Disseminated Intravascular Coagulation

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Introduction

- DIC (aka consumption coagulopathy, defibrination syndrome)
  - Systemic process producing both thrombosis and hemorrhage
  - Initiated by a number of defined disorders
  - Consists of the following components:
    - Exposure of blood to procoagulants
    - Formation of fibrin in the circulation
    - Fibrinolysis
    - Depletion of clotting factors
    - End-organ damage

- Occurs in approximately one percent of hospital admissions

- Treatment is supportive
  - Platelet transfusion
  - Factor replacement
Pathogenesis
Pathogenesis

- Primarily due to an uncontrolled and excessive production of thrombin, leading to widespread and systemic intravascular fibrin deposition
Pathophysiology of the Clinical Manifestations of Disseminated intravascular Coagulation

Intravascular activation of coagulation

- Consumption of clotting factors and platelets
- Fibrin deposition in microcirculation

Secondary fibrinolysis

- Generation of fibrin-degradation products
- Microangiopathic hemolytic anemia
- Ischemic organ damage
- Thrombotic manifestations

Bleeding diathesis
Normal activation of hemostasis

- Begins with exposure of blood to procoagulants
  - Primarily mediated by the extrinsic pathway
    - Involves tissue factor and factor VIIa
    - Ultimately leading to the formation of thrombin
      - Normally localized to the site of injury
      - Inducing platelet aggregation
      - Deposition of crosslinked fibrin to form the hemostatic plug
Generation of thrombin
  - Tightly regulated by the multiple natural antithrombotic pathways existing in plasma and on the endothelial cell surface
    - Ex. antithrombin and tissue factor pathway inhibitor
  - When these mechanisms are overwhelmed by the markedly increased production of thrombin, thrombin may circulate and lead to disseminated intravascular coagulation
  - The widespread deposition of fibrin results in tissue ischemia and consumption of platelets, fibrinogen, prothrombin, and factors V and VIII, which in turn may lead to bleeding
Massive activation of the clotting cascade

Major initiating factors
- Release or expression of tissue factor
  - Usually involving entry of tissue thromboplastins into the circulation
- Extensive injury to vascular endothelium exposing tissue factor
- Enhanced expression of tissue factor by monocytes in response to endotoxin and various cytokines

Intrinsic pathway activation may also occur in some settings
- Appears to contribute more to the development of hypotension than to DIC
Release of tissue plasminogen activator with subsequent generation of plasmin from plasminogen at the site of vascular injury produces

- Compensatory thrombolysis (secondary fibrinolysis)
- Opening of occluded blood vessels
- Release of fibrin degradation products (FDP)
  - Normally the amount of FDP released is small and these are rapidly cleared from the circulation

DIC

- Widespread systemic fibrin deposition
  - Byproducts may enhance bleeding by
    - Interfering with normal fibrin polymerization
    - Binding to the platelet surface glycoprotein IIb/IIIa fibrinogen receptor, interfering with platelet aggregation
Since plasmin can cleave proteins other than fibrin

- Excessive plasmin will lead to proteolytic degradation of fibrinogen and other clotting factors
- Causing consumption coagulopathy, exacerbating the bleeding diathesis
Release of tissue plasminogen activator with subsequent generation of plasmin from plasminogen at the site of vascular injury

- Produces compensatory thrombolysis (secondary fibrinolysis), opening of occluded blood vessels, and the release of fibrin degradation products (FDP)
  - Normally the amount of FDP released is small and these are rapidly cleared from the circulation

In DIC, these byproducts

- Enhance bleeding by interfering with normal fibrin polymerization
- Bind to the platelet surface glycoprotein IIb/IIIa fibrinogen receptor, interfering with platelet aggregation

Plasmin can cleave proteins other than fibrin

- Excessive plasmin will lead to proteolytic degradation of fibrinogen and other clotting factors
  - Causing consumption coagulopathy—exacerbating the bleeding diathesis
Chronic Compensated DIC

- Consequences depend on
  - Cause
  - Rapidity with which the initiating event is propagated
    - If the activation occurs slowly
      - Excess of procoagulants are produced, predisposing to thrombosis
      - If the liver can compensate for the consumption of clotting factors, and the bone marrow maintains an adequate platelet count
        - Bleeding diathesis will not be clinically apparent

- Clinical presentation
  - Primarily thrombotic manifestations
    - Venous and arterial
# Coagulation Parameters in Acute and Chronic Disseminated Intravascular Coagulation

