
Acute systemic disseminated intravascular coagulation

Managing a complex medical condition

In patients with major trauma, DIC approximately doubles the mortality rate. In those with sepsis, 30% to 50% develop DIC. The chance that you will encounter this coagulation disorder during clinical practice is quite high.

Danielle Kruger, PA-C

Acute systemic disseminated intravascular coagulation (DIC) is a complex, acquired, life-threatening coagulation disorder. Its pathophysiology involves uncontrolled intravascular activation of coagulation with secondary fibrinolysis and inevitable consumption of procoagulants and platelets (see Figure 1).¹ In the United States in 1994, there were approximately 18,000 cases of DIC.¹ DIC is not a primary disease; it always occurs secondary to an underlying disorder and may have a broad spectrum of clinical manifestations and multiple etiologies. Because the disease comprises both bleeding and thrombotic events, diagnosis and therapy can be extremely challenging. Successful man-

agement of patients with DIC depends almost entirely on prompt, effective control of the underlying disease.²

Etiology

The causes of DIC may be acute or chronic, systemic or localized, and this syndrome may be the result of a single or multiple conditions¹ (see Table 1, page 31). Infection is the most common cause of DIC. About 10% to 20% of patients with gram-negative sepsis have evidence of DIC, but gram-positive organisms may also be responsible. The endothelium may be disrupted so that tissue factor is released from tissue damaged by trauma, ischemia, infection, surgery, and any other cause of excessive metabolic stress. Hemolysis and the release of tissue material (fat, phospholipids) into the circulation contribute to systemic activation of coagulation in trauma patients.³ With infection, the generalized inflammatory response followed by systemic cytokine production is due to pathogenic exotoxins and components of the microorganism's cell membrane.³ WBCs may also release tissue factor into the circulation in response to endotoxins, immune complexes, or cancer cells. The pathogenesis behind malignancy implicates tissue factor expressed on the surface of tumor cells.^{2,3} Vascular disorders can result in local activation of coagulation factors that can overflow to the systemic circulation and cause DIC.³ Snake venoms and other poisons are capable of activating many components of the hemostatic system.

CME

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Learning objectives

- Review the etiology and pathophysiology of disseminated intravascular coagulation (DIC)
- Discuss the clinical findings of DIC in patients who are predominantly bleeding or predominantly clotting
- Describe the diagnostic workup of DIC and tests to differentiate DIC from other suspected conditions
- Outline the management of DIC, focusing on therapy for the underlying cause

The author is a full-time medicine instructor at Saint Vincent's Catholic Medical Centers PA Training Program, Fresh Meadows, NY. She has indicated no relationships to disclose relating to the content of this article.

Signs and symptoms

DIC can manifest as an acute hemorrhagic disorder associated with excess plasmin formation or, alternatively, as a subacute or chronic disorder that manifests as thrombosis resulting from excess thrombin formation. When taking the history, ascertain symptoms related to the underlying disease process. Also obtain a history of blood loss and hypovolemia, such as from GI bleeding. Look for thromboses in large vessels, as well as microvascular thrombi that cause end-organ damage to the lungs, heart, kidneys, liver, and CNS.¹

Symptoms depend on the compensation capacity of the liver and bone marrow. The patient can be asymptomatic with only laboratory abnormalities or may present with low-grade bleeding or single or multiple thrombotic events, including large-vessel thrombi. Utilize a systematic approach for physical examination in the patient with DIC;^{1,4} evidence will reflect bleeding and/or hypercoagulability state.

- The dermatologic indicators of DIC include petechiae; purpura; epistaxis; gingival, mucosal, or wound bleeding; and hemorrhagic bullae, as well as acral cyanosis, purpura fulminans, localized infarction, and gangrene.
- Bleeding may range from mild and subacute to spontaneous, life-threatening hemorrhage with hypotension, tachycardia, shock, and/or signs of diffuse or localized thrombosis.

- CNS signs include altered mental status, stupor, confusion, and disorientation, although DIC rarely causes focal deficits.
- The respiratory system may demonstrate pleural friction rub, cough, and dyspnea, as well as signs of adult respiratory distress syndrome.
- GI manifestations include hematemesis, hematochezia, melena, and guaiac-positive stools.
- GU abnormalities such as azotemia, oliguria, renal failure, hematuria, metrorrhagia, and uterine hemorrhage may also occur.

