Hematological Issues in Critically Ill Patients with Cancer

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Patients with solid and hematologic malignancies including patients undergoing hematopoietic stem cell transplantation are at risk for bleeding and thrombotic complications. The diagnosis of cancer is often made in the context of a new bleeding diathesis or an unprovoked venous thromboembolism. Patients presenting with major bleeding or thrombotic complications usually require admission to an intensive care unit (ICU). These complications can also be the life-ending event in a cancer patient’s clinical course, making their diagnosis and management even more important for the intensivist. Given the significant advances in the diagnosis and treatment of almost all types of cancers in recent years, the intensivist is likely to encounter an ever-increasing number of cancer patients in the ICU setting with these complications.

Abnormal hemostasis can occur as a consequence of both the pathology and treatment of cancer. Because cancer can have multiple effects on hemostatic equilibrium, treatment of these complications can be more complex than in the general population. This article reviews the physiology of coagulation and fibrinolysis, with special attention to those aspects that are most frequently altered in the setting of malignancy. The pathophysiology of bleeding and thrombotic complications specific to critically ill cancer patients are then detailed, and the diagnostic and therapeutic strategies are discussed. Special emphasis is placed on new cancer medications that have an effect on hemostasis, and on novel clotting and anticoagulant agents that are available to the intensivist for the management of these patients.

PHYSIOLOGY OF NORMAL HEMOSTASIS

Hemostasis is the process that maintains the integrity of a closed, high-pressure circulatory system after vascular damage. Hemostasis is a balanced series of protease
cascades and cellular interactions that ultimately control initiation of thrombin formation, propagation of thrombin activation, activation of endogenous anticoagulants, and fibrinolysis (Fig. 1).¹

Platelet Thrombus Formation

Under physiologic circumstances, thrombus formation is initiated by injury to a vessel wall and the inner endothelial lining, exposing the subendothelial extracellular matrix. This process results in exposure of collagen, fibronectin, von Willebrand factor, and tissue factor (TF) to circulating platelets.²–⁵ These proteins bind platelet receptors, localizing platelets to the site of injury, and initiating a cascade of events resulting in

Fig. 1. Physiology of normal coagulation. Pg, plasminogen; PN, plasmin.
platelet activation. The end result is assembly and activation of the platelet receptor glycoprotein IIb-IIIa (GPIIb-IIIa) on the platelet cell membrane. GP IIb-IIIa is able to bind both von Willebrand factor and fibrinogen, resulting in irreversible platelet adhesion and aggregation and ultimately in rapid formation of a platelet plug at the site of vessel wall injury. Exposed TF initiates the generation of thrombin, which not only converts fibrinogen to fibrin but also activates platelets.

**Fibrin Generation**

Blood coagulation is initiated by TF, culminating in the generation of thrombin and fibrin. TF, a membrane protein expressed on fibroblasts and pericytes in the adventitia and medial smooth muscle cells of the vessel wall, binds activated factor VII (VIIa). VIIa activates factors X and IX. Activated factor IX (factor IXa) then combines with factor VIIIa, which is activated from factor VIII by thrombin, to form a second pathway to activate factor X. Factor Xa complexes with factor Va and prothrombin to form the prothrombinase complex, which then cleaves prothrombin (factor II) to form thrombin (factor IIa), the key enzyme in hemostasis. Fibrin is ultimately generated by cleavage of fibrinogen by thrombin to form fibrin monomers, which then polymerize to form the fibrin clot. This polymer is covalently cross-linked by factor XIIIa (generated from factor XIII by thrombin) to form a chemically stable clot. Thrombin also feeds back to activate cofactors V, VIII, and XI, further amplifying the coagulation system (see Fig. 1).

**Natural Anticoagulant Mechanisms**

Fibrin deposition is limited by an endogenous anticoagulant system. Antithrombin (AT) is a plasma protein member of the serpins (serine protease inhibitors) family that inhibits the activities of all of the activated protease enzymes. Protein C is a vitamin K-dependent protein that proteolyses factor Va and factor VIIIa to inactive fragments. Protein C binds to an endothelial cell protein C receptor (EPCR) and is activated by thrombin bound to thrombomodulin, another endothelial cell membrane-based protein, in a reaction that is modulated by a cofactor, protein S. TF pathway inhibitor is a plasma protein that forms a quaternary complex with tissue factor, factor VIIa, and factor Xa, thereby inhibiting the extrinsic coagulation pathway (see Fig. 1).