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Acute Decompensated DIC

- Dominated by intravascular coagulation
  - Depletion of platelets, fibrinogen, prothrombin, and factors V and VIII
  - Production, via the action of plasmin, of fibrin degradation products, which further interfere with hemostasis

- Clinical consequence
  - Profound systemic bleeding diathesis
    - Bleeding from wound sites, intravenous lines, and catheters, as well as bleeding into deep tissues

- Intravascular fibrin strands cause mechanical shearing of circulating red cells
  - Producing microangiopathic hemolytic anemia
Etiology

- **Most common causes**
  - Sepsis
  - Trauma and tissue destruction
  - Cancer
  - (Obstetrical complications)

- **In two large series of 346 and 118 patients with DIC, the following distribution of causes was noted:**
  - Generalized infection (26 & 40%)
  - Malignancy (24 & 7%)
  - Surgery and trauma (19 & 24%)
  - Liver disease (8%)
  - Miscellaneous (23%)
Major Causes of Disseminated Intravascular Coagulation

**Events that initiate DIC**
- Septicemia — Gram negative and Gram positive
- Crush injury or complicated surgery
- Severe head injury
- Cancer procoagulant (Trousseau's syndrome)
- Acute leukemia, especially promyelocytic
- Complications of pregnancy
  - Amniotic fluid embolism
  - Abruptio placentae
  - HELLP syndrome
  - Eclampsia and severe preeclampsia
  - Dead fetus syndrome
  - Septic abortion
  - Amphetamine overdose
- Giant hemangioma (Kasabach-Merritt syndrome)
- Abdominal aortic aneurysm
- Peritoneovenous shunt
- Acute hemolytic transfusion reaction
  (ABO incompatibility)
- Paroxysmal nocturnal hemoglobinuria
- Snake and viper venoms
- Liver disease
  - Fulminant hepatic failure
  - Reperfusion after liver transplantation
- Heat stroke
- Burns
- Purpura fulminans

**Events that complicate and propagate DIC**
- Shock
- Complement pathway activation
Sepsis

- Nonbacterial
- Bacterial
- Classically recognized as a complication of endothelial damage produced by meningococcemia
- Subsequently described with a variety of Gram negative and Gram positive organisms
  - Ex. Overt DIC occurs in 30-50% of patients with Gram negative sepsis
Animal models of endotoxin-induced DIC

- Evidence that the pathogenesis involves both
  - Thrombin generation
  - Suppression of normal antithrombotic mechanisms
    - Downregulation of the protein C/thrombomodulin system
    - Impaired fibrinolysis

- Clinical Presentation
  - Determined by the balance between thrombin generation, clotting factor depletion, and thrombolysis
Other Factors in Sepsis

- Shock
  - Reduced blood flow
    - Diminishes the beneficial effects of hemodilution
  - Tissue damage
    - Promotes further thrombin formation
- Impaired hepatic perfusion or function
  - Causes inadequate hepatic removal of circulating activated procoagulants
Mechanisms of DIC in Shock

- Extrinsic pathway
  - Primary activating pathway
  - Experimental models
    - Inhibition of tissue factor suppresses the endotoxin-induced generation of thrombin
    - In normal humans given a bolus injection of endotoxin, the administration of tissue factor pathway inhibitor produces a dose-dependent inhibition of the activation of coagulation
Mechanisms of DIC in Shock

- Intrinsic Pathway
  - Endotoxemia activates factor XII
    - Leads to conversion of prekallikrein to kallikrein and kininogen into circulating kinins
      - Mediate increased vascular permeability, vasodilatation, and shock
  - Experimental models
    - Inhibition of intrinsic pathway activation ameliorates the hypotension but not the DIC
Mechanisms of DIC in Shock

- Activation of coagulation
  - Consequence of endothelial damage
    - Enhanced expression and release of granulocyte and macrophage procoagulant substances (ex. tissue factor)
  - May be a direct action of endotoxin and other membrane lipopolysaccharides
  - May be indirect with mediation via activation of cytokines (ex. interleukin-6 and tumor necrosis factor alpha)
Additional mechanism

May be involved in patients with meningococcal sepsis

Associated with high levels of circulating microparticles, originating from platelets or granulocytes, and having procoagulant activity

In one report, the patients with the most severe manifestations had microparticles which when added to normal plasma in vitro generated a substantial amount of thrombin
Mechanisms of DIC in Shock

- Other infections associated with DIC
- Gram positive bacteremias
  - Staphylococcus aureus, Streptococcus pneumoniae, and Clostridia perfringens
- Other
  - Viral infections (eg, varicella, hepatitis) have rarely been associated with DIC
    - Mechanism of this possible association is not known
Acute DIC is a common and potentially serious complication of extensive surgery and trauma.

