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## Editorial

**Disseminated intravascular coagulation (DIC)** is a condition in which blood clots form throughout the body, blocking small blood vessels. Symptoms may include chest pain, shortness of breath, leg pain, problems speaking, or problems moving parts of the body. As clotting factors and platelets are used up, bleeding may occur. This may include blood in the urine, blood in the stool, or bleeding into the skin. Complications may include organ failure.

Relatively common causes include sepsis, surgery, major trauma, cancer, and complications of pregnancy. Less common causes include snake bites, frostbite, and burns. There are two main types: acute (rapid onset) and chronic (slow onset). Diagnosis is typically based on blood tests. Findings may include low platelets, low fibrinogen, high INR, or high D-dimer.

Treatment is mainly directed towards the underlying condition. Other measures may include giving platelets, cryoprecipitate, or fresh frozen plasma. Evidence to support these treatments, however, is poor. Heparin may be useful in the slowly developing form. About 1% of people admitted to hospital are affected by the condition. In those with sepsis, rates are between 20% and 50%. The risk of death among those affected varies from 20 to 50%.

In DIC, the underlying cause usually leads to symptoms and signs, and DIC is discovered on laboratory testing. The onset of DIC can be sudden, as in endotoxic shock or amniotic fluid embolism, or it may be insidious and chronic, as in cancer. DIC can lead to multiorgan failure and widespread bleeding. For more in-depth study of DIC, please turn over and head straight to "**DISEASE DIAGNOSIS**" segment.

When the main article is DIC, it follows that subsidiary articles should also be related to coagulation disorders. So Prothrombin Time gets exhaustive coverage under "**INTERPRETATION**". Many a times individuals taking Warfarin get incongruous reports not tallying with the dosage, the culprit is sometimes the diet, "**TROUBLE SHOOTING**" segments highlights the related facts and aspects.

So much for the informative sections.

Little play and quiz is integral to this communiqué too!



## DISEASE DIAGNOSIS

### DIC (DISSEMINATED INTRAVASCULAR COAGULATION)

#### Background

Disseminated intravascular coagulation (DIC) is characterized by systemic activation of blood coagulation, which results in generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to multiple organ dysfunction syndrome (MODS). Consumption of clotting factors and platelets in DIC can result in life-threatening hemorrhage.

Derangement of the fibrinolytic system further contributes to intravascular clot formation, but in some cases, accelerated fibrinolysis may cause severe bleeding. Hence, a patient with DIC can present with a simultaneously occurring thrombotic and bleeding problem, which obviously complicates the proper treatment.

The subcommittee on DIC of the International Society on Thrombosis and Haemostasis has suggested the following definition for DIC: "An acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."

DIC is estimated to be present in as many as 1% of hospitalized patients. DIC is not itself a specific illness; rather, it is a complication or an effect of the progression of other illnesses. It is always secondary to an underlying disorder and is associated with a number of clinical conditions, generally involving activation of systemic inflammation. Such conditions include the following:

- Sepsis and severe infection (including COVID-19)
- Trauma (neurotrauma)
- Organ destruction (eg, pancreatitis)
- Malignancy (solid and lymphoproliferative/myeloproliferative malignancies)
- Severe transfusion reactions
- Obstetric complications – [Amniotic fluid embolism](#); [abruptio placentae](#); hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; eclampsia
- Retained dead fetus syndrome

- Vascular abnormalities - [Kasabach-Merritt syndrome](#) and large vascular aneurysms
- Severe hepatic failure
- Severe toxic reactions - Envenomations, [transfusion reactions](#), and transplant rejection

Heat stroke and hyperthermia

Hemorrhagic skin necrosis (purpura fulminans)

Catastrophic antiphospholipid syndrome (rare)

DIC is most commonly observed in severe sepsis and septic shock. Indeed, the development and severity of DIC correlate with mortality in severe sepsis. Although bacteremia, including both gram-positive and gram-negative organisms, is most commonly associated with DIC, other organisms (eg, viruses, fungi, and parasites) may also cause DIC.

Trauma, especially neurotrauma, is also frequently associated with DIC. DIC is more frequently observed in trauma patients with the systemic inflammatory response syndrome (SIRS). Evidence indicates that inflammatory cytokines play a central role in DIC in both trauma patients and septic patients. In fact, the systemic cytokine profiles in septic patients and trauma patients are nearly identical.

The symptoms of DIC are often those of the underlying inciting condition (see Etiology). In addition, symptoms of thrombosis, embolism, organ dysfunction, or bleeding may be present.

#### Acute versus chronic DIC

DIC exists in both acute and chronic forms. Acute DIC develops when sudden exposure of blood to procoagulants (eg, tissue factor [TF], or tissue thromboplastin) generates intravascular coagulation. Compensatory hemostatic mechanisms are quickly overwhelmed, and, as a consequence, a severe consumptive coagulopathy leading to hemorrhage develops. Abnormalities of blood coagulation parameters are readily identified, and organ failure frequently results.

In contrast, chronic DIC reflects a compensated state that develops when blood is continuously or intermittently exposed to small amounts of TF. Compensatory mechanisms in the liver and bone marrow are not overwhelmed, and there may be little obvious clinical or laboratory indication of the presence of DIC. Chronic DIC is more frequently observed in patients with solid tumors and in those with large aortic aneurysms.

## Pathophysiology

The hematologic derangements seen in DIC result from the following 4 simultaneously occurring mechanisms:

- Tissue factor (TF) – mediated thrombin generation
- Dysfunctional physiologic anticoagulant mechanisms (eg, depression of antithrombin and protein C system), which cannot adequately balance this thrombin generation Impaired fibrin removal due to depression of the fibrinolytic system – This is mainly caused by high circulating levels of plasminogen activator inhibitor type 1 (PAI-1); however, in exceptional forms of DIC, fibrinolytic activity may be increased and contribute to bleeding
- Inflammatory activation

### Thrombin generation and tissue factor

Thrombin generation is detectable at 3-5 hours after the occurrence of bacteremia or endotoxemia. Ample evidence exists for a pivotal role of the TF/factor VIIa system in the initiation of thrombin generation.

Exposure to TF in the circulation occurs via endothelial disruption, tissue damage, or inflammatory or tumor cell expression of procoagulant molecules (including TF). TF activates coagulation via the extrinsic pathway involving factor VIIa. The TF-VIIa complex activates thrombin, which cleaves fibrinogen to fibrin while simultaneously causing platelet aggregation. The intrinsic (or contact) pathway may also be activated in DIC, though contributing more to hemodynamic instability and hypotension than to activation of clotting.

Thrombin produced by the TF/factor VII pathway amplifies both clotting and inflammation through the following activities:

- Platelet activation, enhancing aggregation and augmenting platelet functions in coagulation
- Activation of factors VIII, V, and XI, yielding further thrombin generation
- Enhanced activation of proinflammatory factors via protease-activated receptors (PARs)
- Activation of factor XIII to factor XIIIa, which augments production of fibrin clots from fibrinogen
- Activation of thrombin-activatable fibrinolysis inhibitor (TAFI), making clots resistant to fibrinolysis; and
- Enhanced expression of adhesion molecules (eg, L-

selectin), thereby promoting the inflammatory effects of white blood cells (WBCs)

Factor VIIa has been implicated as the central mediator of intravascular coagulation in sepsis. Blocking the factor VIIa pathway in sepsis has been shown to prevent the development of DIC, whereas interrupting alternative pathways did not demonstrate any effect on clotting.

Abrogation of the TF/factor VII(a) pathway by monoclonal antibodies specifically directed against TF or factor VIIa activity completely inhibited thrombin generation in endotoxin-challenged chimpanzees and prevented the occurrence of DIC and mortality in baboons that were infused with *Escherichia coli*. Indeed, in most DIC patients, TF antigen is detectable in plasma. Hence, activation of coagulation in DIC is primarily TF-driven; the intrinsic pathway of coagulation appears not to play an important role.

The actual source of the TF has not been established with certainty. TF may be expressed on mononuclear cells in vitro, and its expression on circulating monocytes of patients with severe infection has been demonstrated. In addition, it may be expressed on endothelial cells. Injured endothelial cells express TF, whereas healthy ones do not. However, the importance of endothelial cell TF expression in vivo and its role in the pathogenesis of DIC remain to be determined.

Another source of TF may be polymorphonuclear leukocytes (PMNs) and other similar cell types, though it is unlikely that these cells actually synthesize TF in substantial quantities. On the basis of the observation that TF has been transferred from leukocytes to activated platelets on a collagen surface in an ex-vivo perfusion system, it is hypothesized that this “bloodborne” TF is transferred between cells through microparticles derived from activated mononuclear cells.

### Impaired coagulation inhibitor systems

Thrombin generation is usually tightly regulated by multiple hemostatic mechanisms. However, once intravascular coagulation commences, compensatory mechanisms are overwhelmed or incapacitated. Impaired functioning of various natural regulating pathways of coagulation activation may amplify further thrombin generation and contribute to fibrin formation.

