

# Hemostasis and Blood Forming Organs

## Subcommittee:

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<b>Hemostasis and Blood Forming Organs</b>	
<b>Recommended Curriculum Equivalent: 1.5 hr</b>	
<b>Drugs for Treating Anemia</b>	
<b>Minerals</b>	<b>Vitamins</b>
DEFEROXAMINE FERROUS SULFATE ferrous gluconate iron dextran	CYANOCOBALAMIN FOLIC ACID VITAMIN B <sub>12</sub>
<b>Hematopoietic growth factors</b>	
ERYTHROPOIETINS EPOETIN ALFA Darbepoetin	Myeloid Growth Factors Filgrastim Sargramostim Thrombopoietic Growth Factors Interleukin-11 Thrombopoietin
<b>Learning Objectives</b>	
<p><b>Physiology and pathophysiology</b> Diagram the normal physiological control of hematopoietic growth factors and the effect of kidney failure on erythropoiesis. Relate factors that can lead to abnormal iron balance including genetic hemochromatosis to the iron absorption and transport pathways. Describe the biochemical systems, which are impaired in B-12 and folic acid deficiency, and the role of cyanocobalamin and folic acid in correcting the metabolic defect in DNA thymine and methionine synthesis.</p>	
<p><b>Mechanism of action</b> Explain the molecular mechanism of action of each drug in each drug class.</p>	
<p><b>Actions on organ systems</b> Describe the pharmacological effects of each class of drugs on the hematopoietic system.</p>	
<p><b>Pharmacokinetics</b> Describe the possible etiologies, which should be considered if a delayed or diminished response to doses of recombinant erythropoietin within the recommended dose range occurs. Analyze how the pharmacokinetics and therapeutic effects of epoetin alpha and darbepoetin alpha differs between normal and anemic dialysis patients. Describe the sources, transport, metabolism, storage, and excretion of vitamin B-12 and folic acid. State the factors, which influence the bioavailability of vitamin B-12 and folic acid.</p>	

**Adverse effects, drug interactions and contraindications**

Describe the principal adverse effects and contraindications of the drugs in each class.

Describe the clinically important drug interactions of the drugs in each class.

Identify adverse events associated with erythropoietin use in cancer patients, and black box warning on erythropoietin preparations.

**Therapeutic uses**

Apply the criteria for oral therapy versus parenteral iron therapy to a patient with iron deficiency anemia. Consider the associated side effects and the predicted rates of response to the two therapies.

Summarize the risks of acute iron poisoning in children and its treatment.

Evaluate the pharmacologic management of chronic iron overload disease (e.g. secondary to chronic blood transfusion, iron absorption disturbances, etc.).

Explain the appropriate management of the patient with a megaloblastic anemia in regards to both acute and chronic management, vitamin dosage and expected response.

Compare the possible metabolic reasons why folic acid will correct the erythropoietic lesion but not the neurologic lesion in Addisonian pernicious anemia.

What is the rationale for the use of folic acid in patients with elevated serum levels of homocysteine or spina bifida?

Compare the therapeutic applications for myeloid growth factors with those for thrombopoietic growth factors.

Differentiate approaches to treatment of folic-dependent vs B12- dependent megaloblastic anemia; describe how laboratory tests guide choice of treatment.

Describe cancer vs non-cancer indications for myeloid growth factors. Delineate specific types of cancer where these growth factors are contradicted.

**Notes****Clinical Pharmacology**

In chronic kidney disease, iron absorption from the gastrointestinal tract is often impaired. Intravenous iron may be considered and may decrease the dose of more expensive erythropoiesis-stimulating therapies. Caution in that i.v. high molecular weight iron preparations are associated with increased risk of anaphylaxis.

