sepsis & coagulation [created by Paul Young 02/10/07]

antithrombin III

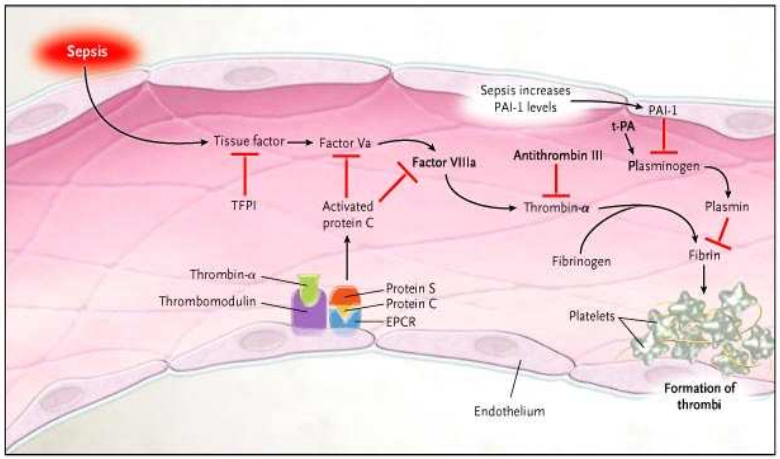
- inhibits multiple components of the intrinsic, extrinsic and final common coagulation pathways (IIa, IXa, Xa, XIa, XIIa, VIIa/TF, and kallikrein)
- in addition to its antithrombotic properties, AT bound to endothelial cell surface heparans stimulates the endothelium to release prostacyclin, anti-inflammatory properties.
- In animal models, AT successfully blocks endotoxin-induced pulmonary leukocyte accumulation and vascular permeability changes

- Kybercept trial of ATIII showed increased mortality for patients receiving AT-III and heparin compared to placebo (36.6% vs 39%)

tissue factor pathway inhibitor

- Extrinsic pathway activation is tightly regulated by TFPI which is a potent inhibitor of tissue factor
  - TFPI was not proven beneficial overall in a large RCT 1754 in sepsis (OPTOMIST trial)
  - mortality 34% in both group. Interestingly, a planned interim analysis after inclusion of 722 patients had shown a large difference in mortality: 29·1% versus 38·9% for TFPI versus placebo, respectively (p=0·06). This difference fell just short of predefined stopping rules, and the trial was continued. Survival in the TFPI group then fell precipitously, and on completion of the study no difference in mortality remained.
  - Subgroup analysis suggests the possibility of a potentially beneficial effect among patients with pneumonia. This has led to a large multicentred study being conducted to investigate the potential usefulness of this agent in this group of patients (CAPTIVATE STUDY)

overview



effect of sepsis on coagulation

- Sepsis-induced procoagulant activity is generally more severe than that which can be produced by trauma.
- The prothrombic diathesis is systemic—that is, thrombin is generated not only by the endothelium, but also by circulating activated monocytes. This creates an essentially unlimited supply of TF.
- Generalized activation of coagulation depletes the body's natural antithrombotic factors: protein C, antithrombin (AT), and TF pathway inhibitor (TFPI)

coagulation cascade

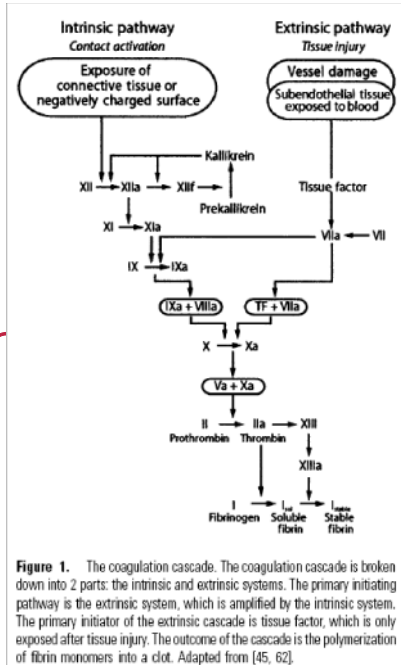
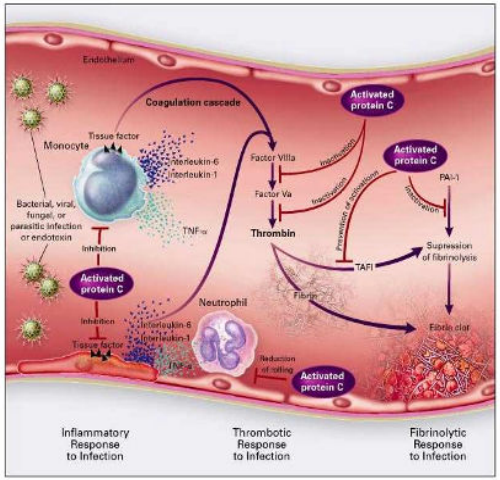


Figure 1. The coagulation cascade. The coagulation cascade is broken down into 2 parts: the intrinsic and extrinsic systems. The primary initiating pathway is the extrinsic system, which is amplified by the intrinsic system. The primary initiator of the extrinsic cascade is tissue factor, which is only exposed after tissue injury. The outcome of the cascade is the polymerization of fibrin monomers into a clot. Adapted from [45, 62].

activated protein C



mechanisms:
(i) inhibition of coagulation system:
- inactivation of factor VIIIa
- inactivation of factor Va
- inactivation of PAI-1
- prevention of activation of TAFI
- inhibition of tissue factor
(ii) inhibition of inflammation:
- inhibition of release of cytokines from monocytes
- inhibition of neutrophil rolling
(iii) inhibition of apoptosis

trials:
- Overall, PROWESS demonstrated an absolute risk reduction of death at 28 days of 6% (from 31% to 26%); for patients with an APACHE-II of >25 the ARR was 13%
- ADDRESS was terminated early because of a lack of effectiveness of therapy. Number needed to cause severe bleeding was 100