Plasma levels of the most important inhibitor of thrombin, antithrombin, are usually markedly reduced in patients with

DIC. This reduction is caused by the following:

- Antithrombin is continuously consumed by ongoing activation of coagulation
- Elastase produced by activated neutrophils degrades antithrombin as well as other proteins
- Further antithrombin is lost to capillary leakage
- Production of antithrombin is impaired secondary to liver damage resulting from underperfusion and micro-vascular coagulation

Low antithrombin levels in DIC are associated with increased mortality, particularly in patients with sepsis. That low levels of antithrombin precede the clinical manifestation of sepsis in prospective studies suggests that antithrombin is indeed involved in the pathogenesis of this disease and associated organ dysfunction.

In addition to the decrease in antithrombin, significant depression of the protein C system may occur. Protein C, along with protein S, also serves as a major anticoagulant compensatory mechanism. Under normal conditions, protein C is activated by thrombin when complexed on the endothelial cell surface with thrombomodulin. Activated protein C combats coagulation via proteolytic cleavage of factors Va and VIIIa and proteolyzes PAR1 when bound to the endothelial cell protein C receptor (EPCR).

Impaired functioning of the protein C pathway is mainly due to down-regulation of thrombomodulin expression or its inactivation by cellular reactive oxygen species on endothelial cells by proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin (IL)-1b. This down regulation has been confirmed in studies in patients with meningococcal sepsis.

In combination with low levels of zymogen protein C (due to mechanisms similar to those described for antithrombin), this process results in diminished protein C activation, which will enhance the procoagulant state. Protein C levels are further reduced via consumption, extravascular leakage, renal loss, and reduced hepatic production and by a reduction in circulating free protein S. The availability of protein S to serve as a cofactor for activated protein C is regulated by the degree it is bound to the complement protein C4B-binding protein.

Animal experiments involving severe inflammation-induced coagulation activation convincingly show that compromising

the protein C system results in increased morbidity and mortality, whereas restoring adequate functioning of activated protein C improves survival and organ failure. Experiments show that mice with a 1-allele targeted deletion of the protein C gene (resulting in heterozygous protein C deficiency) have more severe DIC and organ dysfunction and a higher mortality than wild-type littermates.

Besides being implicated in the physiologic regulation of thrombin formation, activated protein C probably also has important inflammation-modulating effects, which may be of relevance in the pathogenesis of DIC.

TF pathway inhibitor (TFPI) is another anticoagulant mechanism that is disabled in DIC. TFPI reversibly inhibits factor Xa and thrombin (indirectly) and has the ability to inhibit the TF-VIIa complex. Although levels of TFPI are normal in patients with sepsis, a relative insufficiency in DIC is evident. TFPI depletion in animal models predisposes to DIC, and TFPI blocks the procoagulant effect of endotoxin in humans. The role of TFPI in the pathogenesis of DIC has not been fully clarified.

The experimental finding that administration of recombinant TFPI blocks inflammation-induced thrombin generation in humans, along with the observation that pharmacologic doses of TFPI are capable of preventing mortality during systemic infection and inflammation, suggests that high concentrations of TFPI are capable of modulating TF-mediated coagulation. Presumably, however, the endogenous concentration of TFPI is insufficiently capable of regulating coagulation activation and the downstream consequences during systemic inflammation.

### **Defective fibrinolysis**

The intravascular fibrin produced by thrombin is normally eliminated via a process termed fibrinolysis. Experimental models indicate that at the time of maximal activation of coagulation, the fibrinolytic system is largely shut off.

Experimental bacteremia and endotoxemia result in a rapid increase in fibrinolytic activity, most probably caused by release of plasminogen activators from endothelial cells. However, this profibrinolytic response is almost immediately followed by suppression of fibrinolytic activity due to a sustained increase in plasma levels of PAI-1; these effects are mediated by TNF-2 and IL-1. High PAI-1 levels precede DIC and predict poor outcomes.

Notably, strategies that can block endotoxin-induced thrombin generation completely, such as anti-TF antibodies or recombinant hirudin (r-hirudin), have no significant effect on activation and subsequent inhibition of fibrinolysis, which suggests that these 2 processes are independently regulated.

In a study of 69 DIC patients (31 with multiorgan failure), higher levels of tissue plasminogen activator (t-PA) antigen and PAI-1 with depressed levels of  $\alpha_2$ -antiplasmin were observed in patients with DIC and multiorgan failure than in DIC patients without multiorgan failure. This finding supports the conclusion that fibrinolysis is a mechanism vital to the prevention of multiorgan failure.

Playing a key role in the process of coagulation and hemostasis is the vascular endothelium, which is responsible for the production of von Willebrand factor (vWF). vWF mediates the adhesion between the platelet surface receptors and the vessel wall and is increased in cases of thrombotic microangiopathy related to DIC. Impaired control of endothelial cell thrombomodulin expression may result in facilitated thrombin generation, which subsequently results in increased platelet activation and the conversion of fibrinogen to fibrin.

Rare cases of DIC are characterized by a severe hyperfibrinolytic state on top of an activated coagulation system. Examples of such situations are the DIC that occurs as a complication of acute myeloid leukemia M-3 (in the French-American-British [FAB] classification) or the DIC that may occur secondary to some forms of adenocarcinoma. Although hyperfibrinolysis predominates in this situation, disseminated thrombosis is still found in a considerable number of patients at autopsy. Clinically, however, these patients suffer from severe bleeding.

In general, patients with DIC should not be treated with antifibrinolytic agents, because this may increase the fibrinolytic deficit and may result in increased thrombosis.

### Inflammatory activation

Inflammatory and coagulation pathways interact in substantial ways. It is clear that there is cross-communication between the 2 systems, whereby inflammation gives rise to activation of the clotting cascade and the resultant coagulation stimulates more vigorous inflammatory activity.

There are a number of different triggers that can cause a hemostatic imbalance, giving rise to a hypercoagulable state.

Many of the activated coagulation factors produced in DIC contribute to the propagation of inflammation by stimulating endothelial cell release of proinflammatory cytokines. Factor Xa, thrombin, and the TF-VIIa complex have each been demonstrated to elicit proinflammatory action. Furthermore, given the anti-inflammatory action of activated protein C and antithrombin, depression of these anticoagulants in DIC contributes to further dysregulation of inflammation.

### Etiology

Several disease states may lead to the development of DIC (see Tables 1 and 2 below), generally via one of the following two pathways:

- A systemic inflammatory response, leading to activation of the cytokine network and subsequent activation of coagulation (eg, in sepsis or major trauma)
- Release or exposure of procoagulant material into the bloodstream (eg, in cancer, crush brain injury, or in obstetric cases)

In some situations (eg, major trauma or severe necrotizing pancreatitis), both pathways may be present.

**Table 1.** Causes of Acute (Hemorrhagic) Disseminated Intravascular Coagulation.

Type	Cause
Infectious	Bacterial (eg, gram-negative sepsis, gram-positive infections, rickettsial) Viral (eg, HIV, cytomegalovirus [CMV], varicella-zoster virus [VZV], and hepatitis virus) Fungal (eg, <i>Histoplasma</i> ) Parasitic (eg, malaria)
Malignancy	Hematologic (eg, acute myelocytic leukemia) Metastatic (eg, mucin-secreting adenocarcinoma)
Obstetric	Amniotic fluid embolism Abruptio placentae Acute peripartum hemorrhage Preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet

	count (HELLP) syndrome Retained stillbirth Septic abortion and intrauterine infection Acute fatty liver of pregnancy
Trauma	Burns Motor vehicle accidents Snake envenomation
Transfusion	Hemolytic reactions Transfusion
Other	Liver disease/acute hepatic failure* Prosthetic devices Shunts (Denver or LeVeen) Ventricular assist devices
*Some do not classify this as DIC; rather, it is liver disease with reduced blood coagulation factor synthesis and reduced clearance of activate products of coagulation.	

**Table 2.** Causes of Chronic Disseminated Intravascular Coagulation

Type	Cause
Malignancies	Solid tumors Leukemia
Obstetric	Retained dead fetus syndrome Retained products of conception
Hematologic	Myeloproliferative syndromes
Vascular	Rheumatoid arthritis Raynaud disease
Cardiovascular	Myocardial infarction
Inflammatory	Ulcerative colitis Crohn disease Sarcoidosis
Localized	DIC Aortic aneurysms Giant hemangioma (Kasabach - Merritt syndrome) Acute renal allograft rejection

Bacterial infection (in particular, bloodstream infection [BSI]) is commonly associated with DIC. There is no difference in the incidence of DIC between patients with gram-negative sepsis and those with gram-positive sepsis. Systemic infections with other microorganisms, such as viruses and parasites, may lead to DIC as well.

Factors involved in the development of DIC in patients with infections may be specific cell membrane components of the microorganism (lipopolysaccharide or endotoxin) or bacterial

exotoxins (eg, staphylococcal alpha toxin). These components cause a generalized inflammatory response, characterized by the systemic occurrence of proinflammatory cytokines.

Severe trauma is another clinical condition frequently associated with DIC. A combination of mechanisms - including release of tissue material (eg, tissue factor [thromboplastin], fat or phospholipids) into the circulation, hemolysis, and endothelial damage—may contribute to systemic activation of coagulation. In addition, solid evidence indicates that cytokines also play a pivotal role in the occurrence of DIC in trauma patients. In fact, systemic cytokine patterns have been shown to be virtually identical in trauma patients and septic patients.

