AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
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Case Studies in Hematologic Emergencies

A series of cases will be presented that focus on the appropriate methods of identifying life-threatening hematologic emergencies and of initiating the appropriate treatment. This will include laboratory evaluation of anemia, thrombocytopenia, and hemophilia.

- Identify and describe the treatment of life-threatening hematologic emergencies.
- Review the coagulation cascade and the emergent indications for various factors and platelets.
- Learn to anticipate life threats in patients with hemophilia through the prophylactic use of coagulation factors.

WE-118
Wednesday, October 13, 1999
8:00 AM - 8:55 AM
Room # N242
Las Vegas Convention Center

FACULTY

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Case Studies in Hematological Emergencies

Patricia Lee MD FACEP

Case One:

HPI: 24 y/o black male presents with c/o "usual sickle pain" in back, arms, legs and chest.
ROS: Denies F, N/V/D, abdominal pain, headache, SOB.
PE: thin BM, sclera pale, no other focal findings
Lab: Hemoglobin 6.0 (usual baseline 7.5-8.0); retic count 13%; smear reveals 15 NRBC, +sickle cells

Case One: Evaluation of Hemolysis: Sickle Cell Anemia

Evaluation of anemia

- Production - destruction = circulating red blood cell volume
- Assess production patient's corrected absolute reticulocyte count after measuring retic count, RBC count, hematocrit.
- Reticulocytes are early RBC that are mobilized from the BM when more RBC's are needed; Normal retic count = l%
- Normally reticulocytes live in bone marrow for 3 days; spend 1 day in peripheral blood before matured. The more severe the anemia, the reticulocyte is released earlier and the longer the time to maturation.
HCT	Reticulocyte Maturation Time (days)
45%	1.0
35%	1.5
25%	2.0
15%	2.5
- Absolute reticulocyte count = reticulocyte count X RBC count; Absolute reticulocyte count must be corrected by degree of anemia. If the retics spend more than 1 day in peripheral blood, they will be recounted each day and give a falsely elevated value for production.
- Corrected absolute reticulocyte count = $\frac{\text{Abs. Retic count}}{\text{Retic. Maturation time}}$

Evaluation of Hemolysis

- Interpretation of Absolute Reticulocyte Count

	Normal	Aplasia	Hemolysis
% Retics/mm3	1.0	0.5	10
RBCs/mm3	5,000,000	1,500,000	3,000,000
Abs retics/mm3	50,000	75,000	300,000
Retic matn time/days	1.0	2.5	2.0
Corr abs retic ct	50,000	30,000	150,000

- RBC Lifespan: 120 days
- T1/2 - 30 days with normal reticulocyte count of 1-1.5%
  - If reticulocyte count is increased to 5% (3 times normal) there is

destruction of 3 times normal ; T1/2 drops to 30/3 = 10 days
- NRBC's - signify BM attempt to repopulate RBCs

Management of Sickle Cell Anemia:
- Rest, hydration, analgesia
- Retic count if Hgb drops 2 gm/dl from baseline
- Transfusion if hemolysis is excessive
- Hgb < 6 g/dl or drop of more than 3 gm/dl from baseline
- Retic > 12%

Case Two

HPI: 65 year old male with h/o HTN, cardiomyopathy (EF=15%) c/o weakness and SOB, unable to ambulate 10 feet without holding onto wall.
ROS: no CP, abd pain, F/N/V. **PMH**: HTN, arthritis
PE: orthostasis, diaphoretic, pale sclera, PMI displaced 3 cm, abd: benign; rectal-no stool in vault.
LAB: Hgb 7.5 g/dl (baseline Hgb 1 week earlier-10.5 g/dl).
ED COURSE: The patient has a large volume bright red blood per rectum. NGT aspirate- negative. While awaiting GI lab, patient develops increasing dyspnea and mild chest pain unresponsive to O2.

