Hemostasis and Shock

Bleeding Disorders

➢ Vascular Disorders:
• Diagnosis by exclusion
• Lab of limited value

➢ Platelet Disorders:
• Adhesion, Aggregation, Secretion

➢ Coagulation Factor Deficiencies:
• Hemophilias
• Others

Bleeding Disorders

● Clinical Symptoms:

➢ Platelet Symptoms:

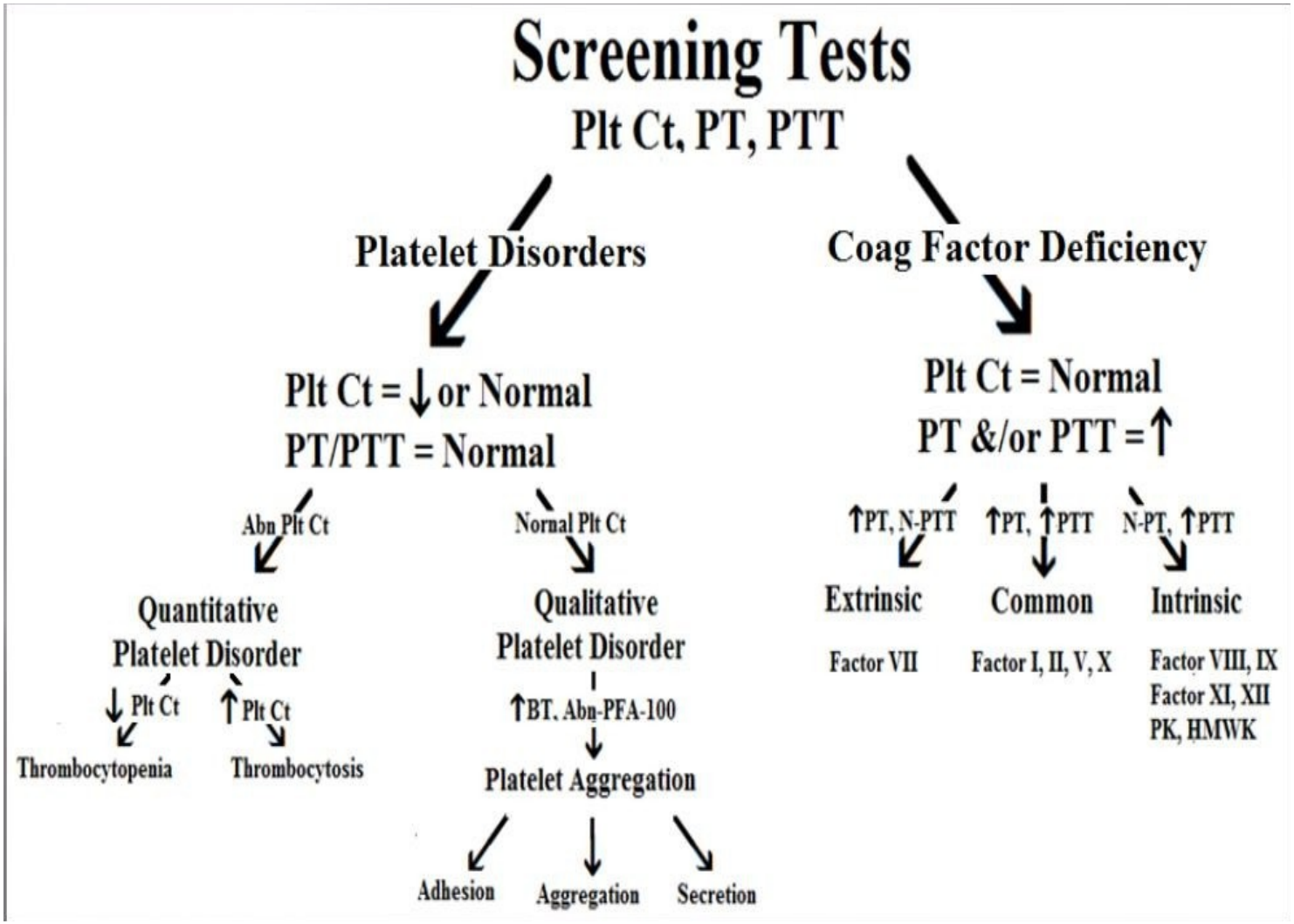
• Petechiae>>Bruising>>Mucosal Bleeding>>Purpura

➢ Indeterminant Symptoms:

• Prolonged Bleeding>>General Bleeding

➢ Coagulation factor Symptoms:

• Resumed Bleeding>>Ecchymoses>>Hemarthroses


Screening Tests
Plt Ct, PT, PTT
Platelet Disorders
Coag Factor Deficiency
Plt Ct = ↓ or Normal
PT/PTT = Normal
Plt Ct = Normal
PT &/or PTT = ↑
Abn Plt Ct
Nornal Plt Ct
↑PT, N-PTT
↑PT, ↑PTT
N-PT, ↑PTT
Quantitative Platelet Disorder
Qualitative Platelet Disorder
Extrinsic
Common
Intrinsic
↓ Plt Ct
↑ Plt Ct
↑BT, Abn-PFA-100
Factor VII
Factor I, II, V, X
Factor VIII, IX
Factor XI, XII
PK, HMWK
Thrombocytopenia
Thrombocytosis
Platelet Aggregation
Adhesion
Aggregation
Secretion

Bleeding Disorders

Platelet Disorders

Platelet Disorders:

● Thrombocytopenia:

➢ Five categories of causes:

- **Increased destruction**

  Short platelet life , ITP , Transplacental, Drug induced , TTP , DIC , artifact

- **Decreased production**

  Bone marrow is not producing platelets adequately

  (Cancer, chemo, radiation, aplastic anemia)

- **Increased splenic sequestration**

  Spleen is removing platelets to fast

- **Dilutional**

  Massive blood transfusions

- **Multifactoral**

  Disorders that affect platelets in multiple ways

Platelet Disorders:

●Thrombocytosis:

➢ **Primary (Pre-leukemias)**

- Essential thrombocythemia (ET)

  Platelets are >400,000 but often >1,000,000/uL

- Polycythemia vera (PV)

  RBC and platelets are elevated

➢ **Secondary (Thrombocytosis from another disorder)**

- Following acute hemorrhage
- Following splenectomy
- Following recovery from alcoholism, cancer, IDA

Platelet Disorders:

