Platelet Disorders

Bleeding Disorders

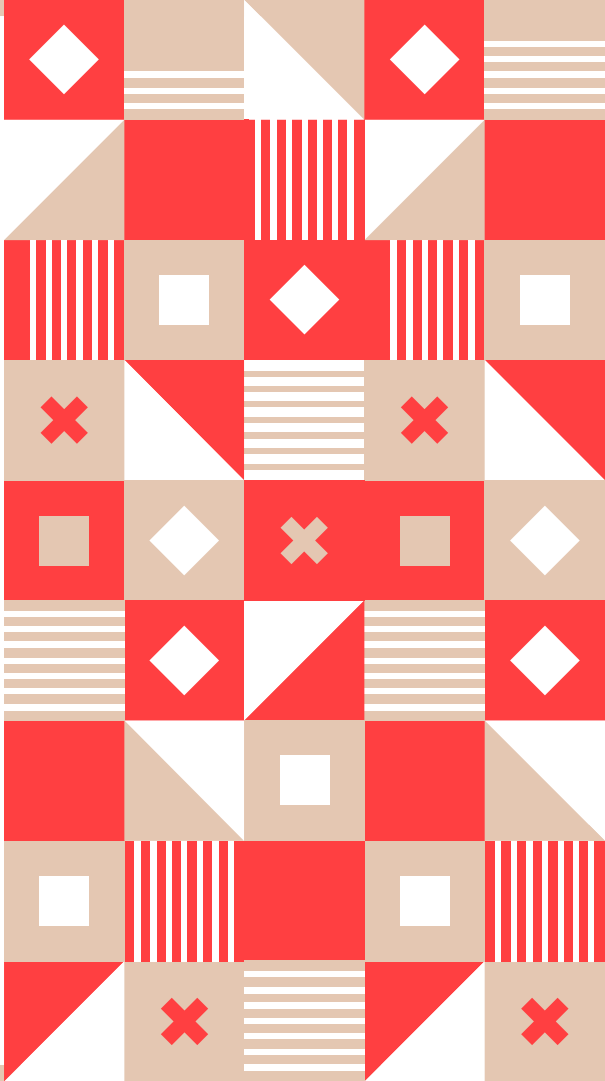
Ghadeer AlMuhaisen, M.D.
Consultant hematopathologist
Mutah University

The most important tests for investigation of suspected coagulopathies

- **Prothrombin time (PT):** assesses extrinsic & common pathways. Time in seconds needed for plasma to clot after addition of tissue thromboplastin (e.g., brain extract) and Ca2+ ions.
- A prolonged PT: deficiency of factors V, VII, or X; prothrombin; or fibrinogen or the presence of an acquired inhibitor (an antibody)
- **Partial thromboplastin time (PTT).** assesses intrinsic & pathways. Time in seconds needed for the plasma to clot after the addition of kaolin, cephalin, and Ca2+.
- A Prolongation of PTT: deiciency of factor V, VIII, IX, X, XI, or XII; prothrombin; or fibrinogen or the presence of an acquired inhibitor
- **Platelet count.**
- Also, specialized tests that measure the levels of specific clotting factors and fibrin split products or assess the presence of circulating anti-coagulants.

Thrombocytopenia

- Platelets count < 150,000 platelets/µL
- Normal count 150,000 - 450,000 platelets/µL
- Posttraumatic Bleeding risk at 20,000-50,000 platelets/µL
- Spontaneous bleeding is unlikely until counts below 5000 platelets/µL



Causes of Thrombocytopenia

- Isolated thrombocytopenia is associated with a bleeding tendency and **normal coagulation tests.**
- Bleeding occurs from small, superficial blood vessels & produces petechiae or large ecchymoses in the skin, the mucous membranes of GI & urinary tracts.
- Larger hemorrhages in the CNS occurs with marked thrombocytopenia
- Clinically important thrombocytopenia is with reduced production or increased destruction of platelets.