**Relevance****USMLE topic**

Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Anemia of Chronic Disease

**Principles of therapeutics**

Treatment of anemia, drugs stimulating erythrocyte production

**AAMC Medical School Objectives**

Project Report X Patient Safety – Table 1

**Topic C:** Drug treatment of common conditions,

**Topic D:** Management of less common but severe medical conditions and emergencies.

<b>Anticoagulant Drugs</b>			
<b>Recommended Curriculum Equivalent: 1 hr</b>			
<b>Drug Classes and Drugs to Consider</b>			
Indirect Thrombin Inhibitors	Direct Thrombin Inhibitors	Factor Xa Inhibitors	Inhibitors of Clotting Factor Synthesis
HEPARIN PROTAMINE SULFATE (antidote)	DABIGATRAN bivalirudin lepirudin	ENOXAPARIN RIVAROXABAN fondaparinux	VITAMIN K (antidote) WARFARIN
<b>Learning Objectives</b>			
<p><b>Physiology and Pathophysiology</b>            Explain the role of the coagulation cascade in the regulation of hemostasis.            Describe the synthesis of the vitamin K-dependent clotting factors, and explain the role of antithrombin in the regulation of hemostasis.            Examine the pathogenesis of venous thrombosis.</p>			
<p><b>Mechanism of Action</b>            Explain the molecular mechanism of action of the drugs in each drug class.            Compare the structural features of unfractionated heparin, direct thrombin inhibitors and factor Xa inhibitors that determine their target specificity.            Relate the structural similarity of warfarin to vitamin K to explain the mechanism of action of inhibitors of clotting factor synthesis.</p>			
<p><b>Actions On Organ Systems</b>            Analyze the effect of heparin on platelet aggregation and plasma lipids.            Explain how the anticoagulant responses to heparin and warfarin are monitored clinically using aPTT and INR, respectively.</p>			
<p><b>Pharmacokinetics</b>            Identify the anticoagulants that are orally effective vs. those that must be given parenterally.            Compare the rates of onset of action of heparin with warfarin in regard to their routes of administration and mechanisms of action.            Apply the effects of warfarin on vitamin K-dependent clotting factor turnover to its anticoagulant activity.            Explain how genetic polymorphisms in <i>CYP2C9</i> and <i>VKORC1</i> can affect the patient response to warfarin.</p>			
<p><b>Adverse Effects, Drug Interactions and Contraindications</b>            State the principal complication of anticoagulant therapy (bleeding) and describe the adverse effects and contraindications of the drugs in each class.            Describe the incidence and time to onset of heparin-induced thrombocytopenia.            Explain how protamine and vitamin K are used as antidotes to excessive bleeding caused by heparin and warfarin, respectively.            Describe the effects of warfarin therapy during pregnancy on the developing fetus.            Discuss the disease, drug, food and herbal interactions with warfarin; explain how dietary vitamin K can affect warfarin therapy.</p>			

**Therapeutic Uses**

Evaluate parenteral and oral anticoagulant therapy for initial and long-term management of patients with venous thrombosis and pulmonary embolism.

Formulate a plan for the pharmacological management of thromboembolic complications from heparin-induced thrombocytopenia.

Apply the goals of warfarin therapy to its use in patients with:

- atrial fibrillation
- prosthetic heart valves
- myocardial infarction
- stroke

Defend the advantages/disadvantages of treatment with dabigatran or rivoraxaban, instead of warfarin for oral anticoagulant therapy.

**Notes****Clinical Pharmacology**

Patients receiving heparin for more than 4 days have an up to 5% risk of developing heparin-induced thrombocytopenia. Non-heparin anticoagulant alternatives are used to treat this condition, including fondaparinux, a factor X inhibitor, that is used off label. Its advantages include once daily, subcutaneous administration and the lack of effect on INR. It is important to remember that fondaparinux has no antidote for its infrequent causation of a major bleeding episode. The drug may also accumulate in patients with renal insufficiency and is contraindicated in patients with a creatinine clearance of < 30 ml/min.

Dabigatran and rivaroxaban were designed as alternatives to warfarin, but both also predispose patients to high risk for stroke, serious bleeding and blood clots. Like fondaparinux, both have no known antidote, accumulate in patients with renal insufficiency, and interact with many of the same drugs that interact with warfarin. As a P-glycoprotein substrate, dabigatran's use must be reconsidered during concurrent administration of drugs that induce or inhibit P-glycoprotein.

**Relevance****USMLE topic**

Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders

**Principles of therapeutics**

anticoagulants

**AAMC Medical School Objectives**

Project Report X Patient Safety – Table 1

**Topic C:** Drug treatment of common conditions,

**Topic D:** Management of less common but severe medical conditions and emergencies.

## Antiplatelet Drugs

**Recommended Curriculum Equivalent: 0.75 hr**

### Drug Classes and Drugs to consider

Cyclooxygenase Inhibitors	ADP P2Y <sub>12</sub> Inhibitors	Phosphodiesterase Inhibitors	GPIIb/IIIa inhibitors	INHIBITORS OF PAR-1
ASPIRIN (acetylsalicylic acid) ibuprofen	CLOPIDOGREL TICLOPIDINE parasugrel	dipyridamole	ABCIXIMAB EPTIFIBATIDE tirofiban	vorapaxar

### Learning Objectives

#### **Physiology and pathophysiology**

Explain the role of platelet aggregation in the regulation of hemostasis.  
Describe the pathogenesis of thrombosis with respect to the platelet activation.

#### **Mechanism of action**

Explain the molecular mechanism of action of each drug in each drug class.  
Describe how inhibition of prostaglandin synthesis affects platelet aggregation, specifically the role of COX-1 and COX-2.  
Compare differences and similarities in mechanism of action for antiplatelet drugs: e.g. aspirin, dipyridamole, clopidogrel, abciximab, vorapaxar.

