Evaluation and management of disseminated intravascular coagulation (DIC) in adults

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INTRODUCTION

Disseminated intravascular coagulation (DIC; also called consumption coagulopathy and defibrination syndrome) is a systemic process with the potential for causing thrombosis and hemorrhage. It can present as an acute, life-threatening emergency or a chronic, subclinical process, depending on the degree and tempo of the process and the contribution of morbidities from the underlying cause. Identifying DIC and the underlying condition responsible for it are critical to proper management.

This topic discusses DIC in adults.

Separate topic reviews discuss:

- **DIC in children** – (See "Disseminated intravascular coagulation in infants and children".)
- **DIC in pregnancy** – (See "Disseminated intravascular coagulation (DIC) during pregnancy: Clinical findings, etiology, and diagnosis".)
- **Differential diagnosis** – (See "Approach to the adult with a suspected bleeding disorder" and "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

PATHOGENESIS

Intravascular coagulation and fibrinolysis — Normal hemostasis ensures formation of a blood clot at the site of vessel injury, followed by resolution of the clot to allow tissue repair. There are multiple feedbacks built into this system to prevent activation of coagulation in the absence of vessel injury and restrict the clot to the site of injury. (See "Overview of hemostasis".)

In DIC, the processes of coagulation and fibrinolysis become abnormally (and often massively) activated, leading to ongoing systemic coagulation and fibrinolysis.

A typical sequence of events includes the following (figure 1):

- **Procoagulant exposure** – Blood is exposed to one or more procoagulants, such as tissue factor (TF), from which it is normally protected. Sources and components of these procoagulants depend on the underlying condition. As examples:
  - Some bacterial products, such as lipopolysaccharides, can activate coagulation [1].
  - In meningococcal sepsis, microparticles containing TF are found in the circulation [2].
  - "Cancer procoagulant" generally refers to TF produced by cancer cells. It can also be a proteolytic enzyme produced by some mucinous tumors and placenta that is capable of activating factor X [3,4]. (See "Cancer-associated hypercoagulable state: Causes and mechanisms", section on 'Procoagulant proteins'.)
  - In trauma, damage to the vascular endothelium and tissues may cause release of procoagulant enzymes or phospholipids.
  - In severe intravascular hemolysis, such as an acute hemolytic transfusion reaction (AHTR) caused by ABO mismatch, coagulation is activated by a combination of processes including TF release (likely by monocytes), generation of cytokines including tumor necrosis factor (TNF) and interleukin 1 (IL-1), and reduced nitric oxide (NO) function [5].
  - In patients with inherited or acquired protein C deficiency, an imbalance between thrombin generation and fibrinolysis may be responsible for overwhelming normal mechanisms that protect against inappropriate coagulation.
  - Neutrophils may contribute to the formation of neutrophil extracellular traps (NETs), which have procoagulant properties. (See 'Extracellular DNA and NETs' below.)

- **Coagulation** – Activation of the coagulation cascade leads to the production of thrombi consisting of fibrin and platelets (figure 2). These can occur in the microvasculature and/or larger vessels. Extensive formation of thrombi in turn leads to consumption of endogenous coagulation factors, producing a "consumption coagulopathy"; and of platelets and anticoagulant factors (eg, protein S, protein C, antithrombin).

- **Fibrinolysis** – Fibrinolysis is activated at sites of thrombus formation, with generation of fibrin degradation products (FDP) that, when present in significant amounts, interfere with both fibrin clot formation and platelet aggregation. (See "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis".)

- **Compensatory changes** – DIC is a dynamic process. The acuity and magnitude of ongoing intravascular coagulation determine whether consumption of coagulation factors and platelets can be compensated adequately by ongoing synthesis of coagulation factors and generation of new platelets in the bone marrow. The two ends of the spectrum between inadequate and adequate compensation are sometimes referred to as acute and chronic DIC.

  - **Acute DIC** – Acute (decompensated) DIC can develop when blood is exposed to large amounts of tissue factor (or other procoagulant substances) over a brief period of time, with significant generation of thrombin. This leads to rapid consumption of coagulation factors that outpaces their production. The fibrin degradation products (FDPs) that are generated in turn disrupt normal fibrin polymerization and fibrinogen binding to platelet surface αIIbβ3 (GPIIbIIIa), thus interfering with both fibrin clot formation and platelet aggregation, and effectively operating as pathologic anticoagulant and anti-platelet agents.

    The consumption coagulopathy, combined with the high concentration of FDPs, leads to the severe bleeding diathesis seen in decompensated DIC, and accounts for the clinical observation that supportive therapy with Fresh Frozen Plasma (FFP) and platelet transfusions by themselves are generally insufficient to completely correct the bleeding diathesis. Clotting times become prolonged and the potential for clinically important bleeding increases [6]. Acute DIC is typically seen in settings such as sepsis, trauma, or acute promyelocytic leukemia. (See 'Acute DIC' below.)

  - **Chronic DIC** – Chronic (compensated) DIC can develop when blood is continuously or intermittently exposed to smaller amounts of tissue factor (or other procoagulant substances). Coagulation factors and platelets are consumed, but production is able to compensate, and the liver is able to clear the FDPs. Clotting times may be normal, and

thrombocytopenia may be mild or absent. Thrombosis generally predominates over bleeding, although many patients are asymptomatic with laboratory-only evidence of increased thrombin generation and fibrinolysis [7]. Chronic DIC is typically seen in patients with advanced malignancy, especially pancreatic, gastric, ovarian, and brain tumors. (See 'Chronic DIC' below and "Cancer-associated hypercoagulable state: Causes and mechanisms".)

- **End organ damage** – Tissue or organ damage may result from reduced perfusion, thrombosis, and/or bleeding. Often, contributions from DIC itself and the condition that precipitated it are intertwined. Organ failure may result in significant morbidity and mortality. (See 'Organ dysfunction' below and 'Recovery and prognosis' below.)

Other vascular factors that may contribute to the pathogenesis of DIC include:

- Endothelial damage, which can result in the release of procoagulant substances and the loss of endothelial antithrombotic properties.
- Reduced local blood flow, which slows diffusion of procoagulant and anticoagulant factors away from the site.
- Reduced organ perfusion, which may delay hepatic clearance of coagulation byproducts.
- Reduced levels of nitric oxide, causing increased vascular tone and enhanced platelet aggregation and activation.
- Involvement of other blood cells. As an example, monocytes are known to secrete TF when stimulated by pathogens.
- In trauma or sepsis, acidosis and hypothermia may interfere with appropriate coagulation because the enzymatic functions of the coagulation factors are pH and temperature-dependent [8].

Extracellular DNA and NETs — Increasing evidence suggests that damage-associated pattern molecules (DAMPs, also called "alarmins") including cell-free DNA (cfDNA), extracellular histones, and DNA-binding proteins play a critical role in the pathogenesis of DIC [9]. DAMPs are released from dying cells or secreted from immune cells in response to infection or tissue injury. (See "An overview of the innate immune system", section on 'Interaction of innate and adaptive immunity'.)

Elevated levels of circulating extracellular cfDNA, normally found at approximately 1 mcg/mL in healthy people, are found in various pathologic conditions including sepsis, trauma, cancer, and autoimmune diseases. Often there is extensive formation of neutrophil extracellular traps (NETs). NETs are web-like structures composed of decondensed chromatin coated with a variety

of cellular proteins such as myeloperoxidase, neutrophil elastase, histones, and high mobility group box 1 protein (HMGB1) that are released from dead or dying neutrophils [10].

NET formation (NETosis) is a complex and incompletely characterized process in which nuclear chromatin becomes decondensed and released into the cytoplasm, followed by rupture of the plasma membrane and expulsion of the cellular contents into the extracellular space. NETosis accompanies a form of lytic cell death distinct from apoptosis and necrosis. Under normal conditions, NETosis appears to be a highly regulated component of innate immunity that is protective against microbial pathogens, but it becomes dysregulated in severe inflammatory conditions. The cfDNA and other nuclear proteins released during NETosis are cytotoxic and play an important role in the pathogenesis of DIC.

NETosis is highly procoagulant. It activates the clotting cascade and influences primary and secondary hemostasis via a number of mechanisms:

- Delivery of tissue factor
- Activation of the contact phase of coagulation by cfDNA
- Cytotoxicity of cfDNA, which activates cell surface Toll-like receptor (TLR9)
- Induction of platelet aggregation by cfDNA
- Proteolytic degradation of anticoagulants such as tissue factor pathway inhibitor (TFPI) via neutrophil elastase
- Cytotoxicity to endothelial cells from DNA binding proteins that are normally excluded from the circulation, such as histones and HMGB1

NET formation has been shown to play an important role in the development and propagation of pathological venous thrombosis [10,11]. An antibody directed at histone proteins has been shown to reduce sepsis-related mortality in animal models [12].

In a 2015 study involving 199 patients with DIC and 20 healthy controls, elevated plasma levels of DNA-histone complexes and double-stranded DNA (dsDNA), considered to be in vivo markers of NETosis, correlated with the severity of coagulopathy in DIC and were independent prognostic factors [13].

ANG-TIE pathway

- **Pathway** – The angiopoietin-tyrosine kinase with immunoglobulin and EGF homology domains (ANG-TIE) pathway is involved in lymphatic and blood vessel development during embryogenesis and controls vascular permeability, inflammation, and physiologic and pathologic responses in adult tissues [14].

- **Proteins** – Angiopoietins 1 and 2 (ANG1 and ANG2) are ligands that bind to the TIE1 and TIE2 (also called TEK) receptors, a subfamily of receptor tyrosine kinases on endothelial cells in this cell signaling pathway. ANG1 is a paracrine ligand expressed by mesenchymal cells and a strong TIE2 agonist that supports endothelial cell survival, vessel stability, and endothelial barrier function, whereas ANG2, expressed by endothelial cells and stored in their Weibel-Palade bodies, acts as a context-dependent weak TIE2 agonist or antagonist and inhibits the ANG1-TIE2 signaling axis.

- **Role in DIC** – Proteomics analysis on plasma samples from septic patients with DIC showed that the circulating ANG2 level was strongly correlated with traditional DIC markers that indicate sequelae of DIC and more accurately predicted patient mortality than these markers [15]. This observation was replicated in a murine endotoxin sepsis model. In that same model, TIE2 activation normalized the prothrombotic responses in the endothelium by inhibiting endothelial tissue factor and phosphatidylserine exposure. Disruption of the ANG-TIE2 axis preceded the development of overt DIC, suggesting that it plays a central role in the pathogenesis of DIC. Targeting the ANG-TIE2 pathway may have therapeutic potential in the treatment of sepsis-associated DIC [16].

