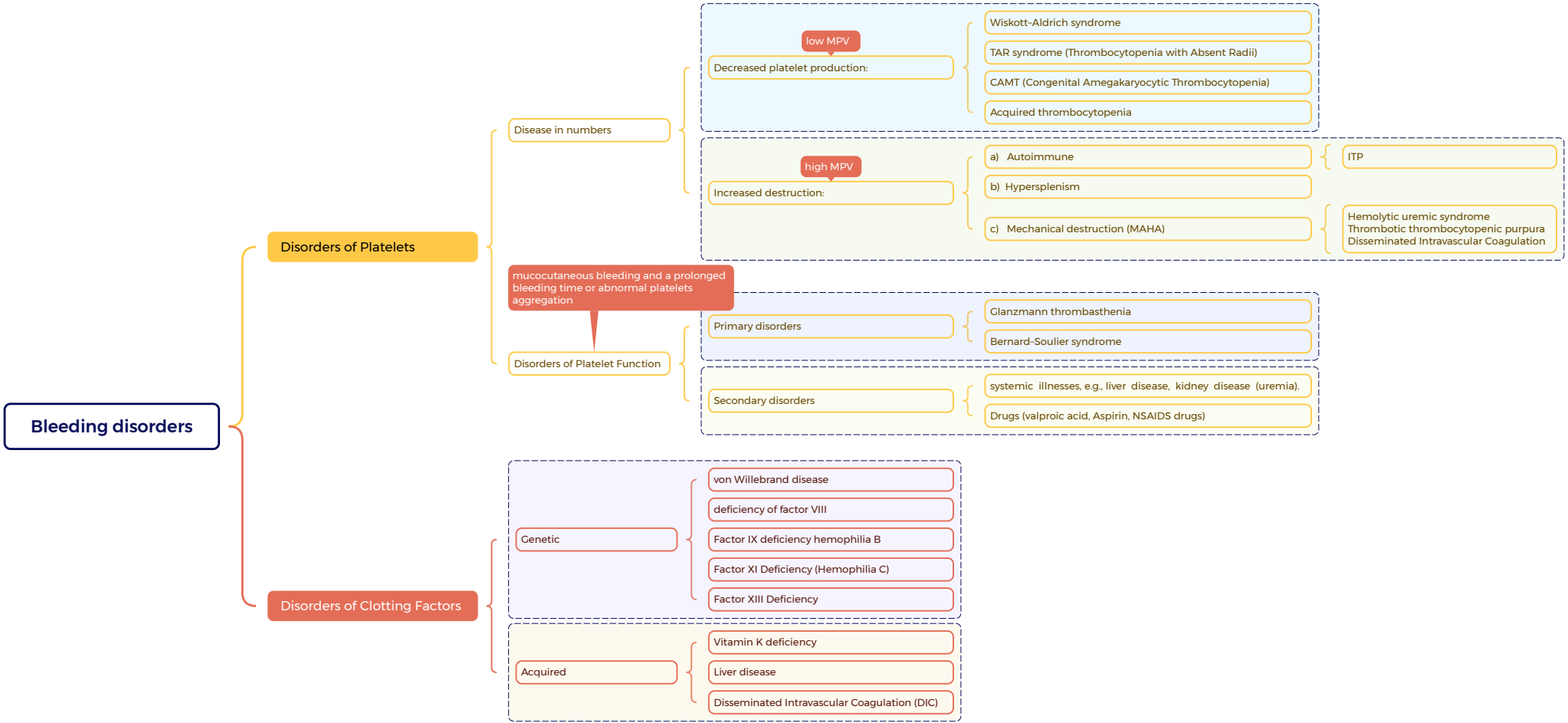

❖ **Mucocutaneous bleeding** is the hallmark of platelet disorders

Disorders of Platelets

1. Decreased platelet production: usually small size platelets or low MPV

CAMT (Congenital Amegakaryocytic Thrombocytopenia)	TAR syndrome (Thrombocytopenia with Absent Radii)	Wiskott–Aldrich syndrome	Acquired thrombocytopenia
? Severe thrombocytopenia in association with orthopedic abnormalities. ? The thrombocytopenia usually improves over time	- Severe thrombocytopenia , but no other congenital anomalies. - The marrow is devoid of megakaryocytes and usually progresses to aplasia of all hematopoietic cell lines. - BM Biopsy :hypoplastic	- An X-linked disorder characterized by hypogammaglobinemia , eczema, and thrombocytopenia - Small platelets are seen on a peripheral blood smear - Otitis media	as a result of decreased production is rarely an isolated finding. It is seen more often in the context of pancytopenia resulting from bone marrow failure caused by infiltrative or aplastic processes.

2-Increased destruction: usually large platelets or high MPV(mean platelet volume):

Immune Thrombocytopenic Purpura	
1. Definition and Epidemiology	• Childhood Immune Thrombocytopenic Purpura is a common acquired bleeding disorder in children. • It is the most common cause of acute onset thrombocytopenia in an otherwise healthy child. • It usually follows an acute viral infection. • Incidence is equal in males and females. • Peak incidence occurs between 1 and 4 years of age.
2. Etiology and Pathophysiology	• Childhood ITP is caused by autoantibodies directed against platelet membrane antigens. • These antibodies are usually IgG or IgM. • During a viral infection: ◦ The immune system initially produces IgM antibodies. ◦ Later, class switching occurs and IgG antibody levels increase over several weeks. • Some IgG antibodies may cross-react with platelet antigens due to structural similarity between viral and platelet antigens. • Platelets become coated with antibodies. • Antibody-coated platelets are: ◦ Recognized and phagocytosed by macrophages of the reticuloendothelial system. ◦ Mainly destroyed in the spleen. • This leads to severe thrombocytopenia, often with platelet counts less than 10,000 platelets per mm^3. • Intravenous immunoglobulin improves thrombocytopenia only in ITP, not in other causes of thrombocytopenia.
3. Clinical Manifestations	• Symptoms usually appear 1 to 4 weeks after a viral illness. • Onset is abrupt. • Common manifestations include: ◦ Petechiae ◦ Purpura ◦ Epistaxis • The thrombocytopenia is usually severe. • There is no significant lymphadenopathy. • There is no hepatosplenomegaly. • The child otherwise appears well.