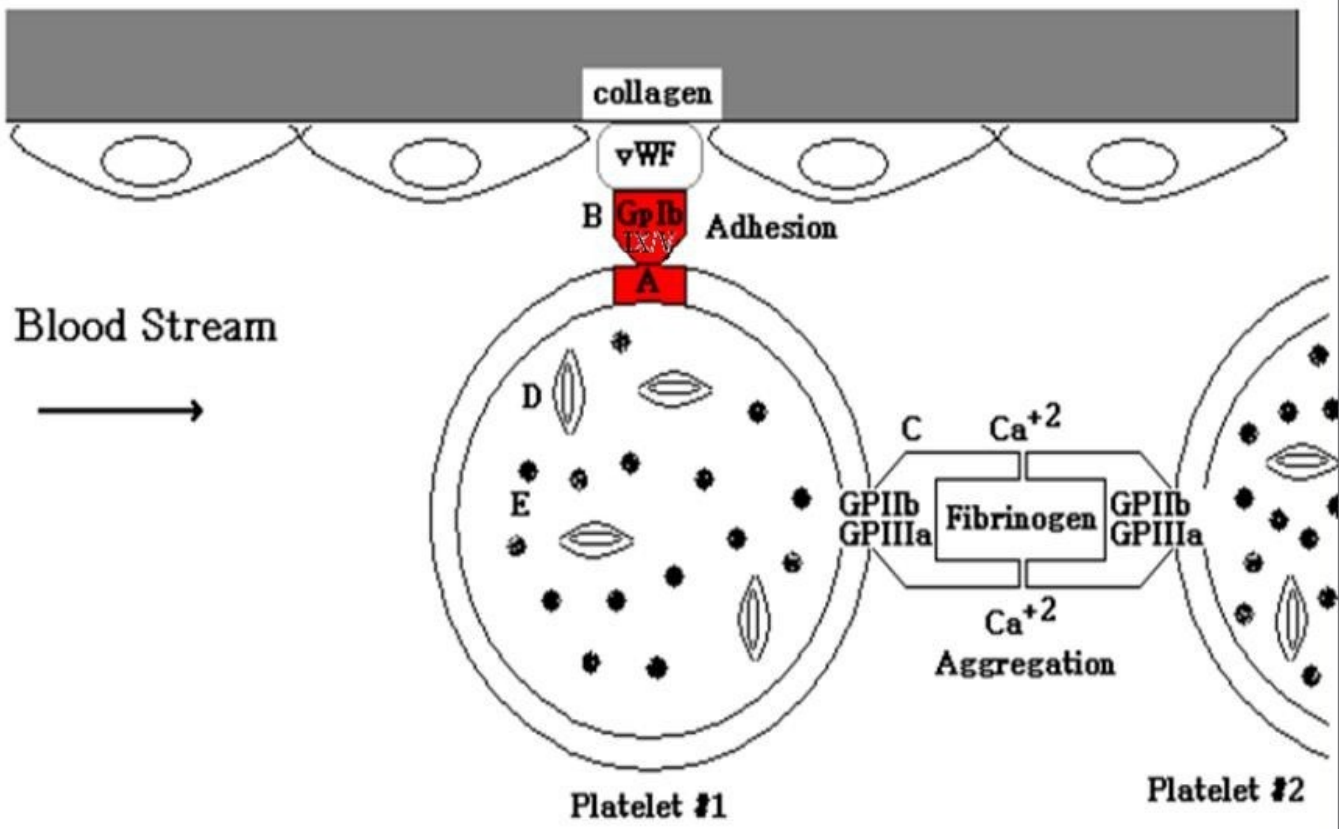
- Inherited Qualitative Disorders

➢ Platelet Adhesion Disorders:

- Bernard Soulier
  - Autosomal recessive
  - Decreased platelet glycoproteins (GPIb/IX/V)
  - Treat with plt transfusions
- Von Willebrand's Disease
  - Autosomal dominant (1 in 10,000)
  - Decrease in plasma & platelet VWF
  - Treat with cryoprecipitate or DDAVP

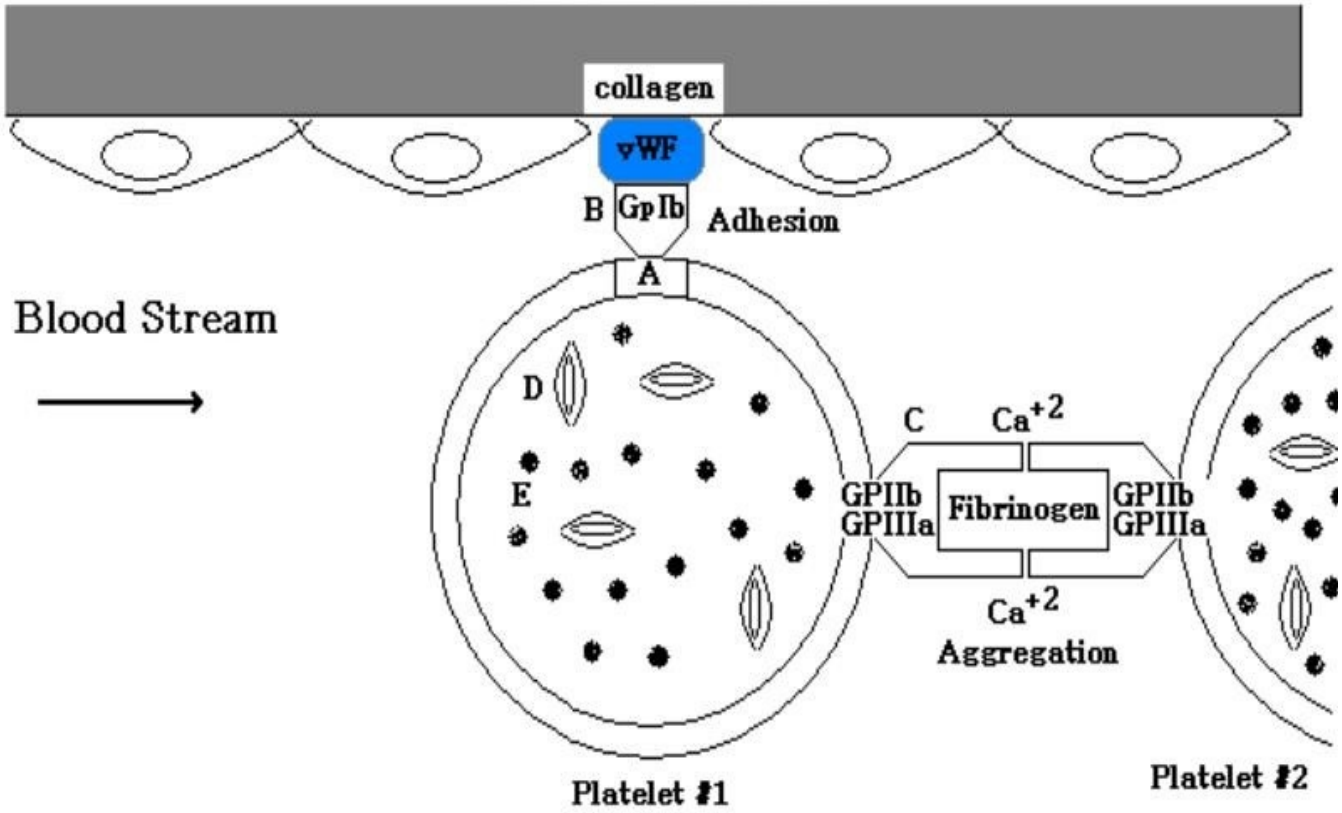
Inherited Platelet Disorders

Bernard-Soulier



Inherited Platelet Disorders

von Willebrand's



Platelet Disorders:

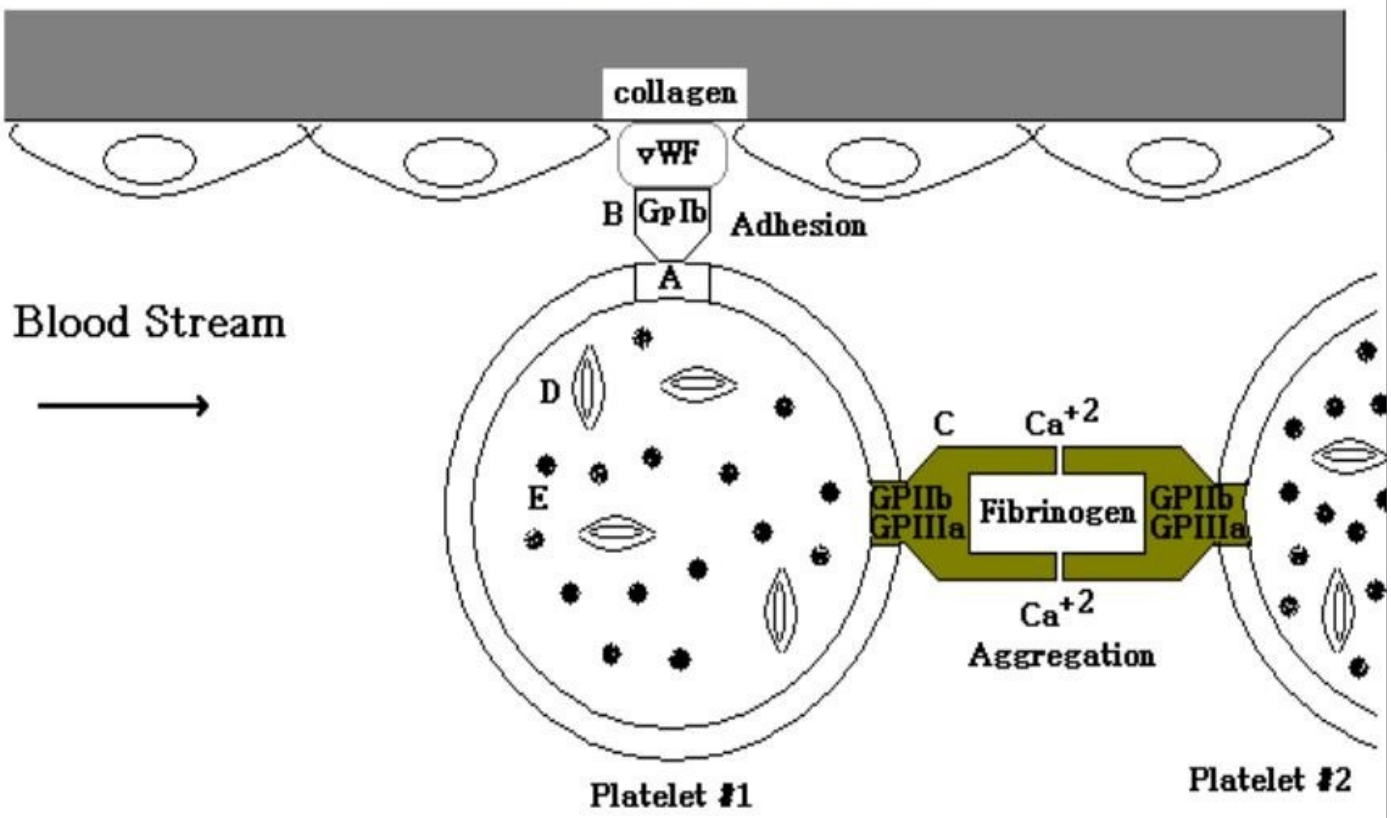
- Aggregation Disorders:

➢ Afibrinogenemia
  - Autosomal recessive
  - Binds GPIIb/IIIa receptors
  - Cryoprecipitate or FFP

➢ Glanzman's Thrombasthenia
  - Autosomal recessive
  - Deficiency of GPIIb/IIIa receptor
  - Platelet transfusions or BMT

Inherited Platelet Disorders

Glanzman's Thrombasthenia



Platelet Disorders:

- Secretion Disorders (Mild Bleeding)

➢ Storage Pool Disease
  - Dense Body Deficiency

➢ Aspirin
  - Inhibits cyclooxygenase enzyme for a week (TXA2)

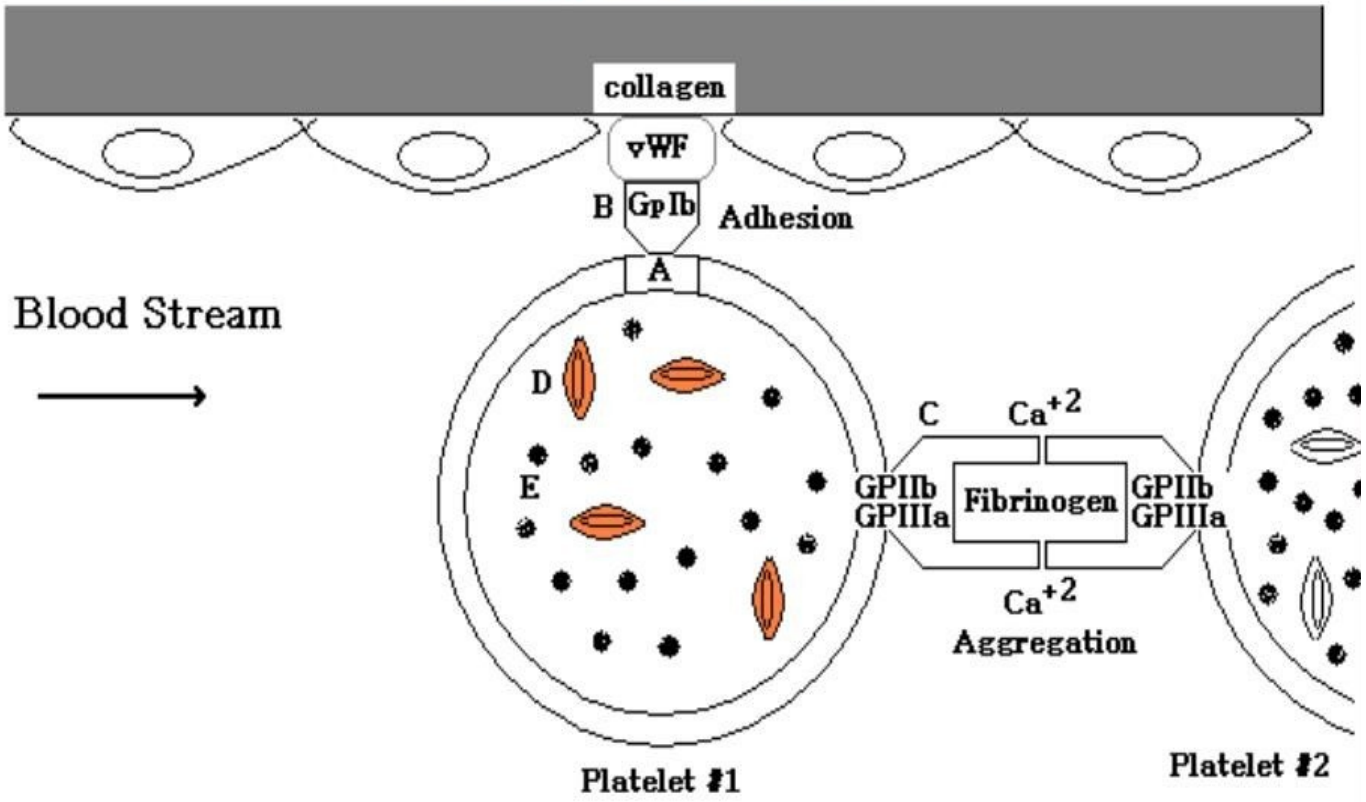
➢ Uremia
  - Renal disease
  - Treat with dialysis or renal transplant

