به نام خدا

Disseminated Intravascular Coagulation

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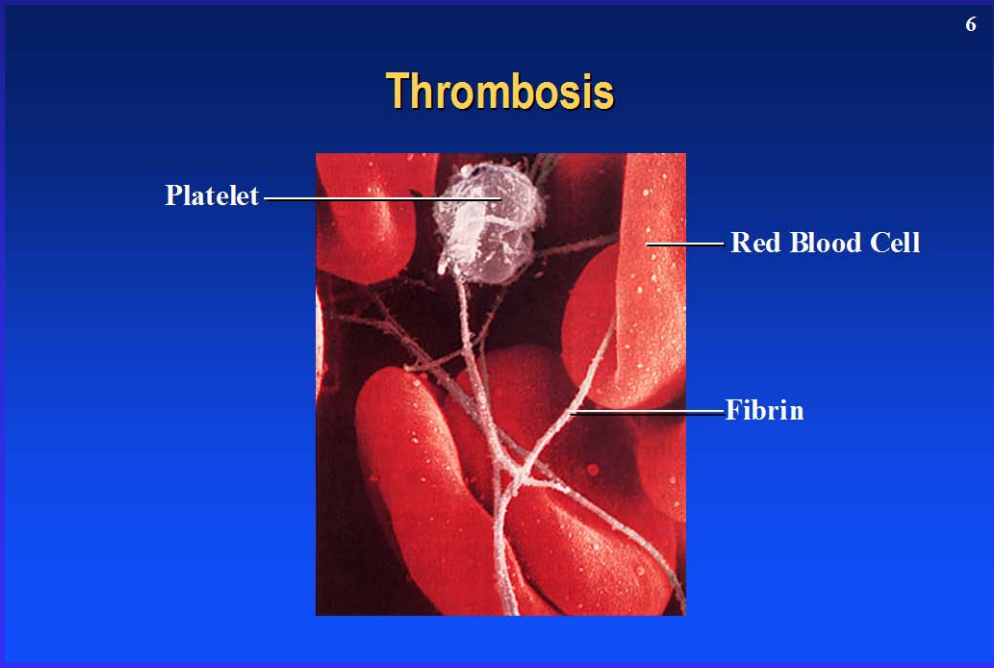
Algorithm for Diagnosis of DIC "DIC Score"

factor	score
Presence of known underlying disorder	No= 0 yes=2
Coagolation test	
Platelets	>100k=0 <100k=1 <50k=2
D-dimer level increased	No=0 moderate=2 strang=3
Pt prolongation (sec)	<3=0 >3but<6 =1 >6=2
Fibrinogen (mg/dl)	>100=0 <100=1
Total score	>= 5 compatible with overt DIC < 5 suggestive of nonovert DIC

DIC

- An acquired syndrome characterized by **systemic intravascular coagulation**
- Coagulation is always the initial event.
- Most morbidity and mortality depends on extent of intravascular thrombosis
- Multiple causes



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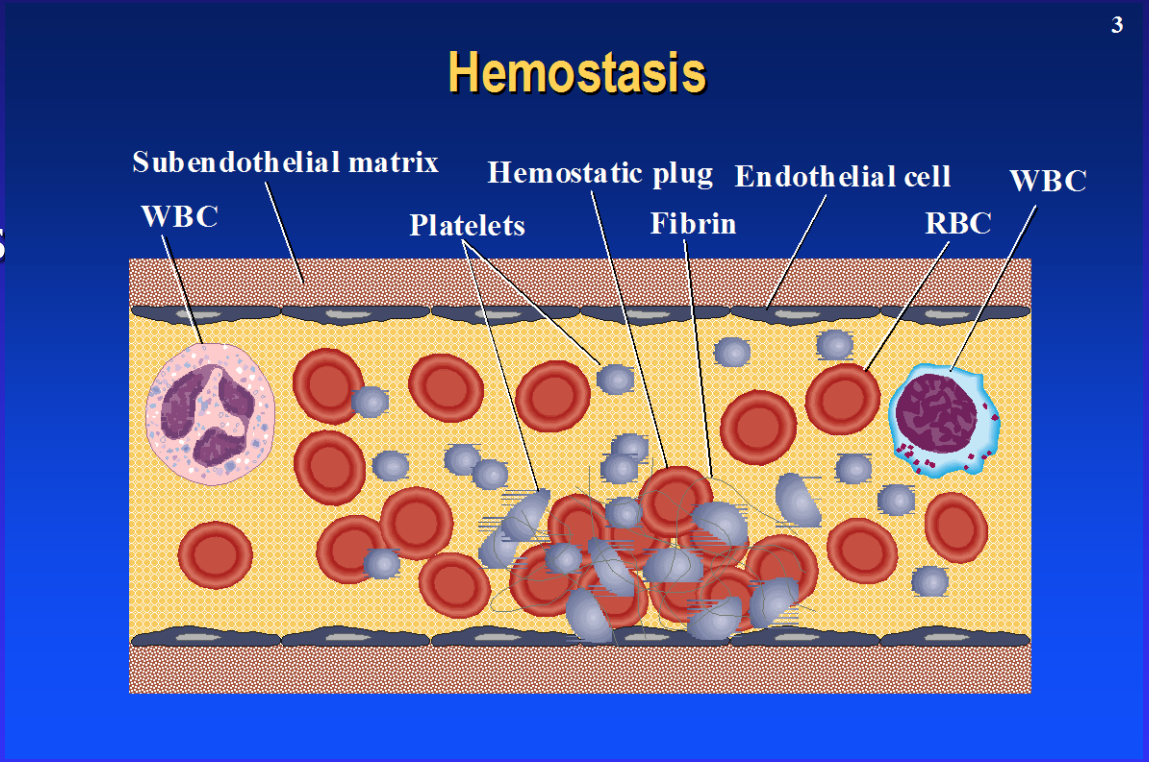
Hemostasis Review