- Release of tissue enzymes and or phospholipids from damaged tissue into the systemic circulation triggers activation of cytokine networks and the hemostatic system.
- Severity of the coagulopathy in these conditions is a predictor of adverse outcome.
- Incidence of DIC among trauma patients who develop the sustained systemic inflammatory response syndrome (SIRS) is greater than 50%.

Occurrence of DIC and SIRS are strong determinants for posttrauma multiple organ dysfunction syndrome.
One study of 159 patients with blunt head injury found a coagulopathy in:
- 41% of those with CT evidence of brain injury
- 25% of those without brain injury
- DIC developed 1-4 hours after injury and was associated with a higher frequency of death

Another study found direct evidence of procoagulant release and thrombin formation in cerebrovenous blood within 6 hours after severe isolated head trauma:
- These changes were associated with increased D-dimer and soluble fibrin concentrations in central venous blood
  - Consistent with activation of both coagulation and fibrinolysis
Malignancy

- 3rd most frequent cause of DIC after infection and trauma
- Accounts for approximately 7% percent of cases
- Malignancy is a hypercoagulable state and DIC is the most common coagulopathy
- Reported in
  - As many as 15% of patients with advanced disease
  - In most patients with acute promyelocytic leukemia (APML)
Obstetrical Complications
Miscellaneous Causes

- Kaposiform hemangioendothelioma
  - Aggressive form of giant hemangioma
  - Frequently complicated by DIC (Kasabach-Merritt syndrome)
    - Initiated by prolonged contact of abnormal endothelial surface with blood in areas of vascular stasis
    - Platelets and fibrinogen are consumed in these hemangiomas, and fibrinolysis appears to be enhanced
    - The DIC is usually chronic and compensated but can transform into fulminant disease
    - Similar phenomenon occurs in approximately 50 percent of patients with hereditary hemorrhagic telangiectasia and in as many as 3 to 4 percent of patients with large abdominal aortic aneurysms
Insertion of a peritoneovenous shunt is frequently complicated by DIC

Due to entry into the blood stream of endotoxin or other procoagulant material in the ascitic fluid

Incidence of DIC in this setting can be minimized by intraoperative drainage of the ascites prior to insertion of the shunt
Miscellaneous Causes

- Acute hemolytic transfusion reactions
  - Destruction of donor erythrocytes by preformed recipient antibodies
    - Usually due to ABO incompatibility which is most often the result of clerical error
- Bites from rattlesnakes and other vipers
  - Snake venoms contain a variety of substances that can affect coagulation
Miscellaneous Causes

- Many coagulation abnormalities are seen in cirrhosis
  - Complicated and intensified by the decreased synthesis of coagulation proteins
  - DIC-like picture can be seen in fulminant hepatic failure and in the reperfusion phase of orthotopic liver transplantation
  - Low-grade, subclinical DIC also appears to be common in patients with cirrhosis, due in part to absorbed endotoxin from the gut
Miscellaneous Causes

- Frequent complication of heat stroke
  - Occurs in 45% of patients admitted to an intensive care unit with near-fatal heat stroke in Chicago
  - 31% percent of patients during the Makkah pilgrimage
  - Presumed mechanism is nonspecific tissue injury with the release of tissue factor
  - Similar mechanism is presumably responsible for DIC associated with burns
Miscellaneous Causes

- DIC may accompany rhabdomyolysis, hyperthermia, acute respiratory distress syndrome, and renal failure in patients with amphetamine overdosage.

- Purpura fulminans, characterized by hemorrhagic skin necrosis, can be associated with DIC.
  - Usually seen in association with homozygous protein C deficiency (neonatal purpura fulminans or acquired protein C deficiency—ex. Meningococcemia).
Clinical Manifestations
Bleeding

- Petechiae and ecchymoses are common in conjunction with blood oozing from wound sites, intravenous lines, catheters, and, in some cases, mucosal surfaces.
  - Can be life-threatening if it involves the gastrointestinal tract, lungs, or central nervous system.
  - After surgical procedures, hemorrhage may develop around indwelling lines, catheters, drains, and tracheostomies, and blood may accumulate in serous cavities.
Acute Renal Failure