4. Laboratory Findings	• Platelet count is markedly reduced. • Red blood cell count is normal. • White blood cell count and differential are normal. • Peripheral blood smear shows isolated thrombocytopenia.
5. Diagnosis	• Diagnosis is usually clinical. • It is based on: ◦ Typical clinical presentation ◦ Isolated thrombocytopenia on complete blood count • Bone marrow examination is not routinely required. • Bone marrow examination is indicated when: ◦ Atypical clinical features are present ◦ There is concern for leukemia or aplastic anemia • Bone marrow study must be performed before starting steroid therapy if indicated. • Bone marrow findings in ITP include: ◦ Increased number of megakaryocytes ◦ Normal erythroid and myeloid cell lines
6. Treatment	• Treatment depends on platelet count and severity of bleeding. **A. Observation** • Therapy is usually not indicated when platelet count is greater than 20,000 per mm^3. • Many children can be safely observed. **B. Medical Treatment** • Indicated in: ◦ Moderate to severe clinical bleeding ◦ Severe thrombocytopenia with platelet count less than 10,000 per mm^3 • Treatment options include: ◦ Prednisone at a dose of 2 to 4 mg per kg per day for approximately two weeks ◦ Intravenous immunoglobulin at a dose of 1 g per kg per day for one to two days ◦ Anti-D immunoglobulin in appropriate patients **C. Platelet Transfusion** • Platelet transfusion is not routinely indicated. • It is reserved for life-threatening bleeding. **D. Splenectomy** • Splenectomy is indicated in acute ITP only for life-threatening bleeding. • In chronic ITP, splenectomy may be considered after failure of medical therapy.
7. Prognosis	• Approximately 80 percent of children have spontaneous resolution within six months of diagnosis. • Serious bleeding, including intracranial hemorrhage, occurs in less than 1 percent of patients.
8. Chronic Immune Thrombocytopenic Purpura	• ITP is classified as chronic when it persists for 6 to 12 months. • Repeated treatments with: ◦ Intravenous immunoglobulin ◦ Intravenous anti-D immunoglobulin ◦ High-dose pulse steroids can delay the need for splenectomy. • Rituximab (anti-CD20 antibody) induces remission in approximately 50 percent of cases. • Thrombopoietin receptor agonists such as Eltrombopag may be used. • Secondary causes of chronic ITP must be excluded, especially: ◦ Systemic lupus erythematosus ◦ Human immunodeficiency virus infection ◦ Primary immune deficiencies • Splenectomy induces remission in 70 to 80 percent of children with chronic ITP. • The risks of splenectomy, including: ◦ Surgical complications ◦ Severe infections due to encapsulated organisms must be weighed against the risk of severe bleeding.

