HYPERCOAGULABLE STATES, FIBRINOLYSIS

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Hypercoagulable states

- Factor V, VII, VIII, IX, fibrinogen, and vWF increase with age.
- Factor VIII elevated in Africans
- Diminished in those of O blood group
- Factor VIII elevated in acute phase responses, pregnancy, oral contraceptive use, or aerobic exercise

Hypercoagulable states

- During pregnancy stasis due to obstruction of inferior vena cava by gravid uterus along with increase in the majority of clotting factors, fibrinogen and vWF is observed.
- Activity of Protein S decreases with simultaneous resistance of protein C.
- In addition, fibrinolytic system is also impaired
- During the first hours of surgery, there is increase in TF, tissue plasminogen activator (tPA) and vWF
- Dysfibrinogenemia

Hypercoagulable states

- Resistance to Activated Protein C
- Factor V Leiden G1691A mutation
- Most common genetic risk factor for deep vein thrombosis
- Found in 60% of affected patients
- But in only up to 15% of Europeans
- Rare in African, South Asian, Australians
- Resists cleavage by protein C.
- Confirm by demonstrating mutation.

Hypercoagulable states

- Protein C deficiency
- Autosomal dominant inheritance
- If due to liver disease or vitamin K deficiency (or warfarin), both Factor VII and Protein C will be diminished proportionately.
- Protein S deficiency
- Autosomal dominant inheritance
- If due to liver disease or vitamin K deficiency (or warfarin), both Prothrombin and Protein C will be diminished proportionately.

Hypercoagulable states

- Prothrombin 20210G-A mutation
- Increased plasma levels of prothrombin
- Predisposing to venous and possibly arterial thromboses.
- Found in 6% of patients with idiopathic venous thrombosis
- But only in 2% of Europeans
- Rare in African, South Asian, Australians

Hypercoagulable states

- Antithrombin III deficiency
- May also predispose to arterial thrombosis.
- Lower levels of ATIII:
- Autosomal dominant inheritance
- Heparin
- Oral contraceptives
- Liver disease
- Nephrotic syndrome
- L-asparaginase use
- DIC
- Warfarin elevates levels of ATIII.

Hypercoagulable states

- Hyperhomocysteinemia
- MTHFR gene mutation
- Increased serum levels predispose to
- Venous and arterial thrombosis
- Atherosclerotic cardiovascular disease.
- Found in up to 25% of patients with venous thrombosis
- But in up to 15% of Europeans
- Elevate levels:
- Phenytoin
- Methotrexate
- Deficiencies of vitamins B_6, B_{12}, and folic acid

Hypercoagulable states

- Antiphospholipid Antibodies
- 3-5% of general population
- High risk for:
- Venous and arterial thrombosis
- Recurrent spontaneous abortions
- Neurologic complications.
- Heterozygous group of antibodies (IgM and IgG)
- Directed against protein-phospholipid (anionic) complexes on which coagulation interactions occur:
- Cardiolipin, beta 2 glycoprotein 1 (B2GP1), and cell-membrane phosphatidylserine

Hypercoagulable states

- Antiphospholipid antibodies may be
- Idiopathic or
- Associated with autoimmune diseases
- Systemic lupus erythematosus
- Drugs
- Hydralazine
- Antiphospholipid syndrome.
- Often associated with immune-mediated thrombocytopenia.
- Anticardiolipin antibodies are not detected in the lupus anticoagulant screen. Often detected by an abnormal RPR in the absence of syphilis.

Deep vein thrombosis

- Prevalence is 5%.
- Low risk of clinically important pulmonary embolism (<1%)
- Confined to the calf veins
- But 15-25% will extend into popliteal or proximal vein
- Moderate to high risk:
- Localized tenderness along the distribution of the deep venous system; or
- Leg swelling or calf swelling at least 3cm larger than the asymptomatic leg
- (or pitting edema confined to the symptomatic leg)

Deep vein thrombosis

- Negative high sensitivity D-dimer assay excludes thrombosis (specificity >90%).
- Positive D-dimer assay in patient at high probability of deep vein thrombosis should be followed by ultrasonography.
- Ultrasonography result guides strategy.

