Disseminated Intravascular Coagulation

Series Editor:
Eric D. Jacobsen, MD
Instructor in Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA

Contributor:
Thomas G. DeLoughery, MD, FACP
Professor of Medicine, Departments of Pathology and Pediatrics, Oregon Health Sciences University, Portland, OR

Table of Contents

Introduction ............................................. 2
Pathogenesis ........................................... 2
Patterns of DIC........................................ 2
Diagnosis.................................................. 3
Treatment............................................... 5
Specific DIC Syndromes.............................. 5
Summary............................................... 9
References............................................. 9

Cover Illustration by Kathryn K. Johnson

Copyright 2010, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of topics and preparation of editorial content. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.
Disseminated Intravascular Coagulation

Thomas G. DeLoughery, MD, FACP

INTRODUCTION

The process of coagulation is finely controlled at many levels to ensure the right amount of hemostasis at the right location. Broadly defined, disseminated intravascular coagulation (DIC) refers to any process that disrupts this fine tuning, leading to unregulated coagulation. Defined this way, DIC may be found in patients with a variety of diseases and can present with a spectrum of findings ranging from asymptomatic abnormal laboratory findings to florid bleeding or thrombosis. It is important to remember that DIC is always a consequence of an underlying pathological process and not a disease in and of itself. This manual reviews concepts common to all forms of DIC and discusses the more common disease states that lead to DIC.

PATHOGENESIS

At the most basic level, DIC is the clinical manifestation of inappropriate thrombin activation. Inappropriate thrombin activation can occur due to underlying conditions such as sepsis, obstetrical disasters, and trauma. The activation of thrombin leads to (1) conversion of fibrinogen to fibrin, (2) activation of platelets (and their consumption), (3) activation of factors V and VIII, (4) activation of protein C (and degradation of factors Va and VIIIa), (5) activation of endothelial cells, and (6) activation of fibrinolysis (Table 1).

Conversion of fibrinogen to fibrin leads to formation of fibrin monomers and excessive thrombus formation. These thrombi are rapidly dissolved by excessive fibrinolysis in most patients, but in certain clinical situations, especially cancer, excessive thrombosis will occur. In patients with cancer, this is most often a deep venous thrombosis, and rarely patients may have severe DIC with multiple arterial and venous thromboses, especially patients with pancreatic cancer. Nonbacterial thrombotic endocarditis can also be seen in these patients.

Because thrombin is the most potent physiologic activator of platelets, there is increased activation of platelets in DIC. These activated platelets are consumed, resulting in thrombocytopenia. Platelet dysfunction is also present. Platelets that have been activated and have released their contents but still circulate are known as “exhausted” platelets; these patients can no longer function to support coagulation. The fibrin degradation products (FDP) in DIC can also bind to GP IIb/IIIa and further inhibit platelet aggregation.

Activation of factors V, VIII, XI, and XIII can promote thrombosis, but they are then rapidly cleared by antithrombin (XI) or activated protein C (V and VIII) or by binding to the fibrin clot (XIII). This can lead to depletion of all the prothrombotic clotting factors and antithrombin, resulting in both thrombosis and bleeding.

Activation of protein C further promotes degradation of factors Va and VIIIa, enhances fibrinolysis, and decreases protein C levels. Activation of endothelial cells, especially in the skin, may lead to thrombosis. Purpura fulminans also may develop in certain patients, especially those with meningococcemia. Endothelial damage will downregulate thrombomodulin, preventing activation of protein C and leading to further reductions in levels of activated protein C.

Finally, activation of fibrinolysis leads to breakdown of fibrin monomers, formation of fibrin thrombi, and increased levels of circulating fibrinogen. In most patients with DIC, the fibrinolytic response is brisk, which explains why most patients with DIC present with bleeding and prolonged clotting times.

