Acute Disseminated Intravascular Coagulation (DIC)

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pathophysiology

general concept of DIC

Normally, clots form locally at sites of vascular damage. These clots are subsequently degraded after tissue damage is repaired. The processes of clot formation and clot degradation (fibrinolysis) are localized and tightly regulated, based on a balance of counterregulatory proteins (procoagulants vs. anticoagulants regulate clot formation; fibrinolytics vs. antifibrinolytics regulate clot breakdown).

The fundamental pathophysiologic signature of DIC is widespread, uncontrolled clot formation. Clotting may be initiated by a variety of factors (e.g., bacterial lipopolysaccharides, tissue factor released by monocytes or the placenta, or damage to the endothelial glycocalyx). The fine balance of procoagulation vs. anticoagulation is broken, leading to widespread disseminated clot formation. This clot burden places a massive
DIC may cause a variety of life threats:

1. Disseminated microvascular thrombosis may cause tissue hypoperfusion and tissue damage. This may be exacerbated by depletion of fibrinolytic proteins, which prevents clots from undergoing thrombolysis (“fibrinolytic shutdown”).
2. Depletion of anticoagulant proteins may predispose patients to form macrovascular thromboses (e.g., deep vein thrombosis and pulmonary emboli).
3. Depletion of procoagulant proteins may lead to hemorrhage.

**different flavors of DIC**

Different causes of DIC tend to cause different problems. Infection and septic shock tend to cause a more prothrombotic form of DIC, which predominantly causes excess clot formation. Alternatively, DIC due to obstetric catastrophes or leukemia tends to cause depletion of fibrinogen leading to hemorrhage. Consequently, DIC is not a monolithic construct – and appropriate treatment often depends on understanding the context.

**acute versus chronic DIC**

- **Acute DIC** results from an acute trigger of coagulation (e.g., sepsis or trauma). This leads to abrupt and exuberant depletion of coagulation factors, leading to hemostatic imbalances.
  - This chapter is predominantly about *acute DIC* – which is more immediately relevant to critical care medicine.
- **Chronic DIC** refers to chronic activation of coagulation, often due to disseminated adenocarcinomas. This causes gradual consumption of coagulation factors, which can be compensated by the production of additional clotting factors. Symptoms and laboratory abnormalities are consequently less notable (this is sometimes termed “chronic compensated DIC”).

**symptoms**

DIC may be asymptomatic, or it may cause bleeding and clotting. Symptoms may be dominated by either bleeding or clotting.

**microvascular thrombosis causes organ failure**

- Microvascular thromboses may be an occult cause of organ failures. *With the exception of the skin, it is often difficult or impossible to tell that microvascular thrombosis is occurring.* The most common manifestations are:
  1. Renal failure is probably the most common.
  2. Acute respiratory distress syndrome (ARDS).
  3. Brain involvement may cause delirium, coma, seizure.
  4. Adrenal failure (Waterhouse-Friedrichsen syndrome) may result from microvascular thromboses, followed by hemorrhagic transformation. The net result is adrenal failure which can precipitate [adrenal crisis](https://emcrit.org/ibcc/adrenal-crisis/).
  5. Skin: purpura fulminans (occlusion of microvasculature in the skin potentially causing gangrene). This signifies an extreme form of DIC which requires aggressive management (more on this [here](https://emcrit.org/ibcc/pf/)).

**macrovascular thrombosis**

- Primarily causes venous thrombosis (e.g., deep vein thrombosis, pulmonary embolism).

**bleeding**

- Petechiae and purpura may occur on the skin.
- Oozing may originate from intravenous catheters or mucus membranes.
- Life-threatening hemorrhage can result from gastrointestinal or intracranial hemorrhage. However, in most forms of DIC, severe bleeding is uncommon.
### DIC screening lab panel

- Complete blood count (CBC)
- INR or PT, PTT
- Fibrinogen
- D-dimer

### D-dimer

- D-dimer is *invariably* elevated in DIC, often dramatically so (e.g., >4,000 ng/mL).
- A normal D-dimer essentially excludes DIC.
- Advanced sepsis-induced DIC may impair fibrinolysis (“fibrinolytic shutdown”), which limits further increases in D-dimer.