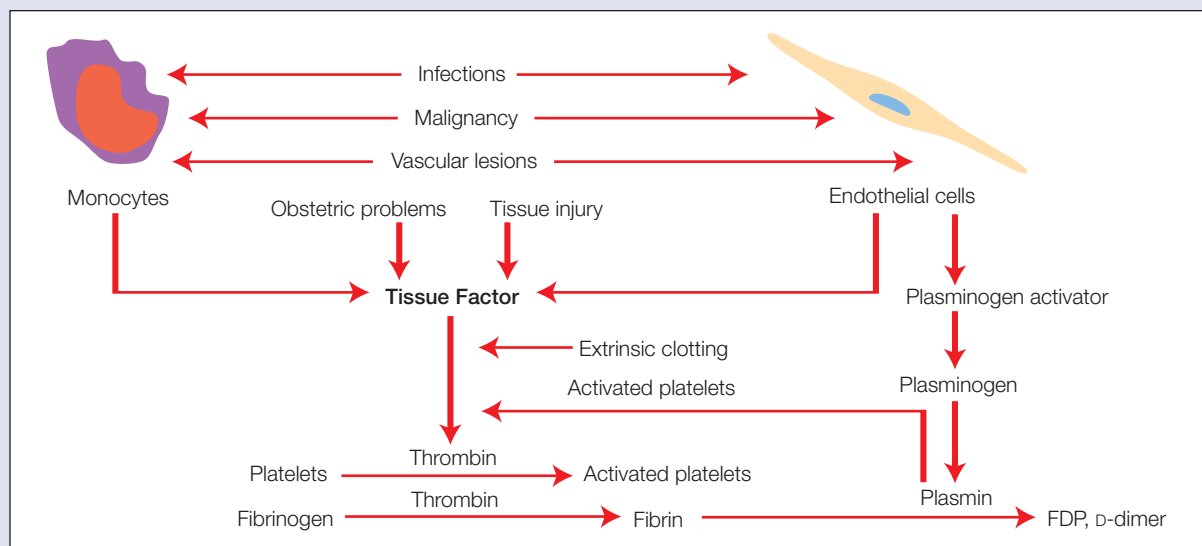
Diagnosis

Acute DIC is diagnosed clinically and confirmed with laboratory evidence. No single laboratory test by itself can be considered diagnostic. At the same time, however, diagnosis of DIC does not require an abnormal result on every laboratory test that is known to produce abnormal results in DIC, especially when the clinical picture is consistent with DIC. Some hospitals may have a specific DIC panel; in those that do not, a diagnosis can often be made from a platelet count, measurement of clotting times, measurement of one or two clotting factor inhibitors (such as antithrombin), and a test for fibrin degradation products (FDPs)⁵ (see Table 2, page 31).

Specific laboratory tests Reduction in the platelet count over several measurements is a sensitive sign of

FIGURE 1

Process of disseminated intravascular coagulation



Coagulation activation by various etiologic factors with subsequent clot breakdown forming FDP & D-dimer

Key: FDP: fibrin degradation products.

Adapted with permission from Messmore HL Jr, Wehrmacher WH. Disseminated intravascular coagulation: a primer for primary care physicians. *Postgrad Med Online*. 2002;111(3). Available at: http://www.postgradmed.com/issues/2002/03_02/messmore.htm. Accessed March 21, 2006.

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Key Points

- DIC always occurs secondary to an underlying disorder, usually infection, and can have a broad spectrum of clinical manifestations and multiple etiologies.
- DIC can manifest as an acute hemorrhagic disorder associated with excess plasmin formation or, alternatively, as a subacute or chronic disorder that manifests as thrombosis resulting from excess thrombin formation.
- The diagnosis of acute DIC is essentially clinical and confirmed with laboratory evidence.
- The mainstay of DIC management is treatment of the underlying disease that predisposes to hypercoagulability.