PATTERNS OF DIC

The clinical manifestations of DIC in a given patient depend on the balance of thrombin activation and secondary fibrinolysis as well as the patient’s ability to compensate for the DIC. Patients with DIC present in 1 of 4 patterns: they can be asymptomatic, presenting with laboratory evidence of DIC but no bleeding or thrombosis, or present with overt bleeding, thrombosis, or purpura fulminans. Asymptomatic presentation is often seen in patients with sepsis or cancer. However, these patients can rapidly become symptomatic with progression.
of the underlying disease. Bleeding in DIC results from a combination of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis. These patients may present with diffuse bleeding from multiple sites (eg, intravenous sites, areas of instrumentation). Despite the general activation of the coagulation process, thrombosis is unusual in most patients with acute DIC. The exceptions include patients with cancer, trauma patients, and certain obstetrical patients. Most often the thrombosis is venous, but arterial thrombosis and nonbacterial thrombotic endocarditis have been reported. Purpura fulminans, a severe form of DIC, is discussed in detail in the Specific DIC Syndromes section.

**DIAGNOSIS**

The diagnosis DIC is not based solely on laboratory testing but rather requires interpreting the appropriate tests in the context of the patient’s presentation and underlying condition (Table 2). Repeat testing is necessary given the dynamic nature of DIC. Screening tests for DIC include the prothrombin time (PT) activated partial thromboplastin time (aPTT), platelet count, and fibrinogen level. The PT-INR and aPTT are usually elevated in severe DIC but may be normal or shortened in chronic forms. One may also see a shortened aPTT in severe acute DIC due to large amounts of activated II and factor X “bypassing” the contact pathway. APTTs as short as 10 seconds have been seen in acute DIC. The platelet count is usually reduced but may be normal in chronic DIC. Serum fibrinogen and platelets are decreased in acute DIC but also may be in the “normal” range in chronic DIC. The most sensitive of the screening tests for DIC is a fall in the platelet count, with low counts seen in 98% of patients and counts under 50,000 cells/µL in 50%. The least specific test is fibrinogen, which tends to fall below normal only in severe acute DIC.

“Specific tests” for DIC allow one to deduce that abnormally high concentrations of thrombin are present. These include the ethanol gel and protamine sulfate tests, measurement of fibrin degradation product (FDP), and D-dimer levels. The ethanol gel and protamine tests detect circulating fibrin monomers. Circulating fibrin monomers are seen when thrombin acts on fibrinogen. Usually the monomer polymerizes with the fibrin clot, but when there is excess thrombin these monomers continue to circulate. Detection of circulating fibrin monomer means there is too much IIa and therefore DIC is present.

FDPs are produced when plasmin acts on the fibrin/fibrinogen molecule to cleave the molecule in specific places. FDP levels are elevated in the setting of increased fibrin/fibrinogen destruction, as occurs with DIC and fibrinolysis. FDP levels are typically mildly elevated in renal and liver disease due to reduced clearance.

When fibrin monomers bind to form a thrombus, factor XIII acts to bind the monomers together to form a dense network of fibrin polymer. One of the bonds created binds the fibrin “D” domains together, creating a bond that is resistant to plasmin. When the thrombus is lysed, this dimer remains and this degradation fragment is known as the D-dimer. High levels of D-dimer indicate that IIa has acted on fibrinogen to form a fibrin monomer that bonded to another fibrin monomer and that this thrombus was lysed by plasmin. Because an elevated D-dimer level can occur due to other causes (eg, exercise, surgery), an elevated D-dimer must be interpreted in the context of the clinical situation.