- Coagulation cascade
- Vascular Endothelium
- Anticlotting Mechanisms
- Fibrinolytic System
- Platelets
- Blood Flow Dynamics



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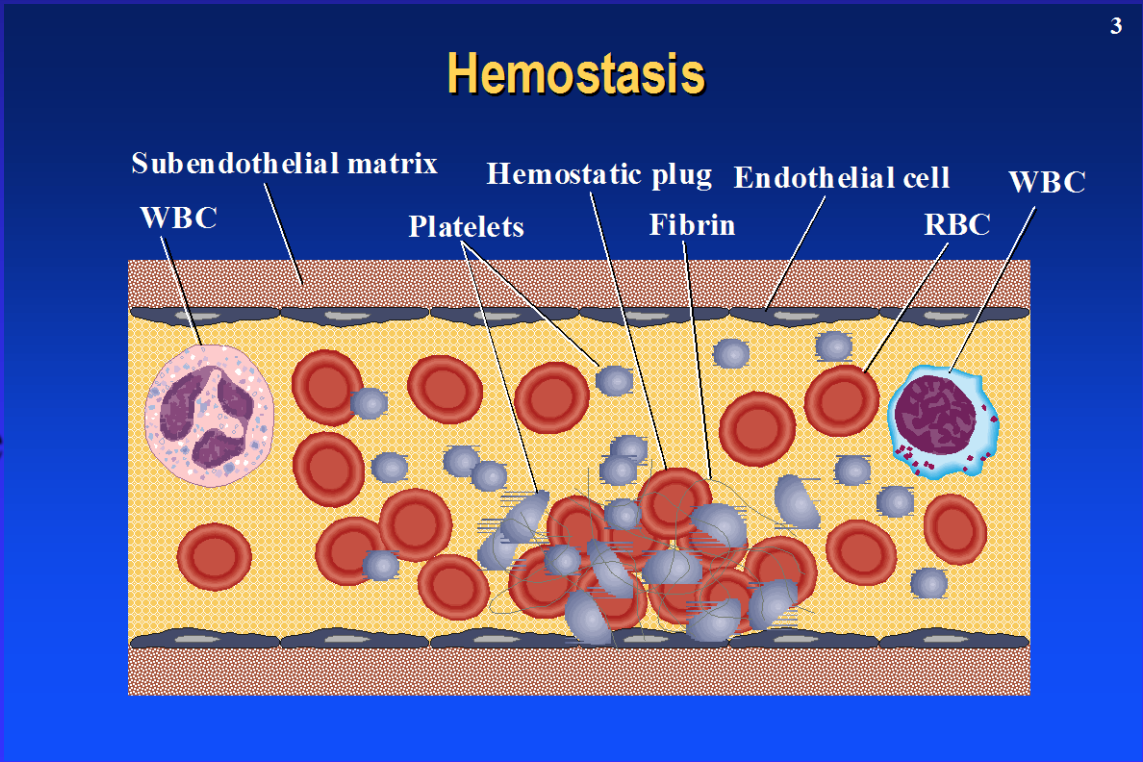
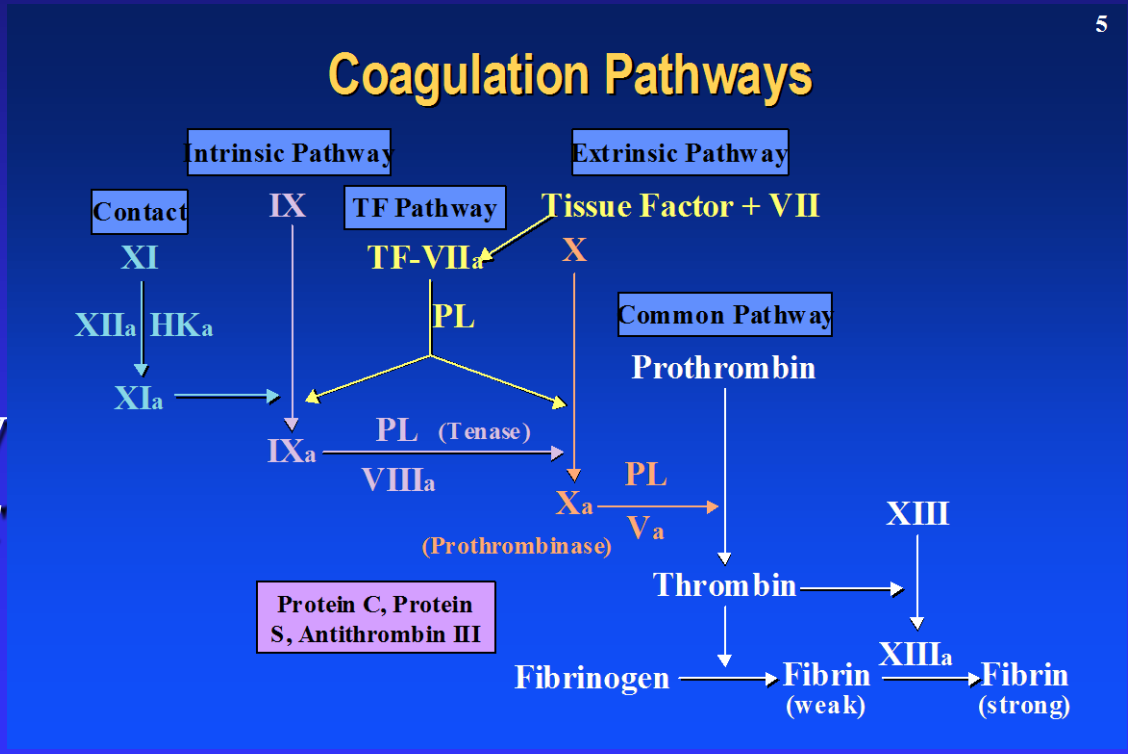
Vascular Endothelium