Decreased Production of Platelets
Generalized Bone Marrow Dysfunction
Aplastic anemia: congenital and acquired Marrow infiltration: leukemia, disseminated cancer
Selective Impairment of Platelet Production
Drug-induced: alcohol, thiazides, cytotoxic drugs Infections: measles, HIV infection
Ineffective Megakaryopoiesis
Megaloblastic anemia Paroxysmal nocturnal hemoglobinuria
Decreased Platelet Survival
Immunologic Destruction
Autoimmune: ITP, systemic lupus erythematosus Isoimmune: posttransfusion and neonatal Drug-associated: quinidine, heparin, sulfa compounds Infections: infectious mononucleosis, HIV infection, cytomegalovirus infection
Nonimmunologic Destruction
Disseminated intravascular coagulation TTP Giant hemangiomas Microangiopathic hemolytic anemias
Sequestration
Hypersplenism
Dilutional
Multiple transfusions (e.g., for massive blood loss)

Immune Thrombocytopenic Purpura (ITP)

- includes two clinical subtypes:

1. *Chronic ITP*: A relatively common disorder, affect women 20-40 years.
2. *Acute ITP*: A self-limited form, seen mostly in children after viral infections.

- **Pathogenesis: Antibodies against platelet membrane glycoproteins IIb/IIIa or Ib/IX complexes (detected in ~ 80% of cases of chronic ITP)**
- Splenectomy→ normalizes the platelet count & induces a complete remission in more than two-thirds of patients.
    - Splenomegaly is not a feature of uncomplicated ITP
    - But the spleen is an important site of anti-platelet antibody production
    - the spleen is major site of the premature destruction of the IgG-coated platelets.
- BM contains increased numbers of megakaryocytes (common to all forms of thrombocytopenia due to accelerated platelet destruction)

Immune Thrombocytopenic Purpura

- The onset of chronic ITP is insidious.
- Common findings: petechiae, easy bruising, epistaxis, gum bleeding, and hemorrhages after minor trauma.
- More serious intracerebral or subarachnoid hemorrhages are uncommon.
- The diagnosis rests on the clinical features; thrombocytopenia, examination of the marrow, and the exclusion of secondary ITP.
- Reliable clinical tests for anti-platelet antibodies are not available.
- Treatment usually involves the use of immunosuppressive agents and, in some cases, splenectomy.

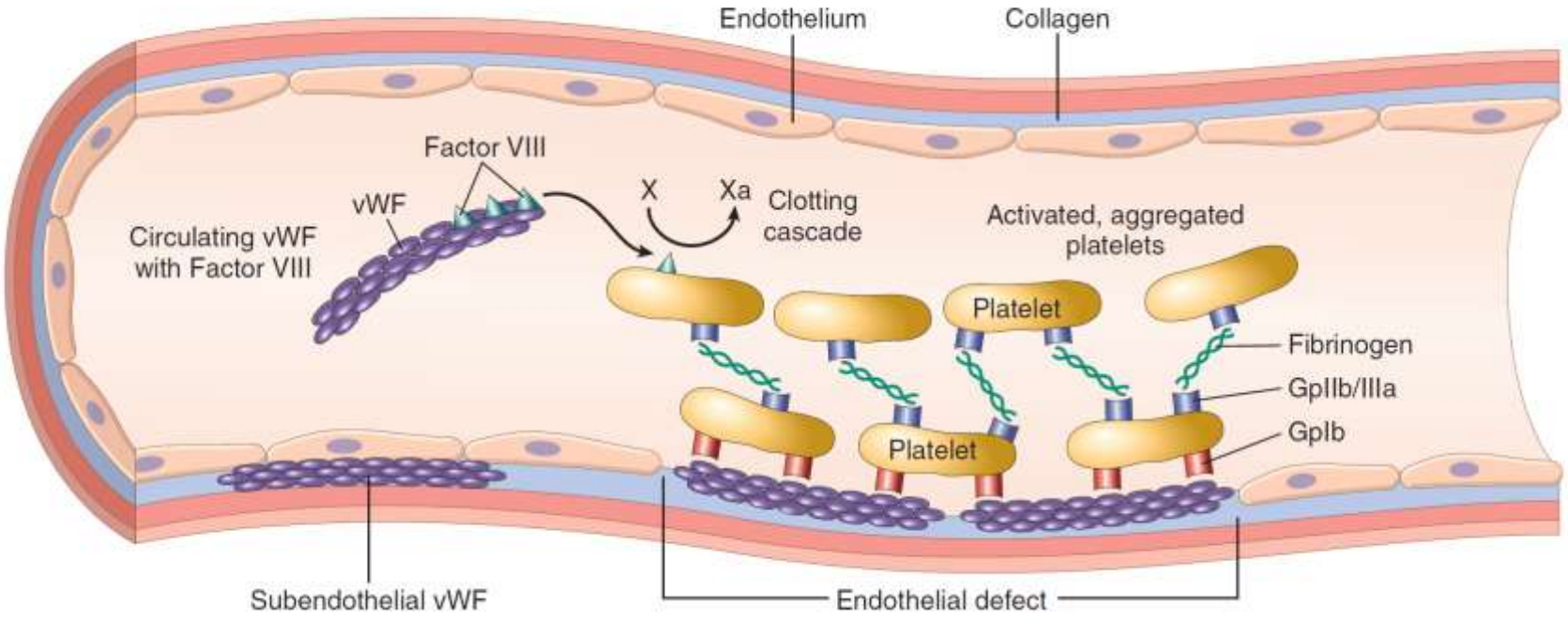
Thrombotic Microangiopathies: TTP and HUS

