EDUCATIONAL COMMENTARY – DISSEMINATED INTRAVASCULAR COAGULATION

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Learning Objectives

Upon completion of this exercise, the participant will be able to:

- explain the coagulation cascade and the role it plays in disseminated intravascular coagulation (DIC).
- identify clinical symptoms and indications that may aid in the diagnosis and treatment of DIC.
- analyze available testing to help optimally identify DIC.

Disseminated intravascular coagulation (DIC) is an acquired syndrome that occurs as a result of an underlying condition. This disorder leads to an imbalance in the coagulation system characterized by the simultaneous activation and consumption of clotting factors and platelets. Consumption results in patient bleeding, while the activation of intravascular coagulation results in fibrin formation and fibrin deposits in the microvasculature, which causes thrombosis.[1]

The Coagulation Cascade

An understanding of the coagulation process is essential to understanding the mechanism of DIC. The process of hemostasis is like a scale that must be kept in balance. If the scale is tipped in one direction the patient will bleed; in the other direction the patient will form a clot. Normal secondary hemostasis is a series of enzymatic reactions resulting in the formation of fibrin. This occurs through the intrinsic and extrinsic pathway. The initiation of the intrinsic pathway occurs when activated factor XII binds to exposed endothelium at the site of injury. In the extrinsic pathway, circulating activated VIIa binds to tissue factor being released from the site of injury. All of these reactions lead to the formation of thrombin. Thrombin's feedback mechanism cleaves fibrinogen, and activates factors V, VIII, XIII, and protein C.

Disseminated intravascular coagulation results from an inappropriate activation of clotting factors or abnormal release of tissue factor into the circulation. The major mechanisms of the coagulation system are activated. The extrinsic pathway is activated as excess tissue factor is released during tissue necrosis and organ failure. This results in the formation of platelet-fibrin-rich thrombi in the vasculature.   Some of the triggers of DIC that activate the intrinsic pathway are liver disease, immune disorders, burns, shock, and obstetric complications; the most common trigger is sepsis.

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Naturally occurring anticoagulants, inhibitors of coagulation, are also impaired. Antithrombin, the most important inhibitor of thrombin, is reduced due to a combination of consumption, degradation, and impaired synthesis. Protein C system is decreased due to impaired synthesis as well as the reduction of protein S, which is a cofactor of protein C. There is also evidence that tissue factor pathway inhibitor (TFPI) does not regulate tissue factor sufficiently. This further triggers the activation of coagulation in DIC.

Plasminogen activators are released due to bacteremia and endotoxemia. However, the fibrinolytic system, which is responsible for the dissolution of a clot, is mostly shut off during DIC. This is due to suppressed activity resulting from an increase in plasminogen activator inhibitor (PAI-1).

In DIC, bleeding occurs due to deficiencies in multiple coagulation factors (coagulation factors are consumed in thrombi and digested by plasmin) and thrombocytopenia (platelets are consumed in the thrombi). Additionally, intravascular fibrin deposits contribute to organ failure and mortality. All of these processes cause the simultaneous formation of both thrombin and plasmin, resulting in the clinical presentation of bleeding and clotting.

Clinical Conditions

Disseminated intravascular coagulation is caused by several clinical conditions. The degree is dependent on the etiology and the acuteness. There are 2 types of DIC: (1) acute hemorrhagic DIC, and (2) chronic or overt DIC.

Acute Hemorrhagic DIC

Acute hemorrhagic DIC develops rapidly—from a few hours to a few days—with a high mortality rate of 54% to 67%. Each patient's presentation varies depending on the etiology and the body's ability to control this coagulopathy. The production of coagulation factors depends on the health of the patient's liver. A patient's presentation also depends on the body's ability to replace coagulation factors and remove fibrin degradation products, as well as the bone marrow's ability to replace platelets.[2]

Acute DIC is often seen with infections. It is a frequent complication of severe sepsis with a high degree of mortality and multiorgan failure. The disseminated microthrombi decrease tissue oxygenation; this can cause organ infarction and necrosis. Acute DIC is more likely to occur in conjunction with bacterial infection, in particular gram-negative sepsis. Other causes include obstetric complications, liver malignancy, tissue injury, and necrosis.

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In acute DIC, excess plasmin formation results in a hemorrhagic state. Patients present with oozing from sites, large subcutaneous hematomas, deep tissue bleeding, and petechiae. Acute DIC may also occur in patients with endotoxemia, extensive tissue trauma, hypotension or shock, and massive surgery. Treatment depends on the symptoms.

Chronic or Overt DIC

Overt DIC is more difficult to diagnosis than acute DIC, and occurs in 10% to 20% of patients. This is a compensated DIC that occurs when fibrin clot formation and the accompanying fibrinolysis are in a steady state because the liver and bone marrow can compensate for the increased use of coagulation factors and platelets. Additionally, fibrin degradation products (FDPs) can still be cleared. Laboratory tests are minimally abnormal.