- Occurs in 25 to 40% of patients with acute DIC
  - Two major mechanisms are involved
    - Microthrombosis of afferent arterioles may produce cortical ischemia or necrosis
    - Hypotension and/or sepsis can lead to acute tubular necrosis
  - Endotoxin-induced endothelial injury may predispose to intrarenal thrombus formation by
    - Directly promoting platelet aggregation
    - Diminishing the release of nitric oxide (endothelium-derived relaxing factor)—which normally inhibits platelet aggregation
    - Increasing the synthesis of plasminogen activator inhibitor type 1, leading to a reduction in fibrinolytic activity
Hepatic Dysfunction

- Jaundice is common in patients with DIC
  - May be due both to liver disease and increased bilirubin production secondary to hemolysis
- Hepatocellular injury may be produced by sepsis and hypotension
Pulmonary Disease

- Pulmonary hemorrhage with hemoptysis and dyspnea may result from damage to the vascular endothelium.
- In addition, sepsis and trauma are causes of acute respiratory distress syndrome (ARDS) as well as DIC.
  - Diffuse pulmonary microthrombosis due to DIC can augment the lung injury associated with ARDS.
A number of neurologic abnormalities can occur in patients with DIC.

- Include coma, delirium, and transient focal neurologic symptoms.
- Microthrombi, hemorrhage, and hypoperfusion all may contribute.
Diagnosis
Acute DIC

- Diagnosis of acute DIC is suggested by
  - History (sepsis, trauma, malignancy)
  - Clinical presentation
  - Moderate to severe thrombocytopenia (less than 100,000/µL)
  - Presence of microangiopathic changes on the peripheral blood smear

- Diagnosis is confirmed by
  - Laboratory studies which demonstrate evidence of both increased thrombin generation (eg, decreased fibrinogen) and fibrinolysis (eg, elevated FDPs and D-dimer)
  - Degree of abnormality in these findings may correlate with the extentiveness of organ involvement
Clinically significant DIC is unlikely if there is no biochemical evidence of accelerated fibrinolysis.

Elevated D-dimer levels, reflecting cross-linked fibrin degradation, are the most common abnormal parameter in patients with DIC.

- Measurement of D-dimer is more specific although somewhat less sensitive than a latex agglutination test for fibrin degradation products.
- Method of choice is the enzyme-linked immunosorbent assay (ELISA).
PT and PTT

- Prolongation of the prothrombin time (PT)
  - Reflects reduced activity of the components of the extrinsic and common pathways
    - Include factors VII, X, V, and prothrombin, which are the most frequently decreased clotting proteins in DIC

- Activated partial thromboplastin time (aPTT)
  - Measures the intrinsic and common pathways of coagulation
    - Is sensitive to deficiencies of factors XII, XI, IX and VIII
    - Less sensitive than the PT to deficiencies of components of the common pathway
Fibrinogen

- Plasma fibrinogen concentration
  - Usually low in acute decompensated DIC
  - May be elevated as an acute phase reactant in certain conditions
    - Thus, a plasma fibrinogen of 200 mg/dL, although within the normal range, may represent a significant decrease in a patient whose baseline level, because of underlying malignancy, sepsis, or inflammation, should be 800 mg/dL
Other Studies

- Thrombin time and reptilase time
  - Usually prolonged due to hypofibrinogenemia and the presence of fibrin degradation products
- Specific assays can also be used to monitor various coagulation factors
  - Factors V and VIII, in addition to fibrinogen, are usually significantly depressed
Acute DIC is also characterized by reduced levels of endogenous coagulation inhibitors such as antithrombin (AT), protein C, and protein S.

- Marked reduction in AT levels at the onset of septic shock may be a sensitive marker of unfavorable prognosis, presumably by permitting persistence of the procoagulant state.

- Another potentially useful marker is measurement of soluble fibrin monomers.
  - However, specific assays for soluble fibrin monomers are not generally available.
Chronic DIC

- Laboratory studies are variable in chronic DIC
- Slower rate of consumption of coagulation factors may be balanced by enhanced synthesis of these proteins
  - Platelet count may be only moderately reduced
  - Plasma fibrinogen is often normal or slightly elevated
  - PT and PTT may be within normal limits
- Diagnosis may be largely based upon evidence of microangiopathy on the peripheral blood smear and increased levels of FDPs and particularly, D-dimer
Acute DIC is a serious complication that is associated with a high mortality rate, determined in part by the underlying disease.

Reported mortality rate ranges from 40 to 80% in patients with severe sepsis, trauma, or burns.