- thrombotic microangiopathies encompasses a spectrum of clinical syndromes:
  - Thrombocytopenic purpura (TTP).
  - Hemolytic uremic syndrome (HUS).
- TTP is associated with the **pentad**: fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, & renal failure
- HUS also is associated with microangiopathic hemolytic anemia and thrombocytopenia, no neurologic symptoms, the dominance of acute renal failure, and frequent occurrence in **children**.
- thrombotic microangiopathies has a widespread formation of platelet-rich thrombi in the microcirculation.
- Platelets consumption → thrombocytopenia + narrowing of blood vessels by the platelet-rich thrombi → a microangiopathic hemolytic anemia.

Thrombotic Microangiopathies: TTP and HUS

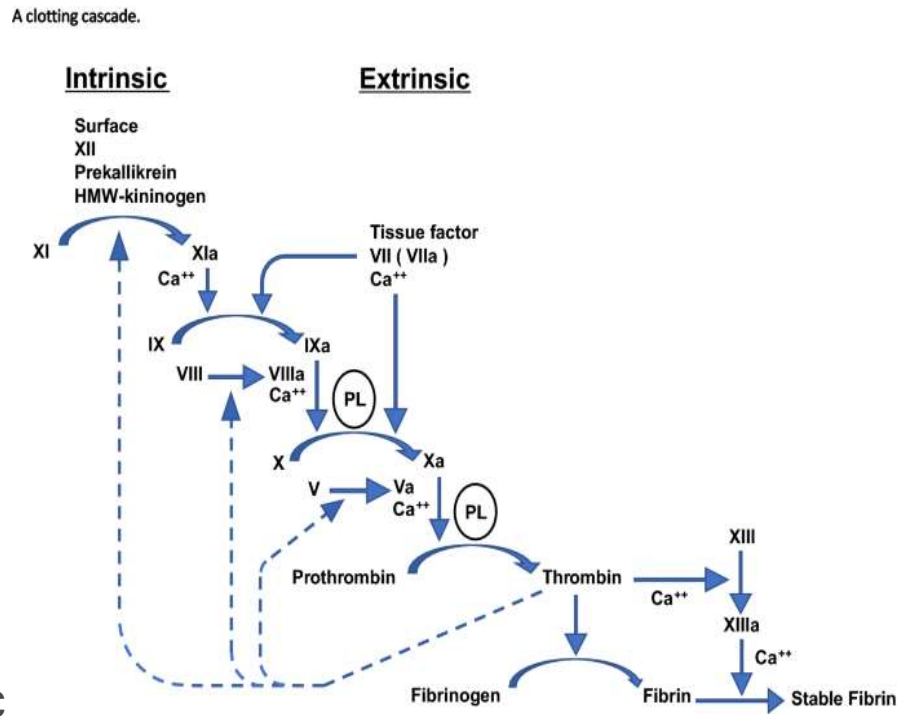
- TTP usually affects adult, pathogenic mechanism:
  1. Inherited: Deficiency of metalloprotease (ADAMTS 13) needed for cleaving very HMW_vWF (multimers).
  2. Sporadic, more common, non-familial acquired: autoantibody against ADAMTS 13.
- HUS more commonly seen in pediatric population, pathogenesis:
  - E. coli O157:H7 (toxin induced endothelial damage)
  - Clinical Picture: Bloody diarrhea followed by acute renal failure.
- Unlike in DIC, in TTP and HUS activation of the coagulation cascade is not of primary importance, and so the results of laboratory tests of coagulation (PT and PTT tests) usually are normal.