**Fibrinolysis**

Fibrinolysis is the protease cascade that leads to breakdown of a fibrin clot (see Fig. 1). The 2 physiologic initiating enzymes are tissue-type and urokinase plasminogen activator (t-PA and u-PA, respectively). Both proteases are capable of activating plasminogen to the active protease, plasmin, which then degrades fibrin into fibrin degradation products (FDP).

 t-PA and plasminogen bind to specific lysine residues within fibrin, and to annexin II on the surface of endothelial cells, monocytes, myeloid lineage cells, and smooth muscle cells. Fibrin binding not only localizes both proteases to the clot but also increases the catalytic efficiency of the single-chain active zymogen form of t-PA. There is convincing evidence that the initiating event for t-PA–mediated fibrinolysis is in fact generation of the fibrin clot itself (see Fig. 1).

In contrast, urokinase is not incorporated into a developing fibrin clot, but is instead localized to the surface of endothelial cells, monocytes, fibroblasts, and many tumor cells via binding to the urokinase-type plasminogen activator receptor (uPAR). As with t-PA, fibrin interactions, binding of single-chain u-PA to uPAR, results in a significant increase in urokinase catalytic efficiency and thus potential for cell surface plasmin generation.
Fibrinolysis is negatively regulated by the serine protease inhibitors (serpins) plasminogen activator inhibitor-1 (PAI-1), PAI-2, and α2-antiplasmin, and by thrombin-activatable fibrinolysis inhibitor (TAFI). When excess plasmin in the blood has saturated all the available α2-antiplasmin, a slower acting inhibitor, α2-macroglobulin, acts as a second-line defense.

**RELATIONSHIP OF THE COAGULATION SYSTEM AND CANCER**

The relationship between the coagulation system and malignancy was first recognized by Bouillaud in 1823 when he described 3 patients with malignancy and fibrin clots, and later by Trousseau in 1865 when he further described the link between cancer and thrombosis. In 1878, Billroth demonstrated cancer cells within a thrombus and theorized that tumor cells spread by thromboembolism. Cancer can affect all 3 aspects of Virchow’s triad, namely changes in blood flow or stasis by physical occlusion of vessels by tumor mass or by increased intravascular cell mass, alteration of the normal hemostatic balance toward a hypercoagulable state, and direct injury to blood vessel endothelium.

Several procoagulant molecules are specifically upregulated in cancer, including TF and cancer procoagulant (CP). TF expression is closely regulated, and present on the surface of endothelium and monocytes or macrophages only with vessel injury. However, cancer produces a proinflammatory state that triggers release of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) that upregulate TF expression in these cell types. CP is a procoagulant vitamin-K independent molecule thought to be specifically expressed by cancer cells, capable of direct factor X activation. In addition to the upregulation of procoagulant molecules, TNF-α and IL-1β also downregulate thrombomodulin, therefore decreasing activation of protein C, and thus the endogenous anticoagulant system, and they also upregulate PAI-1 expression, which decreases effective fibrinolysis.

The propensity toward venous thromboembolism (VTE) in cancer patients is startling. Correcting for all other risk factors, cancer patients have an approximately six-to sevenfold higher risk of VTE than their cancer-free counterparts, and 1 in 7 cancer patients who dies in the hospital will die from a pulmonary embolism. Furthermore, an unprovoked VTE may be a herald sign of malignancy. Recent evidence suggests that patients with splanchnic venous thromboembolism should be tested for JAK2V617F mutation as an early screen for Ph-myeloproliferative disease. A recent meta-analysis indicated that extensive workup for malignancy including abdominal and pelvic imaging may be warranted in cases of otherwise unprovoked VTE. Finally, several reports suggest that prolonged treatment with warfarin may reduce the incidence of certain cancers.