DIC versus other TMAs — DIC is associated with microvascular thrombi that contain fibrin as well as platelets.

In contrast, some of the other thrombotic microangiopathies (TMAs), such as thrombotic thrombocytopenic purpura (TTP) and complement-mediated hemolytic uremic syndrome (HUS), are characterized by platelet-rich microthrombi without significant fibrin clot formation or consumption coagulopathy. Thus, other TMAs generally present with thrombocytopenia and normal coagulation studies.

In some cases, other TMAs are caused by clearly defined endothelial defects:

- TTP is caused by deficiency of the ADAMTS13 protease, which results in accumulation of very long "ultra-large" von Willebrand factor multimers on the endothelial surface that are capable of binding platelets. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)", section on 'TTP pathogenesis'.)

- Complement-mediated HUS is thought to be caused by complement-induced damage to the endothelium. (See "Complement-mediated hemolytic uremic syndrome in children".)

These endothelial defects may promote platelet adherence and activation without exposing the blood to large amounts of procoagulant substances.

Both DIC and other TMAs can produce microangiopathic hemolytic anemia (MAHA), characterized by schistocytes on the peripheral blood smear (picture 1). Schistocytes are formed as red blood cells (RBCs) pass through fibrin strands and microthrombi and become mechanically sheared (picture 2). The extent of microangiopathic hemolysis is often greater in TTP and complement-mediated HUS than it is in DIC.

CAUSES OF DIC

DIC does not occur in isolation. A number of underlying conditions are responsible for initiating and propagating the process (table 1) [8].

Common causes of DIC include the following:

- **Sepsis** from a variety of organisms (bacterial, fungal, viral, and parasitic).

  In a series of 183 consecutive individuals admitted to the hospital with 2019-2020 coronavirus disease (COVID-19) pneumonia (median age, 54 years), coagulation testing revealed evidence of overt DIC (using the ISTH criteria) in only one patient who survived, versus 15 patients (71 percent) who died [17]. The median time from admission to development of DIC was four days (range, 1 to 12 days).

- **Malignancy**, especially acute promyelocytic leukemia, mucinous tumors (eg, pancreatic, gastric, ovarian), and brain tumors.

- **Trauma**, especially to the central nervous system.

- **Obstetric complications**, including preeclampsia, retained dead fetus, acute fatty liver of pregnancy.

- **Intravascular hemolysis**, often due to acute hemolytic transfusion reaction (AHTR) in the setting of ABO incompatible transfusion, but also in other forms of hemolysis such as in severe malaria [18].

The relative frequency of causes has been illustrated by two large case series, which found the most common causes of DIC to be infection, malignancy, and trauma/surgery, each accounting for approximately 10 to 20 percent of cases depending on the study [19,20].

Additional causes are seen less often, but may be considered if none of the above conditions are obviously present, or in certain clinical settings [8,21]. These include:

- Heat stroke

- Crush injuries
- Amphetamine overdose
- Insertion of a peritovenous shunt
- Fat embolism
- Vascular abnormalities, including aortic aneurysm and Kaposiform hemangioendothelioma
- Rattlesnake or other viper bite (considered by some to be another type of coagulopathy and/or thrombotic microangiopathy other than DIC) [22]
- Hereditary homozygous protein C deficiency (purpura fulminans)
- Acute solid organ transplant rejection
- Catastrophic antiphospholipid antibody syndrome (CAPS)
- Visceral leishmaniasis [23]
- Certain forms of heparin-induced thrombocytopenia (HIT) and related syndromes such as COVID-19 vaccine-induced immune thrombotic thrombocytopenia

These conditions are discussed in detail in separate topic reviews.

EPIDEMIOLOGY

DIC is seen in approximately 1 percent of admissions to tertiary care hospitals. In a series of 123,231 patients admitted to university hospitals in Japan, 1286 were diagnosed with DIC (1 percent) [24]. These data may underestimate the incidence of mild, subclinical, or transient DIC. In contrast, the incidence of DIC may be lower in lower acuity settings.

The incidence of DIC in specific medical conditions is illustrated by the following examples:

- **Cancer** – DIC is seen in a significant number of patients with cancer. Malignancies most likely to cause DIC include acute promyelocytic leukemia, pancreatic cancer, and other mucin-producing solid tumors such as gastric, prostate, breast, and ovarian cancer [25]. In a cohort of 1117 patients with various solid tumor malignancies, DIC was diagnosed in 76 (6.8 percent) [26]. Significant risk factors for the development of DIC included age >60 years (odds ratio [OR] 5.1), male sex (OR 4.3), breast cancer (OR 4.0), tumor necrosis (OR 3.4), and advanced stage disease (OR 2.6).

- **Infection** – DIC is common in patients with bacterial sepsis, with increasing likelihood related to the severity of the systemic inflammatory response. In a series of 35 patients who met criteria for systemic inflammatory response syndrome for four or more

consecutive days, DIC was seen in 29 (83 percent) [27]. (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis".)

- **Trauma** – In a review of 136 patients with severe trauma, 42 had DIC (31 percent) [28]. Series of patients with head trauma have reported DIC in approximately 40 percent [29,30].

- **Obstetric complications** – The incidence of DIC in patients with obstetric complications ranges from 20 percent in patients with hemolysis, elevated liver function tests, and low platelets (HELLP syndrome) to 66 percent in patients with amniotic fluid embolism [31,32]. These and other obstetric conditions associated with DIC are discussed in detail separately. (See "Disseminated intravascular coagulation (DIC) during pregnancy: Clinical findings, etiology, and diagnosis".)

CLINICAL MANIFESTATIONS

COVID-19-associated abnormalities — Patients with coronavirus disease 2019 (COVID-19) have been reported to have a number of clinical and laboratory abnormalities that suggest a systemic coagulopathy, likely due to endothelial injury (referred to as endothelialitis or endotheliitis) resulting from the invasion of the SARS-CoV-2 virus into the endothelium, although the mechanisms and risk factors for these changes are not completely characterized. (See "COVID-19: Hypercoagulability", section on 'Virchow's triad'.)

Unlike classical acute DIC, individuals with COVID-19 generally have a high fibrinogen level and a predisposition to thromboembolic rather than bleeding complications. Evaluation and management are discussed separately. (See "COVID-19: Hypercoagulability".)

Acute versus chronic DIC — Acute (decompensated) and chronic (compensated) DIC represent two ends of a pathogenic balance between coagulation factor and platelet consumption, and their production. (See 'Intravascular coagulation and fibrinolysis' above.)

These pathogenic differences translate into differences in clinical and laboratory findings as well (table 2). (See 'Laboratory testing' below.)

Both acute and chronic DIC can be associated with bleeding and/or thrombosis. However, acute DIC is much more likely to present with bleeding, due to consumption of fibrinogen and other procoagulant factors and the disruption of normal fibrin formation and platelet function by the large amount of fibrin degradation products; whereas chronic DIC is more likely to present with

thromboembolic complications because production of procoagulant factors keeps pace with ongoing generation of thrombi. (See 'Bleeding and thrombosis' below.)

Acute DIC — Findings consistent with acute DIC include the following, although none of these findings are highly specific for DIC (table 2):

- Recent history of trauma, sepsis, malignancy (especially acute promyelocytic leukemia), or ABO-incompatible blood transfusion
- Bleeding, especially oozing from sites of trauma, catheters, or drains
- Thrombocytopenia
- Prolonged PT and aPTT
- Low plasma fibrinogen
- Elevated plasma D-dimer
- Abnormalities of other coagulation testing
  - Increased thrombin time
  - Reduced levels of procoagulant factors such as factors VII, X, V, and II (prothrombin)
  - Reduced levels of coagulation inhibitors such as antithrombin (AT), protein C, and protein S [33]
- Microangiopathic changes on peripheral blood smear (picture 1 and picture 3)

In one series of 118 patients with acute DIC, the main clinical manifestations included the following [19]:

- Bleeding (64 percent)
- Renal dysfunction (25 percent)
- Hepatic dysfunction (19 percent)
- Respiratory dysfunction (16 percent)
- Shock (14 percent)
- Thromboembolism (7 percent)
- Central nervous system involvement (2 percent)

Chronic DIC — The following findings are consistent with chronic DIC, although none of these findings are highly specific (table 2):

- History of malignancy, especially pancreatic, gastric, ovarian, or brain tumors
- Venous or arterial thromboembolism, especially without another clear precipitating factor
- Mild or no thrombocytopenia
- Normal or mildly prolonged PT and aPTT
- Normal or even slightly elevated plasma fibrinogen
- Elevated plasma D-dimer

- Microangiopathic changes on peripheral blood smear (picture 1 and picture 3)

Many patients with chronic DIC in the setting of malignancy are asymptomatic, with laboratory-only evidence of low-grade coagulation and fibrinolysis.

Bleeding and thrombosis — Both acute and chronic DIC can be associated with bleeding and/or thrombosis.

- **Bleeding** – Common bleeding manifestations include:

  - Petechiae and ecchymoses
  - Blood oozing from wound sites, intravenous lines, catheters, mucosal surfaces
  - For patients who develop DIC after surgical procedures, accumulation of blood in serous cavities

  The bleeding can be life-threatening if it involves the gastrointestinal tract, lungs, or central nervous system. Bleeding is more likely to occur in acute DIC, but patients with chronic DIC can also have bleeding.

- **Thrombosis** – Thrombosis is more likely to occur in chronic DIC, in the setting of solid tumors, but patients with acute DIC can also have thromboembolic complications. Common thromboembolic manifestations of DIC include:

  - Venous thromboembolism (VTE)
  - Arterial thrombosis with tissue or organ ischemia
  - In patients with chronic DIC in the setting of malignancy, non-bacterial thrombotic endocarditis (marantic endocarditis, Libman-Sacks endocarditis, verrucous endocarditis) and superficial migratory thrombophlebitis (Trousseau's syndrome).

  An exception to the association of malignancy with chronic DIC is acute promyelocytic leukemia, in which patients frequently present with acute DIC (or develop it after initiation of cytotoxic chemotherapy). Life-threatening hemorrhage can result, with a high risk of early hemorrhagic death. (See "Clinical manifestations, pathologic features, and diagnosis of acute promyelocytic leukemia in adults", section on 'Coagulopathy and APL'.)