Both solid tumors and hematologic malignancies may be complicated by DIC. The mechanism by which coagulation is deranged in this situation is poorly understood. Solid tumor cells can express different procoagulant molecules, including TF and a cancer procoagulant. Cancer procoagulant is found in extracts of neoplastic cells and in the plasma of patients with solid tumors. As noted, some tumors are associated with a form of DIC that is characterized by severe hyperfibrinolysis on top of an activated coagulation system.

Acute DIC occurs in obstetric calamities such as placental abruption (abruptio placentae) and amniotic fluid emboli. Amniotic fluid has been shown to be able to activate coagulation in vitro, and the degree of placental separation correlates with the extent of the DIC, suggesting that leakage of thromboplastinlike material from the placental system is responsible for the occurrence of DIC.

Although the coagulation system may be activated in patients with preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, clinically significant DIC occurs in only a small percentage of patients, usually in association with secondary complications.

Vascular disorders, such as large aortic aneurysms or giant hemangiomas (Kasabach-Merritt syndrome), may result in local activation of coagulation. Activated coagulation factors can ultimately “overflow” to the systemic circulation and cause DIC, but systemic depletion of coagulation factors and platelets as a result of local consumption is a more common scenario.

## Epidemiology and Prognosis

DIC may occur in 30-50% of patients with sepsis and it develops in an estimated 1% of all hospitalized patients. DIC occurs at all ages and in all races, and no particular sex predisposition has been noted.

The prognosis of patients with DIC depends on the severity of the coagulopathy and on the underlying condition that led to DIC. Assigning numerical figures to DIC - specific morbidity and mortality is difficult. The following are examples of mortality figures for diseases complicated by DIC:

- Idiopathic purpura fulminans associated with DIC has a mortality of 18%
- Septic abortion with clostridial infection and shock associated with severe DIC has a mortality of 50%
- In the setting of major trauma, the presence of DIC approximately doubles the mortality rate

A retrospective single-center Korean study of women with primary post-partum hemorrhage who presented to the emergency department found that 57 (22.4%) of the 255 patients had overt DIC. Of patients with DIC, 96.5% experienced major adverse events.

DIC criteria based on the Japanese Association for Acute Medicine DIC criteria with the addition of the hemostatic endothelial molecular markers protein C activity and plasminogen activator inhibitor 1 had a sensitivity of 84.6% and a specificity of 80.3% for predicting mortality in a study of 79 patients with severe sepsis or septic shock. Using these criteria, DIC - positive patients also had significantly higher disease severity,

In general, if the underlying condition is self-limited or can be appropriately handled, DIC will disappear, and the coagulation status will normalize. A patient with acute hemorrhagic DIC that is associated with metastatic gastric carcinoma likely has a lethal condition that does not alter patient demise, regardless of treatment. On the other hand, a patient with acute DIC associated with abruptio placentae needs quick recognition and obstetric treatment; the DIC will resolve with the treatment of the obstetric catastrophe.

Obviously, the clinical importance of a severe depletion of platelets and coagulation factors in patients with diffuse, widespread bleeding or in patients who need to undergo an invasive procedure is clear. In addition, the intravascular deposition of fibrin, as a result of the systemic activation of

coagulation, contributes to organ failure and mortality.

Histologic studies in patients with DIC show the presence of ischemia and necrosis due to fibrin deposition in small and medium-sized vessels of various organs. The presence of these intravascular thrombi appears to be clearly and specifically related to the clinical dysfunction of the organ. Specific thrombotic complications that are sometimes seen in the framework of DIC are acral cyanosis, hemorrhagic skin infarctions, and limb ischemia.

In addition, experimental animal studies of DIC show fibrin deposition in various organs. Amelioration of DIC by various interventions appears to improve organ failure and, in some but not all cases, mortality.

Finally, DIC has been shown to be an independent predictor of mortality in patients with sepsis and severe trauma. The presence of DIC may increase the risk of death by a factor of 1.5 to 2.0 in various studies. An increasing severity of DIC is directly related to an increased mortality.

A study utilizing the Japanese Association for Acute Medicine (JAAM) diagnostic criteria for DIC showed that septic patients with DIC had a higher mortality than trauma patients with DIC did (34.7% vs 10.5%).

## Complications

Complications of DIC include the following:

- Acute kidney injury
- Change in mental status
- Respiratory dysfunction
- Hepatic dysfunction
- Life-threatening thrombosis and hemorrhage (in patients with moderately severe-to-severe DIC)
- Cardiac tamponade
- Hemothorax
- Intracerebral hematoma
- Gangrene and loss of digits
- Shock
- Death

## CLINICAL PRESENTATION

### History

The symptoms of disseminated intravascular coagulation (DIC) are often those of the underlying inciting condition (see Etiology). Such conditions may include the following:

- Sepsis or severe infection (with any microorganism)
- Trauma (eg, polytrauma, neurotrauma, or **fat embolism**)
- Organ destruction (eg, severe pancreatitis)
- Malignancy – Solid tumors and **myeloproliferative /lymphoproliferative** malignancies
- Obstetric calamities (eg, amniotic fluid embolism; **abruptio placentae**)
- Vascular abnormalities – **Kasabach-Merritt syndrome** and large vascular aneurysms
- Severe hepatic failure
- Severe toxic or immunologic reactions – Snake bites, recreational drugs, **transfusion reactions**, and **transplant rejection**

In addition to the symptoms related to the underlying disease process, there is typically a history of blood loss through bleeding in areas such the gingivae and the gastrointestinal (GI) system (see Table 3 below). Acutely presenting DIC often manifests as petechiae and ecchymosis, along with blood loss from intravenous (IV) lines and catheters. In postoperative DIC, bleeding can occur in the vicinity of surgical sites, drains, and tracheostomies, as well as within serous cavities.

**Table 3.** Main Features of Disseminated Intravascular Coagulation in Series of 118 Patients.

Features	Affected Patients, %
Bleeding	64%
Renal dysfunction	25%
Hepatic dysfunction	19%
Respiratory dysfunction	16%
Shock	14%
Central nervous system dysfunction	2%

Look for symptoms and signs of thrombosis in large vessels (eg, deep vein thrombosis [DVT]) and microvascular thrombosis (as in renal failure). Bleeding from at least 3 unrelated sites is particularly suggestive of DIC. As many as 25% of patients present with renal failure. Patients with pulmonary involvement can present with dyspnea, hemoptysis, and cough. Comorbid liver disease as well as rapid hemolytic bilirubin production may lead to jaundice. Neurologic changes (eg, coma, obtunded mental status, and paresthesias) are also possible.

**Physical Examination**

With acute DIC, the physical findings are usually those of the underlying or inciting condition; however, patients with the acute disease (ie, the hemorrhagic variety associated with excess plasmin formation) have petechiae on the soft palate, trunk, and extremities from thrombocytopenia and ecchymosis at venipuncture sites. These patients also manifest ecchymosis in traumatized areas.

In patients with so-called chronic or subacute DIC, of which the primary manifestation is thrombosis from excess thrombin formation, the signs of venous thromboembolism may be present.

Circulatory signs include the following:

- Signs of spontaneous and life-threatening hemorrhage
- Signs of subacute bleeding
- Signs of diffuse or localized thrombosis
- Bleeding into serous cavities
- Central nervous system signs include the following:
  - Nonspecific altered consciousness or stupor
  - Transient focal neurologic deficits
- Cardiovascular signs include the following:
  - Hypotension
  - Tachycardia
  - Circulatory collapse
- Respiratory signs include the following:
  - Pleural friction rub
  - Signs of acute respiratory distress syndrome (ARDS)
- Gastrointestinal signs include the following:
  - Hematemesis
  - Hematochezia

Genitourinary signs include the following:

- Signs of azotemia and renal failure
- Acidosis
- Hematuria
- Oliguria
- Metrorrhagia
- Uterine hemorrhage

Dermatologic signs include the following:

- Petechiae
- Jaundice (liver dysfunction or hemolysis)
- Purpura
- Hemorrhagic bullae

- Acral cyanosis
- Skin necrosis of lower limbs (purpura fulminans)
- Localized infarction and gangrene
- Wound bleeding and deep subcutaneous hematomas
- Thrombosis

## DIFFERENTIAL DIAGNOSIS

### Diagnostic Considerations

The differential diagnosis of disseminated intravascular coagulation (DIC) is broad and can include other causes of consumptive coagulopathies, such as trauma and major surgery. In addition, severe liver disease can result in markedly reduced production of coagulation factors and inhibitors. Thrombocytopenia may also occur in this setting secondary to splenic sequestration, resulting in an overall clinical picture quite similar to DIC.

Thrombotic thrombocytopenic purpura (TTP) – hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy superficially like DIC, but distinctly different; in contrast to DIC, the mechanism of thrombosis is not via the tissue factor (TF)/factor VIIa pathway. Results of blood coagulation assays in TTP - HUS are normal. Rather, in TTP - HUS, thrombosis arises from direct platelet activation, usually as a result of widespread endothelial damage or an inherited or acquired impairment of ADAMTS13, a protease that normally cleaves von Willebrand factor (vWF), which results in an ultralarge vWF (ULVWF) that agglutinates/ activates platelets, leading to thrombosis and shearing of red blood cells on the ULVWF.