**Pathophysiology and Management of Bleeding and Thrombosis in Cancer**

Changes in hemostasis often occur with cancer patients, and can be catastrophic, which may result in their admission to the ICU. The mechanisms by which bleeding and thrombosis occur are related both to the effects of tumors on normal organ systems, as a direct effect of altered protein expression by malignant cells, and to the cancer treatment including surgery, chemotherapy, antiangiogenic agents, radiotherapy, and hormonal therapy (Box 1).

**Bleeding complications**

Bleeding in the cancer patient may present as a localized bleeding, mainly as a direct result of tumor invasion to blood vessels, or as a generalized bleeding diathesis. The latter is usually due to severe thrombocytopenia, thrombocytopenathies, coagulation
factor consumption or deficiencies, hyperfibrinolysis, or a combination of all the mentioned factors. Proper management of bleeding in the critically ill patient with cancer depends on the underlying disorder responsible for the bleeding. This article focuses on disorders that can lead to clinically significant or major bleeding in the cancer patient admitted to the ICU.

**Thrombocytopenia** Thrombocytopenia is the most frequently noted hemostatic disorder in patients with cancer, occurring in approximately 10% of cases before ever receiving chemotherapy. In the critical care setting, thrombocytopenia can be the underlying cause for a life-threatening hemorrhage, and can be the reason for delay of administration of therapy. Thrombocytopenia is best understood and treated by consideration of the underlying mechanisms, including (1) decreased platelet production, (2) increased platelet destruction or consumption, and (3) splenic sequestration (Box 2).

To differentiate between these 3 mechanisms of thrombocytopenia, it is important to obtain a detailed history of a patient’s medical history including the time course of development of thrombocytopenia, current medications, presence and type of associated bleeding, and concurrent medical issues. The peripheral smear is of critical importance, as it will facilitate verification of the extent of thrombocytopenia and assist with differentiation between the multiple causes of a low platelet count (Fig. 2). For instance, a spurious low platelet count can be seen with automatic cytometers when there is platelet clumping, platelet satellitism, or platelets of unusual shape or size. Detection of schistocytes or microspherocytes will suggest a microangiopathic process. In cases where there is clinically significant bleeding, it is more likely that thrombocytopenia is a result of impaired platelet production rather than immune mediated peripheral destruction of platelets.
Decreased platelet production

Impaired thrombopoiesis is reliant on hematopoietic stem cell (HSC) differentiation into megakaryocytes under the regulation of thrombopoietin (TPO) acting on the Mpl receptor in conjunction with interleukin (IL)-6, IL-2, and IL-11. As HSCs differentiate into myeloid progenitor cells and eventually to megakaryocytes, they migrate from the bone marrow stem cell compartment to the marrow sinusoids where specific stromal cells produce stromal derived factor-1α (SDF-1α) and fibroblast growth factor-4 (FGF-4), which are critical for platelet production. Any process such as marrow infiltration with malignant cells or chemotherapy that prevents normal maturation of HSCs to mature megakaryocytes, either by altering the bone marrow stroma or preventing precursor cell migration, can alter platelet production. Thrombocytopenia due to decreased platelet production is most

**Box 2**

**Differential diagnosis of thrombocytopenia in patients with cancer**

- **Decreased platelet production**
  - Metastasis to bone marrow
  - Acute and chronic leukemias
  - Lymphomas
  - Plasma cell dyscrasias
  - Cytotoxic chemotherapy
  - Radiation therapy
- **Platelet destruction**
  - Medications
  - Immune mediated
  - Bacterial sepsis
  - Viral, fungal, and protozoal infections
  - Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
- **Splenectomy**
  - Myeloproliferative disorders
  - Lymphomas
  - Chronic lymphocytic leukemias
  - Combination of these mechanisms

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**Fig. 2.** Thrombotic thrombocytopenic purpura (100×).
commonly seen with hematological malignancies. However, bone marrow infiltration from solid tumors such as breast, prostate, and small cell lung cancers also occurs.

**Platelet destruction and splenic sequestration** Increased peripheral destruction of platelets may be drug-induced or sepsis-mediated, and also occurs within the context of disseminated intravascular coagulation (DIC) and thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS).\(^{31}\) Thrombocytopenia secondary to splenic sequestration is usually observed with myeloproliferative disorders, and less commonly with lymphomas and chronic lymphocytic leukemia (CLL). Clinically evident bleeding episodes are more likely to occur when thrombocytopenia is caused by diminished production of megakaryocytes rather than by immune destruction.