Several other tests are sometimes helpful in diagnosing DIC. The thrombin time test is performed

---

Table 1. Consequences of Excessive Thrombin Generation

| Conversion of fibrinogen to fibrin | → | Thrombosis and depletion of fibrinogen |
| Activation of platelets | → | Thrombocytopenia |
| Activation of factors V, VIII, XI, XIII | → | Thrombosis and depletion of coagulation factors |
| Activation of protein C | → | Depletion of factors V and VIII and eventually protein C |
| Activation of endothelial cells | → | Expression of tissue factor |
| Activation of fibrinolysis | → | Lysis of thrombi and depletion of fibrinogen |

Table 2. Testing for Disseminated Intravascular Coagulation

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time-international normalized ratio</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, fibrinogen level</td>
<td>Specific but not sensitive</td>
</tr>
<tr>
<td>Protamine sulfate test: detects circulating fibrin monomers</td>
<td>Sensitive but not specific</td>
</tr>
<tr>
<td>Ethanol gel test: detects circulating fibrin monomers</td>
<td></td>
</tr>
<tr>
<td>Fibrin(ogen) degradation products</td>
<td></td>
</tr>
<tr>
<td>D-dimer test (fibrin degradation product)</td>
<td></td>
</tr>
</tbody>
</table>

---
Disseminated Intravascular Coagulation

by adding thrombin to plasma. Thrombin times are increased in DIC (FDPs interfere with polymerization) and dysfibrinogenemia and in the presence of low fibrinogen levels and the presence of heparin (very sensitive). Reptilase time is the same as thrombin time but is performed with a snake venom that is insensitive to heparin. Reptilase time is elevated in the same conditions as the thrombin time, with the exception of the presence of heparin. Thrombin time and reptilase time are most useful in evaluation of dysfibrinogenemia. F₁₂ is a small peptide cleaved off when prothrombin is activated to thrombin. Thus, high levels of F₁₂ are found in DIC but can be seen in other thrombotic disorders. This test's clinical value remains limited.

A scoring system to both diagnose and quantify DIC has been proposed (Figure).²⁹,¹⁰ This system is especially helpful for clinical trials. One difficulty of using this system in clinical settings is that it requires the measurement of PT, which has not been standardized and often is not reported by clinical laboratories.

**MIMICS OF DIC**

It is important to recognize coagulation syndromes that resemble DIC, especially those with specific therapies that differ from those used to treat DIC. The syndromes most frequently encountered are thrombotic thrombocytopenic purpura (TTP) and catastrophic antiphospholipid antibody syndrome (APS). An important clue to recognizing both these syndromes is that, unlike DIC, there is no primary disorder (eg, cancer, sepsis) that is driving the coagulation abnormalities.

TTP should be suspected when a patient presents with any combination of thrombocytopenia, microangiopathic hemolytic anemia (schistocytes and signs of hemolysis), and end-organ damage.¹¹–¹³ Patients with TTP most often present with intractable seizures, strokes, or sequel of renal insufficiency. Many patients who present with TTP have been misdiagnosed as having sepsis, “lupus flare,” or vasculitis. The key diagnostic differentiator between TTP and DIC is the lack of activation of coagulation with TTP—fibrinogen is normal and D-dimers are minimally or not elevated. In TTP the lactate dehydrogenase level is invariably elevated, often 2 to 3 times normal.¹⁴ The importance of identifying TTP is that untreated TTP is rapidly fatal. Mortality in the pre–plasma exchange era ranged from 95% to 100%. Today plasma exchange therapy is the foundation of TTP treatment and has reduced mortality to less than 20%.¹²,¹⁵–¹⁷

Rarely patients with APS can present with fulminant multiorgan system failure.¹⁸–²¹ Catastrophic APS is caused by widespread microthrombi in multiple vascular fields. These patients develop renal failure, encephalopathy, adult respiratory distress syndrome (often with pulmonary hemorrhage), cardiac failure, dramatic livido reticularis, and worsening thrombocytopenia. Many of these patients have preexisting autoimmune disorders and high-titer antiphospholipid antibodies. It appears that the best therapy for these patients is aggressive immunosuppression with plasmapheresis, followed by intravenous cyclophosphamide monthly.²² Early recognition of this

---

syndrome can lead to quick therapy and resolution of the multiorgan system failure.