Chronic DIC is associated with malignancies, aortic aneurysms, and incomplete abortions. Ten percent to 15% of patients with tumors present with DIC, most likely due to tissue factor expressed on the surface of tumor cells. Disseminated intravascular coagulation is also seen in M3-acute promyelocytic leukemia; the granules of the promyelocytes release a thromboplastin-like substance that releases procoagulants.[1] Survival rates for cancer patients with DIC are lower than cancer patients who do not present with DIC. However, as with other causes, if the underlying disease is appropriately treated, the stimulus for the DIC is removed.[3]

Laboratory Testing

There is no "gold standard" test to specifically identify this coagulopathy. A panel of tests is usually more helpful than a single test. Routine laboratory testing includes the prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, and platelet count. Additionally, schistocytes will be present on the peripheral blood smear. Prolongations of these routine tests are sensitive to DIC; however, they are not specific and can occur with other conditions.

Additional testing looking at FDPs such as the D-dimer can enhance the information available to make a diagnosis. The D-dimer assay detects a specific type of degradation product formed by cross-linking "D" fragments of the fibrin molecule. An elevated level is sensitive for DIC but not specific; increased FDPs are seen in other disorders. The D-dimer result is positive in conditions such as primary fibrinolysis, dysfibrinogemia, and liver disease[4]; therefore, it cannot be used alone to diagnose DIC. A negative result, however, may be helpful in ruling out this condition.

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Laboratory findings considered in distinguishing between DIC and other abnormalities are:

- Thrombocytopenia or a rapidly falling platelet count
- Prolonged PT or APTT or both
- Detection of FDPs in plasma
- Low levels of antithrombin[5]

As shown in **Table 1**, tests are diagnostic in acute cases, while in chronic cases tests are usually normal or slightly abnormal.

TABLE 1. *Reference for Laboratory Findings.*

Laboratory Tests	Acute DIC	Chronic DIC
Screening Tests		
PT and APTT	Usually prolonged	Normal
Fibrinogen level	Usually decreased May be normal Is acute-phase reactive May be in normal range but previously very high; monitor carefully	Usually normal
Confirmatory Tests		
Fibrin degradation products (FDPs), µg/mL	+ >40	+ <40
D-Dimer	Positive	Positive

Source: Castellone DD. Evaluation of bleeding disorders. In: Lehmann CA. *Saunders Manual of Clinical Laboratory Science.* Philadelphia, PA: WB Saunders; 1998. Chapter 40.

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The International Society of Thrombosis and Hemostasis developed a scoring system that improves accuracy in the diagnosis of DIC with 91% sensitivity and 97% specificity.[4] The scoring system is described in **Table 2**.

TABLE 2. *Scoring System for Diagnosing DIC.*

Test	Result	Score
Platelet count	>100	0
	<100	1
	<50	2
Fibrin related marker	No increase	0
	Moderate increase	2
	Strong increase	3
Prolonged PT	<3 sec	0
	>3 sec	1
	>6 sec	2
Fibrinogen	>100 g/dL	0
	<100g/dL	1

If the sum is ≥5 the patient status is compatible with overt DIC. It appears to be valid once linked to coagulation activation markers such as the D-dimer and the consumption of inhibitors.[6]

Treatment

In addition to the symptoms, the underlying disorder must be treated or treatment will fail. For example, in the case of fetal demise, removing the fetus will limit the extent of the DIC. However, when the DIC is caused by sepsis, treatment is more difficult because the organism cannot be removed. Antibiotic therapy must be initiated to minimize the DIC. Whether the patient presents with bleeding or clotting, in regard to DIC, will help determine further treatment.

Prophylaxis will help in preventing venous thromboembolism. Heparin is very effective, but is contraindicated if the cause is hemorrhagic. However, in a patient who is bleeding and has a disorder of consumption, it is important to replace the factors that have been depleted with either plasma or platelets. Patients are treated with fresh frozen plasma (FFP) to replace factors. Small doses of heparin may then be given to prevent the formation of additional clots.

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Using factor concentrates is contraindicated because they may contain activated factors. Additionally, because patients are deficient in inhibitors, treatment with antithrombin concentrate or activated protein C (Xigris® [Eli Lilly, Indianapolis, IN]) can have benefits. Using a recombinant activated protein C decreased mortality from 31% to 25%. In addition to acting as an anticoagulant, protein C also has a direct anti-inflammatory property. It is contraindicated in patients with platelet counts <50,000.

Conclusion

Disseminated intravascular coagulation is a complex disorder that requires immediate attention by both the clinician and the laboratory. Good diagnostic tools and testing algorithms are imperative in order to diagnose and treat the condition.

References

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