7

Hematologic Disorders

■ I. ANEMIA

A. Definition. Anemia is defined as an absolute decrease in the circulating red blood cell (RBC) mass.

B. Etiology
   1. Decreased RBC Production
      a. Deficiency of hematinic agents (i.e., iron, vitamin B_{12}, folate)
      b. Bone marrow failure
   2. Increased RBC Destruction or Loss
      a. Hemolysis
      b. Hemorrhage

C. Diagnostic Evaluation. The approach to the anemic patient in the intensive care unit (ICU) will differ depending on whether the patient was admitted with anemia or if the anemia has developed during the ICU stay.
   1. In the Patient Admitted With Anemia
      a. The symptoms of anemia will depend on the degree of anemia, the rapidity of development, cardiopulmonary reserve, and underlying disease.
      b. As a general rule, a hemoglobin <7 g/dL represents severe anemia, and such patients may present with dyspnea on exertion, lightheadedness, angina, and/or fatigue.
      c. The absence of symptoms in patients with hemoglobin <7 g/dL suggests a gradual onset.
   2. History
      Inquire about previous hematologic values, family, and ethnic history (i.e., sickle cell, thalassemia), history of splenectomy, cholelithiasis at an early age, medications, drugs, alcohol use, dietary habits, gastrectomy, and bleeding history.
   3. Physical Examination
      a. General Appearance: Nutritional status or evidence of specific deficiencies, evidence of chronic illness.
      b. Vital Signs: Tachycardia, postural hypotension, other signs of hypoperfusion (i.e., decreased mental status, low urine output), petechiae, purpura.

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c. Associated Findings: Jaundice, glossitis (i.e., pernicious anemia, iron deficiency), neurologic abnormalities (i.e., vitamin B_{12}, folate deficiency). Lymphadenopathy, hepatomegaly, splenomegaly (i.e., hemolysis, neoplasms, infiltrative disorders). Heart: Listen for flow murmurs, prosthetic valves (i.e., increased RBC destruction). Rectal: Examine stools for blood.

4. Laboratory Evaluation
   Laboratory evaluation usually provides a diagnosis and should always be done in a stepwise manner unless the patient's condition requires emergent transfusion. In this case, a blood sample for RBC indices, peripheral blood smear, and iron, folate, and vitamin B_{12} studies should be obtained before transfusion.
   a. Hemoglobin and hematocrit (Hct) estimate RBC mass and severity of anemia, and in the patient suspected to have active bleeding, they should be monitored serially. Acute blood loss does not influence the Hct immediately.
   b. Mean corpuscular volume (MCV) is a measure of the average size of the RBCs. Classification of the anemia according to the MCV is helpful in generating the differential diagnosis and workup. The smear must be examined to determine whether multiple cell populations are present.
      (1). Low MCV (<80): Generally limits the diagnosis to a few disorders: Iron deficiency, thalassemia, sideroblastic anemia, other hemoglobinopathies, and some cases of anemia of chronic disease.
      (2). High MCV (<100): Megaloblastic anemias, liver disease, alcoholism, drugs (i.e., methotrexate, AZT), and myelodysplastic syndrome.
      (3). Normal MCV: Acute blood loss, hemolytic anemia, pituitary or thyroid failure, aplastic anemia, myelofibrosis, and anemia of chronic disease.
   c. Reticulocyte count is also essential in the evaluation of the anemic patient. It reflects the rate of production of RBCs by the bone marrow. According to the reticulocyte count, anemia can be classified into
      (1). Increased RBC destruction (i.e., bleeding, hemolysis) reflected in a high reticulocyte count
      (2). Decreased RBC production (i.e., iron deficiency, anemia of chronic disease) reflected in an abnormally low reticulocyte count
5. Bleeding should be the first concern in patients who develop anemia while in the ICU. Common sites of bleeding are the gastrointestinal (GI) tract, venipunctures, pulmonary tree, genitourinary tract, and the retroperitoneum. Development of anemia in the ICU should prompt additional investigation (i.e., gastric aspiration to look for blood, stools checked for gross or occult blood, prothrombin time [PT], partial thromboplastin time [PTT], and platelet count).

D. Therapy
1. Patient Acutely Bleeding
   a. General Measures
      (1). Airway management: Assess the need for intubation to prevent aspiration, especially in upper GI bleeding.
      (2). Obtain adequate venous access. Large-bore peripheral catheters allow greater volume administration rates than long central lines.
      (3). Obtain blood for type and cross and diagnostic laboratories, as discussed above.
      (4). Fluid resuscitation: Start with colloids or crystalloids, and continue with whole blood or packed red blood cells as required:

(a). Healthy adult patients can tolerate blood losses up to 20–30% of their blood volume if adequate replacement with crystalloid is provided.
(b). Patients with impaired cardiac reserve, coronary artery disease, or the elderly can develop symptoms with a decrease of about 10% of their blood volume.
(5). Identify the source of bleeding.
(6). Monitor endpoints: Patients with acute bleeding should be closely monitored in the ICU for two goals:
(a). Adequate blood volume replacement: reflected in vital signs, urine output, mental status, central venous pressure (CVP), etc.
(b). Control of bleeding: Follow serial hemoglobin (Hb) and Hct, monitor the bleeding site (GI, genitourinary [GU], etc.).
b. Specific measures will depend on the cause of the bleeding.
2. Patient Not Acutely Bleeding
a. The therapy of anemia will depend on its etiology.
b. A specific hemoglobin concentration should not be used as the only parameter to decide on the need for transfusion. Transfusion of red cells is usually not necessary in patients with either chronic stable anemia or anemia of acute blood loss unless the patient is symptomatic. Patients with chronic anemia, with hemoglobin levels >7 g/dL rarely require blood transfusion, unless cardiopulmonary or cerebrovascular disease is present.
c. The use of erythropoietin/darbepoetin in selected populations (i.e., chronic kidney disease) may be advantageous, if such patient remains the in ICU for several days.