Hemolytic uremic syndrome	Thrombotic thrombocytopenic purpura	Disseminated Intravascular Coagulation
occurs as a result of exposure to a toxin that induces endothelial injury, fibrin deposition, and platelet activation and clearance	platelet consumption, precipitated by a congenital or acquired deficiency of a metalloproteinase that cleaves von Willebrand factor.	

Disorders of Platelet Function

Primary disorders of platelet function may involve receptors on platelet membranes for adhesive proteins.

- Autosomal recessive disorders Characterized by prolonged bleeding time

	Bernard–Soulier syndrome	Glanzmann thrombasthenia
1. Definition	• Bernard–Soulier syndrome is an autosomal recessive inherited platelet disorder. • It is characterized by defective platelet adhesion.	• Glanzmann thrombasthenia is an autosomal recessive inherited platelet function disorder. • It is characterized by a markedly diminished ability of platelets to aggregate and form a stable clot.
2. Pathophysiology	• The disorder is caused by absence or dysfunction of platelet membrane glycoprotein Ib. • Glycoprotein Ib is the receptor for von Willebrand factor, which mediates platelet adhesion to collagen at sites of vascular injury. • As a result: ◦ Platelets fail to adhere to the damaged vascular endothelium. ◦ Primary hemostasis is impaired.	• The disorder results from a deficiency or absence of platelet membrane glycoprotein IIb/IIIa. • Glycoprotein IIb/IIIa is the receptor for fibrinogen. • Fibrinogen is required to cross-link platelets during aggregation. • As a result: ◦ Platelets cannot bind to each other properly. ◦ Platelet aggregation is severely impaired.
3. Platelet Count and Morphology	• Platelet count is mildly decreased (mild thrombocytopenia). • Platelets are large and abnormal in shape. • Blood smear typically shows giant platelets.	• Platelet count is usually normal. • Platelet size and morphology are generally normal.
4. Clinical Features	• Patients may develop severe hemorrhage. • Common manifestations include: ◦ Petechiae ◦ Purpura ◦ Epistaxis ◦ Prolonged bleeding after trauma or surgery	• Patients present with mucocutaneous bleeding, including: ◦ Epistaxis ◦ Gingival bleeding ◦ Menorrhagia ◦ Easy bruising • Bleeding may be severe, especially after trauma or surgery.