TTP-HUS and DIC can usually be distinguished on the basis of their occurrence in different clinical settings (ie, trauma or sepsis for DIC and fever associated with thrombocytopenia and a microangiopathic hemolytic anemia for TTP-HUS). Patients with TTP-HUS do not demonstrate the laboratory abnormalities frequently encountered in DIC (see Workup).

Other thrombotic microangiopathies include chemotherapy - induced or stem cell transplant-associated microangiopathy and HIV-induced TTP.

Thrombocytopenia is present in both DIC and immune thrombocytopenia (ITP). However, ITP is distinct from DIC in terms of its pathophysiologic mechanism and does not involve coagulation activation or microangiopathic hemolytic anemia.

Heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) is another clinical entity with a presentation similar to that of DIC. A subpopulation of patients who have received heparin develop antibodies against platelet antigens (PF4), and a diminution of platelet number can result. If the antibody is particularly reactive with platelets, its direct activation of platelets leads to thrombosis. In HITTS, although the platelet count is decreased, the plasma prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the fibrinogen levels are normal. Thrombosis is observed, but, typically, HITTS does not produce the consumptive coagulopathy of DIC.

Severe COVID-19 often features a coagulation/fibrinolytic abnormality that is marked by an increase in plasma D-dimer levels, and that may progress to DIC. However, the pathophysiology of coagulopathy with COVID-19 is very different from that of septic DIC; the coagulopathy is more localized and has distinct differences from classical DIC or thrombotic microangiopathy syndromes. The clinical presentation in COVID-19 coagulopathy is mostly prothrombotic, with venous and even arterial thromboembolism; hemorrhagic complications are uncommon.

On laboratory testing, the combination of increased D-dimer, thrombocytopenia, and prolonged global coagulation tests in COVID-19 coagulopathy mimics the pattern seen in DIC. However, compared with patients with typical DIC, patients with COVID-19 tend to have a relatively mild thrombocytopenia. Furthermore, in patients with the most severe COVID-19, the prothrombin time is only mildly prolonged; in up to 30% of patients with COVID-19, shortening of PT has been reported. Most patients with COVID-19 coagulopathy will not meet the International Society on Thrombosis and Haemostasis diagnostic criteria for overt DIC.

### Differential Diagnoses

- Dysfibrinogenemia
- Hemolytic-Uremic Syndrome
- Heparin-Induced Thrombocytopenia
- Immune Thrombocytopenia (ITP) in Emergency Medicine
- Thrombotic Thrombocytopenic Purpura (TTP)

## WORKUP

### Approach Considerations

Diagnosis of disseminated intravascular coagulation (DIC) can be difficult, especially in cases of chronic, smoldering DIC, where clinical and laboratory abnormalities may be subtle. No single routinely available laboratory test is sufficiently sensitive or specific to allow a diagnosis of DIC; however, several commonly available laboratory tests often yield abnormal results in DIC. Typically, moderate-to-severe thrombocytopenia is present. Furthermore, the peripheral blood smear can demonstrate evidence of microangiopathic pathology (schistocytes). Scoring systems have been developed to facilitate diagnosis of DIC.

Imaging studies are useful only to detect an underlying cause; the diagnosis of DIC is made by combining the clinical impression with any laboratory abnormalities noted.

No specific procedures help establish a specific diagnosis of DIC. However, a number of different procedures may help to diagnose the underlying causative condition.

### Laboratory Studies

Patients with DIC can present with a wide range of abnormalities in their laboratory values. Typically, prolonged coagulation times, thrombocytopenia, high levels of fibrin degradation products (FDPs), elevated D-dimer levels, and microangiopathic pathology (schistocytes) on peripheral smears are suggestive findings.

Most individual laboratory tests demonstrate high sensitivity for DIC but very low specificity. Furthermore, whereas acute DIC typically overwhelms compensatory anticoagulation mechanisms, resulting in depletion of factors and laboratory derangements, chronic or localized DIC may produce only minimal abnormalities in laboratory tests.

It is essential to keep in mind that laboratory values may represent only a momentary glimpse into a very rapidly changing systemic process and that repeated tests may therefore be necessary in order to make a more clinically certain diagnosis.

### Standard tests

In clinical practice, a diagnosis of DIC can often be made by a combination of the following tests:

- Platelet count
- Global clotting times (aPTT and PT)

- One or two clotting factors and inhibitors (eg, antithrombin)
- Assay for D-dimer or FDPs

### *Platelet count*

Typically, moderate-to-severe thrombocytopenia is present in DIC. Thrombocytopenia is seen in as many as 98% of DIC patients, and the platelet count can dip below  $50 \times 10^9/L$  in 50%. A trend toward decreasing platelet counts or a grossly reduced absolute platelet count is a sensitive (though not specific) indicator of DIC. Repeated platelet counts are often necessary, as a single platelet measurement may indicate a level within the normal range, whereas trend values might show a precipitous drop from previous levels.

The peripheral blood smear can reveal schistocytes, though these are rarely seen to exceed 10% of red blood cells (RBCs). The presence of schistocytes is neither sensitive nor specific for DIC, but in certain instances, it may help confirm a chronic DIC diagnosis when the schistocytes are seen in concert with normal coagulation values and increased D-dimer levels.

### *Clotting times and coagulation factors*

Global clotting times (ie, activated partial thromboplastin time [aPTT] and prothrombin time [PT]) are typically prolonged. In as many as 50% of DIC patients, however, a normal or even an attenuated PT and aPTT may be encountered; consequently, such values cannot be used to exclude DIC. This phenomenon may be attributed to certain activated clotting factors present in the circulation, such as thrombin or Xa, which may in fact enhance thrombin formation.

It should be emphasized that serial coagulation tests are usually more helpful than single laboratory results in establishing the diagnosis of DIC. It is also important to note that the PT, not the international normalized ratio (INR), should be used in the DIC monitoring process; INR is recommended only for monitoring oral anticoagulant therapy.

The prolongation of global clotting times may reflect the consumption and depletion of various coagulation factors, which may be further substantiated by the measurement of selected coagulation factors, such as [factor V](#) and [factor VII](#). Measurement of coagulation factors may be helpful for detecting additional hemostatic abnormalities (eg, those caused by [vitamin K deficiency](#)).

Protein C and antithrombin are 2 natural anticoagulants that are frequently decreased in DIC. There is some evidence to

suggest that they may serve roles as prognostic indicators. Nonetheless, the practical application of measuring these anticoagulants may be limited for most practitioners because the tests may not be generally available.

DIC is associated with an unusual light transmission profile on the aPTT, known as a biphasic waveform. In one study, the degree of biphasic waveform abnormality had an increasing positive predictive value for DIC, independent of clotting time prolongation. In addition, the waveform abnormalities are often evident before more conventionally used laboratory value derangements, making this a quick and robust test for DIC. At present, however, the photo-optical analyzers necessary in clot formation analysis are not widely available.

#### Tests for fibrinogen, D-dimer, and FDPs

Because fibrin activation is a central component of DIC, it would seem logical to assume that if soluble fibrin is elevated, the diagnosis of DIC can be made with confidence. However, soluble fibrin levels are not available to most clinicians within a relevant time frame. Likewise, laboratory assays aimed at differentiating between cross-linked fibrin, fibrinogen, and soluble fibrin have been developed but are not routinely available to the clinician.

The massive fibrin deposition in DIC suggests that fibrinogen levels would be decreased. Accordingly, measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC; however, it is in fact not very helpful. Fibrinogen, as a positive acute-phase reactant, is increased in inflammation, and whereas values may decrease as the illness progresses, they are rarely low. One study demonstrated that in up to 57% of DIC patients, the levels of fibrinogen may in fact remain within normal limits.

In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28%, and hypofibrinogenemia was detected in a very small number of severe cases of DIC only. Sequential measurements of fibrinogen might be more useful and might be more likely to provide diagnostic clues.

Fibrinolysis is an important component of DIC; thus, there will be evidence of fibrin breakdown, such as elevated levels D-dimer and FDPs. D-dimer elevation means that thrombin has proteolyzed fibrinogen to form fibrin that has been cross-linked by thrombin-activated factor XIIIa. When fibrin becomes cross-linked insoluble, a unique D-D domain

neopeptide forms. This cross-linked insoluble fibrin is then proteolyzed uniquely by plasmin to liberate the soluble D-D dimer. Thus, the D-dimer measures prior thrombin and plasmin formation. On the other hand, FDPs only inform that plasmin has been formed and it cleaved soluble fibrinogen, fibrin, or insoluble cross-linked fibrin. D-dimer is the better test for DIC.

Accordingly, testing for D-dimer or FDPs may be helpful for differentiating DIC from other conditions that may be associated with a low platelet count and prolonged clotting times, such as chronic liver disease. Most laboratories have an operational test for D-dimer. In the United States, FDPs are not used as often.

D-dimer or FDPs may be detected by means of specific enzyme-linked immunosorbent assay (ELISA) or latex agglutination assay, allowing rapid and bedside determination in emergency cases. However, some of the available assays for FDPs cross-react with fibrinogen degradation products, and this cross-reactivity may cause spuriously high results. The specificity of high levels of D-dimer and FDPs is therefore limited, and many other conditions (eg, venous thromboembolism, trauma, inflammation, and recent surgery) may be associated with elevated FDP levels.