Competencies

Medical knowledge	◆◆◆◆◆
Interpersonal & communication skills	◆◆
Patient care	◆◆
Professionalism	◆
Practice-based learning and improvement	◆
Systems-based practice	◆◆

For an explanation of competencies ratings, see the table of contents.

DIC.³ Prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) occur in more than 50% of patients because of consumptive deficiency of coagulation factors.¹ Concentrations of fibrinogen, a non-specific acute-phase reactant, are decreased in almost 50% of patients; despite ongoing consumption, however, plasma levels can remain in a normal range for a long time.¹ FDPs are byproducts of fibrinolysis; increased levels are not diagnostic of DIC yet are found in 85% of cases.² High levels may also occur after surgery and in cases of hematoma or of liver or renal failure. D-dimer is a specific marker for fibrin degradation, indicating the presence of thrombin in the circulation prior to fibrinolysis and thus distinguishing DIC from primary fibrinolysis.

Differential diagnoses On peripheral blood smear, there is red cell fragmentation or schistocytes in about 50% of patients with DIC; the mechanism is unknown. When schistocytes are seen in conjunction with thrombocytopenia and prolonged clotting times, other conditions should be considered:

- Idiopathic thrombocytopenic purpura (ITP): Look for recent upper respiratory or GI infection and platelet autoantibodies.
- Hemolytic uremic syndrome (HUS): There is a pre-

dominance of abdominal cramping, vomiting, and the triad of anemia, renal problems, and thrombocytopenia.

- Thrombotic thrombocytopenic purpura (TTP): This condition manifests as the pentad of fever, anemia, renal problems, thrombocytopenia, and neurologic deficits.

Liver disease can mimic DIC and must also be ruled out using levels of Factor V and Factor VIII. Both are low in DIC, while only Factor V is low in liver failure. Tests for FDPs or D-dimer levels are also helpful since these are absent in liver disease.⁴ However, these levels have low specificity as some degree of fibrinolysis occurs in postsurgical patients and in those with infection. Evaluation requires further laboratory tests. Other important tests in a patient with suspected DIC include liver and renal function tests and blood cultures.

Treatment

Treatment of the underlying disease that predisposed the patient to hypercoagulability is the mainstay of DIC management. Initially, the practitioner should monitor vital signs and utilize aggressive support measures, including fluid replacement, oxygen, antibiotics for infections, removal of necrotic tissue, evacuation of retained products of conception, and removal of malignant tumors. The condition will not resolve until the trigger mechanism is removed.

Management can involve replacement of blood products and clotting factors as appropriate for the severity and location of hemorrhage or thrombosis. The optimal regimen for treatment with blood components and the indications for anticoagulant and antifibrinolytic treatments are unknown. There is a lack of well-controlled studies regarding various methods of management; thus treatment continues to be controversial.

Three categories of treatment For purposes of therapy, DIC can be divided into three categories: acute DIC without bleeding or evidence of ischemia, which requires no treatment; acute DIC with bleeding, which requires replacement of deficient clotting components; and acute DIC with ischemia, which necessitates control of the coagulation disorder. There are no specific guidelines for management of the most complicated of cases—acute DIC with manifestations of both bleeding and ischemia. Direct the therapy toward stabilizing the patient’s chief manifestation, which may be thrombotic or hemorrhagic, while working to correct the underlying disease process.⁶

Replacement of deficient clotting components Patients with DIC may be given blood components to replace depleted coagulation factors, platelets, and natural inhibitors of plasmin and thrombin in an attempt to reduce bleeding (see Table 3, page 32). The presumed efficacy of treatment with clotting factors is not based on

randomized controlled trials but is nevertheless considered a rational therapy in bleeding patients.⁵ Although laboratory parameters are important for guiding management, plasma or platelet transfusions should not be given on this basis alone; they are indicated only in patients who have active bleeding and in those who require invasive procedures.^{3,7} If restoring platelets and coagulation factors is indicated, assessing their effects on laboratory parameters will determine whether further treatment is required.