The most common clinical manifestation of thrombocytopenia is mucocutaneous bleeding, which can occur in the form of petechiae, ecchymoses, epistaxis, oral, gastrointestinal, or genitourinary bleeding. Spontaneous bleeding usually does not occur unless the platelet count is less than 10,000/mm\(^3\). However, in the presence of sepsis, uremia, trauma, or surgery, bleeding complications with a higher platelet count may occur.

**ACUTE MANAGEMENT OF THROMBOCYTOPENIA**

The treatment of bleeding associated with thrombocytopenia in the cancer patient is often managed empirically, even when a specifically defined cause cannot be identified. Prophylactic transfusion of platelets is not indicated in patients who are asymptomatic for bleeding unless the platelet count is less than 5000/mm\(^3\). However, in cancer patients undergoing chemotherapy and those with leukemia, prophylactic platelet transfusions are generally beneficial in decreasing the risk of bleeding when the platelet count is less than 10,000/mm\(^3\). For cancer patients undergoing major surgery or invasive procedures such as central venous catheterization, bronchial or endoscopic biopsy, lumbar puncture, thoracentesis, thoracotomy tube placement, and abdominal paracentesis, it is generally recommended that platelet transfusions should be administered in thrombocytopenic patients to a target level of greater than 50,000/mm\(^3\) (see **Box 2**).\(^{35}\) For minor invasive procedures such as arterial puncture or cannulation, prophylactic transfusion is not necessary if the platelet count is at least 20,000/mm\(^3\) and local pressure is applied at the puncture site until hemostasis is achieved. Platelet transfusions are usually indicated in thrombocytopenic patients to keep the platelet count greater than 50,000/mm\(^3\) when evidence of microscopic or gross bleeding is detected, as manifested by either occult blood on stool guaiac tests and mucocutaneous bleeding. The risk of central nervous system bleeding is generally low and bleeding depends on several factors such as underlying causes of thrombocytopenia, coagulation abnormalities, impaired renal or hepatic function, severe sepsis, trauma, and the use of mechanical ventilation. In the event of an intracerebral bleed, a platelet count greater than 100,000/\(\mu\)l is advised (**Table 1**).\(^{36,37}\) Comparative studies have shown that platelets derived from single or random donors produce similar posttransfusion increments, hemostatic benefits, and side effects.\(^{35}\) If a platelet transfusion fails to adequately control bleeding or increase the measured platelet count as anticipated, there are several factors to be considered, including (1) continued bleeding or platelet consumption, (2) alloimmunization, and (3) hypersplenism. In addition to consideration of the clinical scenario, it is helpful to measure platelet count 1 hour and 24 hours following transfusion. If the platelet count increases at 1 hour but is not maintained at 24 hours after transfusion, ongoing bleeding or a platelet consumptive process such as DIC or sepsis is most likely the cause. However, if the
platelet count fails to increase at 1 hour, hypersplenism and alloimmunization are more likely contributing factors. If platelet refractoriness is on the working differential, platelet antibody testing should be performed to look for human leukocyte antigen (HLA) antibodies and appropriate cross-matched platelets obtained.37

THROMBOCYTOPATHIES

Changes in platelet function can also occur in the setting of malignancy, including development of an acquired von Willebrand syndrome, acquired factor VIII deficiency, uremic platelets, and other qualitative platelet defects seen in myeloproliferative disorders such as essential thrombocytopenia and polycythemia vera where marked thrombocytosis can occur.