Case Two: Evaluation of Anemia: Transfusion Criteria
Causes of anemia
- decreased production- e.g. aplasia, infiltrative, impaired or ineffective (B12, folate)
- increased destruction- e.g. immune
- increased sequestration- e.g. hypersplenism

Management
- erythropoietin, Fe, B12, folate, transfusion

Indications for transfusion- Indirect assessment.
- Clinical status - CNS, skin, ABG, urine output, vital signs
- Considerations for decision
  - mechanism - rate, chronicity, extent
  - patient reserve - age, chronicity, cardiopulmonary status
  - physiologic response - VS, mental status, cap refill
  - acute vs. chronic -
    - chronic, treat cause; can tolerate a Hgb of 4-5 g/dl
    - acute- use above indirect measures; transfuse if 20-30% blood loss has occurred or is expected to occur

Case Three:
HPI: 24 y/o F; c/o syncope, heavy vaginal bleeding for 10 days (box of 24 pads Q 2 days), generalized weakness, dizziness, and easy bruising.
ROS: denies abdominal pain, F, LMP 2 wks ago (normal).
PMH: healthy; recent flu.
PE: orthostatic, pale sclera, benign abd, no HSM/ masses; skin-dark bruising on extremities, scattered petechiae under bra and panty lines; pelvic-mod dark blood, uterus-small, no masses, os closed , adnexa-NT, no masses
LAB: pregnancy test neg, UA; Hgb 6.5, wbc 9.4, plat 5000
ED COURSE: IVF given, O2; C/O SOB, weakness, and dizziness

Case Three: Evaluation of Thrombocytopenia: ITP

Causes of thrombocytopenia:

- Abnormal production - e.g. aplasia, infiltrative, ineffective
- Increased destruction- immune (ITP), non-immune (DIC, HUS)
- Sequestration - hypersplenism, ETOH

Evaluate bleeding history

- increased mucosal, lower extremity, pressure sites
- comorbid factors- drugs (ASA, NSAIDS), pregnancy, HIV, previous transfusions

Physical exam findings: petechiae = hallmark; splenomegaly, anemia
Diagnosis: peripheral smear, CBC, BM aspiration, platelet antibody
Management:

- Treat cause. Remove offending agent
- Platelet transfusion prn; Note l u random donor platelets raises platelet count 5-10K;
- Risk of bleeding: >100K small; 50-100K low; <20K high
- Idiopathic Thrombocytopenic Purpura
    - Corticosteroids stabilize vascular integrity
    - Splenectomy if immune destruction
    - IV IgG to block RES
    - Plasmapheresis to remove antibody

Case Four:
HPI: 46 year old female with known von Willebrands disease presents to ED complaining of vomiting blood since last night.
ROS: Denies abd pain, D, F,CP,SOB
PMH: PUD, vonWillebrand's disease
PE: unremarkable, rectal occult blood strongly positive; NGT aspirate-250 cc coffee grounds.

Case Four: vonWillebrand's disease

- von Willebrand factor: major protein mediating primary adherence of platelets to endothelium; vwF also carrier molecule for Factor VIII; auto dominant inheritance;
- Presents as platelet deficiency type bleeding
- Diagnosis: elevated PTT, low VIII:C, low vwF, normal platelet ct, increased bleeding time
- Management DDAVP, Cryoprecipitate

Case Five
HPI: 21 year old male with known hemophilia presents with right knee pain. States awoke with painful swollen knee. No known trauma

ROS: Denies F, CP, SOB, abd pain, skin changes, GU symptoms.
PE: swollen, tender R knee with chronic joint deformity, limited ROM

Case Five: Hemophilia A- Factor VIII deficiency

- Factor VIII- sexlinked; inherit abnormal VIII:C; normal vWF
- Presents with profuse bleeding into joints or internal organs after trauma
- Diagnosis: prolonged PTT, normal PT, low VIII:C; Inhibitors common
- Management: DDAVP, Factor VIII concentrate
- **Guide to Factor VIII replacement**:

Severity	Type of Injury	Factor VIII u/kg
mild	minor trauma, simple hemarthrosis	12.5-25
moderate	IM hematoma, dental extraction, hematuria, GI (mild)	25-50
severe	IC bleed, major surgery, trauma, retro-peritoneal or retropharyngeal bleeding	50

Case SIx:
HPI: 59 y/o male presents with acute CP radiating to left arm with associated N/V, SOB, diaphoresis.
ROS: Denies abd, back pain, F, cough. **PMH**: HTN
PE: diaphoretic, pale, normotensive, lungs: CTA, CV; normal, Abd: benign, Rectal: heme neg
ED course: EKG reveals acute AWMI. Thrombolytics (tPA) are begun. Patient remains in ED for several hours awaiting CCU bed. Forty-five minutes later, patient develops marked RUE weakness. CT reveals small intraparenchymal hemorrhage