■ II. LEUKOPENIA

A. Definitions. Leukopenia is defined by blood leukocyte count below the normal range (in our laboratories <3,800/μL). Neutropenia is defined as absolute neutrophil count <2,000/mL for white patients, and below 1,500/mL for patients who are black or are Yemenite Jews. Lymphopenia is defined as an absolute lymphocyte count <1,500/μL.

B. Etiology
1. Neutropenia (see Table 7.1)
2. Lymphocytopenia (see Table 7.2)

C. Diagnostic Evaluation
1. History
a. Ethnic background: black, Yemenite Jew
b. Family history: Congenital or hereditary defect
c. Medications: Chemotherapeutic agents, antibiotics, etc.
d. Alcohol and dietary history
e. Diet habits: Nutritional deficiency (B_{12}, folate)
f. Underlying illness: Malignancies, human immunodeficiency virus (HIV)
2. Physical Examination
a. General Appearance: Acute distress, mental status, evidence of chronic illness
b. Vital Signs: Fever, hypotension, tachycardia, tachypnea, low urine output (e.g., sepsis)

Table 7.1. Neutropenia: Etiology

False decrease in white blood cells	Counts done long after blood has been drawn
	Disintegration of fragile cells (i.e., blasts, immature white blood cells)
	Presence of paraproteins (monoclonal gammopathies), which can produce white blood cell clumping
Decreased production	Bone marrow injury due to ionizing radiation or drugs
	Bone marrow replacement or destruction by tumor or infection
	Nutritional deficiencies: Vitamin B_{12}, folate
	Congenital stem-cell defects
Increased neutrophil destruction, utilization, sequestration	Hypersplenism Autoimmune Sepsis
Combination (increased destruction and decreased production)	Sepsis Antineutrophil antibodies Drugs Felty's syndrome

Table 7.2. Lymphocytopenia: Etiology

Decreased production	Primary immunodeficiency diseases (HIV)
Increased destruction, utilization, loss	Collagen vascular diseases Acute infections or stress Ionizing radiation Cytotoxic drugs
Unknown mechanisms	Malignancies Chronic infection

c. Associated Findings: Hepato- or splenomegaly, lymphadenopathy, abdominal masses, oral thrush, skin rash, purpura, jaundice, etc.

3. Laboratory Evaluation
   a. Complete blood count and differential (CBC) to assess the degree and type of leukopenia.
   b. Bone marrow aspiration and biopsy are pivotal in the evaluation of the leukopenic patient without obvious cause. Analysis of the bone marrow

(1). Will classify the leukopenia, by revealing the degree of bone marrow cellularity: decreased production, decreased survival, or a combined defect

(2). May indicate the etiology of the leukopenia as in aplastic anemia, bone marrow infiltration (e.g., leukemia), infection, etc.

c. Other laboratory tests that may help in identifying the cause of leukopenia are blood and tissue cultures, vitamin levels, and autoantibodies.

4. Therapy

The mainstay of therapy for the leukopenic patient is to treat the underlying disease. For example, in the patient with suspected drug-induced leukopenia, the offending medications should be discontinued. Vitamin deficiency should also be treated when suspected.

a. Colony-stimulating factors (G-CSF and GM-CSF) represent a line of therapy for the treatment of leukopenia secondary to a decrease in bone marrow production.

b. Transfusions of white blood cell (WBC) concentrates have not been proven to be of benefit in many controlled trials

c. Supportive therapy for the leukopenic patient requires special consideration, particularly in the ICU environment, where there is a higher risk for nosocomial infections:

(1). Granulocyte counts <1,000/μL result in severe immunocompromise.

(2). Patients who are immunocompromised should not receive rectal manipulations. Strict hand washing for caregivers should be enforced. Avoid intramuscular (IM) or subcutaneous (SQ) routes.

(3). If the temperature rises >100.5°F (38.5°C), the patient should be fully examined, pan-cultured, and started on broad-spectrum antibiotics.

■ III. THROMBOCYTOPENIA

A. Definition. Thrombocytopenia is defined as a platelet count <150,000/pL.

B. Etiology (see Table 7.3)

C. Diagnostic Evaluation

1. History

Inquire about bleeding, thrombotic events, mental status changes, alcohol use, drugs and medications, and associated illness.

a. Heparin-induced thrombocytopenia

More common with the use of unfractionated heparin (UFH) rather than low molecular weight heparin (LMWH). More common among surgical rather than medical patients.

2. Physical Examination

a. Vital Signs: Fever, tachycardia, hypotension, tachypnea, oliguria (i.e., sepsis)

b. Skin: Purpura, hematomas, gingival bleeding, lymphadenopathy, hepato- or splenomegaly, abdominal masses

3. Laboratory Evaluation

a. Complete Blood Count and Platelet Count

(1). Platelet counts >50,000/μL in isolation are not associated with significant bleeding problems, and severe spontaneous bleeding is unusual in patients with counts >g20,000/μL in the absence of coagulation factor abnormalities.

Table 7.3. Thrombocytopenia: Etiology

Decreased survival or sequestration	Autoimmune—Primary (ITP); Secondary: collagen vascular disease (SLE); viral infections; drug-induced (heparin, quinidine, sulfas); post-transfusion Hypersplenism (portal hypertension, infiltrative disorders) Thrombotic thrombocytopenic purpura (TTP/HUS) Disseminated intravascular coagulation Sepsis
Decreased production	Primary bone marrow disorders (aplastic anemia, primary thrombocytopenia) Bone marrow infiltration by tumor, infection, etc. Drug induced (alcohol, thiazides, alkylating agents) Infection
Developed while in ICU	Drug-induced (heparin, H_2-blockers, diuretics, antibodies) Disseminated intravascular coagulation Sepsis Post-transfusion

Abbreviations: HUS, hemolytic uremic syndrome; ITP, idiopathic thrombocytopenic purpura; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

(2). Thrombocytopenia associated with anemia suggests thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), or other microangiopathic process.