Deep vein thrombosis

- Patients with documented calf vein thrombosis should either receive anticoagulant treatment to prevent extension
- Or undergo monitoring for proximal extension using serial ultrasound examinations
- If proximal vein thrombosis is absent by objective testing
- 2% new venous thromboembolic events

Deep vein thrombosis

- Untreated proximal vein thrombosis
- 10% fatal pulmonary embolism.
- Inadequately treated proximal vein thrombosis
- 20 to 50 % risk of reduction of recurrent venous thromboembolic events.

Hypercoagulability testing

- Unexplained arterial thrombosis:
- Factor V Leiden
- Prothrombin 2010G
- Unexplained venous thromboembolism:
- Factor V Leiden
- Prothrombin 2010G
- Protein C
- Protein S
- Antithrombin III
- Anti-phospholipid antibodies

Treatment

- Patients with proximal deep vein thrombosis require both:
- Adequate initial anticoagulant treatment with heparin or low molecular weight (LMWH) heparin
- Adequate long-term anticoagulant therapy to prevent recurrent venous thromboembolism.
- Reduces the incidence of recurrent venous thromboembolism during the first 3 months after diagnosis from 25 percent to 5 percent or less.

Heparin

- Heparin catalyzes the activation of ATIII, decreasing the activity of factor Xa and thrombin as a result.
- Low molecular weight heparins (LMWH) such as enoxaparin are equivalent to heparin.
- The major adverse effect of heparin is hemorrhage.
- Immune thrombocytopenia is not a common occurrence.
- Unfractionated heparin may induce antibody formation to platelet factor 4.
- Pro-thrombotic state even if thrombocytopenic as platetlets are activated
- Less likely with low molecular weight heparins.
- Actions reversed with protamine sulfate.

Heparin

- Heparin activity is monitored with the activated PTT (2.0-3.0 times normal as target).
- The activated clotting time may also be utilized.
- LMWH does not require anticoagulant monitoring.
- Synthetic factor Xa inhibitors are as safe and effective as LMWH.
- Intravenous unfractionated heparin remains the preferred approach for initial anticoagulant therapy in patients with severe renal failure.
- Must achieve prolonged APTT values within 24 hours.
- Anticoagulation continues for 5 days.
- Favored in pregnancy.

Venous thromboembolism prophylaxis

- Patient at risk for venous thromboembolism:
- Stomach cancer (very high risk)
- Lung cancer
- Lymphoma
- GYN cancer
- Bladder cancer
- Testicular cancer
- Stratify with Khorana score

Venous thromboembolism prophylaxis

- Khorana score
- If:
- Platelet count >350,000 per fmol
- Hemoglobin <10.0 (or use of growth factors)
- BMI>35
- Pre-chemotherapy white count >11 thousand
- Each of the above counts one except stomach which counts two
- Three or above is high risk for venous thromboembolism

Venous thromboembolism prophylaxis

- Prophylaxis for 7-10 days for short hospital stays with one of the following:
- LMWH
- Low dose UFH
- Fondaparinux
- 28 day course if major surgical procedure, or
- Advanced malignancy receiving chemotherapy
- LMWH preferred
- If previous episode of venous thromboembolism, prophylaxis continued as long as disease is active

Oral anticoagulants

- Long-term anticoagulant therapy is required to prevent a high frequency (15–25%) of symptomatic extension of thrombosis and/or recurrent venous thromboembolic events.
- Oral anticoagulant treatment using a vitamin K antagonist (e.g., sodium warfarin) currently is the preferred approach for long-term treatment.
- Treatment with a vitamin K antagonist is started with initial heparin or LMW heparin therapy and then overlapped for 4 to 5 days
- The dose of vitamin K antagonist should be adjusted to maintain the international normalized ratio (INR) between 2.0 and 3.0.