Case Six: Bleeding s/p thrombolytic

- Streptokinase, tPA, anistreplase, alteplase, used for MI, PE, non-hemorrhagic CVA
- T1/2 tPA - 5 min; streptokinase 23 min, anistreplase-120 min
- Management: Stop thrombolytic
- Supportive care: cryo, FFP, platelet transfusions; EACA

Case Seven:
HPI: 79 year old nursing home patient with h/o CVA and indwelling Foley catheter presents with fever of 103.5C, BP 78/palp.
ROS: unavailable ; **PMH**: unknown
P.E. lethargic, febrile, dehydrated . Lungs: Bilat rhonchi L>R; Abd: benign, no decubiti; GU: Foley cath draining dark brown urine, Rectal: heme pos, Skin: multiple ecchymoses.
LAB: CXR- LLL infiltrate; UA: many WBC, heme pos, bacteria. WBC 24,000; 32% bands, plats-68K.
ED course: One hour after arrival in ED oozing noted at all venipuncture sites, urine with dark red color. BP poorly responsive to IVF resuscitation.

Case Seven: DIC

- Definition: DIC results from control mechanisms being overwhelmed by
  1) massive tissue damage with high levels of tissue factor released
  2) shock and resultant low flow states with loss of hemodilution, and widespread consumption of coagulation factors and platelets
  3) major alterations of endothelium, or
  4) impaired liver function and removal of activated factors
- Comorbid factors: infection, cancer, OB or CVS complications, immune disorders, liver disease, envenomation, transfusion reactions
- Increased FDP, increased D-dimer, decreased FBG
- Management: treat cause
  - supportive care: FFP, cryo, +/- platelets; heparin controversial

Case Eight:
HPI: 49 year old female with known ETOH cirrhosis c/o with weakness and vomiting coffee grounds X 3**.**
ROS: No F/N/V/D, abd pain, CP. **PMH**: cirrhosis, ETOH
PE: normotensive, jaundiced female vomiting coffee grounds and BRB, Abd: NT, distended, + ascites, heme neg stool.
LAB: PT, PTT elevated INR=3.4, Hgb 8.5 g/dl, plt 72K, LFT's elevated
ED course: NGT- 800 cc coffee grounds and BRB - lavaged with l liter NS and not cleared. Repeat BP 88/46.

Case Eight: Alcoholic Liver Disease

- Multiple hemostatic defects due to liver damage and malnutrition - coagulation factor deficiencies, anemia, platelet disorder, fibrinolysis
  - Management: supportive care; address each problem
- Vitamin K deficiency: Factor II, VII, IX, X, Protein C, Protein S
  - management: vitamin K 10 mg po, IM, or IV
    - FFP: 10-20 ml/kg; goal restore factor levels to 30%; give FFP if PT is prolonged 1.5 times the control

Case Nine:
HPI: 45 y/o male brought by paramedics as restrained driver in head-on high speed MVC. + LOC; GCS in field = 8.
PMH: rheumatic fever s/p MVP; medic alert bracelet indicates warfarin
PE: combative, R parietal contusion. No eye opening -pupils 3 mm, reactive. Moves extremities, makes incomprehensible sounds to pain.

Case Nine: Blunt Head Trauma and Coagulopathy

- Give FFP based on history BEFORE CT

Case Ten:
HPI: 18 month old brought by grandmother who says she found him 2 hrs PTA on the floor of her bedroom with an open bottle of warfarin pills scattered about and pill fragments in his mouth. To her count, he may have ingested 10-15 tablets.
ROS: Denies V,D, bleeding in stool, urine, hemoptysis. **PMH**: healthy
PE: laughing, playful infant; nontoxic
Lab: PT, PTT normal

Case Ten: Warfarin Overdose

- Warfarin - interferes with synthesis of vitamin K factors: II, VII, IX, X
  - Many drug interactions, e.g. cimetidine, aminoglycosides, fluroquinolones, macrolides
  - T1/2 - 2.5 days; child requires close observation - referral
  - Management: stop drug, monitor PT;
    - Vit K 10 mg IM, IV, or po
    - FFP as needed 10-20 mg/kg

Case Eleven:
HPI: 63 y/o male brought from home by relatives. Complained earlier in the evening of SOB and chest pain, with visual disturbances. Family states has become increasingly confused.
ROS: Denies F, N/V/D, abdominal or back pain. **PMH**: Denies
PE: stuporous; lungs rales 1/3 up; neuro- non-focal
Lab: Hematocrit- 28%; smear- rouleaux; chemistry lab reports unable to perform requested tests due to viscosity of blood.