  Thromboembolic findings can also occur in patients with malignancy who do not have DIC, due to other causes of hypercoagulability such as chemotherapeutic or biologic agents, indwelling central venous catheters, and/or surgery. This subject is discussed in detail separately. (See "Cancer-associated hypercoagulable state: Causes and mechanisms", section on 'Contributing factors' and "Risk and prevention of venous thromboembolism in adults with cancer", section on 'Incidence and risk factors'.)

Organ dysfunction — DIC can lead to organ dysfunction due to a variety of mechanisms including vascular thrombosis, hemorrhage, and hypoperfusion. This may be especially concerning in individuals with underlying organ dysfunction or organ damage caused by their underlying condition.

- **Kidney failure** – Acute kidney injury occurs in 25 to 40 percent of patients with acute DIC.
- **Liver dysfunction** – Jaundice from liver dysfunction is common in DIC. Preexisting liver failure can exacerbate DIC by impairing hepatic production and/or clearance of clotting factors.
- **Acute lung injury** – Pulmonary hemorrhage with hemoptysis and dyspnea may result from damage to the pulmonary vascular endothelium. Pulmonary microthrombi may contribute to lung injury; this may be especially concerning in patients with acute respiratory distress syndrome (ARDS) due to their underlying condition. (See "Acute respiratory distress syndrome: Clinical features, diagnosis, and complications in adults".)
- **Neurologic dysfunction** – A number of neurologic abnormalities can occur in patients with DIC. These include coma, delirium, and transient focal neurologic symptoms. Microthrombi, hemorrhage, and hypoperfusion all may contribute.
- **Adrenal failure** – Waterhouse-Friderichsen syndrome is a form of adrenal insufficiency that can result from adrenal hemorrhage or infarction. (See "Clinical manifestations of Staphylococcus aureus infection in adults" and "Clinical manifestations of meningococcal infection" and "Causes of primary adrenal insufficiency (Addison disease)".)

Purpura fulminans — Purpura fulminans is a rare, life-threatening condition characterized by DIC, with extensive tissue thrombosis and hemorrhagic skin necrosis. A classic presentation of purpura fulminans is as retiform purpura with branched or angular purpuric lesions (picture 4 and picture 5 and picture 6 and picture 7 and picture 8).

Many patients with this condition have inherited homozygous protein C deficiency. Presentation in early infancy is common, but older patients are also occasionally seen. In contrast, heterozygous protein C deficiency with venous thromboembolism typically does not have DIC as a component of its pathogenesis. (See "Neonatal thrombosis: Management and outcome", section on 'Neonatal purpura fulminans' and "Protein C deficiency", section on 'Neonatal purpura fulminans'.)

Purpura fulminans may also occur in the setting of severe acquired protein C deficiency, such as may occur in patients with severe meningococcal infections. (See "Clinical manifestations of

meningococcal infection", section on 'Purpura fulminans'.)

DIAGNOSTIC EVALUATION

When to suspect DIC — DIC may be suspected in an individual with generalized oozing from multiple intravenous catheter sites or other signs of bleeding, or occasionally in an individual with unexplained thrombosis. Most individuals with DIC have an obvious underlying condition associated with DIC such as sepsis or malignancy, but occasionally DIC is the presenting finding for these conditions.

We do **not** test for chronic DIC routinely in patients with malignancy. We reserve this testing for patients with evidence of unexpected bleeding or thromboembolic complications, and prior to initiating anticoagulant therapy. We also do not test for chronic DIC preoperatively in a patient with cancer if the PT, aPTT, and platelet count are normal.

Laboratory testing — In patients for whom an underlying condition known to be associated with DIC is obvious, the laboratory evaluation typically includes:

- Complete blood count (CBC)
- Review of the peripheral blood smear
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Fibrinogen
- D-dimer

For patients with bleeding or thrombosis, it is appropriate to obtain all of these tests simultaneously. For patients without bleeding or thrombosis, the PT and aPTT may be done first, and fibrinogen and D-dimer done only in those with prolonged PT and aPTT.

Laboratory findings consistent with DIC may include the following, although none are highly sensitive or specific for the diagnosis, and all must be evaluated in the context of the clinical history and other findings:

- **PT and aPTT** – The prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are often prolonged (table 2). These abnormalities are more typical of acute than chronic DIC.

- **Fibrinogen** – Fibrinogen is typically low, especially in acute DIC. Importantly, patients with sepsis, malignancy, and other inflammatory conditions may have markedly increased production of fibrinogen, since fibrinogen functions as an acute phase reactant; thus, a

plasma fibrinogen level within the normal range may represent a substantial consumption (and a significant abnormality) for that patient despite being in the normal range.

- **D-dimer** – D-dimer is typically increased in both acute and chronic DIC.

- **Platelet count** – Thrombocytopenia is common, more typically with acute than chronic DIC. The platelet count is typically mildly to moderately reduced; platelet counts below 20,000/microL are less commonly seen.

- **Blood smear** – Microangiopathic hemolytic anemia (MAHA), with schistocytes and helmet cells seen on the peripheral blood smear (picture 3 and picture 1). These changes may be less pronounced than those seen in other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP). Severe anemia due to microangiopathic hemolysis is uncommon, although most of the underlying conditions responsible for DIC can cause anemia due to other mechanisms (eg, bone marrow suppression, anemia of chronic disease/inflammation). MAHA can be seen in both acute and chronic DIC.

The International Society of Thrombosis and Haemostasis has developed a scoring system to be applied to individuals with an underlying disorder associated with DIC, which incorporates laboratory features including the PT, platelet count, fibrinogen level, and D-dimer; this scoring system has been validated but is not widely used [34,35].

Findings such as thrombocytopenia, low fibrinogen, and elevated D-dimer are considered to be relatively sensitive for the diagnosis but not specific; however data from clinical trials addressing sensitivity and specificity are lacking. Many of the laboratory abnormalities used to support a diagnosis of DIC are present in normal pregnancy, as discussed in detail separately. Some of the other causes of these findings are discussed below. (See "Disseminated intravascular coagulation (DIC) during pregnancy: Clinical findings, etiology, and diagnosis" and 'Differential diagnosis' below.)

Testing is often repeated serially to determine if coagulation and fibrinolysis are worsening or improving. The frequency of testing depends on the severity of clinical findings. Daily or even twice-daily testing may be appropriate in an acutely ill patient with active bleeding or thrombosis; less frequent testing may be reasonable in a patient with laboratory-only findings.

Diagnostic confirmation — DIC is a clinical **and** laboratory diagnosis, based on findings of coagulopathy and/or fibrinolysis in the appropriate setting (eg, sepsis, malignancy). No single laboratory test can accurately confirm or eliminate the diagnosis.

We consider the diagnosis of acute DIC to be established if the patient has laboratory evidence of thrombocytopenia, coagulation factor consumption (eg, prolonged PT, aPTT; low fibrinogen), and fibrinolysis (eg, increased D-dimer), as long as another etiology for these findings does not become apparent. Bleeding or thrombosis are supportive of the diagnosis if present but are not required for diagnosis.

We consider the diagnosis of chronic DIC confirmed if the patient has evidence of fibrinolysis (eg, increased D-dimer) in the absence of another etiology, such as VTE, in an appropriate clinical setting. Typically, this implies the presence of malignancy, although certain other causes, such as a vascular lesion, may be present. Chronic DIC in a patient with malignancy does not necessarily imply the need for a clinical intervention; management is guided by the clinical setting and treatment goals for the individual patient. (See 'Causes of DIC' above.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of DIC includes other conditions associated with bleeding and hypercoagulability, and other causes of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia.

Some conditions, such as liver failure, can be either a cause of DIC or a consequence of DIC. In such cases, the diagnosis of the other condition does not eliminate the possibility of DIC, and vice versa.

- **Severe liver disease** – Liver disease severe enough to impair the hepatic synthesis of coagulation factors can cause a severe coagulopathy.

  Like DIC, severe liver disease is associated with reductions in both procoagulant and anticoagulant factors as well as thrombocytopenia; patients can have bleeding or thrombosis. The coagulation factor reductions and thrombocytopenia in severe liver disease are often caused by a combination of hypersplenism and thrombopoietin (TPO) deficiency, since the liver is the primary site of TPO synthesis.

  Unlike DIC, patients with severe liver disease typically present with a known source of liver injury (eg, acute hepatitis, alcoholic cirrhosis) and abnormal liver function tests, although transaminases may appear to normalize if liver synthetic function is severely impaired. Some clinicians consider factor VIII levels to be helpful because factor VIII is not produced by hepatocytes and thus is often low in DIC and high in severe liver disease. (See "Hemostatic abnormalities in patients with liver disease".)

- **Heparin-induced thrombocytopenia (HIT) and related syndromes** – HIT is a potentially life-threatening complication of heparin exposure due to an autoantibody to a platelet factor four (PF4) epitope created by heparin binding to PF4 (or PF4 binding to heparin sulfate on platelets). Rare cases of spontaneous or autoimmune HIT in the absence of heparin exposure have also been reported. This includes the syndrome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia (VITT).

  Like DIC, patients with HIT can have thrombosis (due to platelet activation by the HIT antibody and/or the underlying condition for which they were receiving heparin) and bleeding (due to heparin or the non-heparin anticoagulant used to treat HIT).

  Unlike DIC, patients with HIT typically have recent heparin exposure and a positive laboratory testing for heparin-PF4 antibodies (HIT antibodies); and patients with HIT do not have global coagulation abnormalities, with the exception of abnormalities caused by their anticoagulant or increased D-dimer associated with thromboembolism. (See "Clinical presentation and diagnosis of heparin-induced thrombocytopenia".)

  For reasons that are not well understood, VITT is more likely to be associated with DIC-like findings including very high D-dimer, low fibrinogen, and mild prolongation of the prothrombin time (PT) and INR. (See "COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT)".)

- **Thrombotic microangiopathy (TMA)** – Thrombotic thrombocytopenic purpura (TTP) and other TMAs (eg, drug-induced TMA [DITMA], hemolytic uremic syndrome [HUS]) present with MAHA and thrombocytopenia due to platelet consumption in microvascular thrombi.

  Like DIC, patients may be acutely ill, thrombocytopenic, and have schistocytes on the peripheral blood smear.