➢ TXA2 Deficiency

➢ Gray Platelet Syndrome
  - No bleeding and normal labs

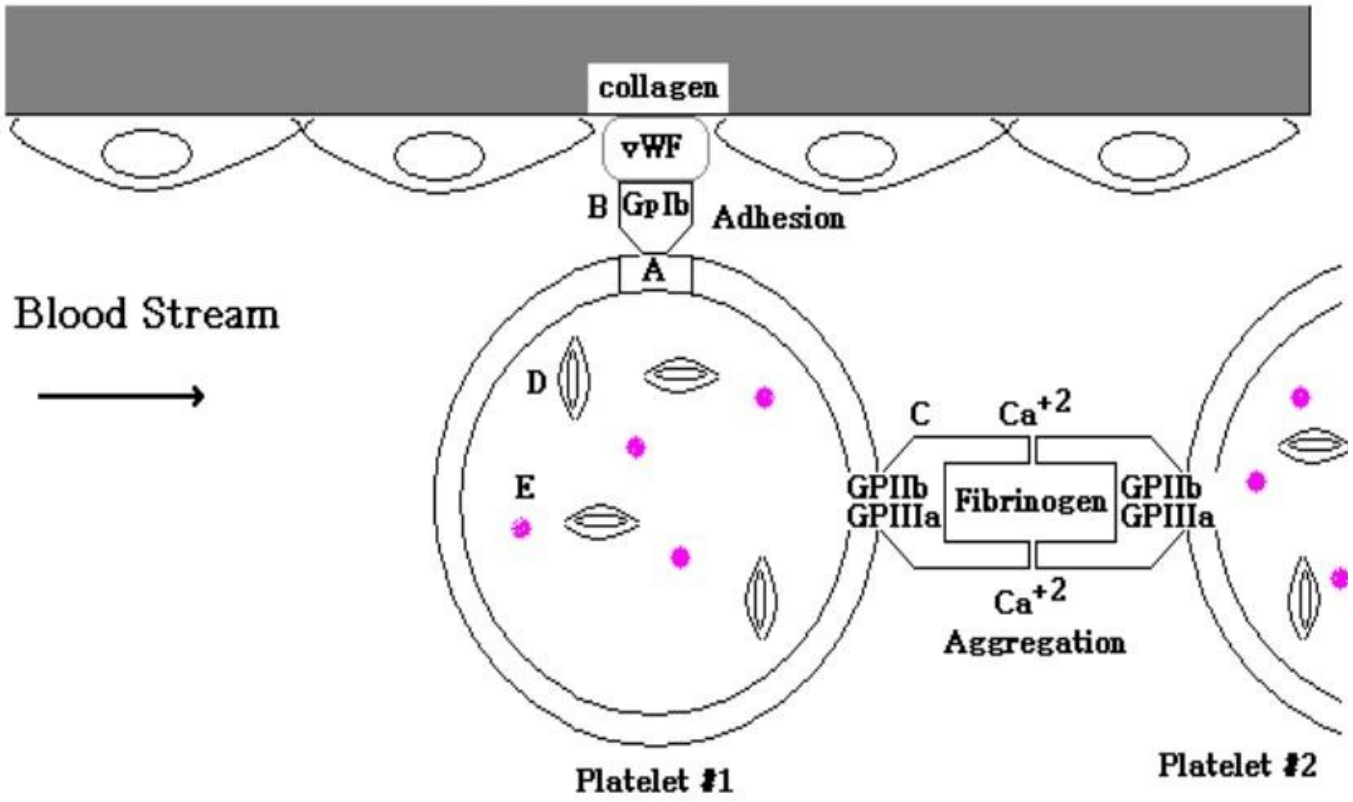
Inherited Platelet Disorders

Storage Pool Disease



Inherited Platelet Disorders

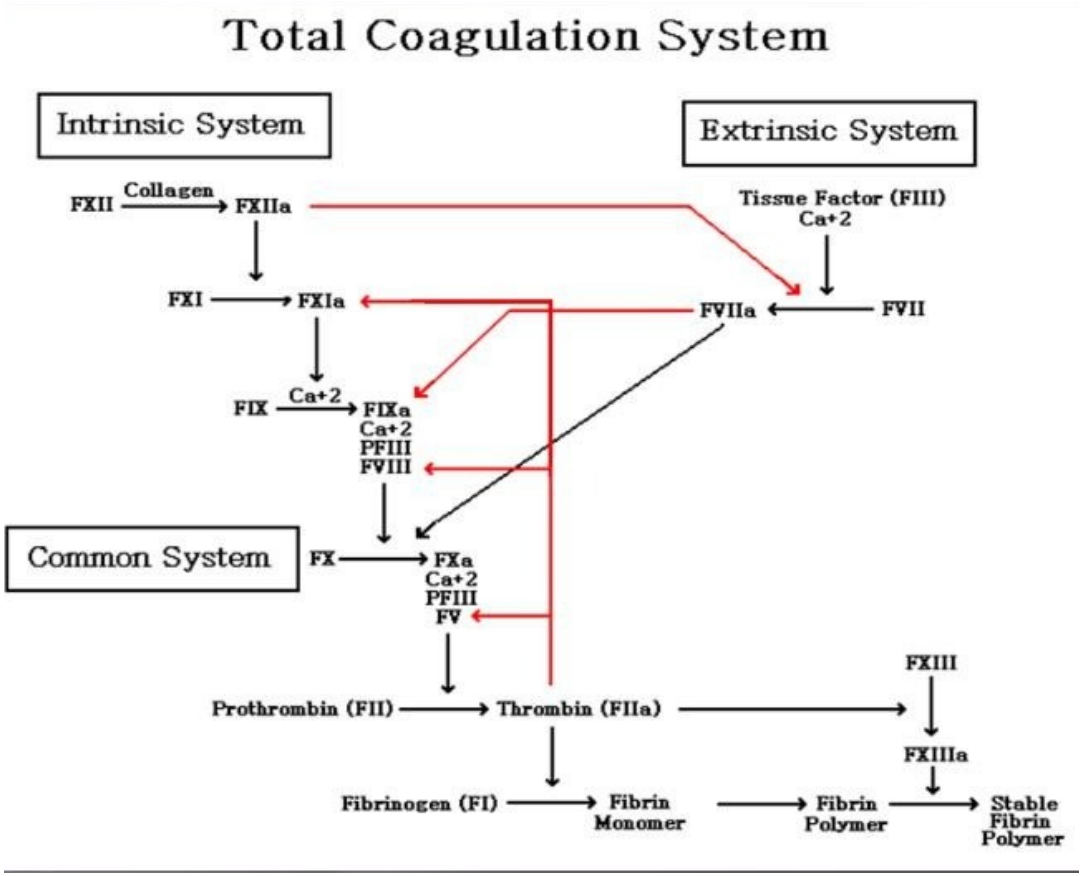
Gray Platelet Syndrome



Bleeding disorders

Coagulation Factor Deficiencies

Coagulation Factor Disorders



Coagulation Factor Disorders

- Intrinsic System Deficiencies
  - X-linked
    - Most common
    - Occurs in males
  - ➢ Factor VIII
    - 1 in 12,500
    - Treated with FVIII concentrate
    - Cryoprecipitate
  - ➢ Factor IX
    - 1 in 50,000
    - Treated with Factor IX concentrate
    - Prothrombin Complex
  - Complications
    - Antibodies and blood borne pathogens (Hep B/C & HIV)