#### **Actions on organ systems**

Identify the site of action of each drug in the platelet aggregation process.

#### **Pharmacokinetics**

Contrast the effects and time course of aspirin with nonsteroidal anti-inflammatory agents (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors on platelet function.  
Demonstrate how manipulation of the dosing regimen for aspirin can reduce adverse effects, particularly on the GI tract.  
Describe difference in routes of administration for different classes of antiplatelet drugs.

#### **Adverse effects, drug interactions and contraindications**

Describe the principal adverse effects and contraindications of the drugs in each class.  
Discuss drug-drug, drug-food, and drug-disease interactions of each drug.  
Explain how concomitant use of NSAIDs, e.g. ibuprofen, can interfere with the antiplatelet actions of aspirin.  
Contrast the effects of reversible with irreversible inhibitors on duration of action.

#### **Therapeutic uses**

Discuss the approach to the management of the patient on short term and long term antiplatelet therapy.  
Explain the role of the platelet glycoprotein IIb/IIIa inhibitors in the diagnosis and management of coronary artery disease.  
Contrast the effects of aspirin, dipyridamole, clopidogrel, and propranolol for primary post MI prophylaxis.  
Compare differences and similarities in appropriate clinical indications for antiplatelet agents.

**Notes**

The antiinflammatory, analgesic and antipyretic effects of aspirin and NSAIDs, including COX-2 inhibitors, are discussed in Analgesics Knowledge Objectives.

**Clinical Pharmacology**

Low-dose enteric-coated aspirin is now considered standard of care to prevent recurrence of a myocardial infarction. In patients with atrial fibrillation and one or more additional risk factors, warfarin was found superior to clopidogrel plus aspirin for stroke risk reduction (ACTIVE W Trial).

In selected patients with CHF in normal sinus rhythm warfarin has no advantage over aspirin for stroke risk reduction (WARCEF trial). It is important to emphasize to patients receiving low-dose enteric-coated aspirin either prophylactically or post-myocardial infarction that concurrent NSAIDs for pain management are contraindicated, and that acetaminophen becomes the first choice non-opioid analgesic for initial pain management.

**Relevance****USMLE topic**

Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders

**Principles of therapeutics**

Anti-platelet drugs

**AAMC Medical School Objectives**  
**Project Report X Patient Safety – Table 1**

**Topic C:** Drug treatment of common conditions,  
**Topic D:** Management of less common but severe medical conditions and emergencies.

<b>Thrombolytic Drugs</b>	
<b>Recommended Curriculum Equivalent: 0.25 hr</b>	
<b>Drug Classes and Drugs to Consider</b>	
Plasminogen Activators	Inhibitors of Fibrinolysis
t-PA ALTEPLASE reteplase tenecteplase	aminocaproic acid
<b>Learning Objectives</b>	
<b>Physiology and pathophysiology</b> Explain the role of plasminogen in thrombolysis Describe the role of thrombolysis in the physiology of hemostasis	
<b>Mechanism of action</b> Contrast the molecular mechanism and site of action of alteplase with aminocaproic acid. Describe the pharmacologic effects of alteplase on thrombi.	
<b>Pharmacokinetics</b> Differentiate between the pharmacokinetic properties of t-PA, alteplase and tenecteplase.	
<b>Adverse effects, drug interactions and contraindications</b> Relate the major adverse effect of thrombolytic drugs to their mechanism of action. Describe the primary contraindications for thrombolytic drugs.	
<b>Therapeutic uses</b> Identify the major indications for thrombolytic drug therapy: Myocardial infarction Ischemic stroke Deep venous thrombosis Pulmonary embolism Discuss aminocaproic acid (EACA), a fibrinolytic inhibitor, which is used routinely along with desmopressin and factor replacement in dental procedures in patients with hemophilia and von Willebrand's disease and for non-dental bleeding episodes in both diseases.	
<b>Notes</b>	
<b>Clinical Pharmacology</b> The plasminogen activator thrombolysis drugs have been studied almost exclusively in acute myocardial infarction patients. These fibrin-specific agents are perceived to be associated with a lower all-cause mortality than the nonspecific thrombolytic drug streptokinase. These drugs are still considered too new to determine their ultimate utility for other thrombotic disorders, and whether or not adverse events are drug class-specific or a reflection of differences among competing marketed products.	
<b>Relevance</b>	

<b>USMLE topic</b> Hematopoietic and Lymphoreticular Systems-Abnormal Processes- Hemorrhagic and Hemostatic Disorders	<b>Principles of therapeutics</b> thrombolytic drugs
<b>AAMC Medical School Objectives</b> <b>Project Report X Patient Safety – Table 1</b>	<b>Topic C:</b> Drug treatment of common conditions <b>Topic D:</b> Management of less common but severe medical conditions and emergencies.