- Vascular endothelium expresses:
  - Thrombomodulin
  - Tissue Plasminogen Activator
  - Tissue thromboplastin/Tissue factor



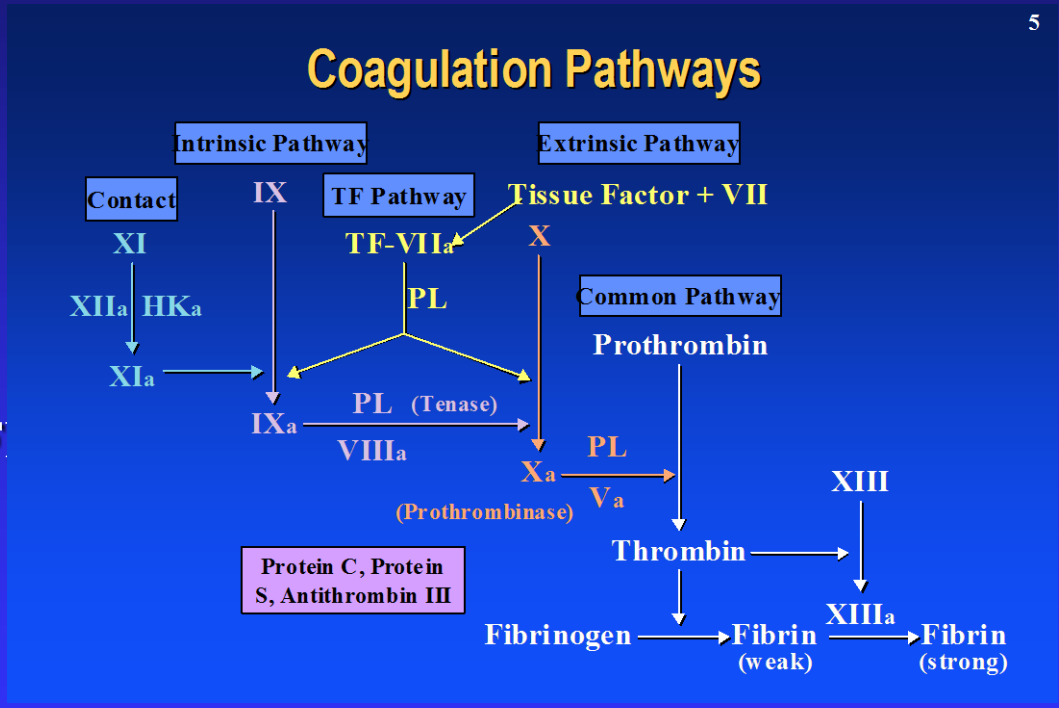
Coagulation

- Intrinsic Pathway
- Extrinsic Pathway
- Common Pathway
- Contact Pathway
- Tissue Factor Pathway
  - ***Primary factor in DIC***



Anticlotting Mechanisms

- Antithrombin III (ATIII):
  - The major inhibitor of the coagulation cascade.
    - Inhibits Thrombin
    - Inhibits activated Factors IX, X, XI, and XII.
  - Activity is enhanced by heparin.
- Tissue factor pathway inhibitor TF



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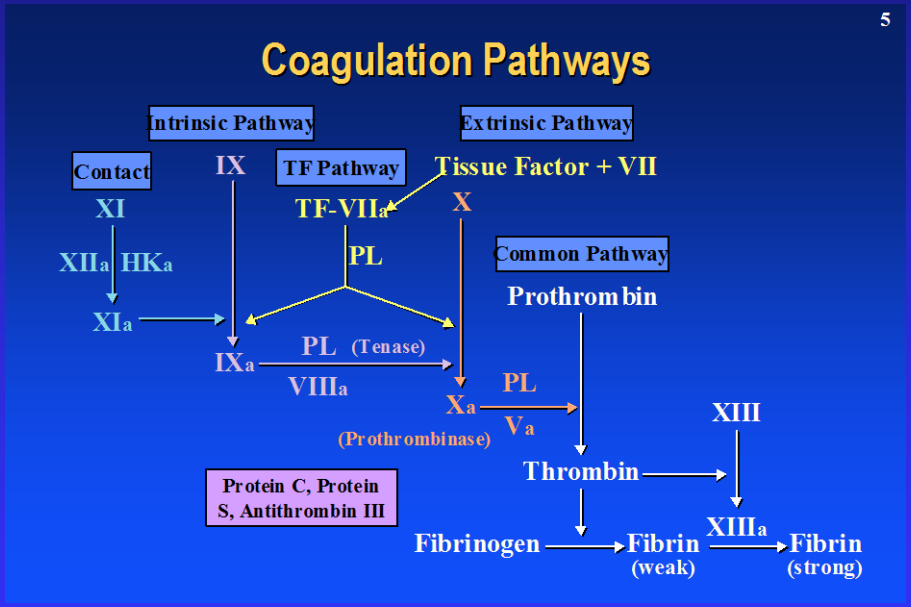
Anticlotting Mechanisms

- Protein C
  - Activated by Thrombin/Thrombomodulin
  - Anticoagulant and fibrinolytic activity.
  - Vitamin K and Protein S are cofactors
- Protein S



