Inflammation and Coagulation

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Coagulation disturbances in Sepsis

- Principally regulated by TNF, IL-1, and IL-6
  - TNF influences coagulation activation via action of IL-6
- Abundant intravascular fibrin formation leads to microvascular thrombosis→widespread ischemic organ damage to organ necrosis and widespread skin necrosis and multiple organ dysfunction syndrome

- Procoagulant mechanisms:
  - Coagulation activation during sepsis is primarily triggered through the Tissue Factor pathway
    - TF on monocytes and probably endothelial cells triggers activation of coagulation in sepsis
    - FVII is activated by TF
    - TF/FVIIa complex activates FX
    - FXa converts prothrombin to thrombin
    - Thrombin activates FV and FVIII
    - Fva enhances Fxa activity to activate prothrombin
  - TFPI rapidly abrogates the TF/FVIIa pathway
  - TF/FVIIa activates FIX
    - In concert w/ FVIIIa takes over function of TF/FVIIa to activate FX
  - Thrombin cleaves fibrinogen to fibrin monomers
  - Thrombin activates FXIII which crosslinks fibrin monomers to form a stable clot
  - Thrombin also activates FXI
    - FXIa activtes FIX
    - FIXa activates more factor X
    - Amplified factor XI also activates thrombin-dependent fibrinolysis inhibitors
    - Cleave off binding sites for plasminogen on fibrin→inhibits fibrinolysis

- Anticoagulant mechanisms:
  - Antithrombin forms antithrombin-thrombin complexes→inactivating thrombin
  - Thrombomodulin
    - Binds thrombin decreasing its procoagulant activity
    - Activates protein C
    - Reduced activity in sepsis due to inflammatory mediators
  - APC
    - Inactivates FVa and FVIIIa
    - Reduced TM activity in sepsis decreases APC activity
- Thrombocytopenia
  - Develops in sepsis due to:
    - Impaired platelet production
    - Increased platelet consumption by tissues
    - Platelet sequestration in the tissues
  - Active phagocytosis of megakaryocytes occurs likely as a result of high levels of macrophage colony stimulating factors

Clinical manifestations and laboratory investigations

- Laboratory markers
  - Increased d-dimer levels
  - Decreased circulating protein C
  - Prolonged coagulation times
    - Due to decreased levels of fibrinogen, prothrombin, and factors II, V, VII, IX and X
      - Consequence of plasmin-induced proteolysis and consumption
  - Decreased platelet count
    - Marker of dysfunction of hemostatic system

Questions

1) Procoagulant mechanisms are predominantly mediated by
   a) vWf
   b) TF
   c) TFPI
   d) FVII
2) A reduction of activated protein C is seen in sepsis due to
   a) Decreased production
   b) Decreased activation
   c) Increased excretion
   d) Increased utilization
3) Thrombin mediated activation of FXIII
   a) Increases activation of FX
   b) Decreases activation of protein C
   c) Cleaves plasminogen binding sites on fibrin
   d) Facilitates fibrin crosslinking
4) Amplification of factor XI decreases clot break down by
   a) Inhibition of protein C
   b) Downregulation of thrombomodulin
   c) Alteration in fibrin preventing plasmin activity
   d) Enhanced thrombin activity
5) List three ways in which thrombocytopenia develops in sepsis
   a) Decreased production
   b) Increased consumption
   c) Sequestration