**TREATMENT**

The main focus of treating DIC is addressing the underlying cause that is driving the thrombin generation.\(^{1,2,4,22,23}\) Fully addressing the underlying cause may not be possible or may take time, and in the meantime it is necessary to disrupt the cycle of thrombosis and/or hemorrhage. In the past, there was concern about using factor replacement due to fears of “feeding the fire,” or perpetuating the cycle of thrombosis. However, these concerns are not supported by evidence, and one must replace factors if depletion occurs and bleeding ensues.\(^{24}\)

Transfusion therapy of the patient with DIC is guided by the 5 laboratory tests that reflect the basic parameters essential for both hemostasis and blood volume status:\(^{25,26}\) hematocrit, platelet count, PT-INR, aPTT, and fibrinogen level. Replacement therapy is based on the results of these laboratory tests and the patient’s clinical situation (Table 3). The transfusion threshold for a low hematocrit depends on the stability of the patient. If the hematocrit is below 30% and the patient is bleeding or hemodynamically unstable, one should transfuse packed red cells. Stable patients can tolerate lower hematocrits and an aggressive transfusion policy may be detrimental.\(^{27,28}\) Due to both the bleeding and platelet dysfunction in DIC, maintaining a platelet count of more than 50,000 cells/µL is reasonable.\(^{23,29}\) The dose of platelets to be transfused is 6 to 8 platelet concentrates or 1 platelepheresis unit. In patients with a fibrinogen level less than 100 mg/dL, transfusion of 10 units of cryoprecipitate is expected to increase the plasma fibrinogen level by 100 mg/dL. In patients with an INR greater than 2 and an abnormal aPTT, one can give 2 to 4 units of fresh frozen plasma (FFP).\(^{23}\) For an aPTT greater than 1.5 times normal, 4 units of plasma should be given. Elevation of the aPTT above 1.8 times normal is associated with bleeding in trauma patients.\(^{30}\) Patients with marked abnormalities, such as an aPTT increased 2 times normal, may require aggressive therapy with at least 15 to 30 mL/kg (4–8 units for an average adult) of plasma.\(^{31}\)

The basic 5 laboratory tests should be repeated after administering the blood products to ensure that adequate replacement therapy was given for the coagulation defects. Frequent checks of the coagulation tests also allow rapid identification and therapy of new coagulation defects in a timely fashion. A flow chart of the test and the blood products administered should also be maintained. This documentation is important in acute situations such as trauma or obstetrical bleeding.

In theory since DIC is the manifestation of exuberant thrombin production, blocking thrombin with heparin should decrease or shut down DIC. However, studies have shown that administration of heparin in most patients leads to excessive bleeding. Currently, heparin therapy is reserved for the patient who has thrombosis as a component of their DIC.\(^{2,24,32}\) Given the coagulopathy that is often present, one should use specific heparin levels instead of the aPTT to monitor anticoagulation.\(^{33,34}\)

### SPECIFIC DIC SYNDROMES

#### SEPSIS/INFECTIOUS DISEASE

Classically, it was believed that gram-negative bacteria can lead to the development of DIC by causing tissue factor exposure via their production of endotoxin, but recent studies indicate that DIC can be seen with any overwhelming infection.\(^{35}\) There are several potential avenues by which infections can lead to DIC.\(^{36}\) As mentioned, gram-negative bacteria produce endotoxin that can directly lead to tissue factor exposure with resulting excess thrombin generation. In addition, any infection can lead to expression of inflammatory cytokines that induce tissue factor expression by endothelium and monocytes. Some viruses and rickettsia can directly infect the vascular endothelium, converting it from an antithrombotic to a prothrombotic phenotype. The hypotension produced by sepsis leads to tissue hypoxia, which results in more DIC. The coagulopathy can range from subtle abnormalities of testing to purpura fulminans. Thrombocytopenia is worsened by cytokine-induced hemophagocytic syndrome.