#### **Specialized tests**

In a specialized setting, molecular markers for activation of coagulation or fibrin formation may be the most sensitive assays for DIC. A number of clinical studies show that the presence of soluble fibrin in plasma has a 90-100% sensitivity for DIC but, unfortunately, a relatively low specificity. As noted (see above) a reliable test for quantifying soluble fibrin in plasma is not available, and one study showed a wide discordance among various assays.

The dynamics of DIC can also be judged by measuring activation markers that are released upon the conversion of the coagulation factor zymogen to an active protease, such as prothrombin activation fragment F1+2 (F1+2). Indeed, these markers are markedly elevated in patients with DIC, but again, the specificity is a problem.

In addition to the known limitations in specificity, many of the more sensitive and sophisticated tests described above are not available to general hematology laboratories. Although these tests may be very helpful in clinical trials or other

research, they often cannot be used in a routine setting.

Evidence also suggests that serum levels of thrombomodulin, a marker for endothelial cell damage, correlate well with the clinical course of DIC, the development of multiple organ dysfunction syndrome (MODS), and mortality in septic patients. Thrombomodulin is elevated in DIC, and such elevation and not only correlates well with the severity of DIC but also can serve as a marker for early identification and monitoring of DIC.

Regardless of the discussion above, most hospitals of all sizes in the developed world have available PT, aPTT, fibrinogen, platelet count, and D-dimer. These tests alone are sufficient to make or exclude a clinical diagnosis of DIC in the practice of medicine.

**DIC Scoring Systems**

The diagnosis of DIC relies on multiple clinical and laboratory determinations. The International Society on Thrombosis and Haemostasis (ISTH) developed a simple scoring system for the diagnosis of overt DIC that makes use of laboratory tests available in almost all hospital laboratories (see the image below, and the [DIC Score](#) calculator.)The presence of an underlying disorder known to be associated with DIC (see [Etiology](#)) is a sine qua non for the use of this diagnostic algorithm.

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation (DIC).

1. Risk assessment: Does the patient have a underlying disorder known to be associated with overt DIC?  
If yes, proceed. If no, do not use this algorithm;
2. Order global coagulation tests (platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers, or fibrin degradation products).
3. Score global coagulation test results:
  - Platelet count (> 100=0, <100=1, <50=2)
  - Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products) (no increase: 0, moderate increase : 2 strong increase: 3)
  - Prolonged prothrombin time (<3 sec.=0, >3 but<6 sec. = 1, >6 sec. =2)

- Fibrinogen level (> 1.0g/L=0, < 1.0g/L=1)
- 4. Calculate score
- 5. If >5: compatible with overt DIC; repeat scoring daily.  
If < 5: suggestive (not affirmative) for non-overt DIC; repeat next 1-2 days.

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation.

A score of 5 or higher indicates overt DIC, whereas a score of less than 5 does not rule out DIC but may indicate DIC that is not overt. Prospective validation studies show this scoring system to be highly accurate for the diagnosis of DIC. The sensitivity of the DIC score for a diagnosis of DIC is 91-93%, and the specificity is 97-98%.

Other analyses show that the DIC scoring system is a strong independent predictor of a fatal outcome in intensive care unit (ICU) patients. In these studies, mortality was higher than 40% in patients with sepsis and DIC (according to the scoring system), compared with about 25% in patients without DIC. For each DIC point in the system, the odds ratio for mortality is 1.29, whereas for each Acute Physiology and Chronic Health Evaluation (APACHE) classification system point, the odds ratio for mortality is 1.07.

Despite the demonstrable utility of the ISTH scoring system for diagnosing overt DIC, concerns have been expressed about its validity for identifying nonovert DIC. In response to these concerns, the Japanese Association for Acute Medicine (JAAM) developed a diagnostic algorithm and scoring system designed for use in critically ill patients (see Table 4 below).

**Table 4.** Japanese Association for Acute Medicine (JAAM) Scoring System for DIC

Clinical conditions that should be ruled out
Thrombocytopenia
Dilution and abnormal distribution
Massive blood loss, massive infusion
ITP, TTP-HUS, HIT, HELLP syndrome
Disorders of hematopoiesis
Liver disease
Hypothermia

Spurious laboratory results	
Diagnostic algorithm for SIRS	
Temperature >38°C or < 36°C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO <sub>2</sub> < 32 mm Hg (< 4.3 kPa) WBC count >12,000 cells/μL, < 4000 cells/ μL, or 10% immature (band) forms	
Diagnostic algorithm	Score
<i>SIRS criteria</i>	
>3	1
0-2	0
<i>Platelet count (× 10/L)</i>	
< 80 or >50 % decrease within 24 hours	3
>80 and < 120 or >30% decrease within 24 hours	1
>120	0
<i>Prothrombin time (value of patient/normal value)</i>	
>1.2	1
< 1.2	0
<i>Fibrin/FDPs (mg/L)</i>	
>25	3
>10 and < 25	1
< 10	0
Diagnosis	
4 points or more	DIC
DIC = disseminated intravascular coagulation; FDP = fibrin degradation product; HELLP = hemolysis, elevated liver enzymes, low platelet count; HIT = heparin-induced thrombocytopenia; HUS = hemolytic uremic syndrome; ITP = idiopathic thrombocytopenic purpura; PaCO <sub>2</sub> = partial pressure of carbon dioxide in arterial blood; SIRS = systemic inflammatory response syndrome; TTP = thrombotic thrombocytopenic purpura; WBC = white blood cell.	

This system has been prospectively validated and has been found to be capable of diagnosing DIC earlier than previous methods could. Furthermore, evidence suggests that early identification of DIC using this scoring system, as well as early and aggressive treatment of DIC and the underlying disorder, can lead to improvements in patient outcome and reductions in mortality.

In a study of the JAAM DIC criteria in 79 patients with severe sepsis or septic shock, Umemura et al reported that the addition of two hemostatic endothelial molecular markers—protein C activity and plasminogen activator inhibitor 1—measured within 12 hours of admission, provided greater prognostic value, predicting mortality with a sensitivity of 84.6% and a specificity of 80.3%. Protein C activity correlated best with mortality, followed by plasminogen activator inhibitor 1. Using those criteria, DIC-positive patients also had significantly higher disease severity.

The Japanese Society on Thrombosis and Hemostasis (JSTH) has developed diagnostic criteria for DIC based on the underlying pathology (basic, hematopoietic, or infectious).

The JSTH criteria are shown in Table 5, below.

Table 5. Japanese Society on Thrombosis and Hemostasis (JSTH) Diagnostic Criteria for DIC Test Results

	Points	
Platelet count (×10/μl)*	80-120	1
	51-80	2
	≤50	3
Fibrin degradation products (FDP; μg/ml)**	10-19	1
	20-39	2
	≥40	3
Fibrinogen (mg/dl)	101-150	1
	≤100	2
Prothrombin time ratio	1.25-1.66	1
	≥1.67	2
Antithrombin (%)	≤70	1
TAT, SF, or F <sub>1+2</sub>	≥2-fold upper limit of normal	1
Liver failure	Acute: Prothrombin time activity 40% or International Normalized Ratio ≥1.5)	

Chronic: Cirrhosis with Child-Pugh B or C (≥ 7 points)-3

F<sub>1+2</sub>= prothrombin fragment 1 + 2; SF=soluble fibrin; TAT=thrombin-antithrombin complex

\*For a platelet count of >50 × 10/μL, add 1 point if the

count decreases  $\geq 30\%$  within 24 h. The maximum score for the platelet count is 3 points.

\*\*For institutions that do not measure FDP, a D-dimer increase of  $\geq 2$ -fold the upper limit of normal scores 1 point.

With the JSTH system, diagnostic scoring for DIC is as follows:

- Basic:  $\geq 6$  points
- Hematopoietic (note that the platelet count is not included in the score calculation):  $\geq 4$  points
- Infectious: (note that the fibrinogen level is not included in the score calculation)  $\geq 5$  points

### Histologic Findings

Grossly, hemorrhage into all tissues (eg, brain, adrenal, lung, kidney) can develop in acute hemorrhagic DIC.

Histologic studies in patients with DIC show the presence of ischemia and necrosis due to fibrin deposition in small and medium-sized vessels of various organs. The presence of these intravascular thrombi appears to be clearly and specifically related to the clinical dysfunction of the organ. Specific thrombotic complications that are sometimes seen in the framework of DIC are acral cyanosis, hemorrhagic skin infarctions, and limb ischemia.

## TREATMENT AND MANAGEMENT

### Approach Considerations

Treatment of disseminated intravascular coagulation (DIC) is controversial, but treatment guidelines have been published and offer broadly similar recommendations. Treatment should primarily focus on addressing the underlying disorder. DIC can result from numerous clinical conditions, including sepsis, trauma, obstetric emergencies, and malignancy. Surgical management is limited to primary treatment of certain underlying disorders.

Management of the DIC itself has the following basic features:

- Monitor vital signs
- Assess and document the extent of hemorrhage and thrombosis
- Correct hypovolemia

Administer basic hemostatic procedures when indicated

Platelet and factor replacement should be directed not at

simply correcting laboratory abnormalities but at addressing clinically relevant bleeding or meeting procedural needs. Heparin should be provided to those patients who demonstrate extensive fibrin deposition without evidence of substantial hemorrhage; it is usually reserved for cases of chronic DIC. Heparin is appropriate to treat the thrombosis that occurs with DIC. It also has a limited use in acute hemorrhagic DIC in a patient with a self-limited condition of acral cyanosis and digital ischemia.

