment of choice for patients with thrombotic thrombocytopenic purpura?
   (A) Administration of corticosteroids
   (B) Transfusion of platelet concentrate
   (C) Plasma exchange
   (D) Administration of thrombopoietin receptor agonists

3. Which of the following is the most appropriate initial treatment for heparin-induced thrombocytopenia?
   (A) Direct thrombin inhibitor
   (B) Warfarin
   (C) Low-molecular-weight heparin
   (D) Platelet transfusion

4. Which of the following conditions cause normocytic anemia?
   1. Renal failure
   2. Endocrine disorders
   3. Chronic diseases
   4. Myelodysplasia

5. Terminal ileal disease (eg, Crohn disease) is associated with deficiency of _______; this deficiency typically develops over _______.
   (A) Folic acid; weeks
   (B) Vitamin B₁₂; weeks
   (C) Folic acid; years
   (D) Vitamin B₁₂; years

6. Iron deficiency, thalassemia, and sideroblastic anemia can cause which of the following conditions?
   (A) Normocytic anemia
   (B) Macrocytic anemia
   (C) Microcytic anemia
   (D) Hemolytic anemia

7. All the following are B symptoms associated with Hodgkin lymphoma, EXCEPT:
   (A) Pruritus
   (B) Fever
   (C) Night sweats
   (D) Weight loss

8. Which stage of Hodgkin lymphoma is characterized by the involvement of lymph node groups above and below the diaphragm but no extranodal sites?
   (A) Stage I
   (B) Stage II
   (C) Stage III
   (D) Stage IV

9. The treatment goal for a patient with aggressive non-Hodgkin lymphoma (NHL) is _______; this subtype accounts for _______ of NHL.
   (A) Palliation; ≈20%
   (B) Cure; ≈20%
   (C) Palliation; ≈50%
   (D) Cure; ≈50%

10. Which of the following drugs used to treat non-Hodgkin lymphoma promotes apoptosis?
    (A) Ibrutinib
    (B) Idelalisib
    (C) Venetoclax
    (D) Rituximab

Answers to Audio Digest Internal Medicine Volume 64, Issue 07: 1-B, 2-D, 3-A, 4-C, 5-D, 6-A, 7-C, 8-A, 9-C, 10-D