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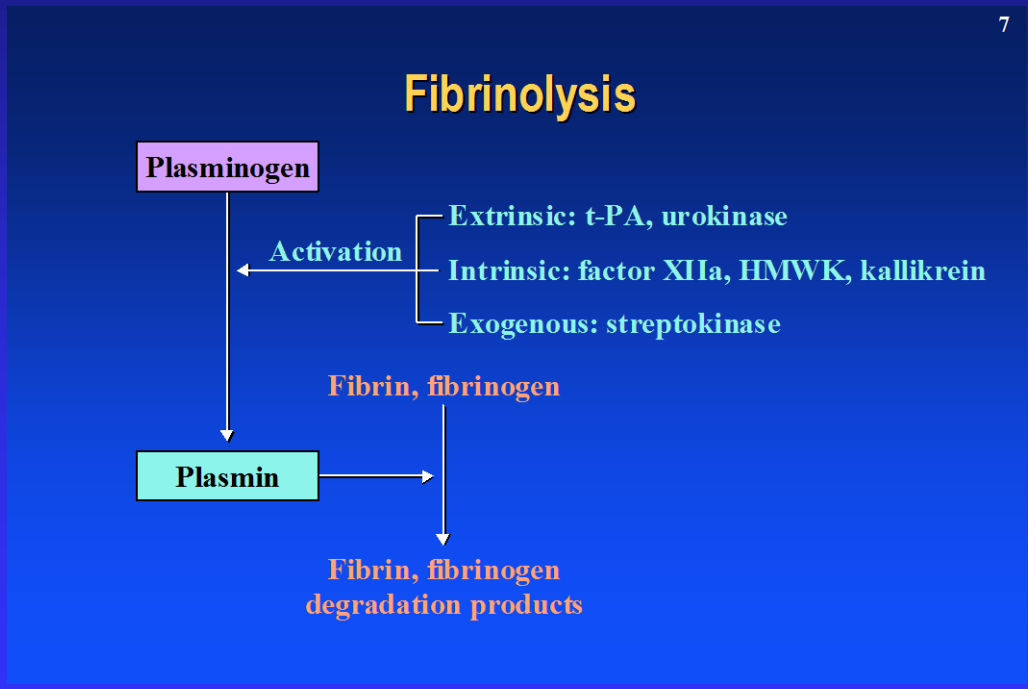
Fibrinolytic System

- Plasmin
  - Produced from Plasminogen by Tissue Plasminogen activator (TPA)
  - Degrades Fibrin and Fibrinogen (Fibrin degradation products, FDP)
  - Degrades Factors V, VIII, IX, XI, and XII.
  - Activity is inhibited by Antiplasmin.



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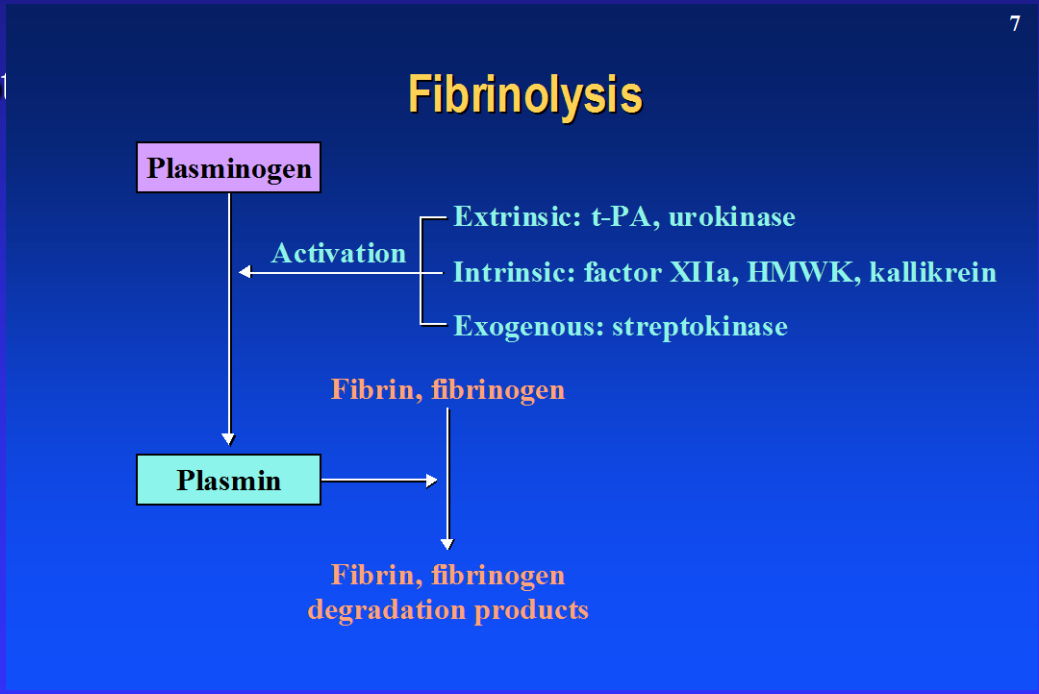
Fibrinolytic Inhibitors

- Antiplasmin
  - Inactivates plasmin rapidly.
    - Acts slowly on plasmin sequestered in the fibrin clot
  - Inactivates factors XI and XII slowly.
- Plasminogen -Activator Inhibitor-1(PAI-1)
  - Inhibits the function of TPA
  - Also has some inhibitory activity against urokinase, plasmin, thrombin, activated Protein C, factors and XII, and kallikrein