(3). Pancytopenia should suggest leukemia, aplastic anemia, or other bone marrow disorder.

b. Peripheral Blood Smear: Note platelet size and other abnormalities (i.e., fragmented RBCs may indicate TTP or DIC; increased platelet size suggests accelerated destruction).

c. Coagulation Evaluation: PT, PTT, D-dimer, fibrin degradation products may indicate the presence of consumption coagulopathy (e.g., DIC).

d. Bone Marrow Aspiration and Biopsy (not always necessary): To assess the number of megakaryocytes and the presence of bone marrow disorders (i.e., leukemia, aplastic anemia, tumor infiltration).

e. For patients with suspected heparin-induced thrombocytopenia 14C-serotonin release assay remains the gold standard. Heparin-induced platelet aggregation tests can also be used as well as the solid phase ELISA immunoassay.

4. Therapy
   Detailed treatment for the various causes of thrombocytopenia is beyond the scope of this chapter. We will concentrate on relevant topics for the acute management of patients in ICU setting.
1. As hemostasis approaches normal at platelet counts >50,000/μL, patients with active bleeding should be transfused (6–10 U) to attempt to achieve levels >50,000/μL.
2. Lumbar puncture and needle organ biopsies (lung, liver, kidneys, etc.) are more hazardous than thoracentesis, paracentesis, and bone marrow biopsy. Transfusion to 50,000/μL before such procedures is indicated.
3. Patients with platelet counts <20,000/μL are at higher risk for hemorrhage. However, there is no clear threshold for prophylactic platelet transfusion.
4. Discontinue all nonessential medications including heparin. Consider changing H_2-blockers to coating agents or antacids. Avoid agents known to inhibit platelet function (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs], ticarcillin, etc.).
5. Avoid trauma, IM and SQ injections, rectal manipulations, hard toothbrush, razors, etc. in thrombocytopenic patients.
6. TTP and HUS deserve special consideration because their management differs.
   a. TTP is a syndrome characterized by microangiopathic hemolytic anemia, fever, fluctuating neurologic deficits, and renal insufficiency. HUS is felt to be a variant of this syndrome in which renal failure is the predominant feature. TTP/HUS should be considered a medical emergency.
   b. Patients with TTP/HUS should not receive platelet transfusions, unless life-threatening bleeding occurs.
   c. Therapy for TTP/HUS includes plasma exchange by plasmapheresis if available, otherwise fresh-frozen plasma (FFP) transfusions. Intravenous (IV) steroids can be used, and in unresponsive cases, vincristine has been recommended.
   d. Heparin-induced thrombocytopenia: The first maneuver is to stop all heparin and heparin-containing products (i.e., heparin-flush). There are a number of alternative anticoagulants to heparin in these patients, such as direct thrombin inhibitors like lepirudin [recombinant hirudin], bivalirudin, or argatroban; fondaparinux; or danaparoids.

■ IV. ANTICOAGULATION AND FIBRINOLYSIS

Anticoagulants and thrombolytic agents are potentially life-saving drugs when used prophylactically or employed therapeutically in critically ill patients.

A. Anticoagulation
   1. Heparin
      a. Mechanism of Action
         Heparin acts by potentiating the activity of the plasma protease inhibitor antithrombin III, which rapidly inhibits the activity of factors XII_a, XI_a, X_a, IX_a, and thrombin (factor II).
      b. Heparin prolongs the thrombin time (TT), bleeding time, PTT, and to a lesser extent the PT.

c. Heparin half-life is 1–3 h, but in patients with pulmonary embolism, clearance is accelerated (20–40%) compared to normals.
d. Indications
   (1). Prophylaxis of deep venous thrombosis (DVT) and pulmonary embolism (PE). All patients in the ICU should be on some form of DVT prophylaxis (commonly, heparin 5,000 U SQ q12 h or low molecular dose heparin (e.g., enoxaparin 40 mg SQ qd). Heparin has proved to be an effective agent in DVT prophylaxis, except after major orthopedic procedures (particularly hip and knee replacement) and after prostate surgery.
   (2). Full anticoagulation (PTT approximately 2 times normal) in pulmonary embolism or DVT, arterial thrombosis, and other disorders. A 5,000–8,000 U IV bolus is commonly used and infusion rates of 1,000 U/h (12–25 U/kg/h).
e. Monitoring of Anticoagulation
   (1). Not required for prophylactic doses.
   (2). For full anticoagulation, the heparin dose should be adjusted to maintain the PTT at 1.5–2.0 times control. To avoid the tendency to under-anticoagulate patients on heparin therapy, a standardized dosing regimen has been developed (Table 7.4).
   (3). Low molecular weight heparin for DVT and acute coronary syndromes (ACS).
   Enoxaparin
   For DVT 1 mg/kg SQ q12 h or
   1.5 mg/kg SQ qd
   For ACS 1 mg/kg SQ q12 h
f. Complications
   (1). Bleeding: Occurs in 7–20% of patients during full-dose heparinization. Hemorrhage typically occurs from the GI, urinary tract, or surgical

Table 7.4. Standardized Protocol for Dosing of Intravenous Heparin

*PTT**	*Dose adjustment*†	*Repeat PTT*
<50	5,000-U bolus, increase infusion by 2,400 U/24 h	6 h
50–59	Increase infusion by 2,400 U/24 h	6 h
60–85	Therapeutic range, no change	Next morning
86–95	High therapeutic range, decrease infusion by 1,920 U/24 h	Next morning
96–120	Stop infusion for 30 min, decrease infusion by 1,920 U/24 h	6 h
120	Stop infusion for 60 min, decrease infusion by 3,840 U/24 h	6 h

* Normal PTT range is 27–35 s.
† Dosing protocol is based on an initial IV bolus of 5,000–8,000 U, followed by continuous infusion of 24,000 U/24 h. The first PTT should be obtained 6 h after the bolus of heparin.

incisions. Less common sites are intracranial, retroperitoneal, soft tissues, nose, and pleural space. Bleeding is associated with the intensity of the anticoagulation (e.g., when the PTT is more than 3 times normal, the risk of hemorrhage is substantially higher).