Case Eleven: Hyperviscosity Syndrome

- Waldenstrom's - increased plasma proteins, serum viscosity high;
  - Management: avoid transfusion, IVF, plasmapheresis
- Hyperleukocytosis: increased WBC seen with leukemia; WBC > 100K
  - Management: avoid diuretics, allopurinol, IVF, alkalinize urine, hydroxyurea, leukapheresis, CNS irradiation
  - Tumor Lysis Syndrome: 1-5 days post therapy; hypoxemia, hypotension, electrolyte abnormalities, renal failure, ARDS
- Polycythemia: Hct 60-80%; treatment- phlebotomy
- Thrombocytosis: Platelets > 1 million; treatment: ASA, apheresis

Case Twelve:
HPI: 56 y/o F brought by daughter for weakness, fever, and confusion.
ROS: Denies N/V/D, CP, neck pain, recent travel, abdominal pain.
PMH: healthy
PE: BP 115/58 HR 112 T 101.5°C RR 20 **Gen**: weak appearance, pale conjunctiva, mild jaundice; **Neuro**: confused, MAEW, no meningismus
Lab: Hgb 6.0 g/dl, plat 18,000, RDW 24.4; schistocytes; BUN 54, Cr 4.8, UA: "tea colored", large protein, 10-15 rbc's

Case Twelve: Thrombotic Thrombocytopenic Purpura (TTP)

- Clinical syndrome with pentad of signs and symptoms: 20% mortality
  - Microangiopathic hemolytic anemia: schistocytes, reticulocytes
  - Thrombocytopenia – 5000-100,000/mm3
  - Renal insufficiency, azotemia, proteinuria, or hematuria
  - Fever
  - Neuro: headace, confusion, CN palsies, seizure, coma
- More common women; typically acute, fulminant course
- Pathogenesis uncertain- abnormal endothelium, inadequate fibrinolysis – microthrombi of platelets and fibrin, physical destruction of rbc's
- Lab reflect hemolytic anemia: anemia, reticulocytosis, elevated indirect

blirubin, elevated LDH, negative direct Coombs, schistocytes, thrombocytopnia; elevated BUN/Cr; UA: proteinuria, hematuria

- Treatment**:** plasma exchange, FFP, steroids, ASA;
  - Avoid platelet transfusion

Case Thirteen:
HPI: 63 y/o female with pancreatic CA c/o swollen, tender LLE X l day.
ROS: No F,N/V/D, abd pain, known trauma, CP, SOB.
PMH pancreatic CA
PE: thin female, LLE warm, erythematous, swollen, tender calf.

Case Thirteen: Hypercoagulable State

Presentation: DVT, PE, venous, recurrent or unusual site thrombosis
Risk factors: BCP, CA, pg, stasis, Protein C or S deficiency, heparin- induced thrombocytopenia, lupus anticoagulant, AT-III deficiency
Diagnosis: Assay for Protein C, Protein S, AT-III; D-dimer
Use of Heparin - binds AT-III and inactives factor X; antagonizes thrombin

- standard heparin (unfractionated -UFH): 80-100 u/kg bolus then 18-20 u/kg/hr maintenance
- low molecular weight heparin (LMWH) - fragmentation of UFH
  - approved for DVT prophylaxis, enoxaparin: acute cornonary syndrome: unstable angina and non-Q wave MI, PE, DVT
    - inhibits Xa; minimal effect on endothelium or platelets or thrombin- fewer hemorrhagic complications;
    - T1/2 is 2-4 times that of UFH and is independent of dose; 1 mg/kg q 12 hrs SC ; therapeutic from first dose; PTT monitoring not needed
  - Side effects: diffuse bleeding, thrombocytopenia, priapism, hypercoagulable, , hyperkalemia, increased AST, ALT with normal bilirubin, osteoporosis, skin necrosis
- Reversal of heparin- protamine sulfate 1 mg/100u heparin
- Hirudin and hirulog – thrombin specific inhibitor; studies ongoing

ED Approach to the Patient with a Bleeding Disorder:

- **Take a good history!!** It is important to **distinguish hereditary from acquired** disorder
- **Excessive profuse/prolonged bleeding after minor injury**; e.g., circumcision, after surgery, with menses, and during **dental** extraction? If no bleeding when wisdom teeth extracted - then not hereditary.
- If **thromboembolism** after childbirth, surgery, and orthopedic procedures- fibrinolytic disorder?