Risk factors for death include:
- Increasing age
- Severity of organ dysfunction
- Hemostatic abnormalities

Not clear if the poor outcome in sepsis and trauma reflects the effects of DIC or the consequences of the systemic inflammatory response.
Treatment

- Correction of the underlying disease and initiating factors
- Hemodynamic support is essential
- Many patients do not require specific therapy for the coagulopathy, either because it is of short duration or because it is not severe enough to present a major risk of bleeding or thrombosis
  - In selected instances, the use of blood component replacement therapy or heparin may be of value
    - There are no controlled studies demonstrating definitive benefit
    - Restoration of physiologic levels of antithrombin may be another therapeutic option
- Antifibrinolytic agents, such as epsilon-aminocaproic acid (EACA) or aprotinin, is generally contraindicated
  - Blockade of the fibrinolytic system may increase the risk of thrombotic complications
Platelet Transfusion and Fresh Frozen Plasma

- Patients with DIC bleed because of thrombocytopenia and coagulation factor deficiency
  - There is no evidence to support the administration of platelets and coagulation factors in patients who are not bleeding or at high risk of bleeding
  - Treatment is justified in patients who have serious bleeding, are at high risk for bleeding (e.g., after surgery), or require invasive procedures
Platelet Transfusion and Fresh Frozen Plasma

- Patients with marked thrombocytopenia (less than 20,000/μL) or those with moderate thrombocytopenia (less than 50,000/μL) and serious bleeding should be given platelet transfusions (1 to 2 units per 10 kg per day)
  - Patients typically show a less than expected rise in platelet count, due to the ongoing consumption

- Patients who are actively bleeding with a significantly elevated prothrombin time (INR) and/or a fibrinogen concentration <50 mg/dL
  - Should receive fresh frozen plasma or cryoprecipitate
  - Preferable to keep the fibrinogen level above 100 mg/dL
Heparin

- Administration of heparin or other anticoagulants to interrupt the underlying coagulopathy in DIC would appear to be a logical therapeutic approach
  - There are no controlled trials indicating benefit
  - Little evidence that the use of heparin improves organ dysfunction
- Additional arguments against the routine use of heparin include potential aggravation of bleeding and the likelihood that it will have reduced effect due to the low levels of AT
Heparin

- Administration of heparin is generally limited to the subset of patients with:
  - Chronic, compensated DIC
  - Predominantly thrombotic manifestations
  - Migratory thrombophlebitis and acral ischemia
Heparin

- **Heparin use in acute DIC**
  - Important to be sure that the patient's antithrombin (AT) level is near normal (ie, 80 to 100 percent)
    - So that the biologically important heparin-AT complex can form and inactivate the serine protease procoagulants, particularly thrombin and factor Xa
  - Usual intravenous bolus heparin injection of 5,000 to 10,000 units should be avoided
    - Aim for an aPTT of about 45 sec
  - If the patient's baseline aPTT is prolonged
    - Aim for further slight prolongation of the aPTT
  - Once there is evidence of heparin effect, replacement therapy with fresh frozen plasma or cryoprecipitate is pursued

- **Heparin use in chronic DIC**
  - Continuous infusion can be used
  - Low molecular weight heparins are also efficacious
Patients with homozygous protein C deficiency or acquired protein C deficiency (eg, due to meningococcemia) may develop purpura fulminans

- Appear to benefit from the administration of protein C concentrate
- In one series of 12 patients with purpura fulminans treated with protein C concentrate, none died despite a predicted mortality rate of 60 to 80 percent

Administration of FFP as a source of protein C is more difficult because of the short half-life of protein C in the plasma

Anecdotal reports that repeated plasma exchange has been helpful in maintaining normal levels of protein C when protein C concentrate is not available
Antithrombin

- Acute DIC is also characterized by reduced levels of endogenous coagulation inhibitors such as antithrombin (AT, formerly known as antithrombin III), protein C, and protein S
- A marked reduction in AT levels at the onset of septic shock may be a sensitive marker of unfavorable prognosis, presumably by permitting persistence of the procoagulant state
- In vitro data shows that AT may decrease the inflammatory response of mononuclear cells and cultured endothelial cells to lipopolysaccharide by decreasing the transcription of genes for mediators such as interleukin-6 and tumor necrosis factor alpha
Antithrombin

- While some clinical studies have suggested that AT therapy is beneficial in patients with severe sepsis or septic shock.
  - Subsequent randomized placebo controlled trial in 2314 patients with sepsis found no benefit, in terms of mortality, from AT administration, and there was an increased risk of bleeding in those who received both AT and heparin.