Oral anticoagulants

- Treatment should be continued for at least 3 months in patients with a:
- First episode of proximal vein thrombosis, or
- Pulmonary embolism secondary to a transient (reversible) risk factor.
- Patients with a:
- First episode of idiopathic deep vein thrombosis, or
- With antiphospholipid antibodies, or
- Thrombophilic condition
- Should be considered for indefinite anticoagulant therapy (but no less than 12 months).

Warfarin

- Warfarin inhibits the γ-carboxylation of vitamin K dependent clotting factors [II, VII, IX, X, proteins C and S].
- Warfarin activity is monitored with the PT [INR >2.0 as target].
- It may take 7 days to stabilize the INR following dosage change.

Warfarin

- Major adverse effect is hemorrhage.
- Risk increases greatly with age.
- In those over 85, risk of intracranial bleeding is 2.5 times greater than those 70-75.
- May be related to cerebral amyloid angiopathy [the cause of 10-15% of spontaneous hemorrhagic strokes].

Warfarin

- As warfarin crosses the placenta, it is not used in pregnancy.
- Effect reversed with intravenous vitamin K or with fresh frozen plasma.
- Drugs commonly prolonging effect are:
- Amiodarone
- Cimetidine
- Metranidazole
- Maintain continuous dosing.

New oral anticoagulants

- Rapid onset (1-4 hours)
- Do not require monitoring.
- Do not use with CYP3A4 inhibitors or inducers.
- Dabigatran is a direct thrombin inhibitor.
- Rivaroxaban is a Factor X^a inhibitor.
- Not inferior to Vitamin K antagonists as anticoagulant therapy.

Fibrinolysis

- The fibrinolytic system is a parallel system which is activated along with activation of coagulation cascade and serves to limit the size of clot.
- Dissolves the fibrin clot into fibrin degradation products (FDPs) by plasmin originating from fibrin bound plasminogen in liver.
- Catalysed by tPA or urokinase plasminogen activator (u-PA) released from vascular endothelium.
- Release of t-PA is stimulated by tissue occlusion, thrombin, epinephrine, vasopressin and strenuous exercise.
- Plasmin activity is tightly regulated by its inhibitor (α-2 antiplasmin)