Factor VIII–von Willebrand factor (vWF) complex



von Willebrand factor (vWF)

- Endothelial cells are the major source of plasma vWF.
- vWF is found in the plasma (in association with factor VIII), in platelet granules, in endothelial cells (cytoplasmic Weibel-Palade bodies) and in the subendothelium
- Factor VIII is synthesized in the liver.
- factor VIII is an essential cofactor for factor IX, which activates factor X in the intrinsic coagulation pathway



von Willebrand disease

- An autosomal dominant disorder.
- Presents as spontaneous bleeding from mucous membranes, excessive bleeding from wounds, and menorrhagia.
- Underrecognized, 1) the diagnosis requires sophisticated tests 2) the clinical manifestations often are mild.
- But prevalent, particularly in Europeans; ~ 1% of US
- The most common inherited bleeding disorder.
- Patients have compound defects in platelet function & coagulation, mostly the platelet defect produces clinical findings.
- Homozygous von Willebrand disease, the deficiency of factor VIII severe enough to produce features resembling hemophilia.

von Willebrand disease

- The effects of the causative mutations vary → divided into several subtypes:

❖ **Type I:** the classic and most common variant. AD.
  - the quantity of circulating vWF is reduced.
  - clinically insignificant decrease in factor VIII levels.

❖ **Type II**: characterized by the selective loss of high–molecular-weight multimers of vWF. (the most active form of vWF)
  - there is a functional deficiency of vWF.
  - Divided to IIA, the multimers are not synthesized (true deficiency) and type IIB, abnormal “hyperfunctional” multimers are synthesized but rapidly removed from the circulation.
  - Can cause spontaneous platelet aggregation (reminiscent TTP), some people with type IIB have mild chronic thrombocytopenia, from platelet consumption.

von Willebrand disease

- Diagnosed by measuring the quantity, size, and function of vWF.
- vWF function is assessed using the **ristocetin** platelet agglutination test.
- Ristocetin somehow “activates” the bivalent binding of vWF and platelet membrane glycoprotein Ib → creating interplatelet “bridges” → platelets clumping (agglutination) → an event that can be measured easily.
- Ristocetin-dependent platelet agglutination serves as a useful bioassay for vWF.

Hemophilia A—Factor VIII Deficiency

- **The most common hereditary cause of serious bleeding.**
- **A**n X-linked recessive disorder caused by reduced factor VIII activity.
- Primarily affects males
- ~ 30% of cases are caused by new mutations; the rest has family history.
- Severe hemophilia A is observed in people with marked deficiencies of factor VIII (activity levels < 1% of normal).
- Milder deficiencies may only become apparent in the face of trauma stresses.
- The varying degrees of factor VIII deficiency are explained by the existence of many different causative mutations.
- 10% of patients with normal factor VIII concentration but low coagulant activity → a mutation that cause production of defective factor VIII.