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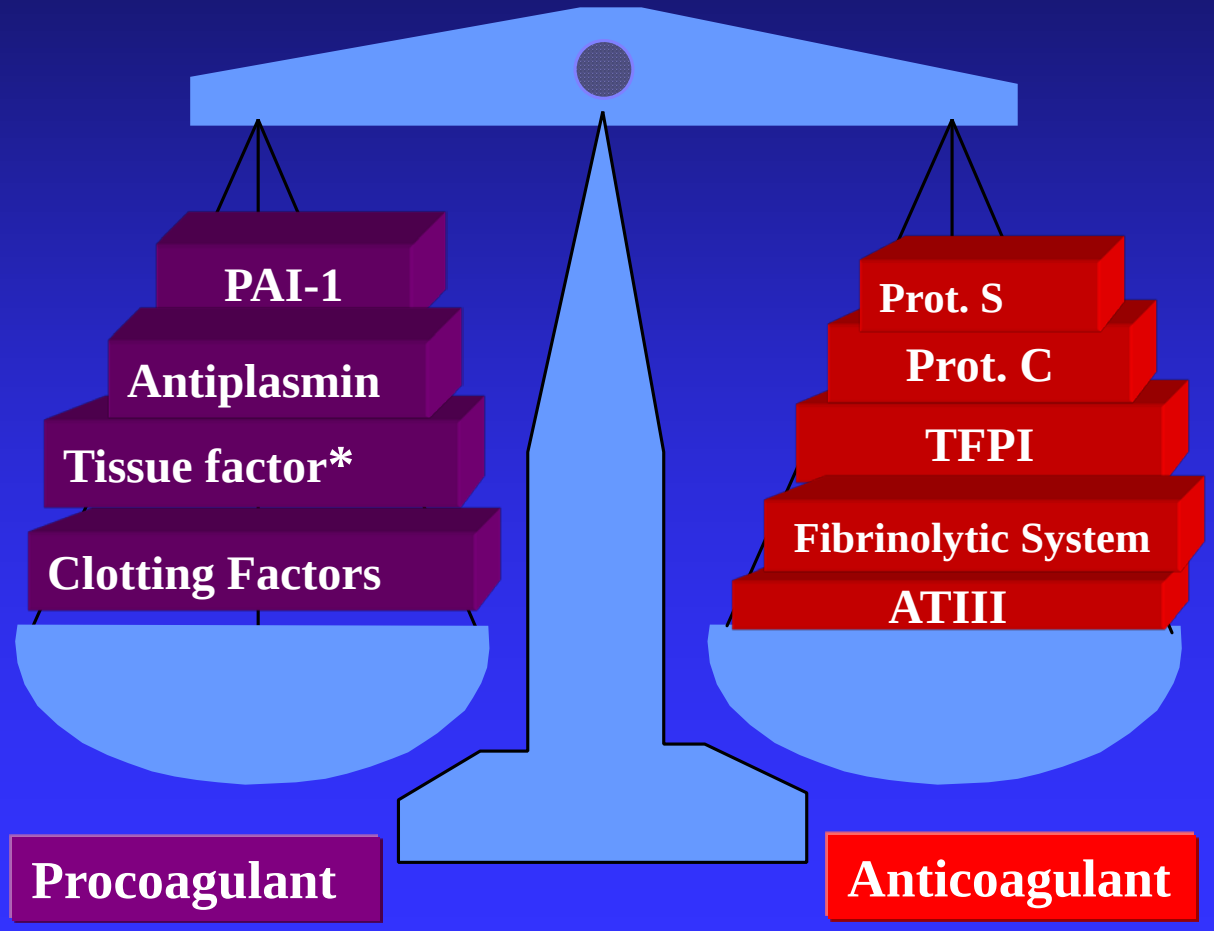
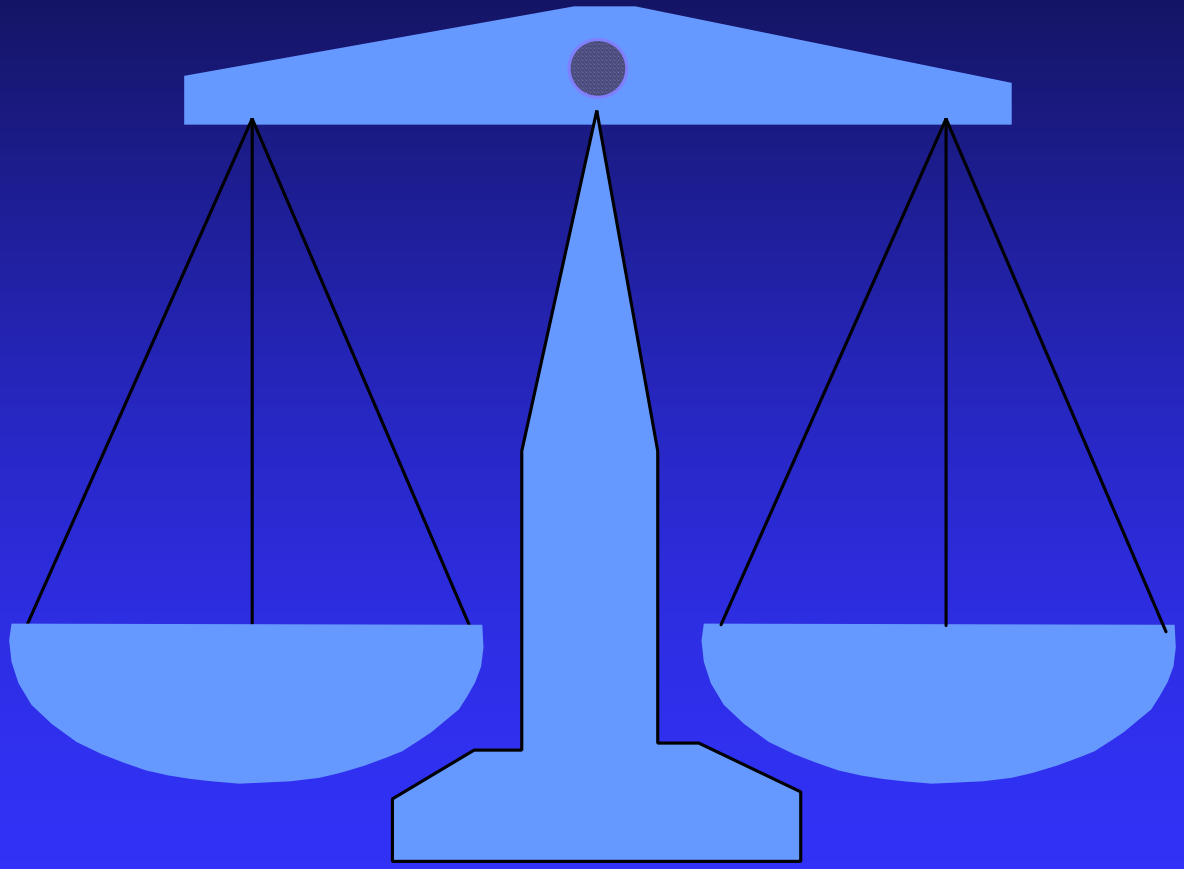
Hemostatic Balance