As with all forms of DIC, empiric therapy directed

---

**Table 3. Transfusion Therapy of DIC: Management Guidelines**

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt; 50,000–75,000 cells/µL</td>
<td>Platelet concentrates or 6–8 packs of single donor platelets</td>
</tr>
<tr>
<td>Fibrinogen &lt; 125 mg/dL</td>
<td>10 units of cryoprecipitate</td>
</tr>
<tr>
<td>Hematocrit &lt; 30%</td>
<td>Packed red cells</td>
</tr>
<tr>
<td>PT/INR &gt; 2.0 and aPTT abnormal</td>
<td>2 to 4 units of FFP</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; FFP = fresh frozen plasma; INR = international normalized ratio; PT = prothrombin time.
Patients with secondary purpura fulminans have been treated with plasma drips, plasmapheresis, and continuous plasma ultrafiltration. 46-49 Heparin therapy alone has not been shown to improve survival. 50 Much attention has been given to replacement of natural anticoagulants such as protein C and antithrombin as therapy for purpura fulminans, but unfortunately randomized trials using antithrombin have shown mostly negative results. 37,41,51-53 Trials using either zymogen protein C concentrates or rhAPC have shown more promise in controlling the coagulopathy of purpura fulminans and improving outcomes in sepsis. 47,54-57 Although bleeding is a concern with use of protein C, most complications occur in patients with platelet counts under 30,000 cells/μL or in those who have meningitis. 58 If rhAPC is used, one should also very carefully monitor other parameters of coagulation (Table 4). Many patients will need debridement and amputation for their necrotic limbs, with one review showing that approximately 66% of patients require amputations. 58

### TRAUMA

Currently, the most common cause of acute DIC is trauma. The coagulation defects that occur in trauma patients are complex in origin. 59 The most common etiologies are dilution of hemostatic factors by fluid or blood resuscitation, hypothermia, tissue damage from trauma, and effects of underlying diseases. Trauma patients are prone to hypothermia, and this can be the major complicating factor in their bleeding. 60,61 Patients may be out “in the field” for a prolonged period of time and be hypothermic on arrival. 52 Packed red cells are stored at 4°C, and the infusion of 1 unit can lower the body temperature by 0.16°C. 63 Hypothermia has profound effects on the coagulation system that are associated with clinical bleeding. 60,64,65 Even modest hypothermia can greatly augment bleeding and needs to be treated or prevented.

The initial management of the bleeding trauma patient consists of obtaining the basic set of coagulation tests. 39,66,67 If the patient is having obvious massive hemorrhage, red cells and plasma should be empirically infused until the results of laboratory tests are received. Since patients with head trauma can develop defibrination, therapy with cryoprecipitate and plasma should be considered. 68 Hypothermia can be prevented by several measures. One is to transfuse the blood through blood warmers. Devices are available that can warm a unit of blood per minute. An increasingly used technique is to perform “damage control” surgery. Patients are initially

---

**Table 4. Treatment of Purpura Fulminans with Recombinant Human Activated Protein C (rhAPC)**

<table>
<thead>
<tr>
<th>Therapy for Purpura Fulminans with Recombinant Human Activated Protein C (rhAPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer rhAPC 24 μg/kg/hr for 96 hours</td>
</tr>
<tr>
<td>Initiate blood product support to maintain:</td>
</tr>
<tr>
<td>An INR &lt; 2</td>
</tr>
<tr>
<td>aPTT less than 1.8 times normal (rhAPC will raise aPTT by 5–7 sec)</td>
</tr>
<tr>
<td>Platelet count over 50,000 cells/μL</td>
</tr>
<tr>
<td>Consider continuous veno-veno hemofiltration</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

at the most likely source of infection and maintaining hemodynamic stability are key to therapy. As discussed below, heparin and other forms of coagulation replacement therapy, with the controversial exception of recombinant human activated protein C (rhAPC), or drotrecogin alfa (activated), are of no benefit.