  Unlike DIC, patients with TTP, DITMA, or HUS have normal coagulation testing because microvascular thrombi in these conditions are primarily platelet-rich and fibrin-poor thrombi, and are not associated with consumption coagulopathy (ie, the PT, aPTT, fibrinogen, and D-dimer are normal in TTP and other TMAs) (table 3). A rare exception may be a patient with a TMA that leads to organ ischemia and in turn causes DIC. Also, unlike DIC, patients with TTP and other TMAs tend to have more severe microangiopathic changes on the blood smear, and other laboratory abnormalities specific to the type of TMA (eg, ADAMTS13 activity level <10 percent in TTP; complement abnormalities in complement-mediated HUS, positive stool studies in Shiga toxin-mediated HUS). (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)"

and "Diagnosis of immune TTP" and "Drug-induced thrombotic microangiopathy (DITMA)".)

- **Hemophagocytic lymphohistiocytosis (HLH)** – HLH is an aggressive and life-threatening syndrome of excessive immune activation. Unchecked immune activation can lead to tissue damage and a very high fatality rate unless treated.

  Like DIC, patients may be acutely ill with cytopenias, prolonged clotting times, low fibrinogen, and increased D-dimer. They may also have fever, liver dysfunction, neurologic changes, and very high ferritin levels.

  Unlike DIC, patients with HLH have evidence of immune activation, with pathogenic variants in one of several immune regulatory genes and often including low or absent natural killer (NK) cell activity, increased soluble interleukin 2 (IL-2) receptor alpha (sCD25) and/or CXCL19, and others. Also unlike DIC, HLH typically requires treatment directed at stopping the immune activation as well as treatment of the underlying cause, if present. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis" and "Treatment and prognosis of hemophagocytic lymphohistiocytosis".)

A list of causes of an elevated D-dimer is included in the table (table 4). A more extensive discussion of other possible causes of abnormal coagulation testing is also presented separately. (See "Clinical use of coagulation tests".)

TREATMENT

Treat the underlying cause — DIC is a process of ongoing thrombin generation and fibrinolysis, and resolution of these abnormalities depends on elimination of the stimulus for these processes.

Thus, the major principle in the management of DIC is treatment of the underlying cause in order to eliminate the stimulus for ongoing coagulation and thrombosis. (See 'Causes of DIC' above.)

Supportive measures — The need for additional supportive measures is individualized for each patient. Examples include the following:

- Hemodynamic and/or ventilatory support – (see "Evaluation and management of suspected sepsis and septic shock in adults" and "Septic shock in children in resource-abundant settings: Rapid recognition and initial resuscitation (first hour)")

- Aggressive hydration for acute hemolytic transfusion reaction – (See "Hemolytic transfusion reactions", section on 'Acute hemolytic transfusion reactions'.)

- Red blood cell transfusion for severe bleeding – (see "Indications and hemoglobin thresholds for RBC transfusion in adults", section on 'Acute bleeding')

Role of systemic therapies — In general, systemic therapies, such as pro-hemostatic or anticoagulant agents, are not used prophylactically to prevent bleeding or thrombosis. However, patients are closely monitored for bleeding and thrombotic complications, and these complications are treated promptly if they occur. (See 'Prevention/treatment of bleeding' below and 'Prevention/treatment of thrombosis' below.)

Our approach is largely based on observational studies and our own experience; there are very few randomized trials to guide therapy in DIC. The management recommendations presented here are largely consistent with a consensus document from the British Committee for Standards in Haematology (BCSH) task force in hemostasis and thrombosis and other international consensus documents [8,36,37].

Prevention/treatment of bleeding — Patients with DIC are at risk of bleeding due to thrombocytopenia, depletion of coagulation factors, and disruption of normal fibrin polymerization and platelet aggregation by fibrin degradation products (FDPs). However, it is not possible to reliably predict which patients will have bleeding. (See 'Pathogenesis' above.)

We do not routinely use prophylactic administration of platelets and coagulation factors in patients who are not bleeding or who are not at high risk of bleeding, as long as the platelet count is ≥10,000/microL. This practice is based on the lack of evidence that bleeding can be prevented by these therapies; the likely transient nature of DIC if the underlying cause is addressed; and the concomitant increased risk of thrombosis in DIC. One international consensus group suggested using a platelet count threshold of 20,000/microL in the absence of bleeding [36].

However, treatment is justified in patients who have serious bleeding, are at high risk for bleeding (eg, after surgery), or require invasive procedures. Importantly, appropriate treatment for bleeding should **not** be withheld for fear of "fueling the fire."

- **Platelet transfusions** – Patients with serious bleeding or need for urgent/emergent surgery and a platelet count <50,000/microL should be given platelet transfusions. Typically, we give one to two units of random donor platelets per 10 kg of body weight, or one single donor apheresis unit daily. Thresholds for specific surgical procedures are presented separately. The increase in platelet count may be less than expected due to

ongoing platelet consumption. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'TTP or HIT' and "Platelet transfusion: Indications, ordering, and associated risks", section on 'Preparation for an invasive procedure'.)

Patients with a platelet count <10,000/microL should be given platelet transfusions due to the increased risk of spontaneous bleeding. This degree of thrombocytopenia is rare in DIC, with the exception of acute promyelocytic leukemia or other conditions associated with severe bone marrow dysfunction.

- **Fresh Frozen Plasma (FFP) or Cryoprecipitate** – Patients with serious bleeding and a significantly prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), or a fibrinogen level <50 mg/dL and serious bleeding, should receive coagulation factor replacement. Options include Fresh Frozen Plasma (FFP), related plasma products such as Plasma Frozen Within 24 Hours After Phlebotomy (PF24), or cryoprecipitate. Cryoprecipitate provides a good source of fibrinogen with significantly less volume load than FFP or PF24 (table 5). (See "Clinical use of plasma components".)

  The specific threshold for transfusion and amount of the product given are individualized to the specific clinical setting and other patient factors such as volume status and severity of bleeding. As an example, the following may be appropriate:

  - If the plasma fibrinogen level is <100 mg/dL, we administer cryoprecipitate to increase it to >100 mg/dL.
  - If the plasma fibrinogen level is >100 mg/dL and the PT or aPTT remains significantly elevated, we administer FFP or PF24. The goal is to reduce bleeding, not to normalize the coagulation tests. Dosing is provided in the table (table 5).

  Case reports have described individuals treated with colloid rather than a plasma product who have developed ischemic gangrene, suggesting that treatment with a non-plasma product might exacerbate the prothrombotic effects of DIC [38].

We do not use antithrombin to treat bleeding in DIC. This practice is based on a trial that randomly assigned 2314 patients with sepsis to antithrombin or placebo and found no difference in mortality [39]. There was an increase in bleeding in patients who also received heparin in this study. A randomized trial testing recombinant thrombomodulin in sepsis-associated DIC also failed to show any benefit over placebo [40]. (See "Investigational and ineffective pharmacologic therapies for sepsis", section on 'Ineffective therapies'.)

Avoid antifibrinolytic agents and PCCs — Antifibrinolytic agents such as tranexamic acid (TXA), epsilon-aminocaproic acid (EACA) or aprotinin is generally **contraindicated** since blockade of the fibrinolytic system may increase the risk of thrombotic complications [41]. However, these agents may be appropriate in patients who have severe bleeding associated with a hyperfibrinolytic state [8].

There are no data regarding the use of prothrombin complex concentrates (PCC) in DIC. In the author's opinion, PCCs are also **contraindicated** in DIC, since administration may trigger more thrombotic complications in the setting of an already hypercoagulable state.

Prevention/treatment of thrombosis — Patients with DIC are at risk of thrombosis because of ongoing stimulation of coagulation, mediated by continuous exposure to tissue factor, thrombin, or other procoagulant substances. (See 'Pathogenesis' above.)

Thrombosis appears to be more common (although still rare overall) with certain infectious causes of DIC such as severe malaria or dengue virus infection. In those cases, thrombosis can be life- or limb-threatening. Digital gangrene of the fingers or toes has been reported [42-45]. Treatment with heparin in such cases is appropriate, although there are no major trials addressing the efficacy or administration of anticoagulants in this setting. (See "Heparin and LMW heparin: Dosing and adverse effects".)

Despite the risk of thrombosis, there is little evidence to support the use of prophylactic anticoagulation in patients with acute or chronic DIC, with the exception of the perioperative period or during a hospital admission for an acute medical illness, as done for patients without DIC. In contrast, anticoagulation is generally appropriate for VTE treatment, with indications similar to individuals without DIC.

Separate topic reviews discuss subjects related to the treatment and prevention of VTE:

- Indications for prophylactic anticoagulation – (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults" and "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)
- Anticoagulation in patients with cancer who have a venous or arterial thromboembolism – (See "Anticoagulation therapy for venous thromboembolism (lower extremity venous thrombosis and pulmonary embolism) in adult patients with malignancy" and "Nonbacterial thrombotic endocarditis".)
- Anticoagulation in individuals with thrombocytopenia – (See "Anticoagulation in individuals with thrombocytopenia".)

- Alternatives to anticoagulation in individuals with contraindications – (See "Overview of the treatment of proximal and distal lower extremity deep vein thrombosis (DVT)", section on 'Patients at high risk of bleeding'.)

As noted, mild to moderate thrombocytopenia from DIC (eg, platelet count 50,000 to 150,000/microL) is not a contraindication to anticoagulation for VTE or arterial thromboembolism (table 6).

Monitoring of anticoagulation in DIC may be complicated because coagulation testing may show baseline elevation in the prothrombin time (PT) or activated partial thromboplastin time (aPTT). Institution-specific guidelines, such as use of heparin levels and/or prolongation above baseline, should be used [46].

Purpura fulminans/protein C deficiency — Patients with homozygous protein C deficiency or acquired protein C deficiency (eg, due to meningococcemia) may develop purpura fulminans. (See 'Purpura fulminans' above.)

Patients with purpura fulminans, including adults, appear to benefit from the administration of protein C concentrate [27,47-50]. In one series of 12 patients with purpura fulminans so treated, none died despite a predicted mortality rate of 60 to 80 percent [27]. Intravenous dosing is 100 IU/kg as an initial bolus followed by 50 IU/kg every six hours until D-dimer normalizes or shows a decreasing trend [50]. (See "Approach to the patient with retiform (angulated) purpura", section on 'Recognition of life-threatening emergencies' and "Treatment and prevention of meningococcal infection", section on 'Protein C concentrate'.)

The administration of FFP as a source of protein C is more difficult because of the short half-life of protein C in the plasma. Two to three units of FFP may be administered approximately every six hours if tolerated.

In contrast, protein C deficiency without purpura fulminans is not an indication for using protein C concentrate.

Protein C concentrate should not be confused with recombinant activated protein C, a product that was evaluated for sepsis and withdrawn from the market in 2011 due to lack of efficacy. (See "Investigational and ineffective pharmacologic therapies for sepsis", section on 'Ineffective therapies'.)