In general, antifibrinolytic agents (eg, tranexamic acid,  $\epsilon$ -aminocaproic acid) should be avoided in DIC because they are known to produce thrombotic complications, such as myocardial infarction and renal artery thrombosis when there is systemic clotting. However, in patients with trauma and massive blood loss, tranexamic acid has been shown to be effective in reducing blood loss and improving survival. Similarly, in massive postpartum hemorrhage, high-dose tranexamic acid has been shown to be effective. Antifibrinolytics also may be useful in cases of DIC secondary to hyperfibrinolysis associated with acute promyelocyticleukemia and other forms of cancer when alpha-2-antiplasmin is uniquely decreased. These agents should always be administered with heparin to arrest their prothrombotic effects.

Administration of activated protein C (drotrecogin alfa) showed benefit in subgroups of patients with sepsis who have DIC, with consideration given to the anticoagulant effects of this agent. However, drotrecogin alfa was withdrawn from the worldwide market on October 25, 2011, after the PROWESS-SHOCK trial failed to show a survival benefit for patients with severe sepsis and septic shock.

Patients with DIC should be treated at hospitals with appropriate critical care and subspecialty expertise, such as hematology, blood bank, or surgery. Patients who present to hospitals without those capabilities and who are stable enough for transfer should be referred expeditiously to a hospital that has those resources.

### Management of Underlying Disease

The management of acute and chronic forms of disseminated intravascular coagulation (DIC) should primarily be directed at treatment of the underlying disorder. Often, the DIC component will resolve on its own once the underlying disorder is addressed.

For example, if infection is the underlying etiology, the

appropriate administration of antibiotics and source control is the first line of therapy. As another example, in case of an obstetric catastrophe, the primary approach is to deliver appropriate obstetric care, in which case the DIC will rapidly subside. If the underlying condition causing DIC is not known, a diagnostic workup should be initiated. Most patients with acute DIC require critical care treatment appropriate for the primary diagnosis, occasionally including emergency surgery.

A DIC scoring system has been proposed by Bick to assess the severity of the coagulopathy as well as the effectiveness of therapeutic modalities. Clinical and laboratory parameters are measured with regularity (every 8

### Administration of Blood Components and Coagulation Factors

Typically, DIC results in significant reductions in platelet count and increases in coagulation times (prothrombin time [PT] and activated partial thromboplastin time [aPTT]). However, platelet and coagulation factor replacement should not be instituted on the basis of laboratory results alone; such therapy is indicated only in patients with active bleeding and in those requiring an invasive procedure or who are otherwise at risk for bleeding complications.

#### Platelets

Platelet transfusion may be considered in patients with DIC and severe thrombocytopenia, in particular, in patients with bleeding or in patients at risk for bleeding (eg, in the early postoperative phase or if an invasive procedure is planned).

The threshold for transfusing platelets varies. Most clinicians provide platelet replacement in nonbleeding patients if platelet counts drop below  $20 \times 10^9/L$ , though the exact levels at which platelets should be transfused is a clinical decision based on each patient's clinical condition. In some instances, platelet transfusion is necessary at higher platelet counts, particularly if indicated by clinical and laboratory findings. In actively bleeding patients, platelet levels from  $20 \times 10^9/L$  to  $50 \times 10^9/L$  are grounds for platelet transfusion (1 or 2 U/kg/day).

#### Coagulation factors

Previously, concerns have been expressed regarding the possibility that coagulation factor replacement therapy

might “add fuel to the fire” of consumption; however, this has never been established in research studies.

It is generally considered that cryoprecipitate and coagulation factor concentrates should not routinely be used as replacement therapy in DIC, because they lack several specific factors (eg, factor V). Additionally, worsening of the coagulopathy via the presence of small amounts of activated factors is a theoretical risk. Specific deficiencies in coagulation factors, such as fibrinogen, can be corrected by administration of cryoprecipitate or purified fibrinogen concentrate in conjunction with fresh frozen plasma (FFP) administration.

Data suggest that the consumption-induced deficiency of coagulation factors can be partially rectified by administering large quantities of FFP, particularly in patients with an international normalized ratio (INR) higher than 2.0, a 2-fold or greater prolongation of the aPTT, or a fibrinogen level below 100 mg/dL. The suggested starting dose is 15 mg/kg.

Repeated measurement of global clotting tests (eg, aPTT and PT) might be useful for monitoring the coagulation defect. In case of a (relative) vitamin K deficiency in the face of consumption, administration of vitamin K may be required.

#### Anticoagulation

Experimental studies have suggested that heparin can at least partly inhibit the activation of coagulation in cases of sepsis and other causes of DIC. However, a beneficial effect of heparin on clinically important outcome events in patients with DIC has not yet been demonstrated in controlled clinical trials. Moreover, antithrombin, the primary target of heparin activity, is markedly decreased in DIC, which means that the effectiveness of heparin therapy will be limited without concomitant replacement of antithrombin.

Furthermore, there are well-founded concerns with respect to anticoagulating DIC patients who are already at high risk for hemorrhagic complications. It is generally agreed that therapeutic doses of heparin are indicated in cases of obvious thromboembolic disease or where fibrin deposition predominates (eg, purpura fulminans or acral ischemia). The use of heparin in chronic DIC where there is preponderance of coagulation without consumption

coagulopathy is well established. In other patients with acryl cyanosis and digital ischemia and DIC, heparin can be safely administered at lower doses. A dose of 4-5 U/kg constant infusion without a 80-U/kg bolus is a safe means to deliver heparin to the DIC without increasing the bleeding risk.

The use of low-molecular-weight heparin (LMWH) has been studied in DIC. Enoxaparin has been used for treatment and prophylaxis of chronic DIC in specific clinical situations. In a multicenter, cooperative, double-blinded trial from Japan that compared dalteparin with unfractionated heparin, the former was associated with a decreased bleeding tendency and reduced organ failure. One randomized clinical trial showed LMWH to be superior for reducing 28-day mortality in patients with severe sepsis.

Patients with DIC may benefit from prophylaxis to prevent venous thromboembolism, which will not be achieved with standard low-dose subcutaneous heparin. Theoretically, the most logical anticoagulant agent to use in DIC is directed against tissue factor activity.

### **Restoration of Anticoagulant Pathways**

Strategies for restoring anticoagulant pathways have primarily involved administration of antithrombin concentrate or recombinant human APC (drotrecogin alfa); however, drotrecogin alfa was withdrawn from the worldwide market on October 25, 2011. Tissue factor (TF) pathway inhibitor (TFPI) and recombinant thrombomodulin (rTM) have also been studied.

### **Antithrombin**

The antithrombin pathway, an important inhibitor of coagulation in normal patients, is largely depleted and incapacitated in acute DIC. As a result, several studies have evaluated the utility of antithrombin replacement in DIC. Most have demonstrated benefit in terms of improving laboratory values and even organ function. To date, however, large-scale randomized trials have failed to demonstrate any mortality benefit in patients treated with antithrombin concentrate.

Most of the randomized controlled trials involved patients with sepsis or septic shock. In the later clinical trials, very high doses of antithrombin concentrate were used to attain

supraphysiologic plasma levels. A series of relatively small trials showed a modest reduction in mortality in antithrombin - treated patients. However, in none of the trials did the effect reach statistical significance.

A large-scale multicenter, randomized controlled trial to directly address this issue showed no significant reduction in mortality of septic patients who were treated with antithrombin concentrate. In this trial, 2114 patients with severe sepsis and associated organ failure were included. Surprisingly, subgroup analyses indicated some benefit in patients who did not receive concomitant heparin, but this observation needs prospective validation.

In another study that evaluated the effects of antithrombin in 23 patients with DIC diagnosed on the basis of the Japanese Association for Acute Medicine (JAAM) criteria (a newly developed diagnostic algorithm for critical illness), patients were treated with either high-dose (60 IU/kg/day; 12 patients) or low-dose (30 IU/kg/day; 11 patients) antithrombin concentrates for 3 days.

On day 0, the patients' backgrounds and antithrombin activity were identical in the 2 groups. However, on day 7, the JAAM DIC score and PT ratio were significantly improved in comparison with those on day 0. However, mortality at 28 days and interaction within the administered antithrombin doses showed no differences.

There were also no differences in the time course of the platelet counts, coagulation and fibrinolytic markers, and DIC scores in the 2 groups. The authors concluded that the effects of antithrombin on prognosis and coagulation and fibrinolytic parameters are independent of the doses administered in patients who have DIC associated with the systemic inflammatory response syndrome (SIRS) or sepsis.

A retrospective Japanese study in 1784 patients with severe sepsis and DIC, 715 of whom received treatment with antithrombin, found a statistically significant association between antithrombin supplementation and lower in-hospital all-cause mortality (odds ratio 0.748,  $P = 0.034$ ). However, that association was not evident on quintile-stratified propensity score analysis or propensity score matching analysis.

In this study, similar results were observed in DIC patients with or without concomitant heparin administration. In addition, although the number of transfusions needed was higher in the group that received antithrombin, the number of severe bleeding complications was not.