DIC

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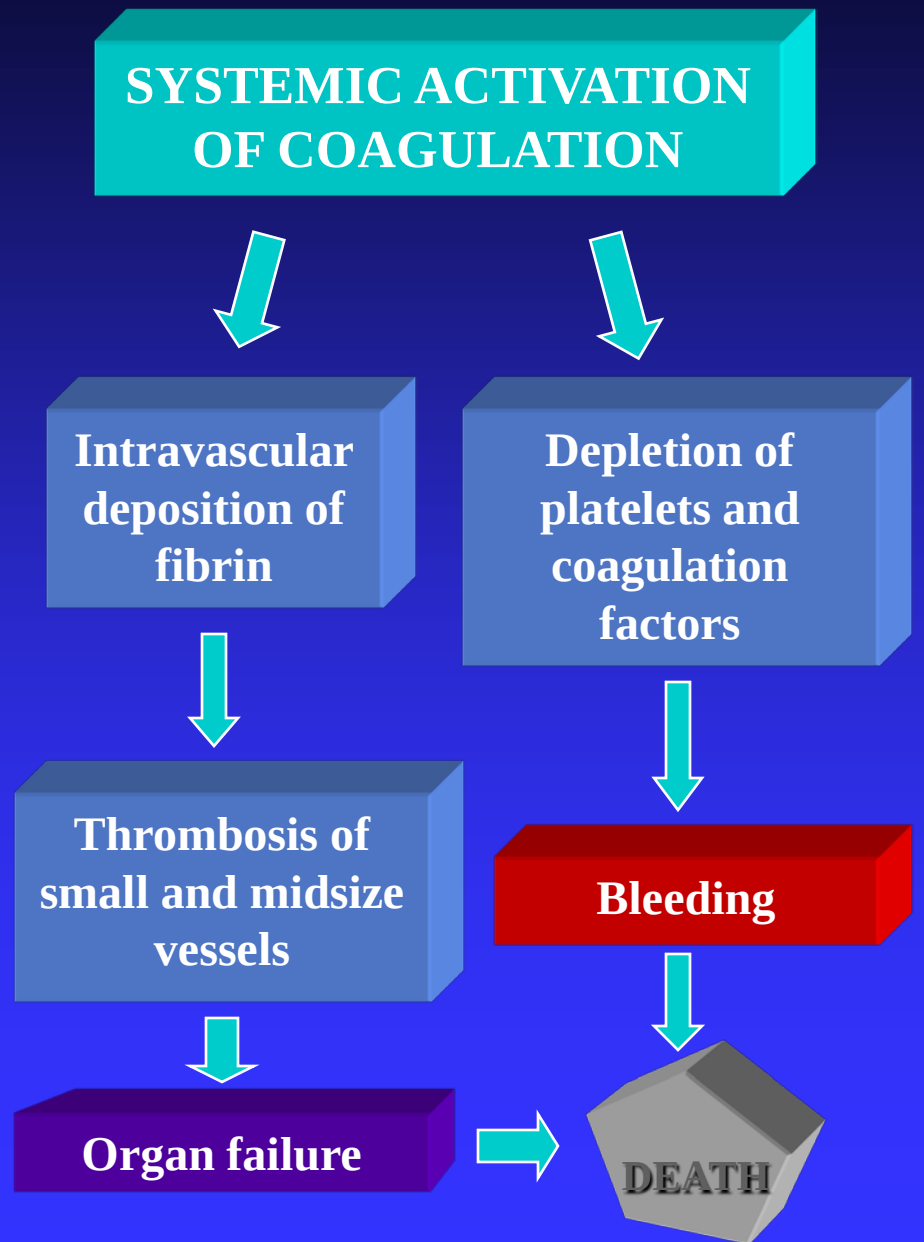
- Coagulation is always the initial event



Pathophysiology of DIC

- Activation of Blood Coagulation
- Suppression of Physiologic Anticoagulant Pathways
- Impaired Fibrinolysis
- Cytokines

Pathophysiology of DIC

- Activation of Blood Coagulation
  - Tissue factor/factor VIIa mediated thrombin generation via the extrinsic pathway
    - complex activates factor IX and X
  - TF
    - endothelial cells
    - monocytes
    - Extravascular:
      - lung
      - kidney
      - epithelial cells