- **Risk factors for hematological emergency**: prolonged immobilization, recent surgery, CHF, arteriosclerosis, malignancy, pregnancy, drug ingestion (acute or chronic, accidental or intentional), ETOH or IV drug use, hepatic insufficiency, HIV, toxins, patient or family history of bleeding or thrombosis, history of transfusions, chemo or radiation.
- **Medications:** ASA inhibits platelet cyclooxygenase; Many OTC meds contain ASA; BCP; NSAIDS, warfarin; heparin, quinidine, many others.
- **Social history**: smoking - thrombotic disorders, alcohol - chronic liver disease, CRF- uremia; drug use, sexual hx- HIV-platelet disorders, anemia, transfusion hx- rbc/plat immune destruction
- Many hematological conditions cause **nonspecific** symptoms.

Physical Exam Clues:

- Look for petechiae, ecchymoses, pallor, icterus, hemarthrosis, chronic joint deformity, chronic joint disease, sternal or bone tenderness, hepato-splenomegaly, and lymphadenopathy, retinal hemorrhage, mucosal bleeding or oozing at catheter sites.

Ask yourself these questions:

- Coagulopathy vs traumatic bleeding?
- Hereditary vs acquired?
- Where is the disorder? Platelet? Coagulation factor? RBC? Fibrinolysis? Vasculitis
- Clinical assessment-- How urgent is treatment?
- What management is needed?

Put it all together:

	Coagulation Factor	Fibrinolytic System	Vascular	Platelet	RBC
Location of bleeding	spontaneous hemarthrosis; deep IM hematoma	multisite; skin, mucus membranes	skin: petechiae or purpura; telangiectasia	skin: petechiae or purpura; mucus membranes: GI bleed, epistaxis, hematuria, etc.	pallor, icterus
Onset of bleeding	delayed or prolonged after trauma	delayed after trauma	prolonged or profuse after trauma	Acute	
Associated Disorders	liver disease	liver disease		liver disease; connective tissue disease; recent viral infection; recent transfusion; CRF	liver disease; HIV; CRF; recent transfusion
Gender	male			female-ITP	

Meds	warfarin heparin	BCP		ASA, heparin, quinidine, NSAID	
Social Hx	ETOH	TOB; ETOH		ETOH HIV risk factors	ETOH

Take Home Points

- Hematological emergencies = non specific complaints
- No substitute for a careful history
- Collect extra samples
- Think situation, location, duration
  - Mucosal, petechiae, LE = platelet defect
  - Deep IM = coagulation factor defect
  - Delayed bleeding = DIC, fibrinolytic defect
  - Atypical thrombus = thrombotic defect
- Goal: 30% factor activity; 50K plats
- Prolongation before bleed: PT>PTT
- SSA: >12% retics + NRBC = severe hemolysis
- Anemia: treat patient not Hgb
- Transfusion is a clinical decision
  - FFP: 10-20 ml/kg
  - Plats: 5-10K rise/unit
  - RBC: 1 gm/dl Hgb rise/unit
- ITP: usually don't bleed
- VWD: DDAVP,, cryo
- Hemophilia: Factor VIII liberally
- Thrombolytics: Discontinue, cryo, FFP
- DIC: treat cause
- ETOH abuse: vit K, FFP, plats
- Blunt Head Trauma and coagulopathy: FFP 1st
- Warfarin: vit K
- Hyperviscosity syndrome: removal or inactivation
- TTP: Plasma exchange, FFP
- Thrombosis: heparin