Critical care patients also develop coagulopathy, which is due to vitamin K deficiency. Since it is depleted because of its increased use, vitamin K may be administered in 10-mg doses on two consecutive days. It is important to supplement folic acid because a deficiency can also develop in acutely ill patients, leading to impaired platelet production.²

Anticoagulant agents are used to treat clinically evident intravascular thrombosis when patients continue to clot 4 to 6 hours after the initiation of primary and supportive therapy.¹

Heparin prevents conversion of fibrinogen to fibrin and inhibits further thrombogenesis but does not actively break down clots.¹ No substantial evidence indicates that heparin therapy reduces morbidity and mortality in DIC.³ Concerns about thrombocytopenia and bleeding continue to limit its use. Heparin does seem to benefit some patients with DIC and should be used with caution at doses based on the severity of disease, its underlying cause, and the extent of thrombosis.

Heparin may be dosed at 80 to 100 units/kg every 4 to 6 hours or 20,000 to 30,000 units/day delivered by continuous infusion.¹ Indications for heparin use in DIC include clinically overt thromboembolism or extensive fibrin deposition; patients may also benefit from prophylaxis to prevent venous thromboembolism.⁵ Monitoring PTT results is mandatory.¹ Heparin is not effective if antithrombin III levels are markedly depleted, and it is often used in combination with replacement therapy because heparin alone can result in bleeding.

Antithrombin III is an alpha 2-globulin that inactivates thrombin, plasmin, and other proteases of coagulation, including factors IXa, Xa, XIa, XIIa, and VIIa.¹ Its importance in physiologic inhibition of coagulation and its anti-inflammatory properties are particularly useful in DIC secondary to sepsis. Most trials have been conducted in patients with sepsis or septic shock, which is the most common cause of acute DIC. In those trials, antithrombin III therapy improved laboratory values, shortened disease duration, and improved organ function.³ In 2001, a trial evaluating the statistical effects of antithrombin III showed no reduction in mortality in patients with sepsis.⁵ Its use for sepsis-related DIC is now controversial.

Activated protein C (APC) is a vitamin K-dependent glycoprotein with anticoagulant and anti-inflammatory properties that is used primarily in septic shock to reduce systemic inflammation by inhibition of thrombosis. In clinical trials of adults with sepsis, APC infusions within 24 hours of diagnosis were associated with significant reductions in the pro-inflammatory cytokines, D-dimer, and sepsis-related mortality.⁸ Protein C can also

TABLE 1
Causes of disseminated intravascular coagulation

Category	Specific diseases
Infection	Disease caused by bacteria, rickettsiae, viruses; hemorrhagic fevers; fungal or parasitic disease (malaria)
Malignancy	Metastatic tumors, hematologic malignancies
Obstetrics	Preeclampsia, placental abruption, amniotic fluid embolism, HELLP syndrome, acute fatty liver of pregnancy
Trauma	Head trauma, motor vehicle accidents, burns, surgery
Vascular disease	Large aortic aneurysms, hemangiomas, massive transfusions
Other	Snake bites, poisons, liver disease, acute hepatic failure

Key: HELLP, hemolysis, elevated liver enzymes, low platelets.
Data from Levi M.³

TABLE 2
Laboratory findings in disseminated intravascular coagulation

Laboratory tests	Result in DIC
Antithrombin III	Decreased
CBC, peripheral smear, and platelet count	Anemia, schistocytes, platelets markedly decreased
D-dimer	Increased
Fibrin degradation products	Markedly increased
Fibrinogen	Decreased
Protein C	Markedly decreased
Prothrombin time, activated partial thromboplastin time	Increased

Data from Furlong M and Furlong B.¹

TABLE 3

Replacement of deficient clotting components

Clotting component	Methods of replacement
Cryoprecipitate	Treatment of choice for fibrinogen levels <80 mg/dL; recommended goal is fibrinogen level of 150 mg/dL in a patient with DIC. Each unit contains 250 mg of fibrinogen and will raise level 6-8 mg/dL.
Fresh frozen plasma	Contains all of the clotting factors, including fibrinogen, as well as the natural anticoagulants protein C and antithrombin III. The recommended dose is 15-20 mL/kg.
Packed RBCs	Transfused to improve blood's oxygen-carrying capacity; each unit is expected to raise hematocrit by 3%. If a patient is transfused with >6 units packed RBCs, fresh frozen plasma and platelets should be administered.
Platelet transfusion	Indicated for a platelet count <20,000. The recommended dose is 1 unit/10 kg of body weight to increase circulating platelets and provide 50 mL of plasma/unit

Data from Kumar R.²

be supplemented via fresh frozen plasma transfusion and is used in the management of sepsis-related DIC.