2. Secondary disorders

? **systemic illnesses, e.g., liver disease, kidney disease (uremia).**
? **Drugs (valproic acid, Aspirin, NSAIDS drugs)**

Disorders of Clotting Factors

1. Congenital Clotting Factor Disorders

- Congenital clotting factor disorders are inherited conditions characterized by deficiency or dysfunction of coagulation factors.
- The most important congenital disorders include:
  - Factor VIII–related disorders
  - Factor IX deficiency
  - Factor XI deficiency
  - Factor XIII deficiency

Factor VIII–Related Disorders

Factor VIII–related disorders include two inherited conditions:
- Hemophilia A
- Von Willebrand Disease

	Hemophilia A (Factor VIII Deficiency)	Von Willebrand Disease
Definition	• Hemophilia A is an inherited disorder caused by a defect in factor VIII procoagulant activity. • Platelet count and platelet function are normal.	• Von Willebrand disease is the most common inherited bleeding disorder. • Estimated prevalence ranges from 1 in 100 to 1 in 10,000.
Inheritance and Epidemiology	• Inheritance is X-linked recessive. • Occurs in approximately 1 in 5,000 to 10,000 male births.	• Inherited in an autosomal pattern. • The gene is located on chromosome 12.

Bleeding Characteristics	• Only about 2 percent of neonates with hemophilia develop intracranial hemorrhage.
	• Approximately 30 percent of affected male infants bleed after circumcision.
	• The hallmark clinical features include:
	  ◦ Hemarthroses, most commonly affecting knees, elbows, and ankles
	  ◦ Deep soft tissue bleeding
	• Bleeding into the iliopsoas muscle may be especially severe due to delayed recognition and large blood accumulation.
	• Central nervous system bleeding is the most feared complication, usually following head trauma.
		• Most patients have mild to moderate mucocutaneous bleeding.
		• Common manifestations include:
		  ◦ Epistaxis
		  ◦ Menorrhagia
		  ◦ Easy bruising
		  ◦ Bleeding after dental extraction or tonsillectomy
		• Hemarthroses are uncommon.
		• Severe bleeding occurs mainly in type III disease.

Severity Classification (Based on Factor VIII Activity)	• Severe hemophilia:
	  ◦ Less than 1 percent factor VIII activity
	  ◦ Spontaneous bleeding
	• Moderate hemophilia:
	  ◦ 1 to 5 percent factor VIII activity
	  ◦ Bleeding occurs with trauma
	• Mild hemophilia:
	  ◦ Greater than 5 percent factor VIII activity
	  ◦ Bleeding occurs after surgery or major trauma
		Types of Von Willebrand Disease
		• Type 1:
		  ◦ Quantitative reduction of von Willebrand factor
		  ◦ Most common type, approximately 85 percent
		  ◦ Autosomal dominant
		• Type 2:
		  ◦ Qualitative abnormality of von Willebrand factor
		  ◦ Autosomal dominant or autosomal recessive
		• Type 3:
		  ◦ Near complete absence of von Willebrand factor
		  ◦ Autosomal recessive

Laboratory Findings	• Activated partial thromboplastin time is prolonged
	  ◦ In mild disease, it may be normal
	• Prothrombin time is normal
	• Platelet count is normal
	• Platelet function tests are normal
	• Factor VIII activity is low
	• Von Willebrand factor level is normal
		• Prolonged bleeding time
		• In type III disease:
		  ◦ Prolonged activated partial thromboplastin time
		• Abnormal von Willebrand factor antigen levels
		• Abnormal von Willebrand factor activity assays
		• Reduced plasma factor VIII activity