Pathophysiology of DIC

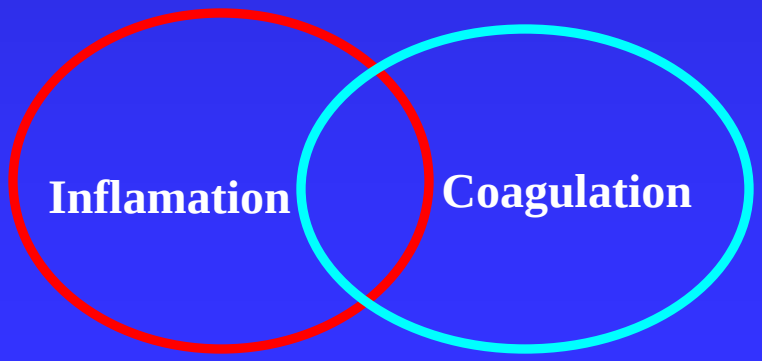
- Suppression of Physiologic Anticoagulant Pathways
  - reduced antithrombin III levels
  - reduced activity of the protein C-protein S system
  - Insufficient regulation of tissue factor activity by tissue factor pathway inhibitor (TFPI)
    - inhibits TF/FVIIa/Fxa complex activity

Pathophysiology of DIC

- Impaired Fibrinolysis
  - relatively suppressed at time of maximal activation of coagulation due to increased plasminogen activator inhibitor type 1

Pathophysiology of DIC - Cytokines

- Cytokines
  - IL-6, and IL-1 mediates coagulation activation in DIC
  - TNF-α
    - mediates dysregulation of physiologic anticoagulant pathways and fibrinolysis
    - modulates IL-6 activity
  - IL-10 may modulate the activation of coagulation



Diagnosis of DIC

- Presence of disease associated with DIC
- Appropriate clinical setting
  - Clinical evidence of thrombosis, hemorrhage or both.
- Laboratory studies
  - no single test is accurate
  - serial test are more helpful than single test

Conditions Associated With DIC

- Malignancy
  - Leukemia
  - Metastatic disease
- Cardiovascular
  - Post cardiac arrest
  - Acute MI
  - Prosthetic devices
- Hypothermia/Hyperthermia
- Pulmonary
  - ARDS/RDS
  - Pulmonary embolism
- Severe acidosis
- Severe anoxia
- Collagen vascular disease
- Anaphylaxis

Conditions Associated With DIC

- Infectious/Septicemia
  - Bacterial
    - Gm - / Gm +
  - Viral
    - CMV
    - Varicella
    - Hepatitis
  - Fungal
- Intravascular hemolysis
- Acute Liver Disease
- Tissue Injury
  - trauma
  - extensive surgery
  - tissue necrosis
  - head trauma
- Obstetric
  - Amniotic fluid emboli
  - Placental abruption
  - Eclampsia
  - Missed abortion

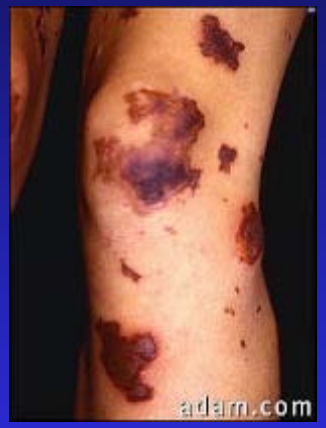
Clinical Manifestations of DIC

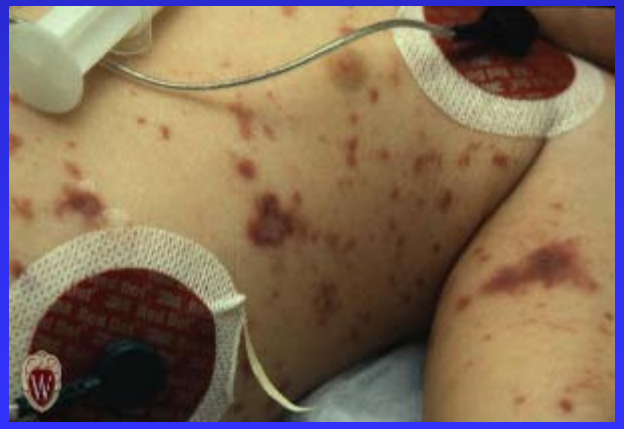
Ischemic Findings are earliest!

ORGAN	ISCHEMIC	HEMOR.
Skin	Pur. Fulminans Gangrene Acral cyanosis	Petechiae Echymosis Oozing
CNS	Delirium/Coma Infarcts	Intracranial bleeding
Renal	Oliguria/Azotemia Cortical Necrosis	Hematuria
Cardiovascular	Myocardial Dysfxn	
Pulmonary	Dyspnea/Hypoxia Infarct	Hemorrhagic lung
GI	Ulcers, Infarcts	Massive hemorrhage.
Endocrine	Adrenal infarcts	

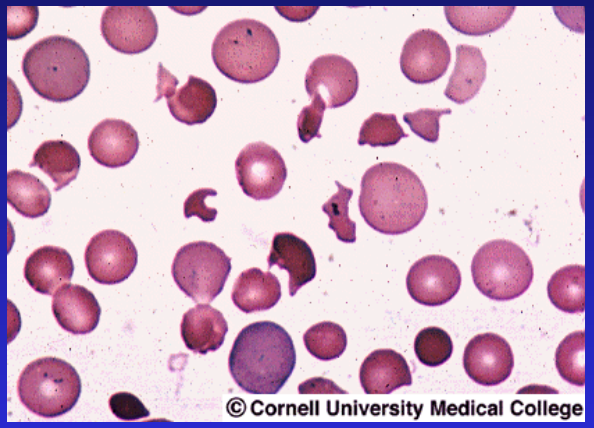
Bleeding is the most obvious clinical finding