**PURPURA FULMINANS**

DIC in association with necrosis of the skin is seen in 2 situations, primary and secondary purpura fulminans. 37,28 Primary purpura fulminans is most often seen after a viral infection. 39 In these patients, the purpura fulminans starts with a painful red area on an extremity that rapidly progresses to a black ischemic area. Acquired deficiency of protein S is found in many patients. 37,40,41 Secondary purpura fulminans is most often associated with meningococcemia infections but can be seen in any patient with overwhelming infection. 52-54 Post-splenectomy sepsis syndrome patients and those with functional hyposplenism due to chronic liver disease are also at risk. 65 Patients present with signs of sepsis, and the skin lesions often involve the extremities and may lead to amputations. As opposed to primary purpura fulminans, those with the secondary form will have symmetrical distal ischemia (toes and fingers) that ascends as the process progresses. Rarely, adrenal infarction (Waterhouse-Friderichsen syndrome) can occur, which leads to severe hypotension. 45

Therapy for purpura fulminans is controversial. Primary purpura fulminans, especially in those with post-varicella autoimmune protein S deficiency, has responded to plasma infusion titrated to keep the protein S level above 25%. 37 Intravenous immunoglobulin has also been reported to help decrease the anti-protein S antibodies. Heparin has been reported to control the DIC and extent of necrosis. 46 The starting dose in these patients is 5 to 8 units/kg/hr. 2
stabilized with control of damaged vessels and packing of oozing sites.\textsuperscript{69} Then the patient is taken to the intensive care unit to be warmed and have coagulation defects corrected.

**PREGNANCY-RELATED DIC SYNDROMES**

**Acute DIC of Pregnancy**

Pregnancy can be associated with the rapid onset of severe DIC in 2 situations, abrupton and amniotic fluid embolism.\textsuperscript{20,71} The separation of the placenta from the uterine wall creates a space for blood to occupy. Because the placenta is rich in tissue factor, this separation leads to activation of coagulation both locally and systemically. Release of blood when this space reaches the vaginal opening can lead to rapid hemorrhage, further augmenting the coagulation abnormalities. Fetal demise due to placental insufficiency can also worsen the DIC. Management depends on the size of the abruption and the clinical status of both mother and fetus.\textsuperscript{70} For severe bleeding and DIC, blood product support is crucial to allow safe delivery. For smaller abruption, close observation with early delivery is indicated.

Amniotic fluid embolism occurs suddenly with the vascular collapse of the woman soon after delivery. Due to the presence of procoagulant rich fluid in the circulatory system, there is often overwhelming DIC. Therapy is directed at both supporting blood volume and correcting hemostatic defects.

**HELLP Syndrome**

The HELLP (hemolysis, elevated liver tests, low platelets) syndrome is a variant of preeclampsia.\textsuperscript{72} Classically, HELLP syndrome occurs after 28 weeks of gestation in a patient suffering from preeclampsia, but can occur as early as 22 weeks in patients with APS.\textsuperscript{73–75} The preeclampsia need not be severe. The first sign of HELLP is a decrease in the platelet count followed by abnormal liver function tests. Signs of hemolysis are present with abundant schistocytes on the smear and a high lactate dehydrogenase level. HELLP can progress to liver failure, and deaths due to hepatic rupture have also been reported. Unlike TTP, fetal involvement is present in the HELLP syndrome, with fetal thrombocytopenia reported in 30% of cases. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will most often result in cessation of the HELLP syndrome, but refractory cases require treatment with dexamethasone and plasma exchange.\textsuperscript{70} Patients should be closely observed for 1 to 2 days after delivery as the hematologic picture can transiently worsen before improving.\textsuperscript{77}

**Acute Fatty Liver of Pregnancy**

Fatty liver of pregnancy also occurs late in pregnancy and is associated with preeclampsia in 50% of cases.\textsuperscript{78,79} Patients first present with nonspecific symptoms of nausea and vomiting but can progress to fulminant liver failure. Patients develop thrombocytopenia early in the course, but in the later stages can develop DIC and very low fibrinogen levels. Mortality rates without therapy can be as high as 90%. Low blood glucose and high ammonia levels can help distinguish fatty liver from other pregnancy complications.\textsuperscript{80} Treatment consists of prompt delivery of the child and aggressive blood product support.