Management	• Prevention of trauma is essential.
	• Mainstay of treatment is factor VIII replacement therapy.
	• Desmopressin acetate:
	  ◦ A synthetic vasopressin analogue
	  ◦ Causes release of stored factor VIII from endothelial cells
	  ◦ Useful in mild hemophilia A
	• Recombinant factor VIII is preferred.
	• Early and appropriate replacement therapy is crucial.
	• Prophylactic therapy starting in infancy:
	  ◦ Greatly reduces the risk of chronic arthropathy in severe hemophilia.
	• In patients with inhibitors:
	  ◦ Recombinant activated factor VII (NovoSeven) may be used.
		• Treatment is directed toward increasing plasma von Willebrand factor levels.
		• Desmopressin acetate:
		  ◦ Induces release of von Willebrand factor from endothelial cells
		  ◦ Effective in most cases of type 1 disease
		  ◦ Not effective in type 2 or type 3 disease
		• Replacement therapy:
		  ◦ Plasma-derived von Willebrand factor concentrates for type 2 and type 3 disease
		• Cryoprecipitate:
		  ◦ Contains von Willebrand factor, fibrinogen, factor VIII, and factor XIII
		  ◦ Used for serious bleeding, major surgery, or type III disease

Dosing Principles	• One unit per kilogram of factor VIII increases plasma factor VIII level by approximately 2 percent.
	• For mild to moderate bleeding, a target level of 40 percent factor VIII is appropriate.
		Functions of Von Willebrand Factor
		• Mediates platelet adhesion to injured subendothelium by binding to:
		  ◦ Platelets
		  ◦ Collagen
		• Acts as a carrier protein for factor VIII, protecting it from degradation.

Complications	• Chronic arthropathy
	• Development of inhibitors to factor VIII
	• Risk of transfusion-transmitted infections with plasma-derived products
	  ◦ Not seen with recombinant factors
		Structure and Synthesis
		• Von Willebrand factor is a large glycoprotein.
		• Synthesized in:
		  ◦ Endothelial cells
		  ◦ Megakaryocytes

Hemophilia B (Factor IX Deficiency)	Factor XI Deficiency (Hemophilia C)	Factor XIII Deficiency

Definition and Epidemiology
• Hemophilia B is caused by factor IX deficiency.
• It is an X-linked recessive disorder.
• Occurs in approximately 1 in 50,000 males.
 	
Clinical Features
• Clinical presentation is similar to hemophilia A.
 	
Laboratory Findings
• Prolonged activated partial thromboplastin time
• Low factor IX activity
• Normal prothrombin time
• Normal platelet count
 	
Management
• Treatment consists of factor IX replacement therapy.
• Recombinant factor IX is preferred.
• One and a half units per kilogram of factor IX increase plasma levels by approximately 1 percent.
	Definition
	• Factor XI deficiency is an autosomal recessive disorder.
	
	Clinical Features
	• Associated with mild to moderate bleeding.
	• Bleeding is usually provoked, such as after surgery or trauma.
	
	Laboratory Findings
	• Prolonged activated partial thromboplastin time.
	
	Management
	• No factor XI concentrate is available in Jordan.
	• Treatment is with fresh frozen plasma.
		Definition and Function
		• Factor XIII is responsible for cross-linking and stabilization of fibrin clots.
		• It has the longest half-life of all clotting factors, approximately ten days.
		
		Clinical Features
		• Poor wound healing
		• Delayed separation of the umbilical stump
		  ◦ This can also be seen in leukocyte adhesion deficiency
		• Increased risk of intracranial hemorrhage
		
		Laboratory Findings
		• Screening coagulation tests:
		  ◦ Prothrombin time is normal
		  ◦ Activated partial thromboplastin time is normal

2. Acquired Clotting Factor Disorders

	Vitamin K Deficiency	Liver Disease	Disseminated Intravascular Coagulation (DIC)

Definition	• Vitamin K is a fat-soluble vitamin.
	• It is essential for hepatic synthesis of:
	  ◦ Procoagulant factors II, VII, IX, and X
	  ◦ Anticoagulant proteins C and S
		• The liver is the major site of production of most coagulation factors.
		• Vitamin K–dependent factors are most severely affected.
			• Disseminated intravascular coagulation is a condition characterized by:
			  ◦ Consumption of clotting factors
			  ◦ Consumption of platelets
			  ◦ Consumption of anticoagulant proteins