COVID-19-specific management — (See "COVID-19: Hypercoagulability", section on 'Management'.)

RECOVERY AND PROGNOSIS

- **Resolution of symptoms** – Unlike bleeding from other causes, such as administration of an anticoagulant, DIC does not resolve immediately once the inciting factor is corrected. Resolution generally requires synthesis of coagulation factors, which are produced at different rates; clearance of anticoagulant factors and fibrin degradation products from the circulation, which depend on hepatic function; and production of new platelets from the bone marrow, which may take several days. (See "Overview of hemostasis" and "Megakaryocyte biology and platelet production", section on 'Platelet production'.)

  Kidney failure generally does not interfere with the resolution of DIC unless there is a component of hepatorenal syndrome or if the kidneys are a major site of thrombosis.

- **Improvement of laboratory findings** – The laboratory abnormalities associated with DIC will usually begin to improve within a few days after the inciting trigger is removed or terminated. Resolution of these abnormalities may take longer if significant liver damage is present, because the liver is the major site of coagulation factor synthesis and clearance.

- **Survival** – The mortality of DIC is highly dependent on the degree of coagulation impairment as well as the treatability of the underlying condition. A marked reduction in antithrombin levels at the onset of septic shock may be a sensitive marker of unfavorable prognosis, presumably reflecting the magnitude of the thrombotic insult and by permitting persistence of the procoagulant state [33,51]. (See 'Diagnostic evaluation' above.)

  The reported mortality rate ranges from 40 to 80 percent in patients with severe sepsis, trauma, or burns [19,28-30,52-54].

  Risk factors for death include increasing age and the severity of the organ dysfunction and hemostatic abnormalities [8,19,21,55-59]. It is not clear, however, if the poor outcome in sepsis and trauma reflects the effects of DIC or the consequences of the systemic inflammatory response. (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis".)

  In one study, the median survival of patients with cancer was lower in those with concomitant DIC versus those without DIC, regardless of the stage of the malignancy (early stage tumors: 16 versus 44 months; advanced stage tumors: 9 versus 14 months) [26].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Disseminated intravascular coagulation (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pathophysiology** – In disseminated intravascular coagulation (DIC), coagulation and fibrinolysis become abnormally (and often massively) activated, leading to ongoing clotting and fibrinolysis, with bleeding and/or thrombosis. Initiating procoagulants may contribute, including tissue factor (TF), bacterial products, microparticles, cell-free DNA (cfDNA), and DNA binding proteins from neutrophil extracellular traps (NETs). Disruption of the endothelial angiopoietin-TIE2 signaling pathway also plays a central role. (See 'Intravascular coagulation and fibrinolysis' above and 'Extracellular DNA and NETs' above and 'ANG-TIE pathway' above.)

- **Causes** – Common causes include sepsis, malignancy, and trauma, as well as obstetric complications and hemolysis from acute hemolytic transfusion reactions (table 1). Additional causes may be considered if none of these conditions are obviously present. (See 'Causes of DIC' above and "Disseminated intravascular coagulation (DIC) during pregnancy: Clinical findings, etiology, and diagnosis" and "Hemolytic transfusion reactions", section on 'Acute hemolytic transfusion reactions'.)

- **Acute versus chronic DIC** – Acute and chronic DIC represent two ends of a spectrum between consumption and production of coagulation factors and platelets (table 2). (See 'Acute versus chronic DIC' above.)

- **Acute DIC** – DIC associated with sepsis, malignancy (especially acute promyelocytic leukemia), or ABO-incompatible blood transfusion is generally acute. Findings include clinical bleeding and consumptive coagulopathy, with thrombocytopenia, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low fibrinogen, elevated D-dimer, and microangiopathic changes on peripheral blood smear (picture 1). (See 'Acute DIC' above.)

- **Chronic DIC** – DIC associated with malignancy (especially pancreatic, gastric, ovarian, or brain tumors) can be chronic. There may be venous or arterial thromboembolism, mild or no thrombocytopenia, normal or mildly prolonged PT and aPTT, normal or slightly elevated plasma fibrinogen, and elevated D-dimer. (See 'Chronic DIC' above.)

- **Laboratory testing** – Individuals with suspected DIC should have a complete blood count (CBC), review of the blood smear, PT, aPTT, fibrinogen, and D-dimer. (See 'When to suspect DIC' above and 'Laboratory testing' above.)

- **Diagnosis** – DIC is a clinical **and** laboratory diagnosis, based on findings of coagulopathy and/or fibrinolysis in the appropriate setting (figure 1). No single laboratory test can accurately confirm or exclude the diagnosis. (See 'Diagnostic evaluation' above.)

- **Differential diagnosis** – The differential diagnosis includes severe liver disease, heparin-induced thrombocytopenia (HIT), other causes of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia such as thrombotic thrombocytopenic purpura (TTP), and hemophagocytic lymphohistiocytosis (HLH). Causes of elevated D-dimer are listed in the table (table 4). (See 'Differential diagnosis' above.)

- **Management**

  - **Treat the underlying condition** – The major management principle is treatment of the underlying cause. (See 'Treat the underlying cause' above.)

  - **Platelet and plasma transfusions** – We do not routinely transfuse platelets and plasma prophylactically as long as the platelet count is ≥10,000/microL. One international consensus group suggested using a platelet count threshold of 20,000/microL in the absence of bleeding. Platelet transfusion is appropriate in patients with serious bleeding, at high risk for bleeding, or requiring invasive procedures. Platelets and/or plasma products should **not** be withheld in these settings for fear of "fueling the fire." In contrast, antifibrinolytic agents (tranexamic acid [TXA], epsilon-aminocaproic acid [EACA], aprotinin) are generally **contraindicated**. (See 'Prevention/treatment of bleeding' above.)

- **Anticoagulation** – There is little evidence to support the use of anticoagulation in patients with acute or chronic DIC, with the exceptions of prophylaxis perioperatively period or during hospital admission, and treatment of venous or arterial thromboembolism. Patients with purpura fulminans appear to benefit from protein C concentrate. (See 'Prevention/treatment of thrombosis' above and "Anticoagulation therapy for venous thromboembolism (lower extremity venous thrombosis and pulmonary embolism) in adult patients with malignancy" and "Nonbacterial thrombotic endocarditis".)

- **Recovery** – Laboratory abnormalities usually begin to improve within a few days after the inciting trigger is terminated. Resolution may take longer if significant liver damage is present. (See 'Recovery and prognosis' above.)

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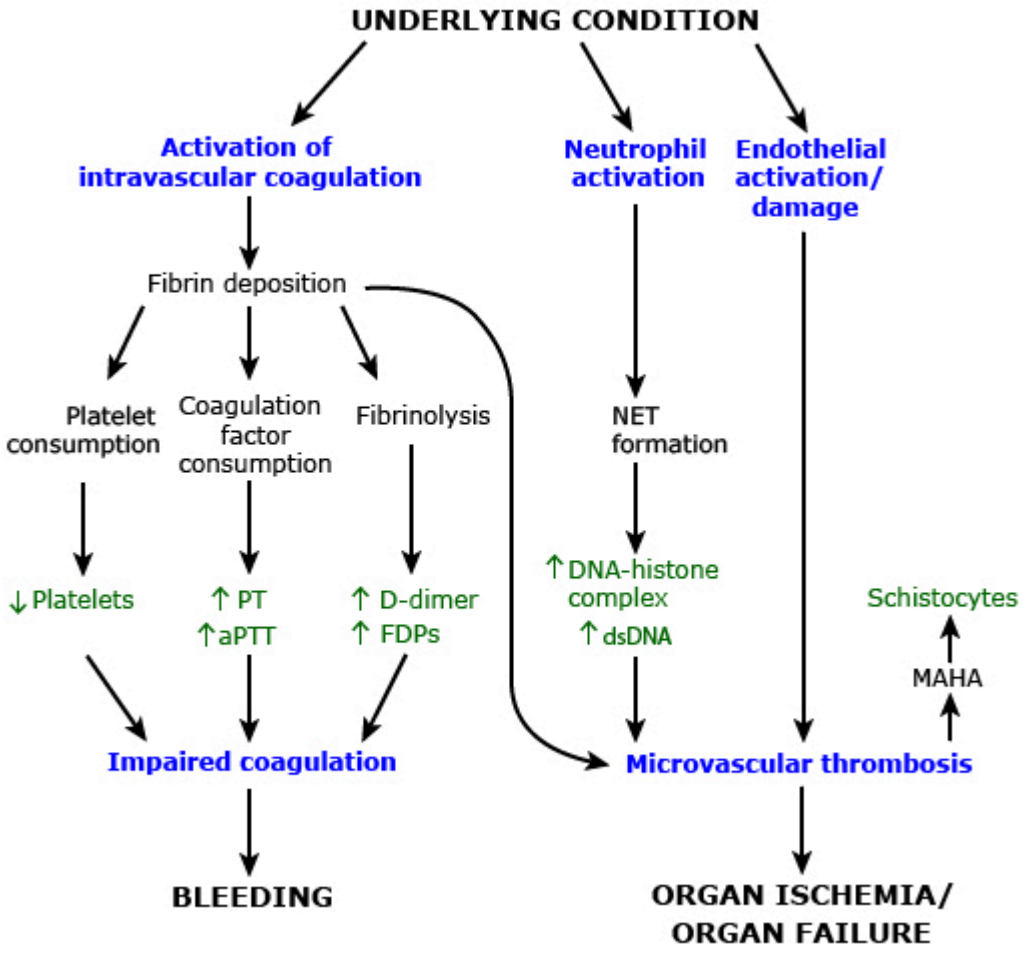
Topic 1306 Version 53.0

GRAPHICS

Pathogenesis of disseminated intravascular coagulation

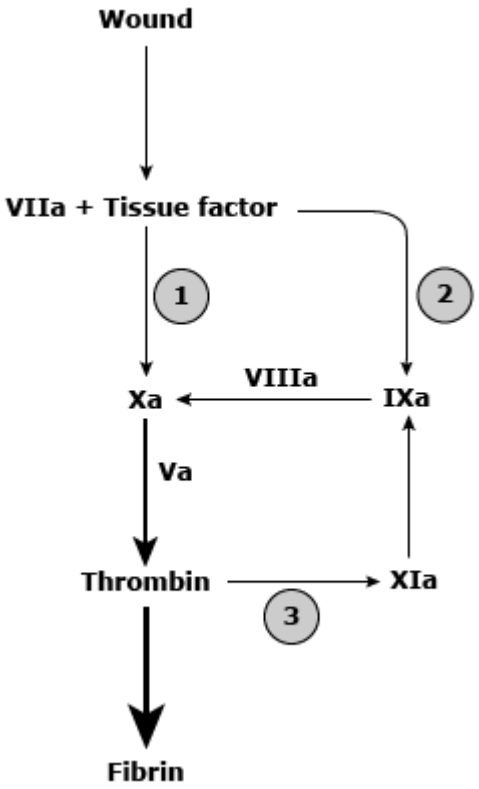


Text in blue refers to pathophysiologic processes; text in green denotes associated laboratory abnormalities. Refer to UpToDate topics on disseminated intravascular coagulation for additional details.