Fibrinolytic system

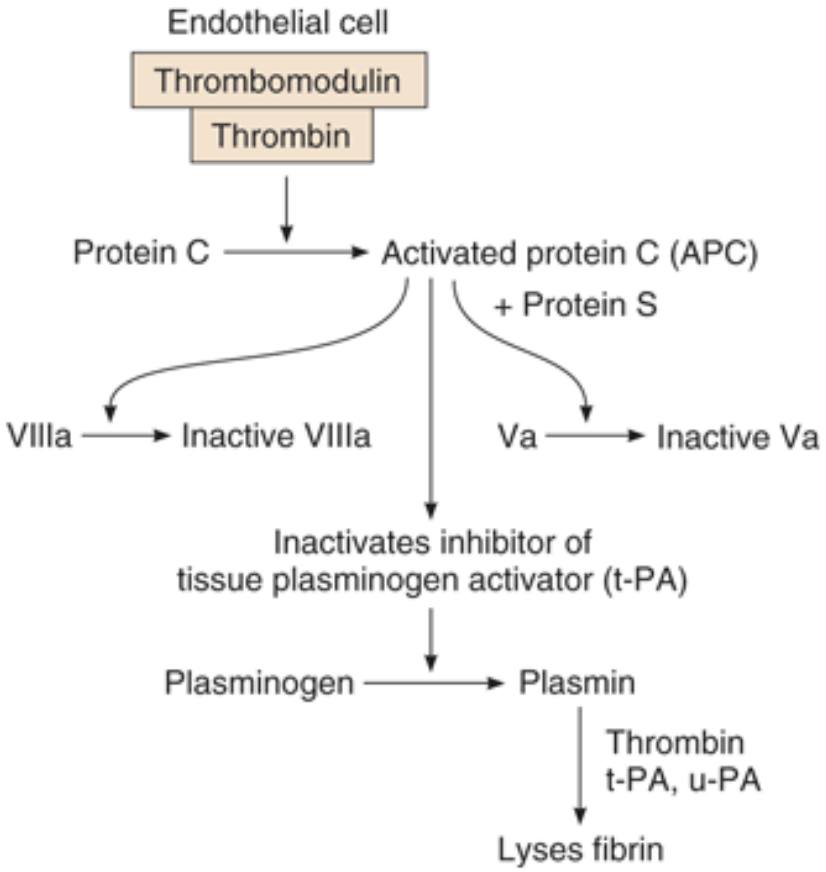


Fig. 32-14
Accessed 03/01/2010

Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fibrinolysis

- Fibrin-based plasminogen (PLG)
- Produced in the liver
- Converted to the serine protease, plasmin (PN)
- through the action of tissue-plasminogen activator (t-PA) or urokinase-plasminogen activator (u-PA).
- The activity of t-PA is greatly enhanced by its assembly with plasminogen through lysine residues on a fibrin-containing thrombus.