### Thrombocytopenia

- Thrombocytopenia may be the most *sensitive* laboratory test for detection of DIC. ([30828800](https://pubmed.ncbi.nlm.nih.gov/30828800)). A down-trending platelet count is often the first laboratory abnormality which to be noted. ([30634199](https://pubmed.ncbi.nlm.nih.gov/30634199)). Of course, thrombocytopenia is *not* specific to DIC: thrombocytopenia is very common in the ICU due to a variety of causes (more on causes of thrombocytopenia [here](https://emcrit.org/ibcc/thrombocytopenia/)).

### INR and PTT abnormalities

- Elevations of INR and PTT support a diagnosis of DIC. However, they can be normal in over half of patients with DIC. ([30634199](https://pubmed.ncbi.nlm.nih.gov/30634199)).
- These abnormalities may not correspond to clinical hypocoagulability (since they measure only clotting factors, but do not reflect deficiencies which may be occurring in anticoagulant factors, such as protein C and protein S).
- In sepsis-induced DIC, PTT prolongation may lag behind PT prolongation as DIC develops. This occurs because the PTT is reduced by elevated factor VIII levels. ([27578502](https://pubmed.ncbi.nlm.nih.gov/27578502)).

### Fibrinogen

- *The fibrinogen is low only in about a quarter of patients with DIC.* ([30634199](https://pubmed.ncbi.nlm.nih.gov/30634199)) Low fibrinogen supports a diagnosis of DIC, but this usually isn’t seen.
- Low fibrinogen is more common in predominantly fibrinolytic types of DIC (e.g., patients with acute promyelocytic leukemia or obstetric-related DIC).
- Sepsis increases fibrinogen levels, so sepsis-induced DIC may have elevated or normal levels of fibrinogen. *Falling* fibrinogen may suggest ongoing DIC with consumption of fibrinogen.
  - *Changes* in fibrinogen over time may be more illuminative than a single value.

### Microangiopathic hemolytic anemia (MAHA) can occur

- Microangiopathic hemolytic anemia can occur due to microthrombi in the capillaries. This causes intravascular hemolysis with the generation of *schistocytes* (fragmented RBCs).

### Role of thromboelastography (TEG) in DIC?

- Patients with DIC often have reduced levels of both clotting factors and also endogenous anticoagulant proteins. This may create a situation where patients appear to be hypocoagulable based on traditional labs (e.g., platelet count and INR) – but they are actually hypercoagulable.
- TEG is a whole-blood integrative test that may help clarify the *overall balance* of coagulation.
TEG often shows hypercoagulability early in the course of DIC (e.g., reduced R-time). Later on, during the course of fulminant DIC, TEG may show hypocoagulability.

**causes of DIC**

Certain forms of DIC tend to cause predominantly thrombosis or hemorrhage – these are indicated below.

**sepsis due to a wide variety of pathogens, most notably:**

- Bacteria *(thrombosis predominates)*
  - Gram-negative bacteria
  - Toxigenic organisms (e.g., group A streptococci)
- Viruses (e.g., viral hemorrhagic fevers)
- Malaria

**direct tissue damage**

- Burns or frostbite
- Heat stroke (thrombosis predominates)
- Surgery
- Trauma (especially involving traumatic brain injury)
- Fat emboli syndrome
- Intravascular hemolysis
  - Hemolytic transfusion reaction
  - Malaria

**malignancy, especially:**

- Acute promyelocytic leukemia (AML-M3) and monocytic leukemia (AML-M5) – Tend to cause a hyperfibrinolytic form of DIC, with prominent bleeding. More on the management of acute promyelocytic leukemia [here](https://emcrit.org/ibcc/apl/).
- Adenocarcinoma (especially pancreas, prostate, lung, gastric, ovary). This is usually a chronic, compensated form of DIC with a tendency towards thrombosis.
- Chemotherapy.

**obstetric catastrophe** *(hemorrhage often predominates)*

- Placental abruption
- Amniotic fluid embolism
- Preeclampsia, HELLP syndrome
- Fetal demise
- Maternal septic shock (e.g., chorioamnionitis, group A streptococcus infection)
- Acute fatty liver of pregnancy