NET: neutrophil extracellular trap; PT: prothrombin time; aPTT: activated partial thromboplastin time; FDPs: fibrin degradation products; dsDNA: double-stranded DNA; MAHA: microangiopathic hemolytic anemia.

Graphic 98047 Version 3.0

Coagulation cascade overview



This schematic shows a revised version of the coagulation cascade that emphasizes the importance of pathways for hemostasis in vivo. Coagulation factors are shown as Roman numerals. Only the activated forms (with the suffix "a") are shown in this diagram for simplicity. Thrombin is activated factor II (factor IIa); unactivated factor II is prothrombin.

Tissue factor exposed at a wound interacts with factor VIIa and initiates clotting by two pathways:

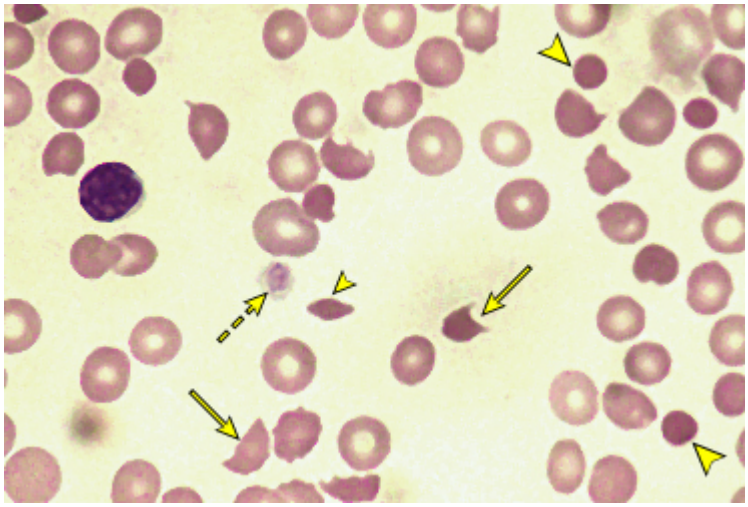
- (1) – Activation of factor X to factor Xa (the extrinsic ten-ase complex).
- (2) – Conversion of factor IX to factor IXa, which activates factor X to factor Xa (the intrinsic ten-ase complex).

Pathways 1 and 2 are equally important.

In a third pathway (3), thrombin also activates factor XI to factor XIa, which can lead to further generation of factor IXa; it serves as an amplification pathway required during severe hemostatic challenges.

Graphic 90873 Version 11.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

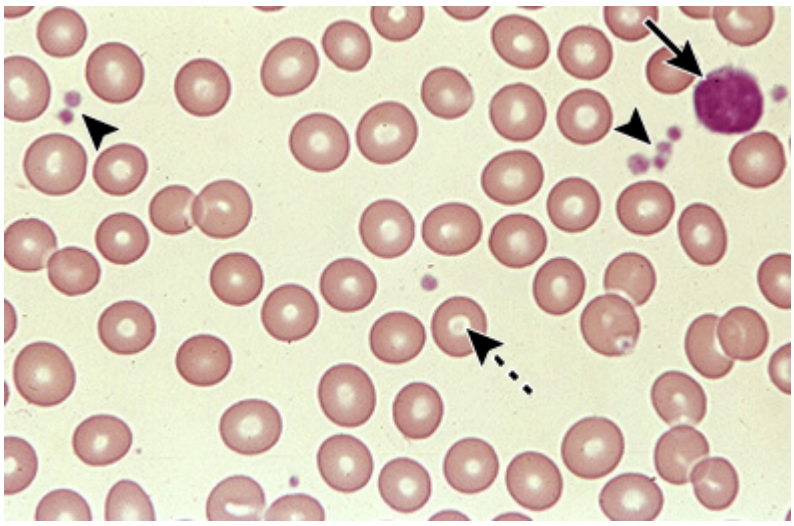


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 8.0

Normal peripheral blood smear



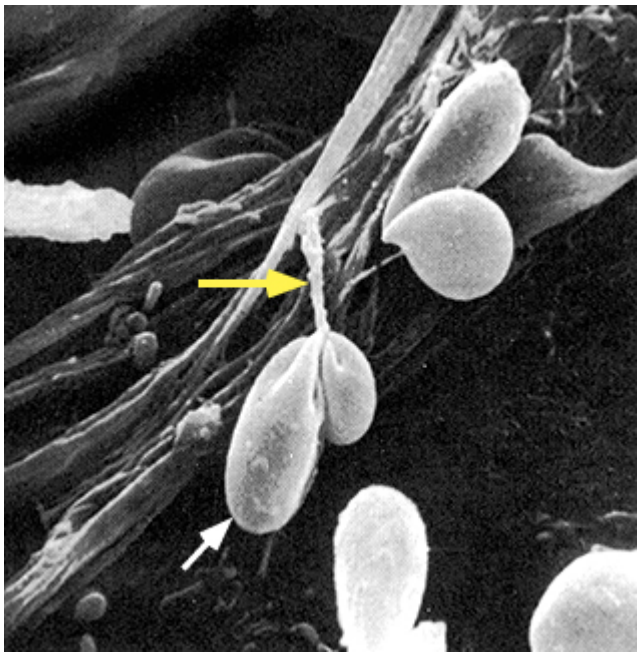
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter

of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Genesis of the schistocyte



This scanning electron microphotograph shows a red blood cell (white arrow) about to be "guillotined" by a fibrin strand (yellow arrow), produced as a result of intravascular coagulation. This results in the formation of a fragmented red blood cell, termed a schistocyte or "helmet cell."

Graphic 81610 Version 3.0

Major causes of disseminated intravascular coagulation (DIC)

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

Refer to UpToDate for further information.

DIC: disseminated intravascular coagulation.

Graphic 58104 Version 4.0

Coagulation parameters in acute and chronic disseminated intravascular coagulation

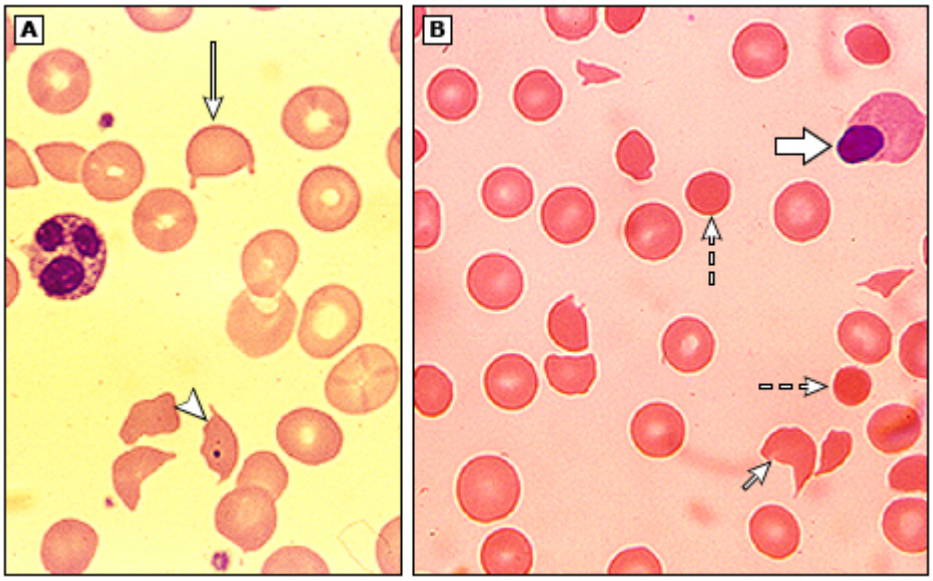
Parameter	Acute (decompensated) DIC	Chronic (compensated) DIC
Platelet count	Reduced	Variable
Prothrombin time (PT)	Prolonged	Normal
Activated partial thromboplastin time (aPTT)	Prolonged	Normal
Thrombin time	Prolonged	Normal to slightly prolonged
Plasma fibrinogen	Reduced	Normal to elevated
Plasma factor V	Reduced	Normal
Plasma factor VIII	Reduced	Normal
Fibrin degradation products	Elevated	Elevated
D-dimer	Elevated	Elevated

In chronic DIC, the thrombin time is more sensitive than PT or aPTT to the effects of increased D-dimer and fibrin degradation products.

DIC: disseminated intravascular coagulation.

Graphic 63831 Version 2.0

Helmet cells in microangiopathic hemolytic anemia

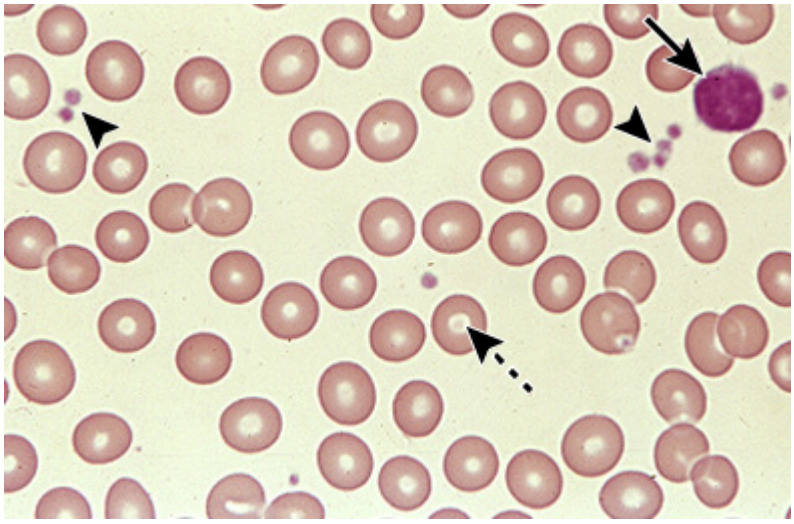


Peripheral smears from two patients with microangiopathic hemolytic anemia, showing a number of red cell fragments (ie, schistocytes), some of which take the form of combat (arrow), bicycle (arrowhead), or football (short arrow) "helmets." Microspherocytes are also seen (dashed arrows), along with a nucleated red cell (thick arrow).