**Retained Dead Fetus Syndrome**

This syndrome is becoming increasingly rare in modern practices. The presence of a dead fetus for many weeks (usually $\geq 5$) can result in a chronic DIC state with fibrinogen depletion and coagulopathy. In some women, these abnormalities worsen at delivery. In a stable patient, a short trial of heparin prior to planning delivery can control the DIC to allow the coagulopathy to stabilize.

**DRUG-INDUCED HEMOLYTIC-DIC SYNDROMES**

A severe variant of the drug-induced immune complex hemolysis associated with DIC has been recognized. Although rare, this syndrome has been reported in patients who receive certain second- and third-generation cephalosporins (especially cefotetan and ceftriaxone).\textsuperscript{81–86} The clinical syndrome starts 7 to 10 days after the drug is administered, and often the patient has received the antibiotic only for surgical prophylaxis. The patient develops severe Coombs’ positive hemolysis with hypotension and DIC. The patients are often believed to have sepsis and often re-exposed to the cephalosporin, resulting in worsening of the clinical picture. The outcome is often fatal due to massive hemolysis and thrombosis.\textsuperscript{83,87–89}

Quinine is associated with a unique syndrome of drug-induced DIC.\textsuperscript{90–93} Approximately 24 to 96 hours after quinine exposure, the patient becomes acutely ill with nausea and vomiting. The patient then develops a microangiopathic hemolytic anemia, DIC, and renal failure. Besides having antiplatelet antibodies, some patients also have antibodies binding to red cells and neutrophils, which may lead to the more severe syndrome. Despite therapy, patients with quinine-induced TTP have a high incidence of chronic renal failure.

Treatment of the drug-induced hemolytic-DIC syndrome is anecdotal. Patients have responded to aggressive therapy, including plasma exchange, dialysis, and prednisone.\textsuperscript{91} Early recognition of the hemolytic anemia
and suspicion that it is drug related is important for early diagnosis so that the drug can be discontinued.

CANCER

Cancers, primarily adenocarcinomas, can result in DIC. The classic Trousseau’s syndrome referred to the association of migratory superficial thrombophlebitis with cancer, but now refers to cancer associated with thrombotic DIC. Highly vascular tumor cells are known to express tissue factor, and some tumor cells can express a direct activator of factor X (“cancer procoagulant”). Unlike many DIC states, DIC caused by cancer presents with thrombosis instead of bleeding. This may be due to the inflammatory state which accompanies cancer, or it may be a part of the chronic nature of cancer DIC biology that allows time for the body to compensate for loss of coagulation factors. In some patients, thrombosis is the first sign of an underlying cancer, sometimes predating the cancer diagnosis by months. Rarely the DIC can result in nonthrombotic endocarditis with microemboli leading to widespread small-vessel thrombosis.

Since there is no effective antineoplastic therapy for many tumors associated with Trousseau’s syndrome, DIC therapy is aimed at suppressing thrombosis. An exception is prostate cancer, where hormonal therapy can markedly decrease the DIC. Because the tumor directly activates coagulation factors, inhibition of active enzymes via heparin has been shown to result in lower rates of recurrence than use of warfarin. Clinical trials have demonstrated that heparin therapy is associated with a lower thrombosis recurrence rate than warfarin. In some patients, the thrombotic process is so vigorous that new thrombosis can be seen within hours of stopping heparin.