**other**

- Post-Cardiopulmonary Resuscitation *(thrombosis predominates)*([29255070](https://pubmed.ncbi.nlm.nih.gov/29255070/))
- Severe collagen vascular disease, vasculitis
- Drug-induced
  - *Heparin-Induced Thrombocytopenia (HIT)*([https://emcrit.org/ibcc/thrombocytopenia/#heparin_induced_thrombocytopenia_and_thrombosis_(HITT)](https://emcrit.org/ibcc/thrombocytopenia/#heparin_induced_thrombocytopenia_and_thrombosis_(HITT))) can cause DIC in ~10% of cases (although the two processes are usually separate)
- Severe hepatitis
- Vascular malformations (e.g., giant hemangiomas or large aortic aneurysms) – hemorrhage predominates.
- *Catastrophic antiphospholipid antibody syndrome*([https://emcrit.org/ibcc/caps/](https://emcrit.org/ibcc/caps/))
isolated sepsis-induced thrombocytopenia vs. DIC

- Sepsis may cause thrombocytopenia via a variety of mechanisms: Impaired platelet production, Increased platelet consumption, (sometimes due to hemophagocytosis), Splenic sequestration of platelets.
- Septic patients often have thrombocytopenia without other abnormalities in their coagulation factors (e.g., normal INR and PTT). Such patients do not have DIC.

Cirrhosis vs. DIC

- Cirrhosis is a risk factor for DIC, because patients with cirrhosis often have reduced levels of coagulation factors and also anti-coagulant proteins (e.g., protein C and protein S). With lower levels of these proteins at baseline, patients with cirrhosis have a delicate balance of procoagulants vs. anticoagulants, which may be more easily disrupted by an acute insult. Thus, cirrhosis may often coexist with DIC.
- However, the two processes are usually separate and can be sorted out.
- Abnormalities which can occur due to cirrhosis:
  - Cirrhosis commonly causes thrombocytopenia and reductions in clotting factor levels (e.g., elevation of INR).
  - Rarely, patients with cirrhosis may fail to clear endogenous tPA, leading to ongoing fibrinolysis (accelerated intravascular coagulation and fibrinolysis AICF) – a condition which can closely mimic DIC.
- Diagnostic clues to sort out DIC vs. cirrhosis
  - (1) Comparison to baseline coagulation factors: if coagulation tests (e.g., thrombocytopenia) are at their baseline level, then acute DIC is unlikely. (29255070)
  - (2) Most patients with cirrhosis have only mildly elevated D-dimer. Thus, profoundly elevated D-dimer may favor DIC. However, markedly elevated D-dimer also does occur in accelerated intravascular coagulation and fibrinolysis (AICF), as a complication of cirrhosis (more on this here).
  - (3) Factor VIII levels: Factor VIII is produced by endothelial cells. In cirrhosis, factor VIII levels will remain normal or elevated. Alternatively, in DIC, factor VIII will be reduced along with other coagulation factors.

HIT (heparin-induced thrombocytopenia) vs. DIC

- A useful feature to sort out HIT vs. DIC is chronicity. DIC usually occurs gradually, beginning around the time of admission. Alternatively, HIT tends to begin abruptly, more than five days after exposure to heparin. The 4-T score may be used to more precisely quantify the risk of HIT (below).
- Most patients with HIT do not have DIC. However, severe HIT may trigger DIC in ~10% of cases.
- **HIT alone** typically causes the following pattern of findings:
  - Platelet counts aren't profoundly reduced (e.g., platelets >20,000/uL)
  - INR and fibrinogen levels are normal.
- **HIT complicated by DIC** may cause the following pattern:
  - Platelets may be profoundly reduced (e.g., platelets <20,000/uL)
  - INR prolongation and hypofibrinogenemia may occur
- More on HIT [here](https://emcrit.org/ibcc/thrombocytopenia/#heparin_induced_thrombocytopenia_and_thrombosis_(HITT)).

**primary thrombotic microangiopathies (e.g., TTP, HUS) vs. DIC**

- Both DIC and thrombotic microangiopathies may lead to anemia, schistocyte formation, and thrombocytopenia. However, schistocyte formation is considerably more exuberant in primary thrombotic microangiopathy, compared to DIC.
- Patients with TTP, HUS, or drug-induced thrombotic microangiopathy should have normal coagulation factors (e.g., INR, PTT, fibrinogen), because clots are composed of platelets and don't involve activation of the coagulation system. Similarly, the D-dimer should be normal or only slightly elevated.[(29255070)](https://pubmed.ncbi.nlm.nih.gov/29255070/)

**catastrophic antiphospholipid antibody syndrome (CAPS) vs. DIC**

- This can be challenging, because CAPS causes DIC in ~25% of cases.
- Features which may suggest CAPS include:
  - A history of connective tissue disease (especially antiphospholipid antibody syndrome).
  - A history of pregnancy loss, or illness onset during pregnancy.
  - Recent withdrawal of anticoagulation.
  - Skin manifestations (e.g., livedo reticularis or cutaneous necrosis).
- More on the diagnosis of CAPS [here](https://emcrit.org/ibcc/caps/).