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50715 Version 5.0

Normal peripheral blood smear



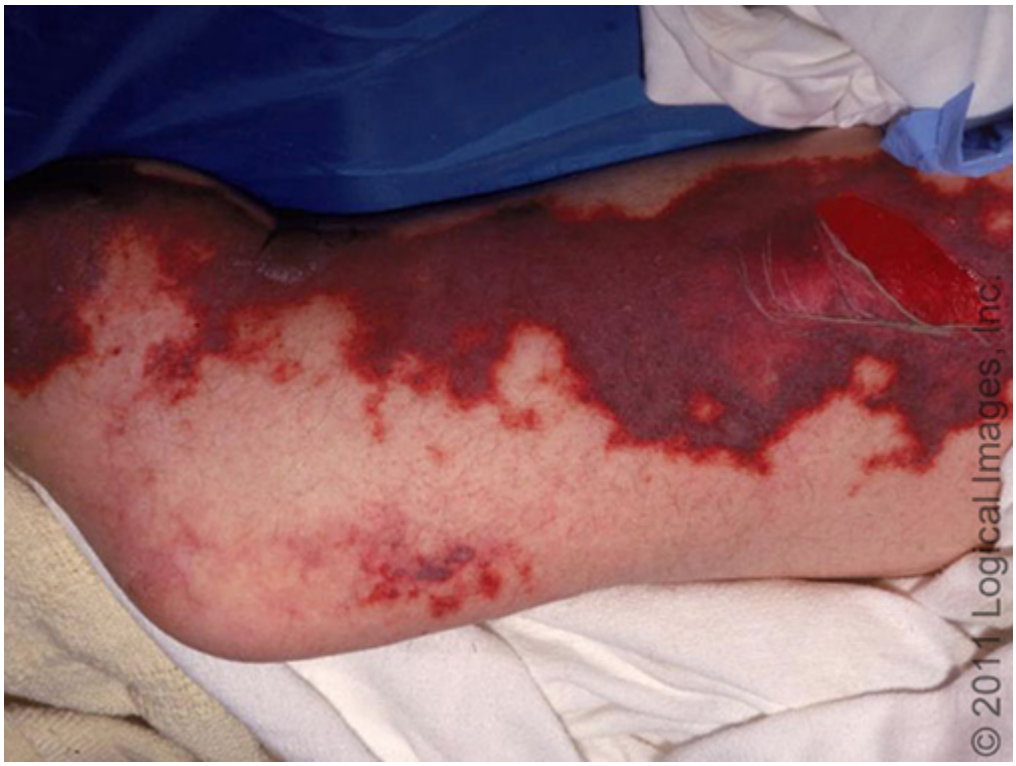
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter

of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

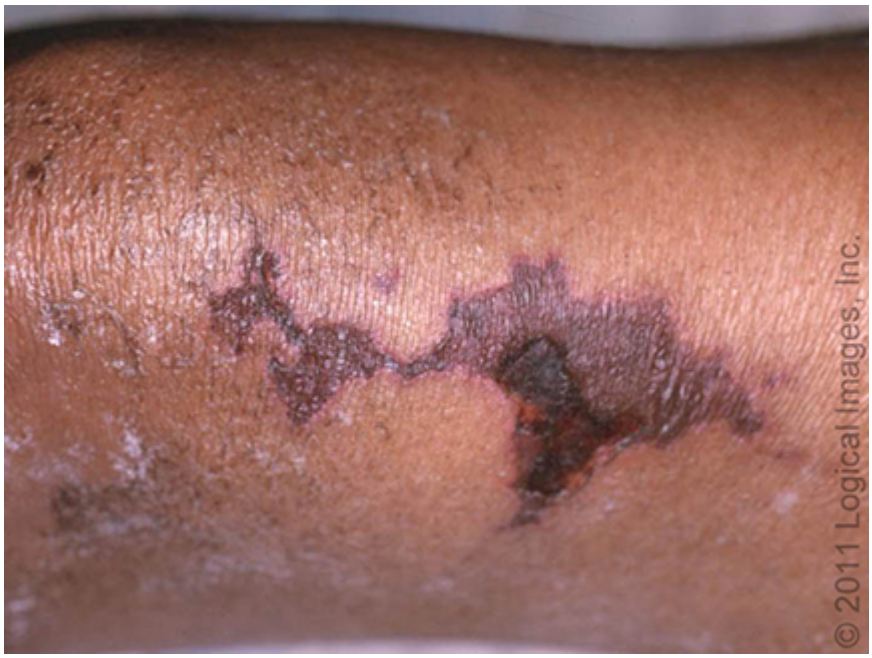
Purpura fulminans



A large, retiform, purpuric lesion is present on the leg. Purpura fulminans is characterized by the presence of extensive purpura.

Graphic 57103 Version 5.0

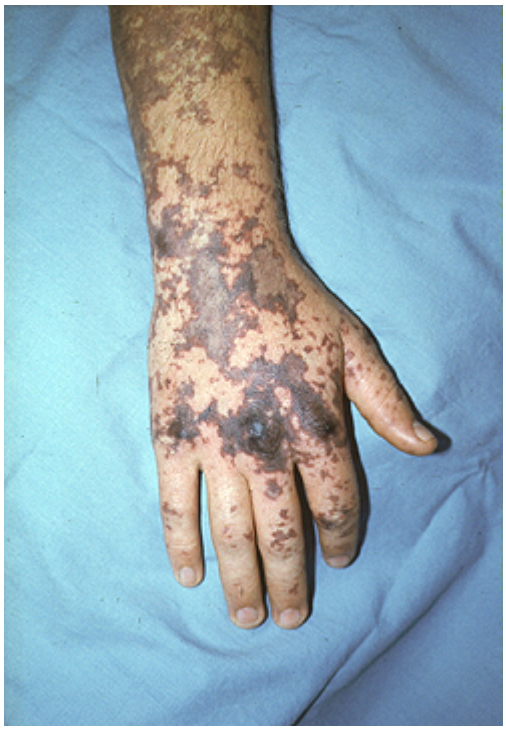
Purpura fulminans



Sharply demarcated, purpuric lesions were present in this patient with purpura fulminans.

Graphic 53920 Version 5.0

Acute meningococcemia

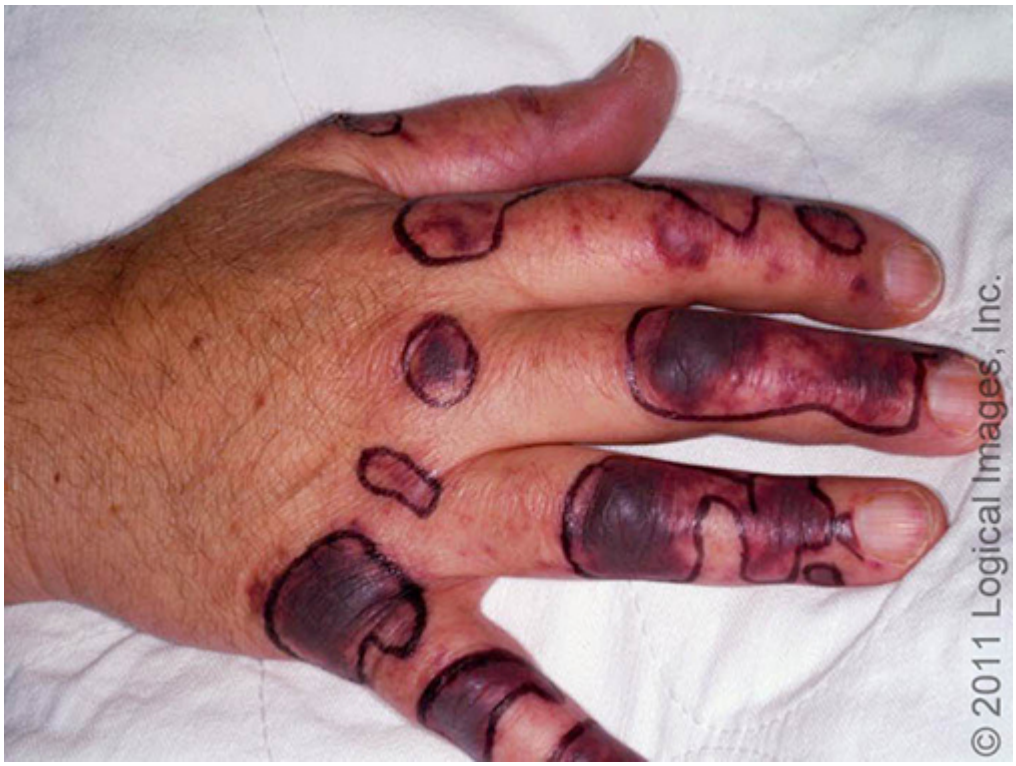


Skin lesions in acute meningococcemia can begin as papules but quickly progress to petechiae and purpura. As seen here, the purpuric lesions can coalesce.

Courtesy of Charles V Sanders. (The Skin and Infection: A Color Atlas and Text, Sanders CV, Nesbitt, LT Jr [Eds], Williams & Wilkins, Baltimore, 1995).