Coagulation Factor Disorders

X-Linked Coagulation Disorders (Intrinsic Factor Deficiencies)		
LAB TEST	**FVIII**	**FIX**
Platelet count	Normal	Normal
Bleeding Time/PFA-100	Normal	Normal
Aggregation ADP	Normal	Normal
Aggregation Collagen	Normal	Normal
Aggregation Epi	Normal	Normal
Aggregation Ristocetin	Normal	Normal
PT	Normal	Normal
PTT	Prolonged	Prolonged
vWF:Ag	Normal	Normal
FVIII Assay	Decreased	Normal
FIX Assay	Normal	Decreased

Coagulation Factor Disorders

- Autosomal Intrinsic Disorders
  - ➢ Factor XI (Hemophilia C)
    - • Rare but most common in Ashkenazi Jewish
    - • Mild bleeding in homozygotes
  - ➢ Factor XII (Hagaman Disease)
    - • No bleeding but significant risk of thrombosis
  - ➢ Prekallikrein & HMWK
    - • No bleeding symptoms (Incubated PTT)
- Treatment usually not required

Coagulation Factor Disorders

Autosomal Intrinsic Factor Deficiencies				
Test	**XI**	**XII**	**PK**	**HMWK**
Plt	N	N	N	N
BT/PFA-100	N	N	N	N
PT	N	N	N	N
PTT	↑	↑	↑	↑
TT	N	N	N	N
Fib	N	N	N	N
FA	↓	↓	↓	↓
FDP	N	N	N	N

Coagulation Factor Disorders

- Fibrinogen Defect (Common Factor Deficiencies)

➢ Inherited

- Autosomal Recessive (Dominant for Dysfibrinogenemia)

➢ Three defects

- Afibrinogenemia
  - Homozygous mutation with little to no detectable amount
  - Umbilical bleeding, surgery, trauma, rare hemarthrosis
- Hypofibrinogenemia
  - Heterozygous mutation with 20-100mg/dLfibrinogen
  - Few if any bleeding symptoms
- Dysfibrinogenemia
  - Abnormal form of fibrinogen synthesized at normal levels
  - No bleeding in most and mild bleeding in some

➢ Treat with cryoprecipitate or FFP

Coagulation Factor Disorders

Fibrinogen Disorders (Common Factor Deficiencies)			
Test	**Afib**	**Hypo**	**Dys**
Plt	N	N	N
PFA-100	N	N	N
BT	↑	N	N
PT	↑	N	N
PTT	↑	N	N
TT	↑	↑	↑
Fib	0	↓	?
FA	NA	NA	NA
FDP	N	N	N

Coagulation Factor Disorders

Common Factor Disorders			
Test	**II**	**X**	**V**
Plt	N	N	N
BT/PFA-100	N	N	N
PT	↑	↑	↑
PTT	↑	↑	↑
TT	N	N	N
Fib	N	N	N
FA	↓	↓	↓
FDP	N	N	N

Coagulation Factor Disorders

- Extrinsic Factor Deficiencies
  - ➢ Factor VII Deficiency
    - Incidence
      - 1 in 500,000 (Moderately rare)
    - Factor (Protein) levels
      - Homozygote = <10%
      - Heterozygote = 40-60%
    - Clinical Symptoms
      - Varied symptoms from manifesting late to severe
    - Treatment
      - Fresh Frozen Plasma
      - Prothrombin Complex

Coagulation Factor Disorders

Extrinsic Factor Deficiencies	
Test	**VII**
Plt	N
BT	N
PT	↑
PTT	N
TT	N
Fib	N
FA	↓
FDP	N

Coagulation Factor Disorders

- Factor XIII Deficiency
  - ➢ Incidence
    - Extremely Rare
  - ➢ Clinical Symptoms
    - 25% have umbilical bleeding
    - Bleeding following trauma and surgery
    - Keloid Formation (abnormal scaring)
  - ➢ All coagulation tests are normal
    - Abnormal urea solubility test (5M)
  - ➢ Treatment
    - Fresh Frozen Plasma

Coagulation Factor Disorders

X-linked Intrinsic			Autosomal Intrinsic				Common			Ext.	N/A
Test	**VIII**	**IX**	**XI**	**XII**	**PK**	**HMWK**	**II**	**X**	**V**	**VII**	**XIII**
Plt	N	N	N	N	N	N	N	N	N	N	N
BT	N	N	N	N	N	N	N	N	N	N	N
PT	N	N	N	N	N	N	↑	↑	↑	↑	N
PTT	↑	↑	↑	↑	↑	↑	↑	↑	↑	N	N
TT	N	N	N	N	N	N	N	N	N	N	N
Fib	N	N	N	N	N	N	N	N	N	N	N
FA	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
FDP	N	N	N	N	N	N	N	N	N	N	N

Coagulation Factor Disorders

- Disseminated Intravascular Coagulation (DIC)
  - ➢ 1ry Disease that triggers massive coagulation
    - Releases thromboplastin (trauma, pregnancy, cancer)
    - Exposure of collagen (trauma, BP, sepsis, cancer)
    - Exposure of enzymes (toxins, venoms)
    - Consumes platelets and coag factors
    - Activates fibrinolysis
  - ➢ Acute DIC
    - 80-90% - bleeding
  - ➢ Chronic DIC
    - 10-20% - thrombosis
  - ➢ Treatment
    - 1ry Disease + replacement therapy (RBC, Plt, FFP)

Coagulation Factor Disorders

Lab Test	DIC
Platelet Count	Decreased ↓↓
PT	Prolonged (↓)
aPTT	Prolonged (↓)
Thrombin Time	Prolonged (↓)
Fibrinogen	Decreased
FDP/D-dimer	Increased ↑↑
Fibrin Monomer	Increased
Fibrinopeptides	Increased
Plasminogen	Decreased
Antithrombin III	Decreased
Factor Assays	↓ in all factors
Blood Smear	Schistocytes

Acquired Coagulation Disorders

- Liver Disease
  - ➢ Causes
    - Cancer, Hepatitis, Alcoholism
      - Decreased production
  - ➢ Treatment
    - Treat primary disease
    - FFP
    - Platelets

Acquired Coagulation Disorders

Lab Test	DIC	Liver Disease
Platelet Count	Decreased ↓↓	Decreased ↓
PT	Prolonged (↓)	Prolonged
aPTT	Prolonged (↓)	Prolonged
Thrombin Time	Prolonged (↓)	Prolonged
Fibrinogen	Decreased	Decreased
Factor Assays	↓ in all factors	↓ in all factors
FDP/D-dimer	Increased ↑↑	Increased ↑
Fibrin Monomer	Increased	Normal
Fibrinopeptides	Increased	Normal
Plasminogen	Decreased	Normal
Antithrombin III	Decreased	Normal
Blood Smear	Schistocytes	No Schistocytes