**DIC scoring systems can help determine if coagulation abnormalities are consistent with DIC**
Several DIC scoring systems exist. The International Society of Thrombosis and Hemostasis (ISTH) score (shown below) is the most widely utilized and accepted.

Scoring systems can help provide an objective metric to evaluate the patient's laboratory abnormalities, but they are neither the end-all nor be-all of diagnosis.

Early in the process of DIC, the patient may not quite reach a positive DIC score (sometimes called 'non-overt DIC'). If there is ongoing concern regarding DIC, coagulation labs may be repeated in 12-24 hours to determine if the patient is developing DIC. Often changes in serial labs may be more illuminating than a single set of labs (e.g., a fibrinogen which is actively falling from 300 mg/dL to 100 mg/dL is more worrisome than a fibrinogen which is stably low at 100 mg/dL).

### sepsis induced coagulopathy (SIC)

**what is sepsis-induced coagulopathy (SIC)?**

- Sepsis-induced coagulopathy essentially refers to DIC caused by sepsis.
- Sepsis tends to cause a particular form of DIC, with the following characteristics:
  - Hypercoagulability and microvascular thrombosis are usually the predominant problems.
  - Fibrinogen levels are generally within the normal range.
  - Fibrinolysis is suppressed, which may lead to impairment of the breakdown of microthrombi.
- The Sepsis-Induced Coagulopathy score is designed specifically to detect DIC in the context of sepsis (table below).
- For patients with sepsis, the Sepsis-Induced Coagulopathy score is more sensitive than the ISTH DIC criteria. For example, patients will generally meet sepsis-induced coagulopathy criteria before they deteriorate and meet ISTH DIC criteria. However, patients with Sepsis-Induced Coagulopathy seem to have the same mortality as patients meeting the more stringent ISTH DIC criteria – suggesting that the increased sensitivity of the Sepsis-Induced Coagulopathy score may not come at the cost of impaired specificity. Unfortunately, since there is no gold standard to diagnose DIC, it's impossible to definitively tell which scoring system is ideal!
how should sepsis-induced coagulopathy be used clinically?

- The utility of Sepsis-Induced Coagulopathy is unclear, because currently there are no proven therapies for this. Consequently, it's unclear how aggressively this diagnosis should be sought. We are probably “missing” many septic patients with sepsis-induced coagulopathy, but does this actually matter?
- One way that Sepsis-Induced Coagulopathy could be used is as a screening tool for DIC among patients with sepsis (figure below).
- It must be borne in mind that many disease processes can cause thrombocytopenia plus a mildly elevated INR. Therefore, patients meeting the criteria for sepsis-induced coagulopathy don't necessarily have DIC. Rather, these patients should be thoughtfully investigated with other differential diagnostic possibilities borne in mind (e.g., cirrhosis, heparin-induced thrombocytopenia).
**Some specific types of DIC require different management:**

- Patients with DIC due to acute promyelocytic leukemia (APML) require specific treatment described [here](https://emcrit.org/ibcc/apl/).
- Patients with purpura fulminans require a specific management strategy described [here](https://emcrit.org/ibcc/pf/).
- Patients with pregnancy-associated DIC and clinical bleeding often need aggressive factor replacement, with an emphasis on maintaining adequate fibrinogen levels.

**Treat the underlying disorder**

- The most important principle of DIC management is to treat the underlying cause.
- DIC due to septic shock is perhaps the most notable example of this – treatment should overall focus on the basic tenets of sepsis care.

**Platelet transfusion**

- Platelet transfusion should generally be avoided, unless:
  - Platelets <10,000/uL.
  - There is a planned procedure with a *substantial* risk of bleeding.
  - There is active bleeding.
- For patients with active bleeding or a pending procedure, transfusion to >30,000-50,000/uL may be reasonable.[29255070](https://pubmed.ncbi.nlm.nih.gov/29255070/)
- Due to ongoing platelet consumption, results from platelet transfusion may be disappointing.