- u-PA acts independently of fibrin.

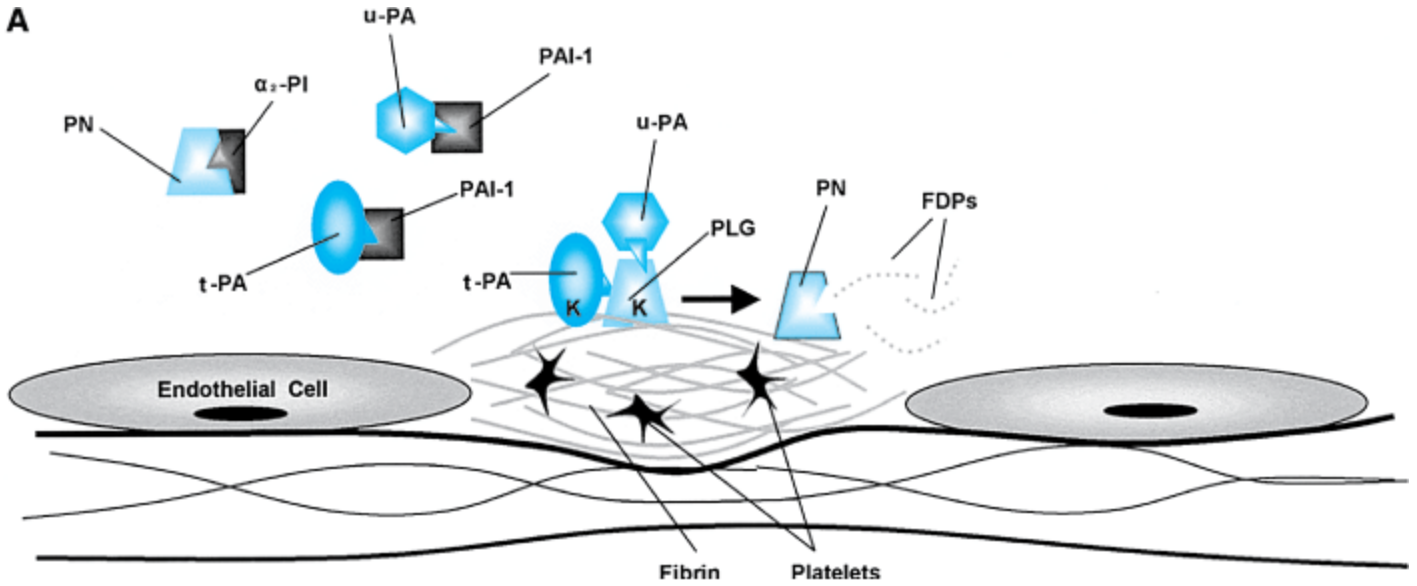
Fibrinolysis

- Both t-PA and u-PA can be inhibited by plasminogen-activator inhibitor-1 (PAI_1), the main physiologic regulator of PA activity.
- Other serine protease inhibitors include α_2-antiplasmin and α_2-microglobulin (also inhibits thrombin).
- By binding to fibrin, plasmin is protected from its major inhibitor PAI_2.
- Bound plasmin degrades cross-linked fibrin, giving rise to soluble fibrin degradation products (FDPs).