Clinical Manifestations of DIC





Microscopic findings in DIC



- Fragments
- Schistocytes
- Paucity of platelets

Laboratory Tests Used in DIC

- ***D-dimer****
- ***Antithrombin III****
- F. 1+2*
- Fibrinopeptide A*
- Platelet factor 4*
- ***Fibrin Degradation Prod***
- ***Platelet count***
- Protamine test
- Thrombin time
- Fibrinogen
- ***Prothrombin time***
- ***Activated PTT***
- Protamine test
- Reptilase time
- Coagulation factor levels

*Most reliable test

Laboratory diagnosis

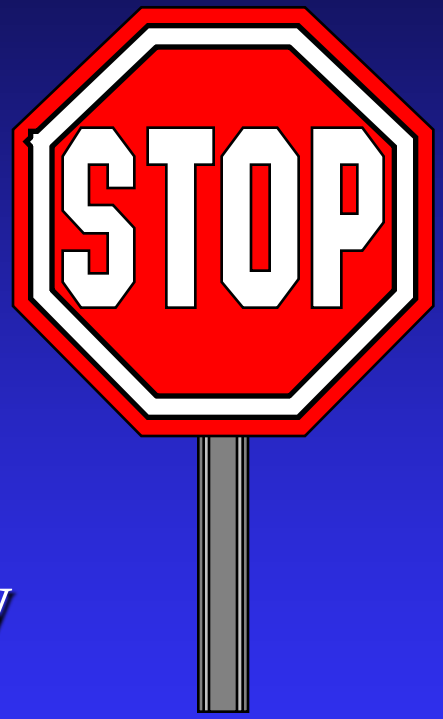
- Thrombocytopenia
  - plat count <100,000 or rapidly declining
- Prolonged clotting times (PT, APTT)
- Presence of Fibrin degradation products or positive D-dimer
- Low levels of coagulation inhibitors
  - AT III, protein C
- Low levels of coagulation factors
  - Factors V,VIII,X,XIII
- Fibrinogen levels not useful diagnostically

Differential Diagnosis

- Severe liver failure
- Vitamin K deficiency
- Liver disease
- Thrombotic thrombocytopenic purpura
- Congenital abnormalities of fibrinogen
- HELLP syndrome

Treatment of DIC

- **Stop the triggering process .**
  - *The only proven treatment!*
- Supportive therapy
- No specific treatments
  - Plasma and platelet substitution therapy
  - Anticoagulants
  - Physiologic coagulation inhibitors



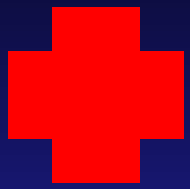
Plasma therapy

- Indications
  - Active bleeding
  - Patient requiring invasive procedures
  - Patient at high risk for bleeding complications
- ***Prophylactic therapy has no proven benefit.***
- ***Cons:***
- Fresh frozen plasma(FFP):
  - provides clotting factors, fibrinogen, inhibitors, and platelets in balanced amounts.
  - Usual dose is 10-15 ml/kg

Platelet therapy

- Indications
  - Active bleeding
  - Patient requiring invasive procedures
  - Patient at high risk for bleeding complications
- Platelets
  - approximate dose 1 unit/10kg

Blood



- Replaced as needed to maintain adequate oxygen delivery.
  - Blood loss due to bleeding
  - RBC destruction (hemolysis)

Coagulation Inhibitor Therapy

- Antithrombin III
- Protein C concentrate
- Tissue Factor Pathway Inhibitor (TFPI)
- Heparin

Antithrombin III

- The major inhibitor of the coagulation cascade
  - Levels are decreased in DIC.
  - Anticoagulant and antiinflammatory properties
- Therapeutic goal is to achieve supranormal levels of ATIII (>125-150%).
  - Experimental data indicated a beneficial effect in preventing or attenuating DIC in septic shock
    - reduced DIC scores, DIC duration, and some improvement in organ function
  - Clinical trials have shown laboratory evidence of attenuation of DIC and trends toward improved outcomes.
  - ***A clear benefit has not been established in clinical trials***.

Protein C Concentrates

- Inhibits Factor Va, VIIa and PAI-1 in conjunction with thrombomodulin.
- Protein S is a cofactor
- Therapeutic use in DIC is experimental and is based on studies that show:
  - Patients with congenital deficiency are prone to thromboembolic disease.
  - Protein C levels are low in DIC due to sepsis.
  - Levels correlate with outcome.
  - ***Clinical trials show significantly decreased morbidity and mortality in DIC due to sepsis.***

Tissue Factor Pathway Inhibitor

- Tissue factor is expressed on endothelial cells and macrophages
- TFPI complexes with TF, Factor VIIa,and Factor Xa to inhibit generation of thrombin from prothrombin
- TF inhibition may also have antiinflammatory effects
- *Clinical studies using recombinant TFPI are promising.*

Heparin

- Use is very controversial. Data is mixed.
- May be indicated in patients with clinical evidence of fibrin deposition or significant thrombosis.
- Generally contraindicated in patients with significant bleeding and CNS insults.
- Dosing and route of administration varies.
- Requires normal levels of ATIII.

Antifibrinolytic Therapy

- Rarely indicated in DIC
  - Fibrinolysis is needed to clear thrombi from the micro circulation.
  - Use can lead to fatal disseminated thrombosis.
- May be indicated for life threatening bleeding under the following conditions:
  - bleeding has not responded to other therapies and:
  - laboratory evidence of overwhelming fibrinolysis.
  - evidence that the intravascular coagulation has ceased.
- Agents: tranexamic acid, EACA

Summary

- DIC is a syndrome characterized systemic intravascular coagulation.
- Coagulation is the initial event and the extent of intravascular thrombosis has the greatest impact on morbidity and mortality.
- Important link between inflammation and coagulation.
- Morbidity and mortality remain high.
- ***The only proven treatment is reversal or control of the underlying cause.***

Thanks