**Fibrinogen supplementation**

- Profoundly low fibrinogen levels may increase the risk of bleeding, including intracranial hemorrhage.
- It may be reasonable to attempt to maintain fibrinogen levels above 50-80 mg/dL (a target that may be personalized to some extent, depending on the risk of bleeding vs. thrombosis).
For patients with active bleeding or a planned procedure, targeting a fibrinogen level >150 mg/dL may be reasonable. Various sources recommend targets ranging from >100 mg/dL to >200 mg/dL, with little supporting evidence. The target may be individualized for a specific patient, when considering the overall risks of hemorrhage and the state of coagulation (e.g., for patients with marked thrombocytopenia, a higher fibrinogen target may compensate for the thrombocytopenia to a certain degree).

Fibrinogen levels may be supported using cryoprecipitate or fibrinogen concentrates.

coonagulation factor replacement (e.g., fresh frozen plasma)

- This is confusing, because traditional labs (e.g., INR) don't reflect the true coagulation tendency of the blood. INR measures only clotting factors (while ignoring endogenous anticoagulants such as protein C and protein S).
- Thromboelastography is likely a better tool to determine the true balance of coagulation. The use of thromboelastography for patients with DIC has not been specifically studied. However, thromboelastography has a proven track record for management of patients with enormously complex coagulopathies in the operating room (e.g., hepatic transplantation, multiple trauma patients, cardiopulmonary bypass operations) – many of whom doubtless had DIC. Thus, it is a logical extension that thromboelastography could be used to tailor blood product selection in the intensive care unit.
- When possible, it may be better not to treat INR and PTT values. However, in patients with active bleeding or planned procedures, factor replacement is indicated if thromboelastography reveals enzymatic coagulopathy (e.g., with prolonged R-time). If thromboelastography isn't available, INR may need to be used as a blunt indicator of whether coagulation factors might potentially be needed.
- Fresh frozen plasma (FFP) has traditionally been used for coagulation factor repletion. However, prothrombin complex concentrates may be another option (especially in patients with volume overload).

vitamin K administration

- It may be difficult to determine whether vitamin K deficiency exists (since INR prolongation results from DIC).
- If vitamin K deficiency is suspected, then vitamin K should be administered empirically (e.g., 10 mg intravenously infused over 30-60 minutes).

DVT prophylaxis

- DVT prophylaxis should be provided to all critically ill patients, unless contraindicated. Contraindications may include:
  - Active bleeding.
  - Profound thrombocytopenia (e.g., platelet count <30,000/uL).
  - Profound hypofibrinogenemia (e.g., fibrinogen <80 mg/dL).
  - Planned procedure with high concern regarding bleeding (e.g., neurosurgery, lumbar puncture).
- Subgroup analysis of the SCARLET and KYBERSEPT trials investigating antithrombin III and thrombomodulin anticoagulation suggest that these anticoagulants were potentially beneficial – but only among patients not taking concomitant heparin. This indirectly suggests that heparin could provide benefits analogous to more expensive, designer anticoagulants.
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therapeutic heparin anticoagulation

- Rationale:
  - Theoretically, anticoagulation with heparin could impede ongoing thrombosis and thereby stop the primary abnormality of DIC (disseminated activation of coagulation).
  - Unfortunately, research into therapeutic heparin anticoagulation has generally been unimpressive. Thus, heparin anticoagulation isn't indicated in most cases of DIC.
- Indications for heparin anticoagulation:
  - (1) Clinical thrombosis (e.g., DVT or pulmonary embolism).
  - (2) Purpura fulminans (this subset of DIC requires an entirely different treatment strategy; more on this here).
- When possible, heparin infusions should be monitored using an anti-Xa level. Patients will often have an elevated PTT at baseline, which may confuse the use of PTT to monitor heparin dosing.
- Patients with DIC may often have heparin resistance, due to low levels of antithrombin III. Higher doses of heparin may be required than usual. More on heparin resistance here.
When possible, try to avoid the use of blood products to “fix labs” in a patient with asymptomatic DIC (although this may be warranted for profoundly low platelet count or fibrinogen level).

- Sepsis-associated DIC generally causes patients to be prothrombotic. Therefore, holding DVT prophylaxis for patients with mild-moderate thrombocytopenia (e.g., platelet count >30,000) may be inadvisable.

**Going further:**

- [Understanding sepsis-induced DIC](https://emcrit.org/pulmcrit/sepsis-dic/) (blog, PulmCrit)

**references**