Hemophilia A—Factor VIII Deficiency

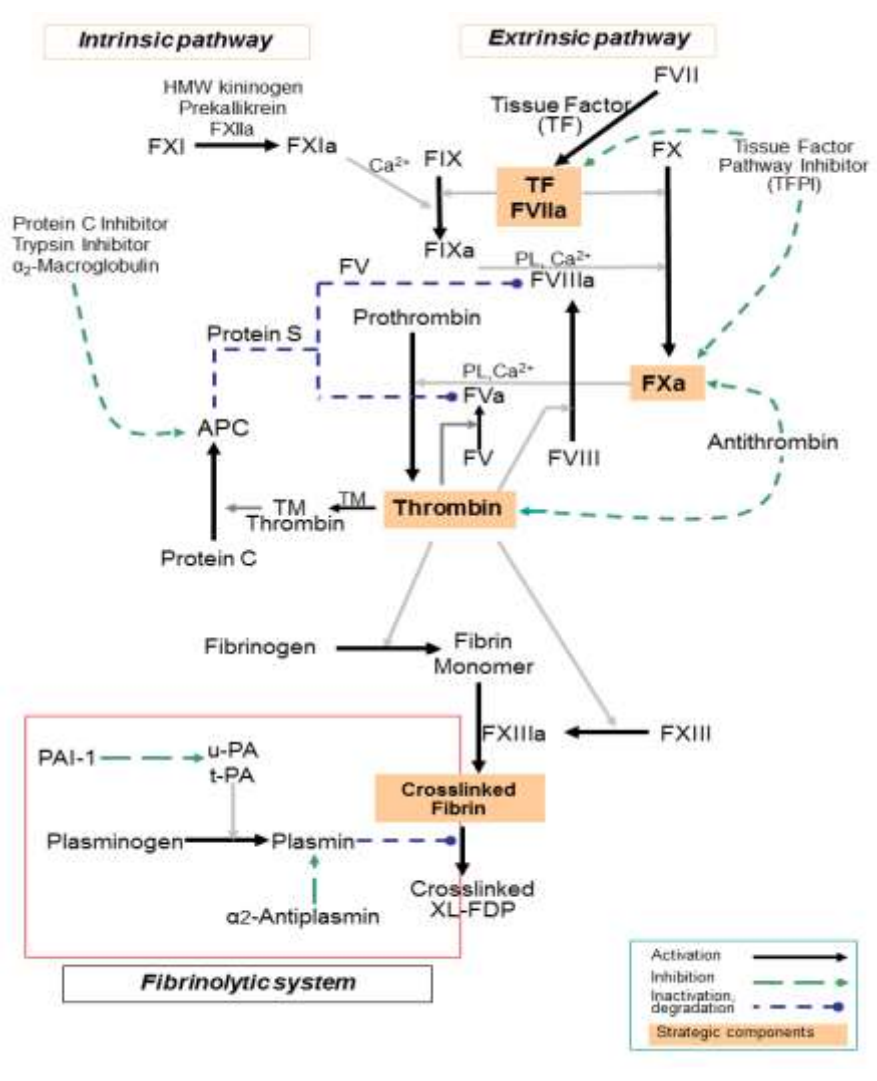
- **Presentation**: easy bruising and massive hemorrhage after trauma or operative procedures.
- Bleeding sites: joints *(hemarthroses), soft tissue, brain*
- Petechiae are characteristically absent.
- A prolonged PTT that is corrected by mixing the patient's plasma with normal plasma.
- Specific assays of factor VIII is used to confirm the diagnosis.
- Hemophilia A is treated with factor VIII infusions.