Causes	• Dietary deficiency is rare, except during early infancy.
	• Conditions that impair fat absorption:
	  ◦ Pancreatic insufficiency
	  ◦ Biliary obstruction
	  ◦ Prolonged diarrhea
	• Medications that interfere with vitamin K metabolism:
	  ◦ Cephalosporins
	  ◦ Rifampin
	  ◦ Isoniazid
	  ◦ Warfarin
			• DIC is always secondary to another condition.
			• Local causes:
			  ◦ Large hemangiomas, such as Kasabach–Merritt syndrome
			• Systemic causes:
			  ◦ Sepsis
			  ◦ Hypothermia
			  ◦ Malignancy
			  ◦ Heat stroke
			  ◦ Snakebite
			  ◦ Severe burns

Clinical Features	• Bruising
	• Oozing from skin puncture sites
	• Bleeding into internal organs
	• Serious bleeding is characteristic in early and late forms
	• Central nervous system bleeding may occur occasionally
			• Cutaneous and internal organ bleeding
			• Bleeding from puncture sites and surgical incisions
			• Skin petechiae and ecchymoses
			• Tissue necrosis and infarction
			• Anemia due to microangiopathic hemolysis
			• In neonates:
			  ◦ Bleeding from venipuncture sites
			  ◦ Gastrointestinal bleeding
			  ◦ Intraventricular hemorrhage

Hemorrhagic Disease of the Newborn	**Timing**
	• Early onset:
	  ◦ Occurs within 24 hours after birth
	• Classic form:
	  ◦ Occurs during the first week of life
	• Late onset:
	  ◦ Occurs between 1 and 3 months of age
			• Widespread activation of the coagulation cascade occurs.
			• This leads to:
			  ◦ Intravascular deposition of fibrin
			  ◦ Tissue ischemia and necrosis
			• Consumption of procoagulant factors results in:
			  ◦ Generalized hemorrhage
			• Microvascular thrombosis causes:
			  ◦ Hemolytic anemia

Laboratory	• Prolonged prothrombin time
	• Prolonged activated partial thromboplastin time
		• Prolonged prothrombin time
		• Prolonged activated partial thromboplastin time
		• Thrombocytopenia
			• Thrombocytopenia
			• Prolonged prothrombin time
			• Prolonged activated partial thromboplastin time
			• Reduced levels of clotting factors:
			  ◦ Especially fibrinogen and factors II, V, and VIII
			• Peripheral blood smear shows:
			  ◦ Fragmented red blood cells
			  ◦ Helmet-shaped cells
			  ◦ Schistocytes
			• Increased fibrin degradation products
			• Increased D-dimer levels

Management	• Administration of vitamin K is the primary treatment.
	• Intramuscular vitamin K given after birth:
	  ◦ Prevents hemorrhagic disease of the newborn
	• In severe bleeding:
	  ◦ Fresh frozen plasma may be required
		• Administration of vitamin K
		• Fresh frozen plasma as needed
		• Platelet transfusion when indicated
			• Treatment of the underlying cause is essential.
			• Supportive therapy includes:
			  ◦ Fresh frozen plasma
			  ◦ Platelets
			  ◦ Fibrinogen replacement as needed
			• Heparin may be used when:
			  ◦ The underlying cause cannot be corrected
			  ◦ Thrombosis predominates

POISON	ANTIDOTE
Acetaminophen	*N*-Acetylcysteine
Benzodiazepine	Flumazenil
β-Blocking agents	Glucagon
Carbon monoxide	Oxygen
Cyclic antidepressants	Sodium bicarbonate
Iron	Deferoxamine

POISON	ANTIDOTE
Lead	Edetate calcium disodium (EDTA) BAL (British anti-Lewisite [dimercaprol]) Succimer (2,3-dimercaptosuccinic acid ([DMSA])
Nitrites/ methemoglobinemia*	Methylene blue
Opiates	Naloxone
Organophosphates	Atropine Pralidoxime (2 PAM; Protopam)