A recombinant form of antithrombin, antithrombinyl-gamma, is being developed as an alternative to antithrombin derived from human plasma. In a randomized, open-label trial in 222 patients with sepsis-induced DIC, the safety and efficacy of antithrombin gamma were comparable to that of plasma-derived antithrombin.

### ***Tissue factor pathway inhibitor***

The TFPI mechanism of coagulation inhibition has received attention as a potential therapy in sepsis-associated DIC. Indeed, initial results from animal studies have been very promising in demonstrating the ability of TFPI to arrest DIC and to prevent the mortality and end-organ damage witnessed in untreated animals. However, a large phase III trial of TFPI in humans with DIC did not show any mortality benefit.

### ***Recombinant thrombomodulin***

In Japan, rTM is widely used for treatment of DIC. Thrombomodulin binds with thrombin, and the resulting complex allows the conversion of protein C to APC. Additionally, thrombomodulin can also bind high-mobility group B (HBGM-1), which inhibits the inflammatory process.

rTM has shown beneficial effects on DIC parameters and clinical outcome in initial trials. It was evaluated in a randomized controlled study involving 234 subjects and was found to yield significantly improved control of DIC in comparison with unfractionated heparin, particularly with respect to the control of persistent bleeding diathesis.

However, a meta-analysis by Zhang et al found that in patients with infection complicated by DIC, treatment with rTM does not decrease short-term mortality: the risk ratio for 28- or 30-day mortality was 0.81 in randomized controlled trials and 0.96 in observational studies. In a systematic review and meta-analysis by Yamakawa et al of rTM for sepsis-induced DIC, pooled relative risk of 28-30 day

mortality was 0.81 (95% CI, 0.62–1.06) in randomized controlled trials, indicating a non-significant reduction in mortality, and 0.59 (95% CI, 0.45–0.77) in observational studies; results suggested that the probability of rTM therapy having a beneficial effect increases with increasing baseline risk.

Inoue et al reported benefit with rTM treatment of DIC caused by noninfectious complications of allogeneic hematopoietic stem cell transplantation, such as acute graft-versus-host disease or thrombotic microangiopathy. In 12 episodes of DIC in 10 patients, the recovery rate was significantly higher than in historical controls.

### **Long-Term Monitoring**

Outpatient medications may include antiplatelet agents for those with low-grade DIC, antibiotics appropriate to the primary diagnosis, or both. Patients who recover from acute DIC should follow up with their primary care provider or a hematologist. Patients with low-grade or chronic DIC may be treated by a hematologist on an outpatient basis after initial assessment and stabilization. Chronic DIC in patients with cancer can be managed with subcutaneous heparin or low molecular weight heparin.

### **Medication Summary**

The goals of pharmacotherapy in cases of disseminated intravascular coagulation (DIC) are to reduce morbidity and to prevent complications. Therapy should be based on etiology and aimed at eliminating the underlying disease. Treatment should be appropriately aggressive for the patient's age, disease, and severity and location of hemorrhage or thrombosis. Treatment of acute DIC includes anticoagulants, blood components, and antifibrinolytics. Hemostatic and coagulation parameters should be monitored continuously during treatment.

Base therapeutic decisions on clinical and laboratory evaluation of hemostasis. In cases of low-grade DIC, therapy other than supportive care may not be warranted or may include antiplatelet agents or subcutaneous heparin; treatment decisions should be based on clinical and laboratory evaluation of hemostasis.

## INTERPRETATION

### Prothrombin Time

#### Specimen Collection

Standard laboratory coagulation-based testing has traditionally been used to obtain measurements of PT to ensure reliable results. However, due to the high turnaround time of up to 90 minutes, point-of-care (POC) devices, with a turn-around time of approximately 5 minutes, are becoming more desirable. POC devices are of great value in the emergency and operating room settings where clinical diagnosis and intervention are time-sensitive. With increased prescribing of vitamin K-antagonists (VKAs) like warfarin, point-of-care devices have also been more convenient for patients and general practitioners to monitor medication effectiveness. With point-of-care devices, monitoring anticoagulation therapy can take place at thrombosis centers, primary care provider offices, and even by the patients themselves. Although point-of-care devices have been shown to underestimate hemostatic abnormality, point-of-care devices are generally reliable in non-emergency settings. Coagulation tests must be performed using plasma samples and not serum as clotting factors get removed in serum preparations. Standard percutaneous phlebotomy is the recommended method used to collect venous blood samples. However, blood samples may also be obtained from indwelling intravenous lines when necessary.

#### Procedures

Phlebotomists collect venous blood samples in plastic tubes with a light blue top that contains 3.2% sodium citrate. Sodium citrate serves to chelate the calcium in the blood sample and prevents the activation of the coagulation cascade. This chelation keeps the blood sample in stasis until ready to be tested. Tube filling must be to within 90 percent of the full collection volume with blood to sodium citrate ratio of 9 to 1. The tube is then gently inverted a few times to mix the sodium citrate solution with the blood. The tube should not be shaken to avoid hemolysis that would lead to inaccurate results. Once the blood sample is ready to be tested, calcium chloride is then added to restore the calcium required for coagulation activation. Clot formation can then be detected mechanically or optically depending on the instrumentation used.

#### Indications

Indications for obtaining PT are:

- Monitoring vitamin K-antagonists (VKA) such as warfarin is the most common indication for PT
- Evaluation of unexplained bleeding
- Diagnosing disseminated intravascular coagulation (DIC)
- Obtaining baseline value before initiating anticoagulation therapy
- Assessment of liver synthesis function and to calculate the model for end-stage liver diseases (MELD) score in liver disease

#### Potential Diagnosis

Causes for a prolonged PT include:

- Liver disease
  - Liver disease or liver dysfunction leads to a decreased production of most coagulation factors. A decreased production of coagulation factors leads to prolonged PT and physical manifestations that can include petechiae and easy bruising.
- Vitamin K deficiency
  - Vitamin K is a necessary component in factors II, VII, IX, and X. A deficiency in vitamin K will lead to a decrease in these factors and prolong PT. Potential causes that can lead to decreased vitamin K levels include malnutrition, prolonged antibiotic use, and impairments with fat absorption.
- Factor deficiency
  - Inherited diseases that lead to a decreased production of factors II, VII, IX, and X will lead to a prolonged PT.
- Disseminated Intravascular Coagulation (DIC)
  - DIC causes a system-wide activation of coagulation, depleting available coagulation factors leading to an increase in PT.
- VKA therapy
  - VKA therapy inhibits factors II, VII, IX, and X and causes a prolonged PT.

- Antiphospholipid antibodies
  - Antiphospholipid antibody syndrome (APS) characteristically presents with recurrent thromboembolic events and/or pregnancy loss along with detected antiphospholipid antibodies (APA). APA causes an increased conversion of prothrombin to thrombin in vivo, leading to an overall decrease in prothrombin. Low prothrombin levels can lead to an increased PT result.:
- Storage and temperature
  - Blood samples for PT testing are only acceptable if stored for less than 24 hours at either room temperature or 4 degrees Celsius
  - Prolonged cold storage at 4 degrees Celsius or lower can activate Factor VII, which can lead to shortened PT results
- High lipid levels
  - Patients with hypercholesterolemia or hypertriglyceridemia have a shorter PT measurement due to more elevated fibrinogen and factor VII levels

### Normal and Critical Findings

The reference ranges for PT vary by laboratory since different facilities use reagents or instruments. However, in most laboratories, the normal range for PT is 10 to 13 seconds. The normal INR for a healthy individual is 1.1 or below, and the therapeutic range for most patients on VKAs is an INR of 2.0 to 3.0. An increased PT/INR for patients on VKAs may suggest a super-therapeutic level and will require medication dose adjustments to prevent bleeding.

### Interfering Factors

- Polycythemia with a hematocrit greater than 55%
  - Elevated hematocrit greater than 55% leads to a decrease in plasma of the blood sample, thereby reducing the coagulating factors available. The sodium citrate levels must be readjusted to prevent artificially prolonged PT measurements, to account for this decreased plasma
- Underfilled tubes
  - Similar to polycythemia, underfilled tubes also will lead to an artificially prolonged PT measurement.
  - Samples obtained from indwelling catheters may suffer contamination as these lines often require a flush with heparin or other solutions that would artificially prolong coagulation times[8]
- Anticoagulants
  - All direct acting anticoagulants prolong PT
    - Argatroban
    - Dabigatran
    - Rivaroxaban
    - Apixaban
    - Edoxaban

### Complications

- Standard percutaneous phlebotomy to obtain blood samples can cause localized pain, bleeding, and bruising.
  - A decreased PT/INR suggests:
  - Increased intake of supplements that contain vitamin K
  - High intake of vitamin K-rich foods
  - Fasting may reduce factors II, VII, and X, subsequently decreasing PT

### Patient Safety and Education

As the use of VKAs increases, it is vital to educate patients on the importance of routine monitoring of PT/INR. Proper monitoring will allow for medication adjustments and prevention of adverse events. If patients are self-monitoring with POC devices, sufficient education and training is necessary for the patient and/or family members who will assist the patient. The cognitive capacity of patients must also be evaluated to ensure the proper use of POC devices.