Hemophilia B—Factor IX Deficiency

- Severe factor IX deficiency is an X-linked disorder.
- Indistinguishable clinically from hemophilia A, but much less common.
- The PTT is prolonged.
- The diagnosis is made using specific assays of factor IX.
- It is treated by infusion of recombinant factor IX.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- **A complication of a wide variety of disorders → caused by systemic activation of coagulation →formation of thrombi throughout the microcirculation.**
- Platelets and coagulation factors are consumed and, secondarily, fibrinolysis is activated:
  - tissue hypoxia and microinfarcts caused by numerous microthrombi
  - a bleeding disorder related to pathologic activation of fibrinolysis and the depletion of the elements required for hemostasis (consumptive coagulopathy)



Obstetric Complications

Abruptio placentae
Retained dead fetus
Septic abortion
Amniotic fluid embolism
Toxemia

Infections

Sepsis (gram-negative and gram-positive)
Meningococcemia
Rocky Mountain spotted fever
Histoplasmosis
Aspergillosis
Malaria

Neoplasms

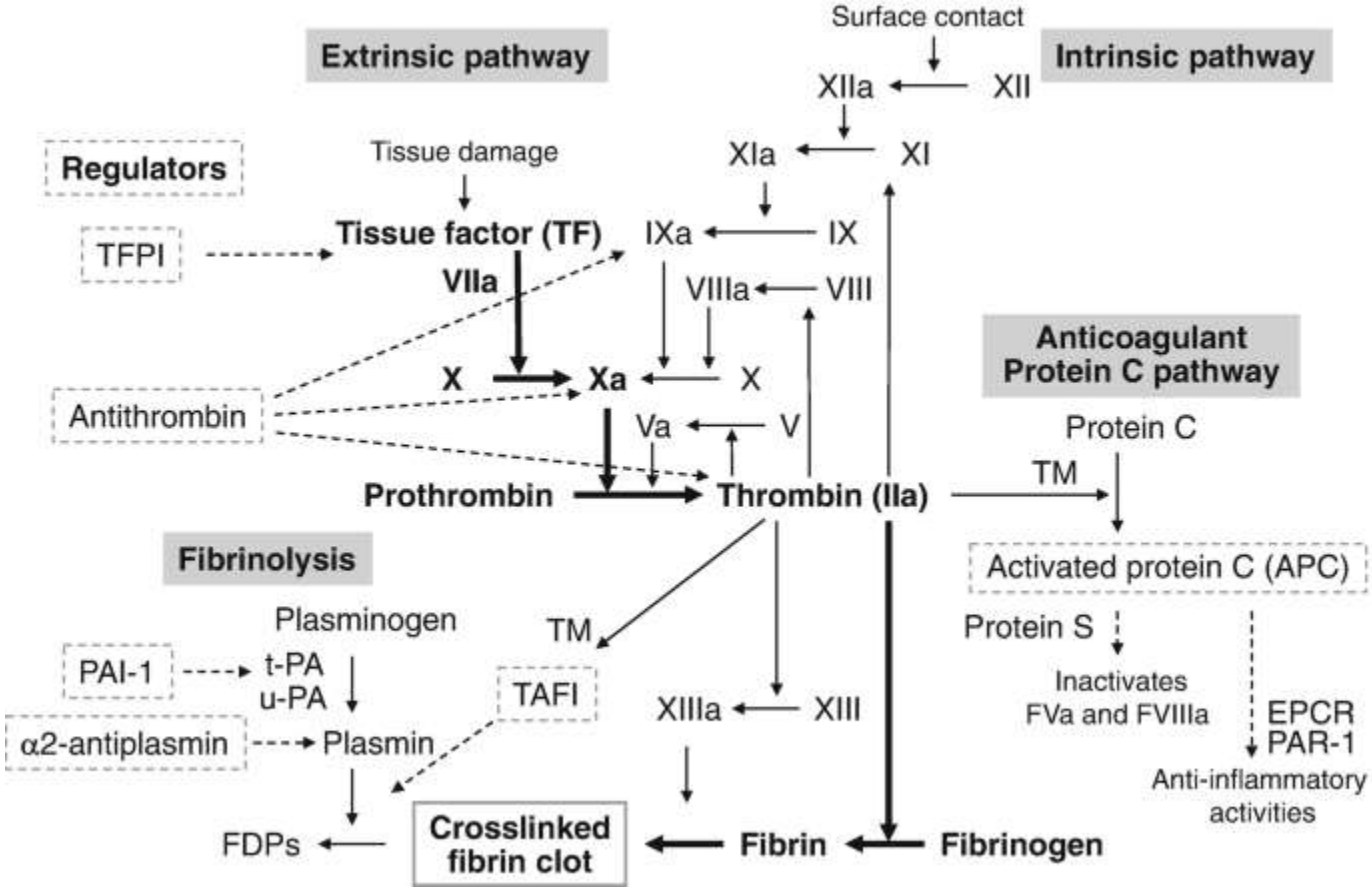
Carcinomas of pancreas, prostate, lung, and stomach
Acute promyelocytic leukemia