(2). Thrombocytopenia: Heparin use is associated with thrombocytopenia in 5–30% of patients, and its incidence is higher with the use of bovine lung heparin.

(a). If thrombocytopenia is mild (>100,000/μL), not associated with bleeding or thrombotic events, heparin therapy can be continued.

(b). Severe thrombocytopenia can occur but is rare. It may be associated with bleeding or paradoxic thrombotic events. Diagnosis is made by detection of heparin-dependent immunoglobulin G (IgG). Treatment consists of discontinuation of *all* heparin use and *avoid* platelet transfusion.

(3). Osteoporosis can be seen with long-term use of heparin.

(4). Hypoaldosteronism rarely is seen.

(5). Antidote: Heparin is generally undetectable in patient's plasma within 3 h after discontinuation of therapy. In the rare instance in which anticoagulation must be reversed more rapidly, protamine sulfate can be used.

2. Warfarin

Warfarin (Coumadin) is the most frequently used oral anticoagulant in the United States. Sometimes the transition to chronic oral therapy is begun before the patient leaves the ICU or must be initiated because of heparin-induced thrombocytopenia, or as DVT prophylaxis in certain cases. The physician caring for the critically ill can also encounter patients who have accidentally or purposely overdosed with warfarin.

a. Mechanism of Action: Warfarin interferes with the hepatic vitamin K-dependent carboxylation of factors II, VII, IX, and X. It also inhibits the synthesis of the anticoagulant factors protein C and S and may thereby be thrombogenic. The antithrombotic effects of warfarin occur only after several days of treatment. In patients on IV anticoagulation therapy, who require chronic oral anticoagulation, heparin and warfarin should be overlapped for at least 48 h.

b. Indications

(1). Prophylaxis of DVT and PE, especially in those patients in whom heparin has not proved to be effective

(2). For chronic anticoagulation therapy

c. Dosing

(1). Loading Dose: 5–10 PO qd for 2–4 days

(2). Maintenance Dose: 2–15 mg PO qd to keep INR (International standardized ratio) therapeutic

d. Complications

(1). Bleeding occurs in 2.4–8.1% of patients chronically anticoagulated. The risk is dose related and proportional to the prolongation of the PT. Treatment consists of FFP transfusions. Vitamin K replacement is only recommended for warfarin overdose, because of its delayed onset of action, and because it makes reinstitution of warfarin therapy complicated.

(2). Warfarin skin necrosis secondary to a paradoxic hypercoagulable state due to the warfarin-induced protein C reduction.

B. Fibrinolysis

1. Fibrinolytic therapy has an expanding role in the treatment of many thromboembolic disorders. Many fibrinolytic drugs are currently marketed: streptokinase (SK), anisoylated plasminogen-streptokinase activator complex (APSAC), urokinase (UK), recombinant human tissue-type plasminogen activator (rt-PA), reteplase, and TNK among others. All drugs activate the fibrinolytic system by converting plasminogen to the active enzyme plasmin. Plasmin degrades fibrin and dissolves the thrombus.
2. Indications
   a. Acute Myocardial Infarction (AMI): Thrombolytic therapy for AMI is discussed in Chapter 3, "Cardiovascular Disorders."
   b. Pulmonary Embolism: While the effectiveness and role of thrombolytic agents in AMIs are firmly established, their use in venous thromboembolism remains infrequent and controversial, mainly because of the fear of a negative benefit/risk ratio. SK, UK, and tPA have been shown to be more effective than heparin alone in accelerating clot lysis and improving pulmonary tissue perfusion. Current recommendations for the use of fibrinolysis in PE are for patients with massive pulmonary embolism and persistent systemic hypotension in whom rapid resolution of pulmonary obstruction is desired. It is still questionable if there is significant improvement to survival in those patients.
   c. Deep Venous Thrombosis: Even more debated is the use of thrombolytic agents in the treatment of DVT. Potential advantages of fibrinolysis over anticoagulation include prevention of PE by lysing the source of thrombus in situ, rapid restoration of normal venous circulation with a prompt resolution of symptoms, and prevention of valve damage, which would otherwise result in chronic venous insufficiency. Risks include a much higher incidence of bleeding.
3. Dosage for Selected Thrombolytic Regimens
   a. Pulmonary Embolism
      UK: 4,400 U/kg bolus, followed by 4,400 U/kg/h for 24 h
      UK: 15,000 U/kg bolus over 10 min
      SK: 250,000 U over 30 min, followed by 100,000 U/h for 24 h
      rt-PA: 100 mg as continuous peripheral infusion over 2 h
      Selective use of lysis in the pulmonary artery directed by catheter (the Varon-Strickman procedure) can also be used.
   b. Deep Venous Thrombosis
      SK: 250,000 U over 30 min, followed by 100,000 U/h for 48–72 h
      rt-PA: 0.5 mg/kg over 4–8 h
      rt-PA: 0.05 mg/kg/h for 24 h
   c. Myocardial Infarction (See Section III)
4. Monitoring
   a. Clinical monitoring should include serial neurologic examinations to detect central nervous system (CNS) bleeding and frequent vital signs to detect bleeding. All puncture sites should be examined frequently.
   b. Laboratory monitoring should include Hb/Hct, platelet, fibrinogen, PT, PTT.
5. Complications
   a. Bleeding: The greatest limitation of the thrombolytic drugs and the factor that has limited their acceptance for the treatment of DVT and PE is the incidence of bleeding.

b. Allergic Reactions: Reactions including skin rashes, fever, and hypotension are rare and usually are associated with the use of SK and APSAC. The induction of antibodies against streptococcal antigens can occur after the administration of SK or APSAC or after streptococcal infection, which may neutralize the fibrinolytic activity of SK.