### Clinical Significance

PT, along with INR, are important measurements to monitor patient coagulation status, especially patients who are on VKAs. However, although PT/INR is useful in monitoring coagulation status, they are rarely used alone. PT/INR use is typically in conjunction with activated partial thromboplastin time (aPTT), which evaluates the intrinsic and common pathways of coagulation. PT/INR and aPTT results together can help in diagnosing various hematologic disorders.

## TROUBLESHOOTING

### What to know about the warfarin diet

People taking the blood thinning medication warfarin may need to moderate vitamin K levels in their diets. Vitamin K may interfere with the effectiveness of warfarin.

A doctor may prescribe warfarin to someone who has had a blood clot in the past, as they are at a higher risk of blood clots in the future. Other factors that increase the chances of a blood clot include:

- obesity
- pregnancy
- long periods of inactivity
- smoking
- irregular heartbeat
- trauma
- older age
- chronic inflammatory diseases
- diabetes
- high blood pressure
- high cholesterol

Warfarin works by slowing the production of clotting factors, which the body makes by using vitamin K from food. Levels of vitamin K in a person's diet could influence the effects of warfarin.

It is possible that vitamin-K rich diets can reduce the effectiveness of warfarin.

### The warfarin diet



Asparagus is high in vitamin K.

Vitamin K, which is in some foods, has an important role in blood clotting, and how warfarin works.

The liver uses vitamin K to produce clotting factors, which are cells that help to control bleeding and enable blood clots to form.

Warfarin disrupts this clotting process by inhibiting an enzyme in the liver that uses vitamin K to form clotting factors.

Warfarin can reduce the chances of a dangerous blood clot forming by increasing the time it takes for the liver to produce clotting factors.

It is possible that eating a diet rich in vitamin K could reduce the effect of warfarin on clotting factors.

The American Heart Association (AHA) suggest that eating vitamin K-rich foods may counteract the effects of warfarin, and lower the prothrombin time. This is the time it takes for a blood clot to form.

The AHA's list of 19 foods high in vitamin K includes:

- amaranth leaves
- asparagus
- broccoli
- Brussels sprouts

- coleslaw
- collard greens
- canned beef stroganoff soup
- endive
- garden cress
- kale
- kiwifruit
- lettuce
- mustard greens
- soybeans
- spinach
- Swiss chard
- tuna fish in oil
- turnips
- vegetable drinks

It is not necessary to cut out foods that contain vitamin K entirely. The foods that contain vitamin K also have other nutritional properties that contribute to a healthful diet.

It is important to note that the guidance varies on how much vitamin K people on warfarin can consume.

For example, a recent systematic review<sup>Trusted Source</sup> suggests a diet that restricts vitamin K intake is unlikely to improve the efficacy of warfarin. The authors suggest that keeping vitamin K levels consistent may be more beneficial.

The average person only needs a small amount of vitamin K, around 60 to 80 micrograms (mcg) per day. As this amount is so small, it can be easy for vitamin K levels to fluctuate across different days, creating a problem for people on warfarin.

Keeping vitamin K levels stable, and within a normal

range, may reduce its effect on the actions of warfarin. Keeping a food diary and being aware of foods that are high in vitamin K can help a person keep track.

### Alcohol and warfarin



Share on Pinterest Drinking alcohol can be harmful for people taking warfarin.

Alcohol can also affect the action of warfarin and, therefore, the risk of developing blood clots.

High levels of alcohol consumption can alter the way the body metabolizes warfarin.

The AHA suggest that, on average, men should drink no more than one or two drinks per day, and women should drink no more than one drink per day.

Examples of one drink are a 12-oz beer, a 4-oz glass of wine, 1/5 oz of 80-proof spirits, or 1 oz of 100-proof spirits.

Drinking too much alcohol can be particularly harmful for people taking warfarin. A study of 570 people<sup>Trusted Source</sup> in 2015 found that alcohol misuse has links to a higher risk of major bleeding in people taking warfarin.

## BOUQUET

### IN LIGHTER VEIN

Husband and wife were having dinner at a fancy restaurant...

As the food was served, Husband said:  
"The Food looks delicious, let's eat."

Wife: Honey.. You say prayer before eating at home.

Husband: That's at home sweetheart... Here the chef knows how to cook.



**1 Kid asked me  
What is Stress??**

**I Locked him in a Room  
with High Speed Internet  
and 1% Battery.**



Teacher : Sani, if you had 5 dollars and you asked your mother for another 5, how many dollars would you have?

Sani : 5 dollars Sir!

Teacher : You don't know your Arithmetic.

Sani : But Sir, you don't know my mother!



## WISDOM WHISPERS

YOU HAVE TO GROW  
FROM THE INSIDE OUT.  
NONE CAN TEACH YOU,  
NONE CAN MAKE YOU  
SPIRITUAL. THERE IS NO  
OTHER TEACHER, BUT  
YOUR OWN SOUL.

True  
confidence  
has no room  
for jealousy  
and envy.  
When you  
know you are  
great, you  
have no  
reason to  
hate.

SUCCESS IS NO ACCIDENT.  
IT IS HARD WORK,  
PERSEVERANCE, LEARNING,  
STUDYING, SACRIFICE  
AND MOST OF ALL, LOVE  
OF WHAT YOU ARE DOING  
OR LEARNING TO DO.

You learn more  
from failure than  
from success.  
Don't let it stop  
you. Failure builds  
character.

## BRAIN TEASERS

1. What are the causes for prolonged APTT?

- A. Hemophilia
- B. Vitamin K deficiency
- C. Liver disease
- D. Presence of circulating anticoagulants
- E. DIC disease (chronic or acute)
- F. All of the above.

2. What is the full form of APTT?

- A. Activated partial thromboplastin time
- B. Activated proper thrombin test
- C. Assorted partial thromboplastin test
- D. Amplified partial thromboplastin time.

3. What is the full form of INR?

- A. International normalized ratio (INR)
- B. Internal normal ratio
- C. Intrinsic normalized ratio
- D. Indian normalized ratio.

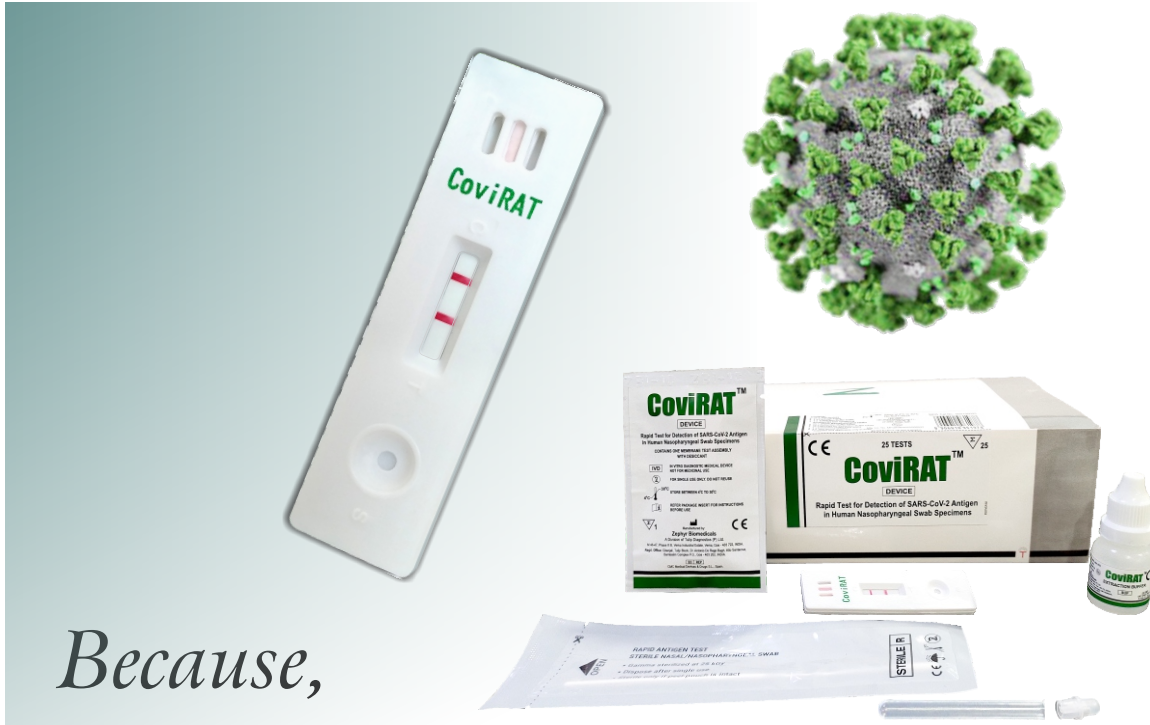
4. What is the normal reference range for clotting time?

- A. 5–10 minutes
- B. 8–15 minutes
- C. 5–8 minutes
- D. 5–12 minutes.



# CoviRAT

## RAPID ANTIGEN TEST for COVID-19



*Because,*

# Only **Sensitivity** Matters!

**In comparison with RT-PCR confirmed specimen**

	<b>Sensitivity</b>	<b>Specificity</b>
<b>Evaluation in USA</b>	96.3%	100 %
<b>Evaluation in India</b> (RT-PCR positive specimens with Ct<30)	95.4%	96.36%

## Highest Correlation with RT-PCR Test!

**Better Testing System For Better Diagnostics**

Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA.  
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