Acquired Coagulation Disorders

- Vitamin K Deficiency in adults
  - Causes of Vitamin K Deficiency
    - Poor Diet
      - Lack of green leafy vegetables
    - Antibiotic Therapy
      - Sterilizes gut
    - Malfunctioning Liver
      - Cannot complete g-carboxylation
- Vitamin K Deficiency in newborns
  - Hemorrhagic Disease of the Newborn
    - Causes
      - Immature Liver
      - Sterile Gut
      - No food by mouth
    - Clinical Manifestations
      - Bleeding from umbilical cord or circumcision

Acquired Coagulation Disorders

Lab Test	DIC	Liver Disease	Vitamin K Def.
Platelet Count	Decreased ↓↓	Decreased ↓	Normal
PT	Prolonged (↓)	Prolonged	Prolonged
aPTT	Prolonged (↓)	Prolonged	Prolonged
Thrombin Time	Prolonged (↓)	Prolonged	Normal
Fibrinogen	Decreased	Decreased	Normal
FDP/D-dimer	Increased ↑↑	Increased ↑	Normal
Fibrin Monomer	Increased	Normal	Normal
Fibrinopeptides	Increased	Normal	Normal
Plasminogen	Decreased	Normal	Normal
Antithrombin III	Decreased	Normal	Normal
Factor Assays	↓ in all factors	↓ in all factors	↓ II, VII, IX, X
Blood Smear	Schistocytes	No Schistocytes	No Schistocytes

Shock- Definition

➢ State in which diminished cardiac output or reduced effective circulating blood volume impairs tissue perfusion and leads to cellular hypoxia.

Shock

➢ With insufficient delivery of oxygen and glucose, cells switch for aerobic to anaerobic metabolism.

➢ If perfusion is not restored in timely fashion, cell death ensues.

Types of Shock

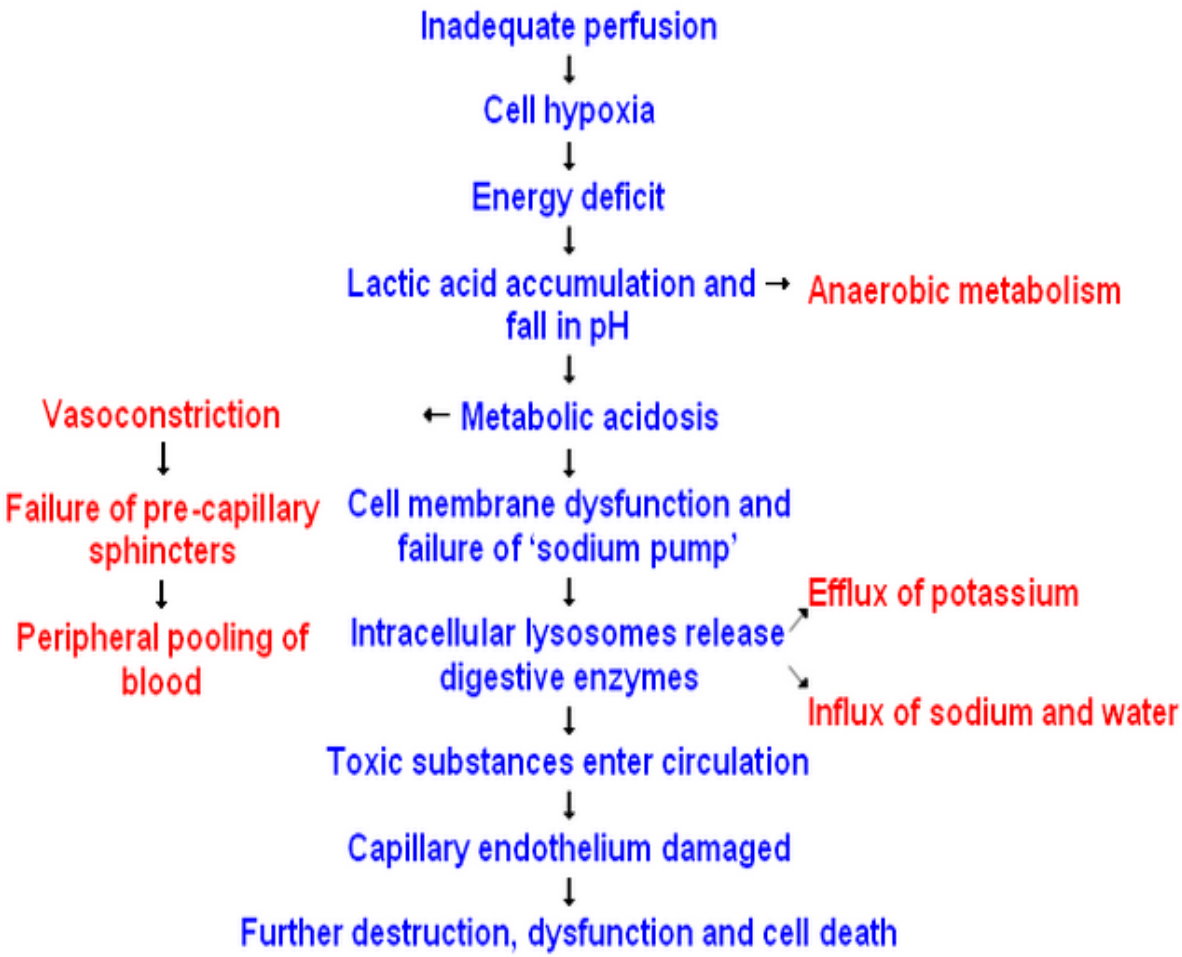
1. Hypovolemic Shock (Hemorrhagic/ Non- Hemorrhagic)
2. Cardiogenic Shock
3. Septic Shock
4. Anaphylactic Shock
5. Neurogenic Shock

Distributive shock

Table 4.3 Three Major Types of Shock

Type of Shock	Clinical Examples	Principal Pathogenic Mechanisms
Cardiogenic	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
Hypovolemic	Hemorrhage Fluid loss (e.g., vomiting, diarrhea, burns, trauma)	Inadequate blood or plasma volume
Septic	Overwhelming microbial infections Gram-negative sepsis Gram-positive septicemia Fungal sepsis Superantigens (e.g., toxic shock syndrome)	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades

Pathophysiology of Shock



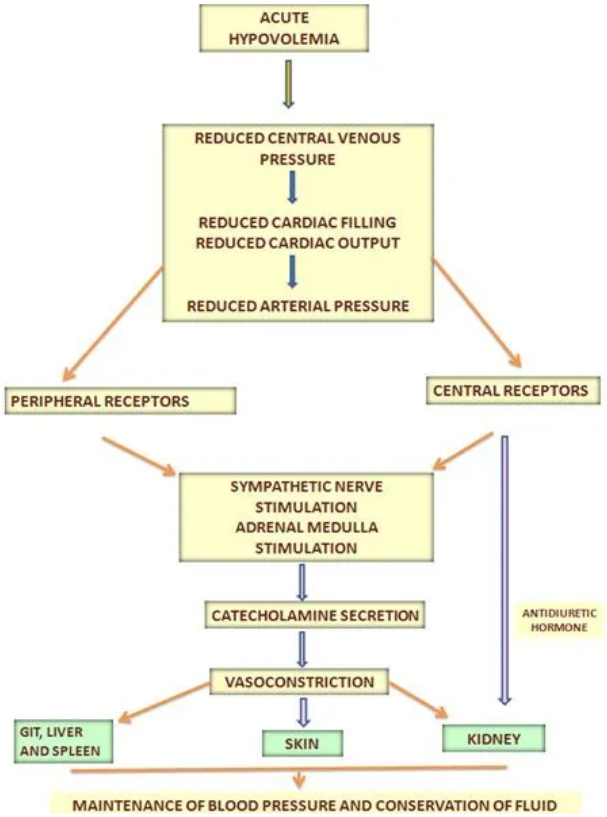
Stages of Shock

- Initial Non-progressive Phase (Reversible)
- Progressive Phase (Intermediate)
- Irreversible Phase (Decompensated Stage)

Stages of Shock

- **Initial Non-progressive Phase:**

- Compensatory mechanism to maintain the homeostasis so that blood supply to vital organs is maintained.
- By neuro-humoral mechanism which maintains blood pressure and cardiac output.
- Widespread vasoconstriction of vessels except coronary and cerebral vessels.
- Fluid conservation by kidney.
- Tachycardia.



Stages of Shock

- **Progressive phase:**

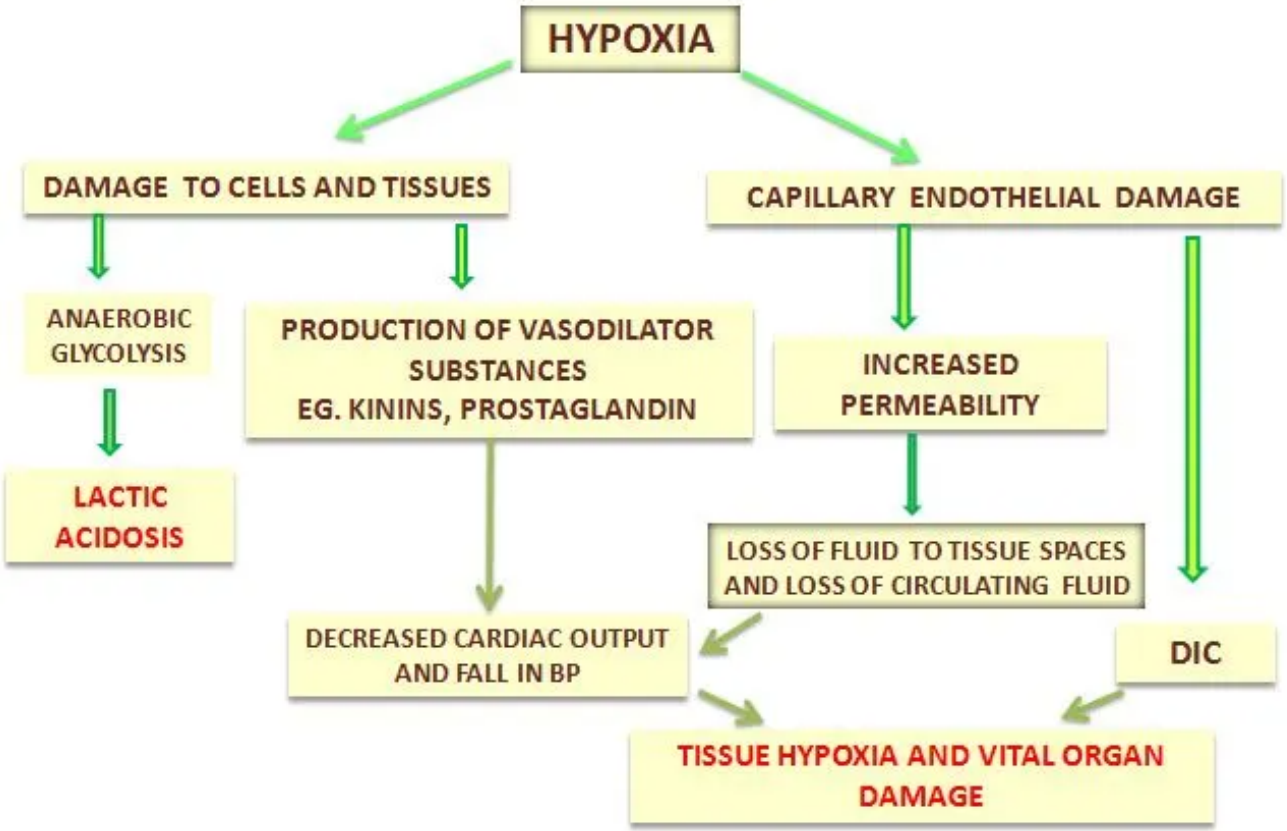
➢ As the stage advances there is failure of compensatory mechanism, dilatation of arterioles, venules and capillary bed.

➢ Because of this fluid leaks out of capillaries into interstitium and there is sludging of blood.

➢ This reduces the tissue perfusion leading to hypoxia.

➢ Initially body tissue except brain and heart suffers from hypoxia.

Stages of Shock



Progressive phase

Stages of Shock

- **IRREVERSIBLE PHASE (DECOMPENSATED STAGE):**

➢ Cellular injury and tissue injury is so severe that condition does not revert back to normal even after correcting hemodynamic defects.

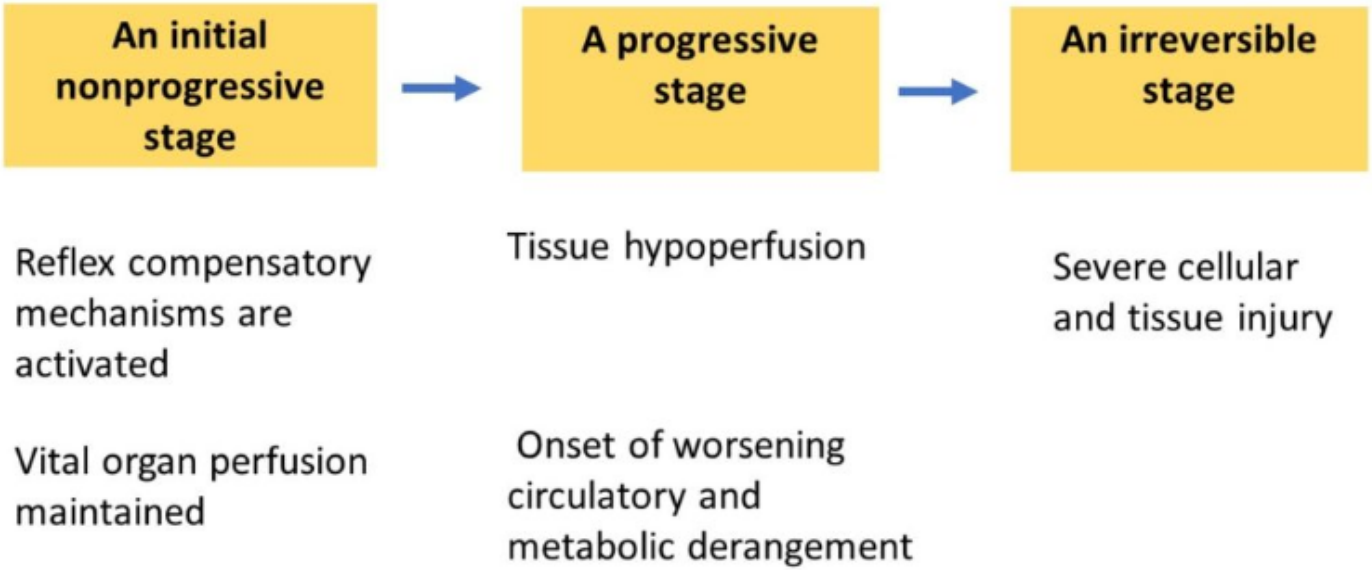
➢ Hypoxic and ischemic cell injury – causes leakage of lysosomal enzymes which further aggravates condition.