Fibrinolysis

- Endothelial cells, monocytes, and macrophages express the u-PA receptor (u-PAR) and annexin 2, a coreceptor for t-PA and PLG that augments the efficiency of plasmin generation.
- Circulating monocytes and macrophages also have cell surface-enolase, a potential receptor for PLG.
- Tranexamic acid is a competetive inhibitor of plasminogen activation.
- At high doses it inhibits plasmin.

Fibrinolysis



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

Fig. 127-1 Accessed 03/02/2010

Fibrinolysis

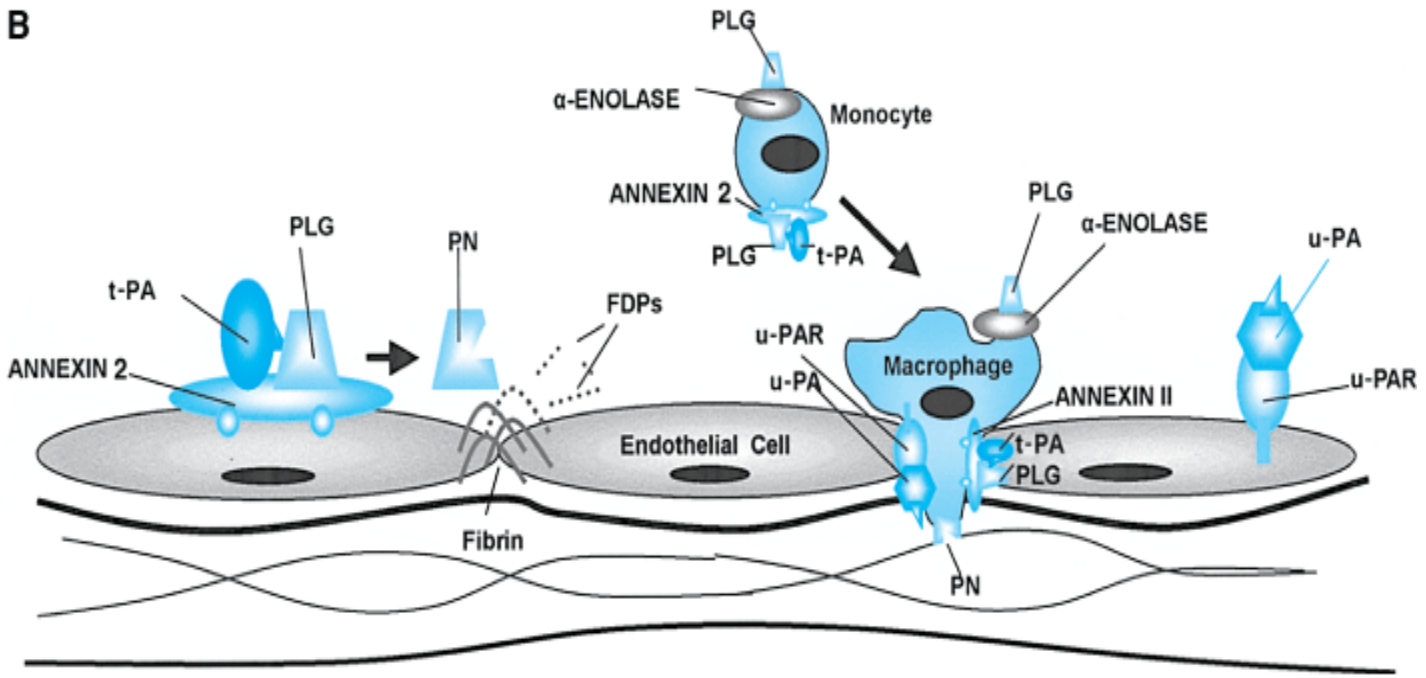


Fig. 127-1 Accessed 03/02/2010

Fibrinolysis

- Fibrinolytic activity lowest in the morning.
- Thrombin time abnormal in the presence of heparin and in the presence of fibrin split products.
- A negative D-dimer assay excludes active fibrinolysis.
- A positive D-dimer assay has little predictive value.

- Lupus anticoagulant may be associated with a positive RPR.
- Prothrombin and partial thromboplastin times are abnormal;
- Thrombin time is normal.

Fibrinolytic therapy

- Fibrinolytic therapy is but one part of a combined antithrombotic strategy.
- Thrombolytic therapy is given as soon as the patient presents with acute symptoms.
- Accelerates thrombus dissolution by increasing fibrinolysis
- The change in thrombus size results from a balance of fibrinolysis with concurrent fibrin formation and platelet deposition.

Fibrinolytic therapy

- Fibrinolytic therapy is administered in combination with an anticoagulant to block fibrin formation and with an antiplatelet agent to limit continued platelet deposition.
- Anticoagulant therapy is routinely continued after completion of fibrinolytic therapy to prevent thrombotic reocclusion stimulated by the procoagulant effects of the original lesion and by prothrombotic effects of fibrinolytic therapy itself.

Fibrinolytic therapy

- Those most likely to respond and benefit:
- Acute myocardial infarction: Within 12 hours of onset.
- Stroke: Ischemic stroke within 3 hours of symptom onset
- Acute occlusions of peripheral arteries as well as distal arterial obstruction not correctable by surgery .
- Large proximal deep venous thrombi with symptoms for <7 days.
- Massive or sub-massive pulmonary embolism with hemodynamic compromise .

Fibrinolytic therapy

- Tissue plasminogen activator (tPA) is fibrin specific
- Major contraindications :
- Risk of intracranial bleeding
- Recent head trauma
- Central nervous system surgery
- History of stroke or subarachnoid bleed
- Intracranial metastatic disease
- Risk of major bleeding
- Active gastrointestinal
- Active genitourinary bleeding
- Major surgery or trauma within 7 days
- Dissecting aneurysm

Fibrinolytic therapy

- Relative contraindications
- Pregnancy
- Severe uncontrolled hypertension
- Remote history of bleeding from any site