ACUTE PROMYELOCYTIC LEUKEMIA

The hemostatic defects in patients with acute promyelocytic leukemia (APL) are multiple. Most, if not all, patients with APL have evidence of DIC at the time of diagnosis. Patients with APL have a higher risk of death during induction therapy as compared with patients with other forms of leukemia, with death most often due to bleeding. Once in remission, APL patients have a higher cure rate than most patients with leukemia. APL is also unique among leukemias in that biological therapy with retinoic acid or arsenic is effective in inducing remission and cure in most patients.

APL patients can present with pancytopenia due to leukemic marrow replacement or with diffuse bleeding due to DIC and thrombocytopenia. Life-threatening bleeding such as intracranial hemorrhage may occur at any time until the leukemia is put into remission. The etiology of the hemostatic defects in APL is complex and is thought to be the result of DIC, fibrinolysis, and the release of other procoagulant enzymes. The diagnosis of APL can be straightforward when the leukemic cells are promyelocytes with abundant Auer rods, although some patients have the microgranular form without obvious Auer rods. The precise diagnosis requires molecular methods. Upon diagnosis of APL, one should obtain a complete coagulation profile, including INR, aPTT, fibrinogen, platelet count, and D-dimers. Change in fibrinogen levels tends to be a good marker of progress in treating the coagulation defects.

Therapy of APL involves treating both the leukemia and the coagulopathy. Currently, the standard treatment for APL is trans-retinoic acid (ATRA) in combination with chemotherapy. This approach will induce remission in over 90% of patients, and a sizable majority of these patients will be cured of their APL. ATRA therapy will also lead to early correction of the coagulation defects, often within the first week of therapy. This is in stark contrast to the chemotherapy era when the coagulation defects would become worse with therapy. Rare reports of massive thrombosis complicating therapy with ATRA exist, but the relationship to either the APL or ATRA is unknown.

Therapy for the coagulation defects consists of aggressive transfusion therapy support and possible use of other pharmacologic agents to control DIC. One should try to maintain the fibrinogen level at over 100 mg/dL and the platelet count at over 50,000 cells/μL. Controversy still exists over the role of heparin in therapy of APL. Although attractive for its ability to quench thrombin, heparin use can lead to profound bleeding and has fallen out of favor.

SNAKEBITES

Snake envenomation can lead to direct activation of multiple coagulation enzymes, including factors V, X, thrombin, and protein C as well as lead to cleavage of fibrinogen. Envenomation can also activate coagulation and damage vascular endothelium. The DIC can be enhanced by widespread tissue necrosis and hypotension. The key to management of snake bites is administration of specific antivenom. The role of factor replacement is controversial but indicated if there is clinical bleeding. One confounder is that some snake venoms, especially rattlesnake, can induce reversible platelet aggregation that corrects with antivenom.

LOCAL VASCULAR ABNORMALITIES

Abnormal vascular structures, including vascular...
Disseminated Intravascular Coagulation
tumors, vascular malformations, and aneurysms, can lead to localized areas of thrombin generation that can “spill-over” into the general circulation, leading to DIC. The diagnosis Kasabach-Merritt phenomenon should be reserved for children with vascular tumors such as angioma or hemangioendothelioma. Therapy depends on the lesion. Embolization to reduce blood flow of vascular malformations can either be definitive or stabilize the patient for surgery. Aneurysms can be repaired by surgery or stenting. Rare patients with aneurysms with significant coagulopathy may require heparin to increase the fibrinogen level before surgery. Kasabach-Merritt disease can respond to steroids or therapy with vincristine or interferon.

SUMMARY

At the most basic level, DIC is the excess activity of thrombin. However, the clinical presentation and therapy can differ greatly depending on the primary cause. Both diagnosis and therapy involve close coordination of laboratory data and clinical assessment.

REFERENCES


Copyright 2010 by Turner White Communications Inc., Wayne, PA. All rights reserved.