■ V. BLOOD AND BLOOD PRODUCTS TRANSFUSION

Transfusion therapy may be associated with several immediate and delayed adverse effects. Therefore, risks and benefits must be carefully weighed before any blood product is administered. The use of blood components should be guided by a rational diagnostic and therapeutic approach.

A. Whole Blood. Whole blood stored >24 h contains few viable platelets or granulocytes; factors V and VIII are decreased, but stable clotting factors are maintained. One unit is 450 mL and transfused to an average-sized adult will increase the hemoglobin by 1.0 g/dL and Hct by 3%.
   1. Indications: Symptomatic anemia with massive hemorrhage
   2. Risks
      a. Allergic reactions
      b. Infectious diseases (i.e., HIV, hepatitis B)
      c. Febrile reactions
      d. Volume overload
      e. Noncardiogenic pulmonary edema

B. Packed Red Blood Cells. Removal of 200–250 mL of plasma from whole blood results in packed RBCs (PRBCs). Transfusion of 1 U of PRBCs will increase the Hb and Hct by the same amount as will 1 U of whole blood. One unit is 250–300 mL.
   1. Indications: Symptomatic anemia
   2. Risks: Same as for whole blood (see above).

C. Packed Red Blood Cells, Leukocyte Poor. Most of the WBCs are removed from the packed RBCs by saline washing.
   1. Indications
      a. Symptomatic anemia and allergic or febrile reaction from leukocyte antibodies
      b. Patients with paroxysmal nocturnal hemoglobinuria
   2. Risks
      Same as for whole blood (see above).

D. Fresh-Frozen Plasma. FFP is separated from freshly drawn whole blood and then frozen, with a volume of 200–250 mL. Rich in all coagulation factors; 1 mL supplies approximately 1 U of coagulation activity. FFP should be ABO compatible; Rh type or cross-matching is not required.
   1. Indications
      a. Bleeding due to coagulation factor deficiency
      b. Treatment of TIT and HUS
      c. Rapid reversal of vitamin K deficiency or warfarin overdose

2. Risks
   Same as for whole blood (see above).

E. Cryoprecipitate. Cryoprecipitate is made by thawing a unit of FFP at 4°C. A white precipitate forms; most of supernatant plasma is removed and refrozen. The volume is 10 mL. A pack of cryoprecipitate contains von Willebrand's factor, lesser amounts of factor VIII, fibrinogen, factor XIII, and fibronectin. ABO compatibility is preferred.
   1. Indications
      a. von Willebrand's disease
      b. Mild-to-moderate hemophilia A
      c. Factor XIII deficiency
      d. Fibrinogen deficiency
   2. Risks
      a. Infectious disease
      b. Hyperfibrinogenemia
      c. Allergic reactions

F. Platelets. Platelet packs are obtained from whole blood; 1 U contains at least 5.5×10^{10} platelets/mm^3 in approximately 50 mL volume. In a normal 70-kg adult, 1 U of platelets should increase platelet count by 5,000–10,000/mm^3.
   1. Indications
      a. To correct bleeding secondary to thrombocytopenia or abnormal platelet function
      b. Prophylactically (e.g., in patients with chemotherapy-induced thrombocytopenia, the threshold is somewhat controversial: 10,000–20,000/mm^3), and before invasive procedures (target counts of 50,000/mm^3)
   2. Risks
      a. Infectious diseases
      b. Allergic reactions
      c. Alloimmunization

G. Complications of Transfusion Therapy
   1. Disease transmission: HIV, hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), Chagas' disease, malaria.
   2. Allergic reactions characterized by fever, chills, urticaria, and respiratory distress. These events are secondary to antileukocytic antibodies or antibodies against antigenic proteins in donor plasma. Therapy is symptomatic (acetaminophen; antihistamines; rarely, epinephrine or glucocorticoids are needed).
   3. Red Cell Transfusion Related
      a. Acute Hemolytic Reactions: Fever, chills, back pain, nausea, vomiting, hypotension, dark urine, chest pain. Acute renal failure with hemoglobinuria and DIC may occur. If suspected
         (1). Inform the blood bank.
         (2). Stop transfusion.
         (3). Replace all IV tubing.
         (4). Send clotted and ETDA-treated blood samples from patient's blood along with the remainder of the unit of blood to the blood bank for cross-match.
         (5). Send blood samples for DIC screen, bilirubin, and free hemoglobin.

(6). Management
(a). Intravascular volume expansion plus mannitol to keep urine output >100 mL/h or 1 cc/kg/h.
(b). Alkalization of urine with IV bicarbonate to keep urine pH >7.0 to avoid hemoglobin tubular precipitation.
(c). Treatment of DIC

b. Delayed Hemolytic Transfusion Reactions: 24 h to 25 days post-transfusion. These are secondary to an amnestic (1–3 days) or primary (7–25 days) antibody response to RBC antigens. Patients usually develop a drop in the Hb and Hct with an increase in bilirubin. Coombs' test is positive.
c. Noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), caused by antileukocytic antibodies.
d. Coagulopathy associated with a large volume of PRBC transfusions, secondary to dilution of platelet and coagulation factors. Treatment consists of FFP and platelet transfusions.
e. Citrate intoxication, also seen with large-volume transfusion of PRBCs. Patients present with hypocalcemia, hypotension, and drop in cardiac output. Treatment: IV calcium.

4. Volume Overload: Especially in patients with congestive heart failure (CHF). Diuretics may be needed after transfusion.
5. Platelet alloimmunization develops in patients who have received multiple transfusions. Approximately 75% of patients receiving platelets on a regular basis will become alloimmunized to platelet antigens. Increments <20% of expected generally indicate alloimmunization. Patients may respond to single-donor platelets, but HLA-matched platelets may be needed.