Normal Hemostasis-Brief Overview

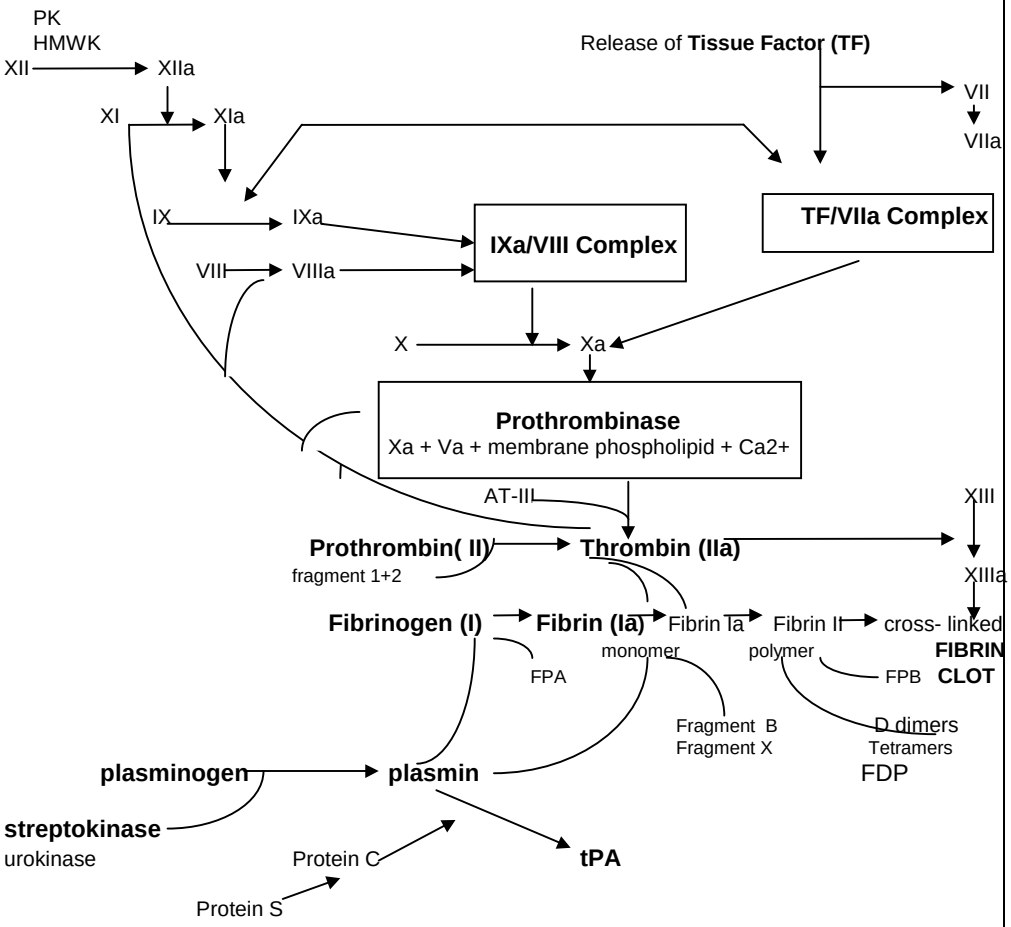
- **Role of Platelets:** binds to subendothelial receptor (GMP-140); exposed receptors cause granule release(vWF, FBG, ADP, thrombospondin) inducing more adherence, aggregation, activation, and granule release: secretes thromboxane A2 -vasoconstrictor -slows blood flow
- **Role of Endothelium:** surface receptors to platelets, activates neutrophils and monocytes; secretes endothelin (vasoconstrictor) and nitric oxide (vasodilator & platelet inhibitor);
- **Role of Coagulation Factors**

Factor

I	**Fibrinogen**
II	**Prothrombin**
III	**Tissue thromboplastin**
IV	**Calcium**
V	**Labile factor (Proaccelerin**
VI	**not assigned**
VII	**Proconvertin**
VIII	**Anti-hemophilic A Factor**
IX	**Anti-hemophilic B (Christmas) Factor**
X	**Stuart-Prower factor**
XI	**Plasma thromboplastin antecedent**
XII	**Hageman factor (contact factor)**
XIII	**Fibrin stabilizing factor**

Intrinsic Pathway
surface contact

Extrinsic Pathway
Tissue trauma



- **Role of Fibrinolysis**: Plasminogen converts to plasmin by tPA and urokinase. TPA is more fibrin specific than streptokinase or urokinase. Proteins C and S are vitamin K dependent. Thrombin, thrombomodulin, Protein S, and phospholipid combine to activate Protein C ---->degrades VIIa and Va, and enhances tPA by inactivating plasminogen activator inhibitor.

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