Graphic 52107 Version 6.0

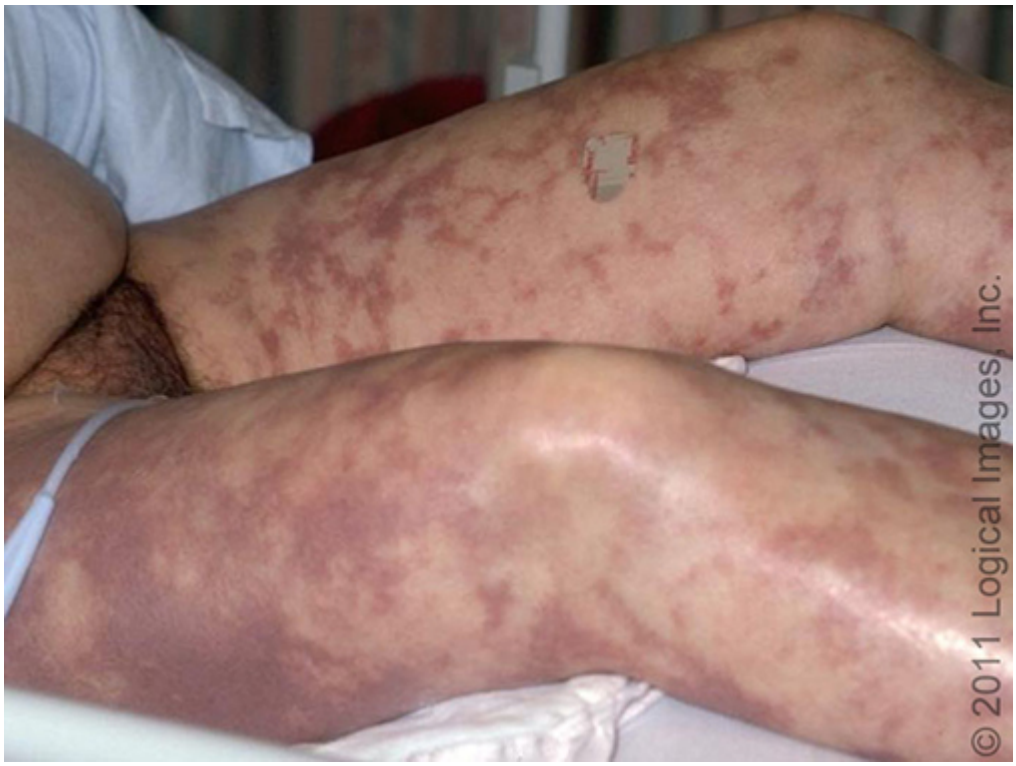
Acral purpura in disseminated intravascular coagulation



Multiple purpuric lesions are present on the hand of this patient with disseminated intravascular coagulation. Several lesions exhibit a retiform shape.

Graphic 74453 Version 7.0

Retiform purpura in disseminated intravascular coagulation



Widespread retiform purpura are present in this patient with disseminated intravascular coagulation.

Graphic 61719 Version 6.0

Laboratory diagnosis of abnormal fibrinolysis

Test	Primary hyperfibrinolysis	DIC	TTP
CBC and blood smear	Normal	Thrombocytopenia, MAHA	Thrombocytopenia, MAHA
PT and aPTT	Normal or prolonged	Prolonged	Normal
Fibrinogen	Decreased	Decreased	Normal
D-dimer or FDP*	Increased	Increased	Normal
Antithrombin	Normal	Decreased	Normal
Euglobulin clot lysis time	Shortened	Shortened	Normal
ADAMTS13 activity	Normal	Normal or mildly reduced¶	Severely deficient (usually <10%)Δ

Refer to UpToDate topics on disorders of fibrinolysis, DIC, and TTP for additional details.

DIC: disseminated intravascular coagulation; TTP: thrombotic thrombocytopenic purpura; CBC: complete blood count; MAHA: microangiopathic hemolytic anemia, characterized by anemia, laboratory markers of hemolysis, and schistocytes on the blood smear; PT: prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation products; ADAMTS13: von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

* FDP is not routinely measured.

¶ ADAMTS13 activity may be mildly reduced (activity, 20 to 60%) in the setting of acute illness.

Δ Refer to UpToDate for a discussion of the role of ADAMTS13 activity testing in the diagnosis of TTP.

Graphic 78455 Version 9.0

Causes of high plasma D-dimer

Condition	Mechanism
Thromboembolism: ▪ Arterial • Myocardial infarction • Stroke • Acute limb ischemia • Intracardiac thrombus ▪ Venous • Deep vein thrombosis • Pulmonary embolism ▪ Disseminated intravascular coagulation (DIC)	Intravascular thrombosis and fibrinolysis
Inflammation: ▪ COVID-19 ▪ Other severe infections ▪ Sepsis ▪ DIC	Activation of the acute inflammatory response and coagulation pathway, intravascular thrombosis and fibrinolysis
Surgery/trauma	Tissue ischemia, tissue necrosis
Liver disease	Reduced clearance of fibrin degradation products
Kidney disease	Multiple, including renal vein thrombosis and nephrotic syndrome
Vascular disorders: ▪ Vascular malformations ▪ Sickle cell disease vaso-occlusion	Intravascular thrombosis and fibrinolysis
Malignancy	Multiple, including vascular abnormalities, cancer procoagulant, and microvascular thrombosis
Thrombolytic therapy	Fibrin breakdown
Pregnancy: ▪ Normal pregnancy ▪ Preeclampsia and eclampsia	Physiologic changes in the coagulation system Microvascular thrombosis and fibrin deposition

Plasma D-dimer is a product of clot breakdown, released upon degradation of polymerized, crosslinked fibrin (if non-crosslinked fibrinogen was degraded, D-monomers would be released). Elevated plasma D-dimer levels indicate that coagulation has been activated, fibrin clot has formed, and clot degradation by plasmin has occurred. There are many causes of elevated D-dimer; identification of the underlying cause requires correlation with other findings, including the clinical picture and other laboratory results. Refer

to UpToDate for further explanation of fibrinogen domain structure and pathophysiology of the disorders listed here.

COVID-19: coronavirus disease 2019; DIC: disseminated intravascular coagulation.

Graphic 60881 Version 5.0

Blood components: Indications and dosing in adults

Component (volume)	Contents	Indications and dose
Whole blood (1 unit = 500 mL)*	RBCs, platelets, plasma	▪ Rarely required. ▪ May be appropriate when massive bleeding requires transfusion of more than 5 to 7 units of RBCs (increasingly used in early trauma management).
RBCs in additive solution (1 unit = 350 mL)	RBCs	▪ Anemia, bleeding. ▪ The increase in hemoglobin from 1 unit of RBCs will be approximately 1 g/dL; the increase in hematocrit will be approximately 3 percentage points.
FFP or other plasma product¶ (1 unit = 200 to 300 mL)	All soluble plasma proteins and clotting factors	▪ Bleeding or expected bleeding (eg, emergency surgery) in individuals with deficiencies of multiple coagulation factors (eg, DIC, liver disease, massive transfusion, anticoagulation with warfarin or warfarin overdose if not corrected by vitamin K and/or PCC, depending on the clinical setting). ▪ Bleeding in individuals with isolated factor deficiencies (most often factor V) if a factor concentrate or recombinant factor is not available. ▪ Therapeutic plasma exchange in TTP (as a source of ADAMTS13). ▪ In the rare event that FFP is used to replace a clotting factor, the dose is 10 to 20 mL/kg. This dose will raise the level of any factor, including fibrinogen, by close to 30%, which is typically sufficient for hemostasis.
Cryoprecipitate, also called "cryo" (1 unit = 10 to 20 mL)	Fibrinogen; factors VIII and XIII; VWF	▪ Bleeding patients with acquired hypofibrinogenemia, which may be due to cardiac surgery, liver transplant, postpartum hemorrhage, or trauma with massive transfusion. ▪ DIC. ▪ Uremia if DDAVP (desmopressin) is ineffective. ▪ The increase in plasma fibrinogen from 1 unit of Cryoprecipitate per 10 kg body weight will be approximately 50 mg/dL. ▪ Cryoprecipitate is generally provided in pools containing 5 units, and most patients receive 1 to 2 pools.
Platelets (derived from whole blood or apheresis) (1 unit of apheresis	Platelets	▪ The platelet count increase from 5 to 6 units of whole blood-derived platelets or 1 unit of apheresis platelets will be approximately 30,000/microL in an average-sized adult.

platelets or a 5 to 6 unit pool of platelets from whole blood = 200 to 300 mL)		

Refer to UpToDate topics on these products and on specific conditions for details of use. Frozen blood products (FFP, Cryoprecipitate) take 10 to 30 minutes to thaw. It may take the same amount of time to perform an uncomplicated crossmatch.

DIC: disseminated intravascular coagulation; FFP: Fresh Frozen Plasma; PCC: prothrombin complex concentrate; RBCs: red blood cells; TTP: thrombotic thrombocytopenic purpura; VWF: von Willebrand factor.

* 450 mL blood and 63 mL citrate-phosphate-dextrose (CPD) anticoagulant-preservative solution.

¶ Other plasma products include:

- Plasma Frozen Within 24 Hours After Phlebotomy (PF24)
- Thawed Plasma

PF24 may be used interchangeably with FFP for all of the indications listed above, with the exceptions of factor VIII deficiency or protein C deficiency, which are treated with recombinant products or plasma-derived factor concentrates. In the rare event that specific factor concentrates are unavailable and these deficiencies must be treated with a plasma product, FFP should be used.

Thawed Plasma may be used interchangeably with FFP for all of the indications listed above, with the exception of factor VIII deficiency without access to factor VIII concentrates, in which FFP should be used, or factor V deficiency, in which FFP or PF24 should be used.

Graphic 53854 Version 23.0

Possible contraindications to anticoagulation

Possible contraindication	Factors to consider
Active, clinically significant bleeding	Site and degree of bleeding (eg, nosebleeds and menses generally are not a contraindication; active intracerebral bleeding is almost always an absolute contraindication), interval since bleeding stopped
Severe bleeding diathesis	Nature, severity, and reversibility of bleeding diathesis
Severe thrombocytopenia (platelet count <50,000/microL)	Absolute platelet count, platelet count trend, and platelet function (eg some individuals with ITP and a platelet count in the range of 30,000 to 50,000 may tolerate anticoagulation if needed)
Major trauma	Site and extent of trauma, time interval since event (eg, for a patient with a mechanical heart valve it may be appropriate to anticoagulate sooner after trauma than a patient with a lesser indication)
Invasive procedure or obstetric delivery (recent, emergency, or planned)	Type of procedure and associated bleeding risk, interval between procedure and anticoagulation
Previous intracranial hemorrhage	Time interval since hemorrhage and underlying cause (eg, trauma or uncontrolled hypertension)
Intracranial or spinal tumor	Site and type of tumor, other comorbidities
Neuraxial anesthesia	Interval since spinal/epidural puncture or catheter removal, other alternatives for anesthesia; traumatic procedures are more concernin
Severe, uncontrolled hypertension	Absolute blood pressure and blood pressure trend

This list does not take the place of clinical judgment in deciding whether or not to administer an anticoagulant. In any patient, the risk of bleeding from an anticoagulant must be weighed against the risk of thrombosis and its consequences. The greater the thromboembolic risk, the greater the tolerance for the possibility of bleeding and for shortening the time interval between an episode of bleeding and anticoagulant initiation. Refer to UpToDate content on the specific indication for the anticoagulant and the specific possible contraindication for discussions of these risks.

ITP: immune thrombocytopenia.

Graphic 107527 Version 4.0