■ VI. DISSEMINATED INTRAVASCULAR COAGULATION

A. Definition. Disseminated intravascular coagulation (DIC) is a dynamic pathologic process triggered by activation of the clotting cascade with resultant generation of excess thrombin within the vascular system. Most consider DIC to be a systemic hemorrhagic syndrome; however, this is only because hemorrhage is obvious and often impressive. What is less commonly appreciated is the significant amount of microvascular thrombosis and, in some instances, large-vessel thrombosis that occurs. This thrombosis is usually the more life-threatening insult.

B. Etiology (see Table 7.5)

Table 7.5. Disseminated Intravascular Coagulation: Etiology

Obstetric accidents (amniotic fluid embolism, abruptio placentae)
Intravascular hemolysis
Sepsis
Malignancy
Trauma
Vascular disorders

C. Diagnostic Evaluation. Since DIC is associated with an underlying disease state, the clinical evaluation will be directed toward identifying (1) primary illness; (2) the status of the coagulation system; and (3) the focal and systemic consequences of the DIC-associated hemorrhage and/or thrombosis.
   1. Clinical Findings Associated With the Primary Illness
      These findings will vary according to the precipitating event: obstetrical accident, infection, malignancy, etc.
   2. Clinical Findings Associated With the Coagulation Status
      a. Bleeding from venipuncture sites, mucous membranes, hemorrhagic bullae, hematuria, GI bleeding, etc.
      b. Purpura, petechiae, subcutaneous hematomas
   3. Clinical Findings Associated With End-Organ Thrombosis and Hemorrhage
      a. Lungs: respiratory distress, hypoxia, ARDS
      b. Kidneys: proteinuria, renal insufficiency
      c. Liver: Budd-Chiari syndrome, hepatitis, hepatic failure
      d. Skin: necrosis, acrocyanosis
      e. CNS: mental status changes, neurologic deficits
   4. Laboratory Evaluation
      a. Peripheral blood smear will show fragmented RBCs, thrombocytopenia, with large platelets.
      b. Prolonged PT and PTT.
      c. Thrombocytopenia is usually around 60,000/μL, but values ranging between 3,000 and 100,000/μL can be seen.
      d. Decreased fibrin level.
      e. Decreased anti-thrombin III level.
      f. Elevated levels of fibrin degradation products (FDP).
      g. Elevation of D-dimer neoantigens is a specific test for degradation products of fibrin, whereas nonspecific FDP may be either fibrinogen or fibrin derived.

D. Therapy. The treatment of DIC is confusing and still controversial. Therapy must be individualized according to the cause of DIC, severity of hemorrhage, severity of thrombosis, hemodynamic status, and age.
   1. The most important and effective treatment for DIC is removal of the triggering disease process (i.e., evacuate the uterus, control of shock, control of infection, removal of tumors, chemo- or radiotherapy, or other indicated therapy).
   2. In cases of obstetric complications, anticoagulation is rarely needed, and evacuation of the uterus usually stops the intravascular clotting process.
   3. If the patient continues to bleed or clot significantly after 6 h of initiation of therapy directed to stop or blunt the triggering event, anticoagulation therapy may be indicated. There is general agreement on the need for anticoagulation in acute promyelocytic leukemia and perhaps DIC with solid tumors. We favor the use of low-dose, subcutaneous heparin at doses of 80–100 U/kg q6 h. Other anticoagulant modalities available are IV heparin and anti-thrombin III concentrates.
   4. If the patient continues to bleed after reasonable attempts to treat the triggering event of the DIC, and if anticoagulation therapy has been initiated, clotting factor depletion is the most probable cause of bleeding and replacement therapy should be considered.
   5. The experimental use of thrombomodulin appears promising.

■ VII. HEMOLYTIC SYNDROMES

A. Definition. Premature destruction of red blood cells. This process may occur either because of abnormal factors in the intravascular environment or because of defective red blood cells.

B. Etiology (see Table 7.6)

C. Diagnostic Evaluation
1. History and Physical Examination
   Clinical manifestations will depend on the underlying disorder, on the severity of the anemia, and on whether the hemolysis is intravascular or extravascular.
   a. Intravascular hemolysis can present as an acute event with back pain, dyspnea, chills, fever, tachycardia, dark urine, and hypotension, and it may result in renal failure.
   b. Extravascular hemolysis is usually less dramatic and may be accompanied only by jaundice and splenomegaly.
2. Laboratory Evaluation
   a. Elevated reticulocyte count.
   b. Peripheral blood smear can provide a diagnosis in cases of spherocytosis; microangiopathic disorders will show the presence of fragmented RBCs; Heinz bodies suggest enzymatic defects; or the presence of anisocytosis or sickle cells is consistent with hemoglobinopathies.

Table 7.6. Hemolytic Syndromes: Etiology

Acquired haemolytic disorders	Immune hemolytic anemia Warm-antibody (idiopathic, neoplasia, collagen vascular disorder, drugs)
	Cold-antibody (idiopathic, *mycoplasma* infection, lymphoproliferative disorder, paroxysmal cold hemoglobinuria
	Microangiopathic hemolytic anemia (TTP, DIC, eclampsia)
	Direct toxic effect (malaria, clostridial infection)
	Splenomegaly Membrane defects Paroxysmal nocturnal hemoglobinuria Spur cell anemia
Hereditary hemolytic disorders	Membrane defects (spherocytosis, elliptosis)
	Enzyme defects (G_6PD deficiency) Thalassemias Hemoglobinopathies

c. Other laboratory data suggestive of hemolysis are
   (1). Hemoglobinuria (indicative of intravascular hemolysis)
   (2). Hemoglobinemia (indicative of intravascular hemolysis)
   (3). Low levels of haptoglobin
   (4). Elevated lactic dehydrogenase (LDH)
   (5). Positive Coombs' test

D. Sickle Cell Disease. Sickle cell disease is a heterogeneous group of defects of hemoglobin synthesis, all of which can cause clinically significant illness due to sickling of red cells. Sickle hemoglobin (Hb S) is less soluble when deoxygenated and forms polymers that precipitate inside the RBCs, leading to membrane abnormalities, decreased deformability, and increased blood viscosity.