Massive Tissue Injury

Trauma
Burns
Extensive surgery

Miscellaneous

Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease


Extrinsic pathway
Surface contact
Intrinsic pathway
XIIa
XII
Regulators
Tissue damage
XIa
XI
TFPI
Tissue factor (TF)
IXa
IX
VIIa
VIIIa
VIII
Anticoagulant
Protein C pathway
X
Xa
X
Antithrombin
Va
V
Protein C
TM
Prothrombin
Thrombin (IIa)
Fibrinolysis
Activated protein C (APC)
Plasminogen
TM
Protein S
PAI-1
t-PA
u-PA
TAFI
XIIIa
XIII
Inactivates
FVa and FVIIIa
EPCR
PAR-1
α2-antiplasmin
Plasmin
Anti-inflammatory
activities
FDPs
Crosslinked
fibrin clot
Fibrin
Fibrinogen

DIC usually is triggered by either

The release of tissue factor or thromboplastic substances into the circulation

- obstetric complications (placenta)
- some cancer cells.
- gram-negative & -positive sepsis endotoxins or exotoxins stimulate the release of tissue factor from monocytes

Widespread endothelial cell damage

- deposition of AntiG/AntiB complexes (e.g. SLE),
- Temperature extremes (e.g. heat stroke or burn injury).
- Infections (e.g., meningococci or rickettsiae
- Systemic inflammatory response syndrome (SIRS) triggered by sepsis & other systemic insults.

DIC, two main consequences.