Bleeding complications of therapy

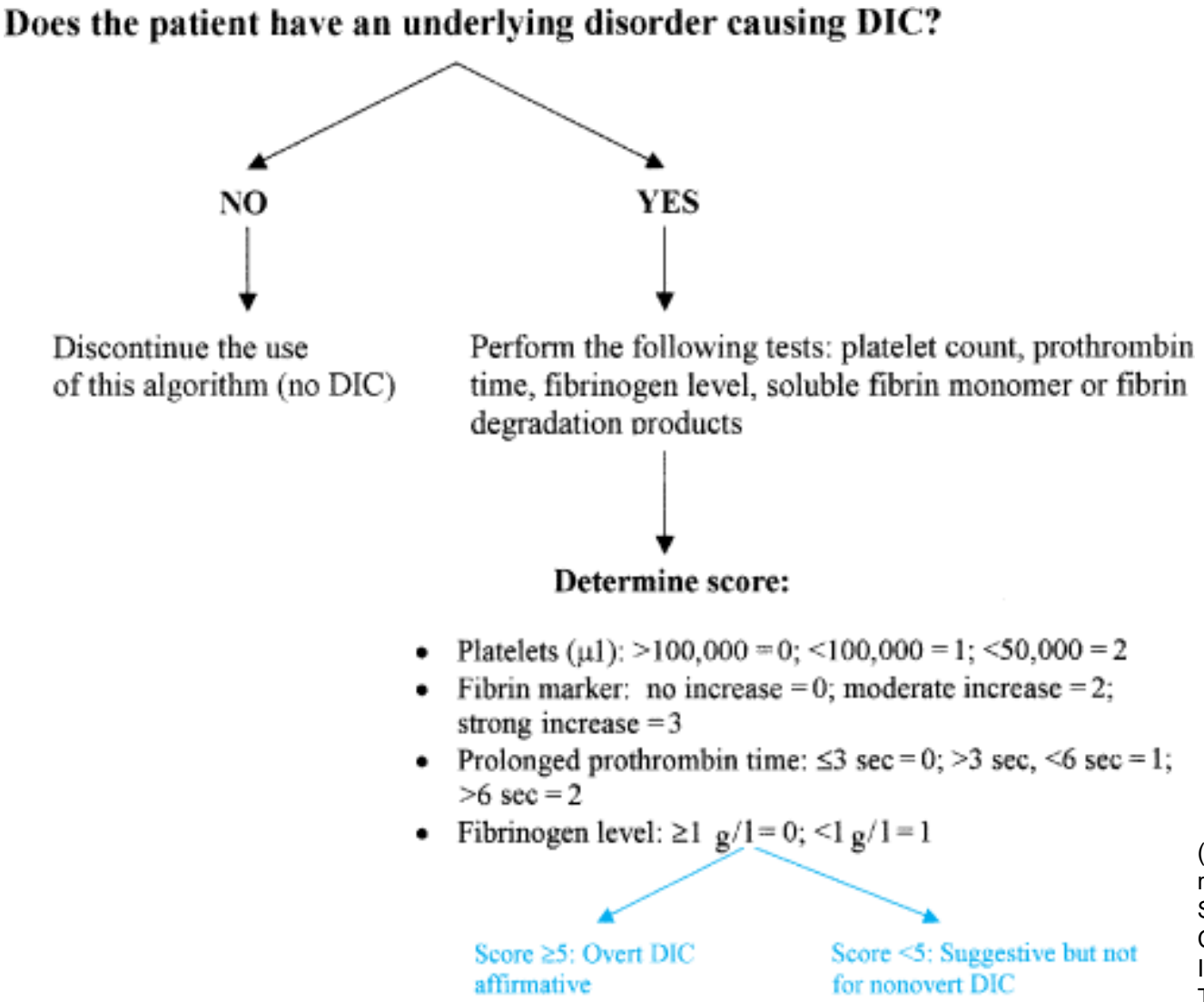
- Discontinue the fibrinolytic agent, (all have short half-lives).
- An antifibrinolytic (anti-plasmin) agent such as ε-aminocaproic acid (EACA) can be administered to block fibrinolysis and may be administered if the fibrinolytic agent remains in the blood.

Bleeding complications of therapy

- Fibrinogen replacement often is needed to correct the plasminemia and can be accomplished by administration of 5 to 10 bags of cryoprecipitate.
- Fresh-frozen plasma can be used to replace other hemostatic proteins.
- Replacement treatment should be monitored with repeated coagulation tests.
- Heparin effect can be reversed by administration of protamine sulfate, and desmopressin may be of some value in reversing platelet dysfunction.
- All other anticoagulant and antiplatelet agents should be discontinued.

Bleeding complications of therapy

- Administration of platelet concentrates can also be useful because fibrinolytic therapy results in platelet dysfunction from proteolysis of surface proteins.
- Replacement of platelets, however, may not be of consistent value because the circulating fibrin(ogen) degradation products induced by fibrinolytic therapy can inhibit the function of infused platelets.



(Adapted from the recommendations of the Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis.)