1. Clinical Manifestations
   The clinical manifestations of sickle cell disease are secondary to vasoocclusive phenomena, which may lead to microinfarctions with resultant painful crises, and eventually, chronic organ damage.
2. Diagnosis
   Demonstration of sickling under reduced oxygen tension. Hemoglobin electrophoresis should be performed to discriminate homozygous SS from AS and to determine the presence of other abnormal hemoglobins.
3. Treatment
   The treatment of sickle cell disease is supportive and limited to management of acute and chronic complications. Frequently, these patients need to be admitted to the ICU due to the severity and life-threatening dimension of their acute attacks.
   a. Early antibiotic treatment at the first evidence of infection. Pneumococcal sepsis is a leading cause of mortality. Other prevalent pathogens include: *Escherichia coli, Haemophilus influenzae, Salmonella* sp., *Shigella* sp., *and Mycoplasma pneumoniae.*
   b. Painful crises: IV hydration; adequate analgesia (usually, a regular schedule of opioids is necessary); oxygen administration is indicated when hypoxemia is present; correction of acidosis.
   c. Look for precipitating events (i.e., infections, surgery, dehydration, trauma, cold temperatures, alcohol ingestion). When abdominal pain is one of the manifestations, other causes of abdominal pain must be ruled out (i.e., acute abdomen, hepatobiliary disease).
   d. Acute chest syndrome: Characterized by pleuritic chest pain, fever, cough, hypoxia, and pulmonary infiltrates. Lung scans and pulmonary angiograms are usually of no help. In addition, the latter test is associated with added risk because of possible induction of sickling by the hypertonic contrast media. Differentiation between pneumonia and infarction is often difficult. Features favoring infarction include painful bone crisis, clear chest radiograph at onset, lower lobe disease, and negative blood cultures. Treatment includes oxygen therapy, mechanical ventilation when indicated, empiric antibiotic therapy, and correction of acidosis.
   e. Sickle cell crisis associated with cerebrovascular accidents or repeated venoocclusive crisis may benefit from transfusion or exchange transfusion to keep the Hb S levels <39%.

E. Autoimmune Hemolytic Anemia

1. Warm-Antibody Autoimmune Hemolytic Anemia
   Warm-antibody autoimmune hemolytic anemia (AHA) is usually extravascular and IgG mediated. This type of hemolytic anemia can be seen in the ICU not

only in patients admitted with collagen vascular diseases or lymphomas but also in drug-induced hemolytic anemias.

a. Diagnosis is made by signs of hemolysis and positive direct Coombs' test.
b. Treatment
   (1). If the suspected mechanism is drug induced, all non-essential medications should be discontinued.
   (2). Sixty percent of cases will respond to steroid therapy (e.g., prednisone 1.0–1.5 mg/kg PO daily).
   (3). Splenectomy will increase the success rate to ≈80–90%.
   (4). Cytotoxic drugs are reserved for patients who fail to respond to steroid plus splenectomy.
   (5). Transfusions are indicated only in severe cases of anemia. In emergency situations, most patients can be managed with careful transfusion (ABO- & Rh-compatible blood) administered slowly while watching for reactions.

2. Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia (MAHA) is a syndrome caused by traumatic intravascular hemolysis. Intraluminal deposition of fibrin strands in small vessels is presumed to be responsible for the red cell destruction.

a. Etiology includes DIC, TTP, HUS, malignant hypertension, vasculitis, and eclampsia.
b. Diagnosis
   (1). Evidence of hemolysis (reticulocytosis, elevated LDH, depressed haptoglobin, etc.)
   (2). Fragmented RBCs in the peripheral blood smear
c. Treatment

   Therapy is directed toward the underlying disorder. Management of TTP, HUS, DIC is discussed elsewhere. Transfusion is rarely indicated.

3. Glucose-6-Phosphate Dehydrogenase Deficiency

This is a hereditary deficiency of the enzyme glucose-6-phosphate dehydrogenase deficiency (G-6PD) in the red cells. It is a sex-linked disorder that affects men and rarely women of Mediterranean, African, or Chinese ancestry. The disease is associated with episodic hemolysis.

a. Clinical Manifestations
   (1). Hemolytic episodes are sometimes triggered by infections or the ingestion of some drugs (e.g., sulfonamides, antimalarials, nitrofurantoin, nalidixic acid, etc.).
   (2). Patients present with acute intravascular hemolysis associated with hemoglobinemia, hemoglobinuria, decreased haptoglobin, and jaundice.
   (3). Peripheral vascular collapse can occur in severe cases.
   (4). Hemolysis is usually self-limited, even if the exposure to the oxidant agent continues, since only the older G-6PD-depleted population of RBCs is affected.
b. Diagnosis

   Definitive diagnosis requires measurement of levels of the enzyme. Diagnosis must be made several weeks after the episode, because enzyme levels can be normal during the hemolytic event due to the presence of high numbers of young red cells that are relatively rich in G-6PD.
c. Therapy
   (1). Transfusion therapy, as indicated.

(2). Protection of renal function during hemolytic episodes: IV hydration to maintain a good urine output, alkalinization of urine (to keep urine pH >7.0).
(3). Prevention of hemolytic episodes can be accomplished by identifying deficient individuals, treating infections promptly, and avoiding exposure to oxidant agents.

■ VIII. USEFUL FACTS AND FORMULAS

Patients in the ICU frequently have hematologic problems. These include anemia, coagulopathies, and thrombocytosis, to name just a few. In evaluation of these patients, many laboratory tests and indices are obtained. The following formulas will aid the critical care practitioner in evaluating these hematologic parameters:

A. **Red Blood Cells.** The *mean corpuscular volume* (*MCV*) indicates the average volume of a single RBC in a given blood sample and is calculated as follows:

$$\text{MCV} = \frac{\text{Hct}(\%) \times 10}{\text{RBC}(10^{12}/\text{L})}$$

The *mean corpuscular hemoglobin* (*MCH*) indicates the average weight of hemoglobin per erythrocyte:

$$\text{MCH} = \frac{\text{Hb(g/dL)} \times 10}{\text{RBC}(10^{12}/\text{L})}$$

The *mean corpuscular hemoglobin concentration* (*MCHC*) indicates the average concentration of hemoglobin in the RBCs of any specimen:

$$\text{MCHC} = \frac{\text{Hb(g/dL)}}{\text{Hct}(\%)} \times 100$$

The *red blood cell volume* can be calculated via a radionuclide study:

$$\text{RBC volume} = \frac{\text{cpm of isotope injected}}{\text{cpm/mL RBC in sample}}$$

where cpm = counts per million.