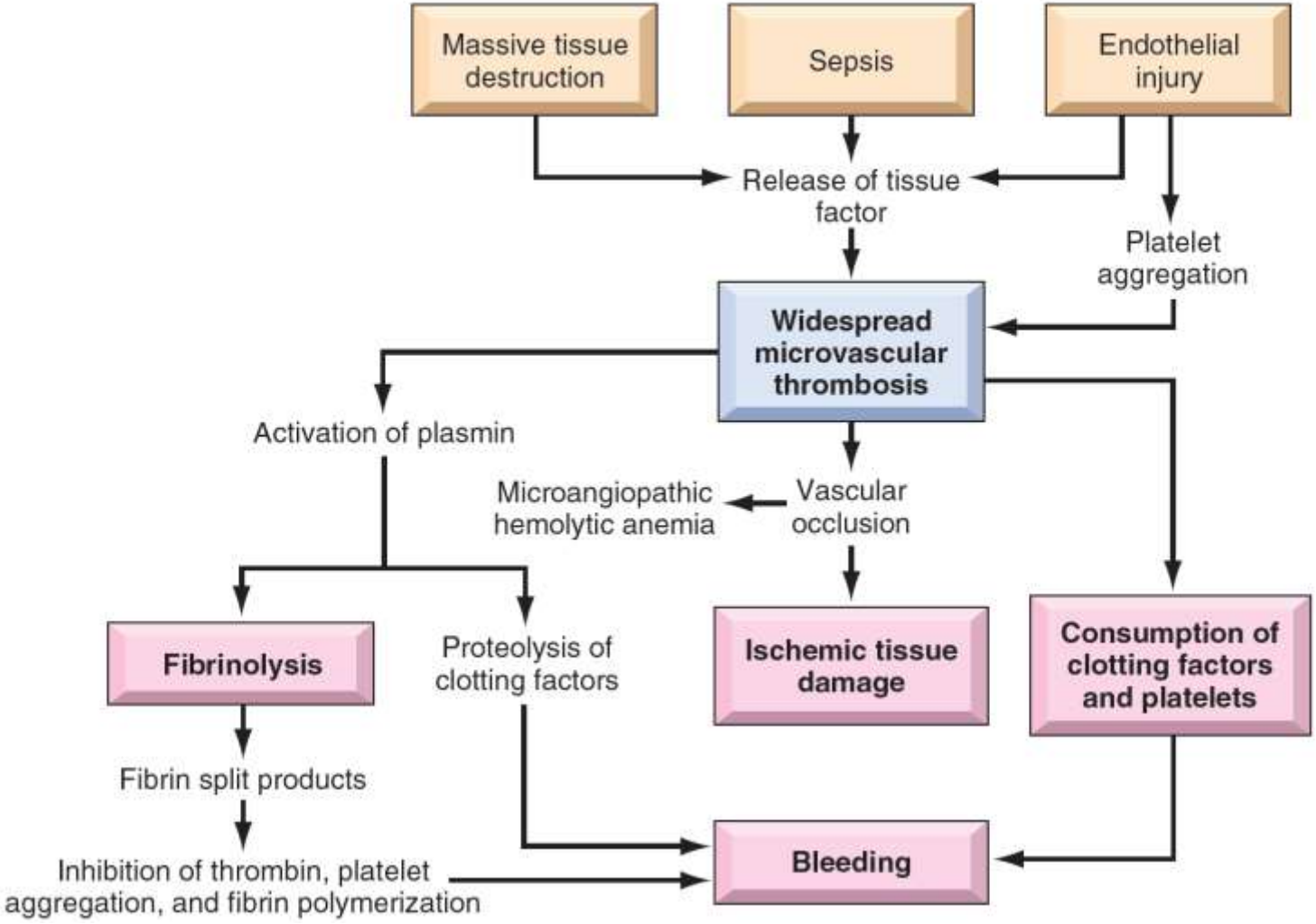
- **First, widespread fibrin deposition within the microcirculation:**

1. Obstruction → ischemia (more severely affected or vulnerable organs)
2. hemolysis → RBCs are traumatized while passing through vessels narrowed by fibrin thrombi *(microangiopathic hemolytic anemia)*.

- **Second, platelets & clotting factors depletion and the secondary release of plasminogen activator:**

Superimposed bleeding tendency?

- Plasmin cleaves not only to fibrin (fibrinolysis) but also to factors V and VIII, (reducing their concentration)
- Fibrinolysis creates fibrin degradation products → inhibit platelet aggregation→ have anti-thrombin activity.
- all of which contribute to the hemostatic failure


Massive tissue destruction
Sepsis
Endothelial injury
Release of tissue factor
Platelet aggregation
Widespread microvascular thrombosis
Activation of plasmin
Microangiopathic hemolytic anemia
Vascular occlusion
Fibrinolysis
Proteolysis of clotting factors
Ischemic tissue damage
Consumption of clotting factors and platelets
Fibrin split products
Inhibition of thrombin, platelet aggregation, and fibrin polymerization
Bleeding

DIC Clinical

- Depending on the balance between clotting and bleeding tendencies, the range of possible clinical manifestations is enormous, usually:
  - Acute DIC (in obstetric complications) is dominated by **bleeding**.
  - Chronic DIC (in cancer) tends to manifest with signs and symptoms related to **thrombosis**.
- The abnormal clotting usually is confined to the microcirculation, but large vessels are involved on occasion.

- The manifestations may be minimal, or there may be shock, acute renal failure, dyspnea, cyanosis, convulsions, and coma.

- The prognosis varies widely depending on the nature of the underlying disorder and the severity of the intravascular clotting and fibrinolysis.
- Acute DIC can be life threatening and must be treated aggressively with anticoagulants such as heparin or the coagulants contained in fresh frozen plasma.
- Chronic DIC is sometimes identified unexpectedly by laboratory testing.

In either circumstance, definitive treatment must be directed at the underlying cause