➢ Myocardial infarction and synthesis of Nitric oxide further worsens condition.

➢ Intestinal ischemia causes microbes from intestinal flora to enter the circulation which produces superimposed bacteremic shock.

➢ Acute tubular necrosis occurs in kidney.

Stages of Shock- Summary



Clinical Consequences of Shock

- **Hypovolemic and Cardiogenic shock:**
  - Hypotension and weak rapid pulse
  - Tachypnea
  - Cool, clammy, cyanotic skin

- **Septic shock :**
  - Warm and flushed skin due to peripheral vasodilation.

Clinical Consequences of Shock

➢ The prognosis varies with the **origin of Shock and its Duration.**

➢ Progressively Cardiac, Cerebral, Pulmonary, Renal dysfunction ultimately may lead to **multiorgan failure and death** if timely appropriate management is missed.

Pathogenesis of Septic Shock

- Most commonly triggered by gram positive bacilli, followed by gram negative bacilli and fungi.
- Substances from these microorganisms stimulate and activate macrophages , neutrophils, dendritic cells, endothelial cells and complements which results in **INFLAMMATORY & COUNTER INFLAMMATORY RESPONSE** leading to Septic shock which leads to organ failure and death.

Pathogenesis of Septic Shock

- Inflammatory mediators are increased, by innate and adaptive immune cells which results in arterial vasodilation, vascular leakage, and venous blood pooling thereby causing **tissue hypoperfusion, cellular hypoxia, and metabolic derangements** which finally leads to organ failure and death.

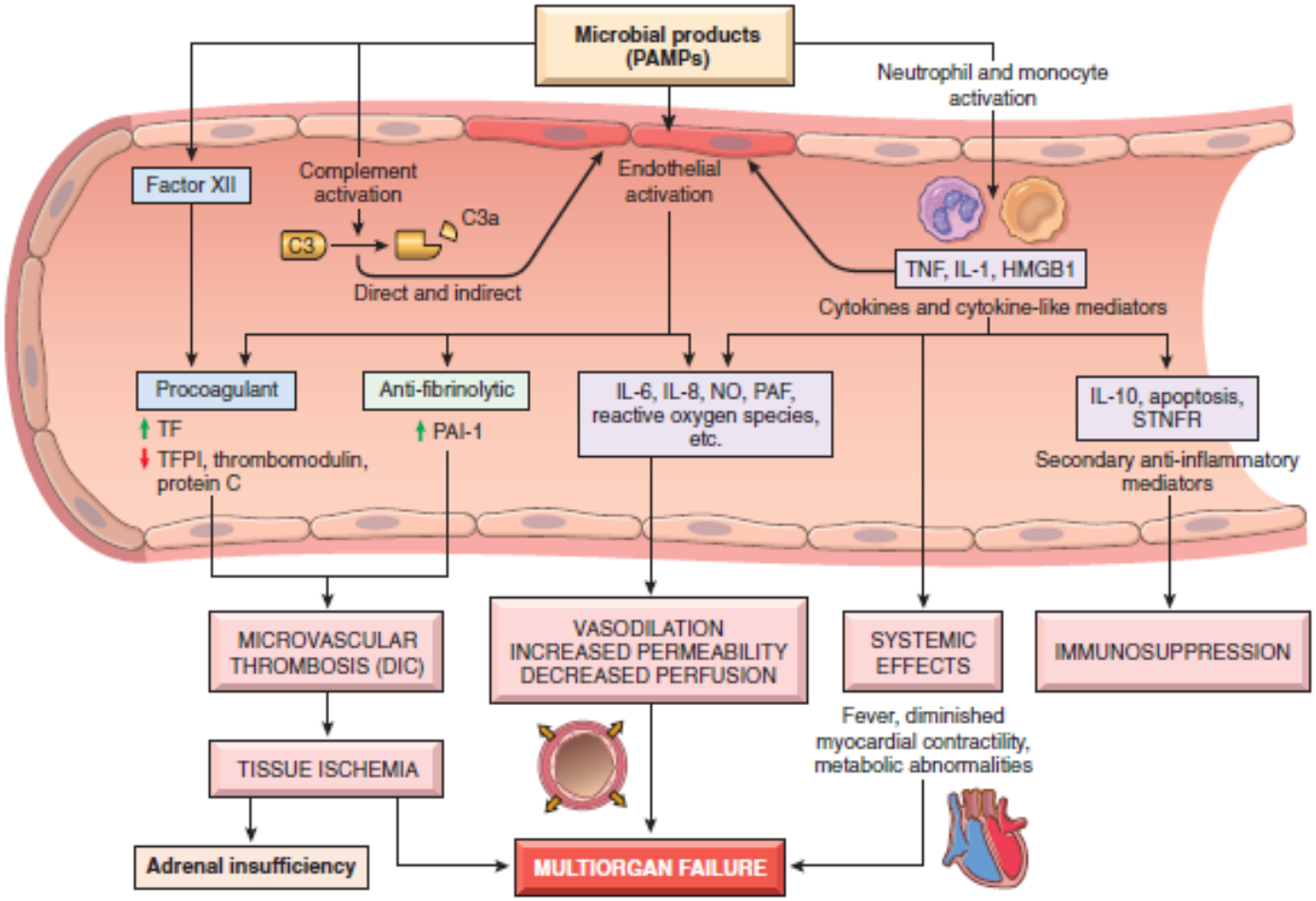


Fig. 4.19 Major pathogenic pathways in septic shock. Microbial products activate endothelial cells and cellular and humoral elements of the innate immune system, initiating a cascade of events that lead to end-stage multiorgan failure. Additional details are provided in the text. *DIC*, Disseminated intravascular coagulation; *HMGB1*, high-mobility group box 1 protein; *NO*, nitric oxide; *PAF*, platelet-activating factor; *PAI-1*, plasminogen activator inhibitor-1; *PAMP*, pathogen-associated molecular pattern; *STNFR*, soluble tumor necrosis factor receptor; *TF*, tissue factor; *TFPI*, tissue factor pathway inhibitor.

➢ Neurogenic Shock:

Due to sudden anxious or painful stimuli. Traumatic brain injury, Spinal cord injury, Spinal anesthesia can cause neurogenic shock. Loss of sympathetic tone, balance tipped towards parasympathetic system. Decreased Heart rate (unique feature).

➢ Anaphylactic Shock:

Due to Type I hypersensitivity reaction. Role of mast cells, histamine.

THANK YOU

Questions ???