B. **Reticulocyte Counts**. To calculate the *percentage of reticulocytes,* usually based on counting 1,000 RBCs, the following formula is commonly utilized:

$$\text{Reticulocytes}(\%) = \frac{\text{Number of reticulocytes}}{\text{Number of RBCs observed}} \times 100$$

The *actual reticulocyte count* (*ARC*) reflects the actual number of reticulocytes in 1 L of whole blood:

$$\text{ARC} = \frac{\text{Reticulocytes}(\%)}{100} \times \text{RBC count } (\times 10^{12}/\text{L}) \times 1{,}000$$

The corrected reticulocyte count (CRC) is calculated as

$$\text{CRC} = \text{Reticulocytes } (\%) \times \frac{\text{Hct(L/L)}}{0.45\text{L/L}}$$

The reticulocyte count is usually viewed in relation to the degree of anemia. The *reticulocyte production index* (*RPI*) is a frequently used correction method:

$$\text{RPI} = \frac{(\text{Measured Hct/Normal Hct}) \times \text{Reticulocyte count}}{\text{Maturation time in peripheral blood}}$$

The *maturation factor* varies according to the hematocrit in the manner shown in Table 7.7.

A normal RPI is 1.0; an RPI of 3.0 or more represents adequate response of the marrow to anemia. An RPI of < 2.0 represents an inadequate response in the presence of anemia.

C. **Anemias**. The RBC indices (MCV, MCHC, MCH) are frequently utilized to classify anemias (see Table 7.8).

Table 7.9 depicts the laboratory differentiation of microcytic anemias.

D. **Hemolytic Disorders**. Table 7.10 depicts some of the common RISC morphologic abnormalities encountered in patients with *hemolytic disorders:*

Table 7.7. Maturation of Reticulocytes in Peripheral Blood

Hematocrit	*Maturation time in days*
0.41–0.50	1
0.30–0.40	1.5
0.20–0.39	2
0.10–0.19	2.5

Table 7.8. RBC Indices in Hypochromic and Microcytic Anemias

	MCV (fl)	*MCHC (g/dL)*	*MCH (pg)*
Normal	83–96	32–36	28–34
Hypochromic	83–100	28–31	23–31
Microcytic	70–82	32–36	22–27
Hypochromic-microcytic	50–79	24–31	11–29

Table 7.9. Differentiation of Microcytic Anemias

Abnormality	*Ferritin*	*Serum iron*	*TIBC*	*RDW*
Chronic disease	N/↑	↓	↓	N
Iron deficiency	↓	↓	↑	↑
Sideroblastic anemia	N/↑	↑	**N**	N
Thalassemia	N/↑	N/↑	N	N/↑

N = Normal; ↑ = increased; ↓ = decreased
Abbreviations: RDW, red cell distribution width; TIBC, total iron-binding capacity.

Table 7.10. RBC Morphologic Abnormalities in Hemolytic Disorders

Abnormality	*Hemolytic disorder*	
	Congenital	*Acquired*
Fragmented cells (schistocytes)	Unstable hemoglobins (Heinz body anemias)	Microangiopathic processes
		Prosthetic heart valves
Permanently sickled cells	Sickle cell anemia	
Spur cells (acanthocytes)	Abetalipoproteinemia	Severe liver disease
Spherocytes	Hereditary spherocytosis	Immune, warm-antibody type
Target cells	Thalassemia Hemoglobinopathies (Hb C)	Liver disease
Agglutinated cells		Immune, cold agglutinin disease

E. **Human Hemoglobins**. Table 7.11 depicts the normal human hemoglobins at different stages of life.

To convert colorimetric readings into grams of Hb/dL (g/dL) using a standard curve set up with the same equipment and reagents used for specimen or calculate specimen concentration (C_u) based on *Beer's law,* the following formula is utilized:

$$C_u(g/dL) = 301\frac{(A_u \times C_s)}{A_s} \times \frac{1}{1{,}000} = \frac{0.301(A_u \times C_s)}{A_s}$$

Table 7.11. Normal Human Hemoglobins at Different Stages of Life

Hemoglobin	*Molecular structure*	*Stage*	*Proportion (%)*	
			Newborns	*Adults*
Portland	$\zeta_2\gamma_2$	Embryonic	0	0
Gower I	$\zeta_2\varepsilon_2$	Embryonic	0	0
Gower II	$\alpha_2\varepsilon_2$	Embryonic	0	0
Fetal (F)	$\alpha_2\gamma_2$	Newborn/adult	80	<1
A_1	$\alpha_2\beta_2$	Newborn/adult	20	97
A_2	$\alpha_2\delta_2$	Newborn/adult	<0.5	2.5

where A_u = the absorbance of the unknown; C_s = the concentration of the standard (usually 80 mg/dL); and A_s = the absorbance of the standard run most recently under the same conditions as the patient specimen.

To calculate the fraction of *hemoglobin F as a percentage,* the following formula is used:

$$\mathrm{HbF}(\%) = \frac{\mathrm{A_{test}}}{\mathrm{A_{dilutedtotal}} \times 5} \times 100$$

where A = absorbance, 5 = the additional dilution factor.

To calculate the *percentage of hemoglobin A_2*:

$$\mathrm{HbA_2}(\%\mathrm{oftotal}) = \mathrm{AfractionI} \times 100\%$$