Fig. 121-2 Accessed 03/02/2010

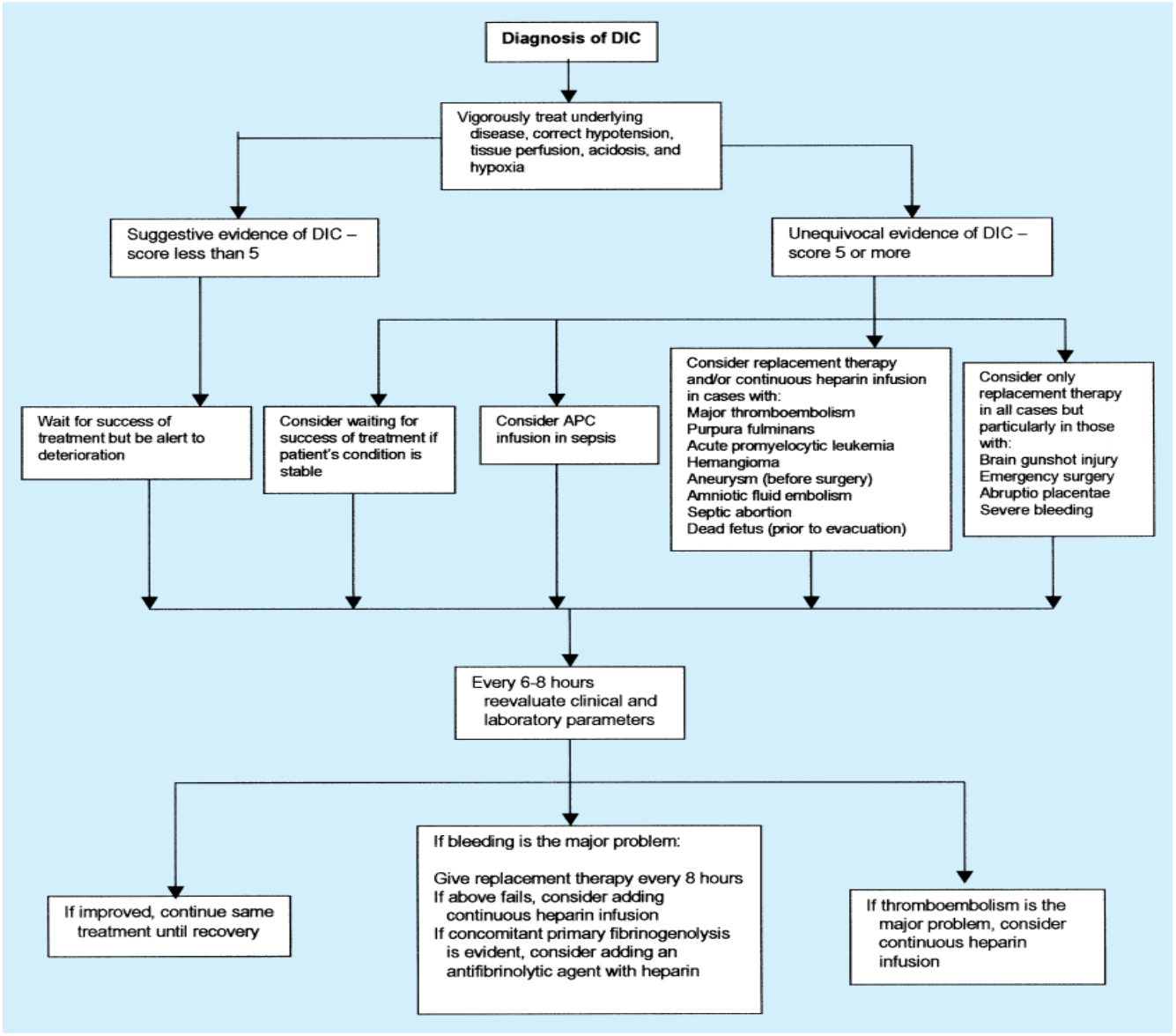


Fig. 121-3 Accessed 03/02/2010