Antifibrinolytic agents

Historically, this class of drugs has been used to treat serious bleeding, particularly in patients with hemophilia. Aminocaproic acid and tranexamic acid inhibit fibrinolysis via inhibition of plasminogen activator and through antiplasmin activity. These drugs should be administered before an operation to patients with a propensity for serious bleeding. In DIC, these agents are used only after the failure of all other therapies and when an increase in plasmin has been documented.² By mechanism of action, the drug should result in a decreased rate of fibrinolysis, controlling bleeding by increasing the fibrinogen level. Preexisting thrombi are not broken down. Efficiency in reducing bleeding is uncertain; this treatment may even set the stage for hypercoagulability. Heparin is often combined with these drugs.

Treatments under investigation

Gabexate mesylate is a synthetic inhibitor of serine proteases, including thrombin and plasmin. Gabexate has not yet been examined in controlled trials in the United States.

Recombinant tissue plasminogen activator (rtPA) induces clot-specific fibrinolysis to improve peripheral perfusion, which is especially useful in thrombus-implicated organ failure. Little direct hemodynamic effect and few bleeding complications occur. Because of concerns about hemorrhagic complications, however, use of rtPA is generally reserved for intractable cases.

Plasmapheresis removes circulating endotoxins, cytokines, and inflammatory cell mediators and can assist in control of fluid balance when excessive volumes of

blood products may be needed. Using fresh frozen plasma and cryoprecipitate as replacement fluid will increase fibrinogen concentrations and shorten PT and PTT.

Hirudin, an anticoagulant found in leech saliva, is the most potent inhibitor of thrombin and can promote local bleeding for hours. Its clinical benefits in DIC have not yet been evaluated.

Glucocorticoids may have a role in treating DIC via their anti-inflammatory effect or as immunosuppressive therapy if an antibody inhibitor of protein C is present.

Prognosis

Both the underlying condition and the severity of DIC influence prognosis. In some cases, DIC resolves completely within hours after the underlying condition is corrected, such as in placental abruption or amniotic fluid embolism. In other cases, however, such as sepsis, DIC may persist for days after the underlying condition has been addressed, and supportive measures may be necessary. □

REFERENCES

- Furlong M, Furlong B. Disseminated intravascular coagulation. eMedicine.com. 2005. Available at: <http://www.emedicine.com/emerg/topic150.htm>. Accessed March 3, 2006.
- Kumar R. Disseminated intravascular coagulation. *JACM (Journal Indian Academy of Clinical Medicine)*. 2001;2(1):73-77.
- Levi M. Coagulation: consultative hemostasis. I. Disseminated intravascular coagulation: new concepts, new controversies. 2002. *Hematology*. Available at: <http://www.asheducationbook.org/cgi/content/full/2002/1/335>. Accessed March 3, 2006.
- Messmore HL Jr, Wehrmacher WH. Disseminated intravascular coagulation: a primer for primary care physicians. *Postgrad Med Online*. 2002;11(3). Available at: http://www.postgradmed.com/issues/2002/03_02/messmore.htm. Accessed March 21, 2006.
- Levi M. Current understanding of disseminated intravascular coagulation. *Br J Haematol*. 2004;124(5):567-576.
- Labelle CA, Kitchens CS. Disseminated intravascular coagulation: treat the cause, not the lab values. *Cleve Clin J Med*. 2005;72(5):377-378, 383-385, 390.
- Baglin T. Fortnightly review: Disseminated intravascular coagulation: diagnosis and treatment. *BMJ*. 1996;312:683-686.
- Schlesinger K, Ragni M. DIC, inflammation, sepsis and activated protein C (APC). Institute for Transfusion Medicine. 2002. Available at: <http://www.itxm.org/TMU2002/Issue3.htm>. Accessed March 21, 2006.