Acquired von Willebrand Syndrome

Several types of cancer have been reported in association with acquired von Willebrand syndrome (aVWS). Among the lymphoproliferative disorders, monoclonal gammopathy of undetermined significance (MGUS) is the condition most frequently associated with aVWS. MGUS can also be associated with multiple myeloma, Waldenstrom macroglobulinemia, CLL, hairy cell leukemia, and non-Hodgkin lymphoma. Among the myeloproliferative disorders, essential thrombocytopenia is the most common, with polycythemia vera and chronic myeloid leukemia being less frequent. Solid tumors including Wilms tumors and carcinomas have also been associated with aVWS.38–40

The clinical manifestations of aVWS are similar to those seen in patients with the hereditary form of the disease, except for the notable absence of a family history or lifelong personal history for bleeding. Spontaneous mucocutaneous and gastrointestinal bleeding may be present; postsurgical bleeding may also occur. Laboratory screening tests generally reveal a prolonged activated partial thromboplastin time (aPTT) and a normal to borderline prolonged bleeding time. Plasma vWF antigen, vWF ristocetin cofactor activity, ristocetin-induced platelet aggregation, and vWF collagen binding activity are generally decreased. Laboratory tests usually fail to demonstrate inhibitory activity against vWF or factor VIII. Treatment is directed to the underlying malignancy and supportive measures including corticosteroids,

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<td>Critical platelet counts and recommendations for transfusion in cancer patients</td>
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<td><strong>Platelet count threshold</strong></td>
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<td>Mucocutaneous or gastrointestinal bleeding</td>
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<td>Leukemias</td>
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These recommendations are intended to serve as general guidelines. Actual treatment will vary depending on specific circumstances.
deamino-8-d-arginine vasopressin (desmopressin acetate [DDAVP]), factor VIII/vWF concentrate, and intravenous immunoglobulin (IVIg). Recombinant factor VII (rFVIIa, NovoSeven) has also been used.\textsuperscript{41}

**Acquired Factor VIII Inhibitors**

Autoantibodies to factor VIII can develop in patients with lymphoproliferative and myeloproliferative\textsuperscript{42} disorders, plasma cell dyscrasias, and solid tumors. The most common presentation is bleeding into the skin or muscles in patients with no previous history of bleeding diathesis. Most patients present with severe bleeding; life-threatening hemorrhage is more commonly seen in the first several weeks of presentation but can occur at any time if treatment is not initiated.\textsuperscript{38–40} The hallmark laboratory finding is a prolongation of the aPTT in the presence of a normal prothrombin time (PT). Plasma mixing studies demonstrate an aPTT that remains prolonged after incubation at 37°C for 1 to 2 hours. Contamination of the blood sample with heparin, which frequently is the inadvertent result of instillation for maintaining vascular access line patency, may artifactually prolong the aPTT and affect the mixing tests. Heparin that has entered the sample may be removed with the enzyme reptilase or resin absorption, after which the plasma may be retested. A prolonged thrombin time in the presence of a normal reptilase time confirms the suspicion of heparin contamination. After a mixing study confirms the presence of an inhibitor and other nonspecific inhibitors have been ruled out, the factor VIII activity should be measured. If the factor VIII activity is low, the titer of the factor VIII antibody should be ascertained. The strength of an inhibitor can quantified by using the Bethesda assay, which measures residual factor VIII activity after incubation of normal plasma with serial dilutions of patient plasma for 2 hours at 37°C. The inhibitor titer in Bethesda units (BU) represents the reciprocal of the dilution of the patient’s plasma that leads to 50% inhibition in the assay described. The goals in the treatment of acquired factor VIII inhibitors in patients with cancer are twofold: (1) management of the acute bleeding and (2) elimination of the autoantibody against factor VIII. The acute bleeding can be managed with desmopressin acetate if there is a low inhibitor titer (<5 BU) or with human or porcine factor VIII. Factor VIII bypassing agents such as recombinant human factor Vila, or activated prothrombin complex concentrate are used in case of moderate- to high-titer inhibitor (>5 BU). Immunosuppressive therapy such as corticosteroids, cyclophosphamide, vincristine, cyclosporine, and intravenous immunoglobulin (IVIg) may be used in addition to the treatment of the underlying cancer. Rituximab should be considered in patients who are resistant to first-line therapy or cannot tolerate standard immunosuppressive therapy. It has been proposed that rituximab should be included as first-line therapy in combination with prednisone for patients with an inhibitor titer greater than 5 but less than 30, and in addition to prednisone and cyclophosphamide for those patients with a titer greater than 30.\textsuperscript{40} Plasmapheresis may be helpful to transiently remove the autoantibody (typically IgG) from circulation.\textsuperscript{31,43}

**Uremia**

Acute and chronic renal failure are frequent comorbidities in the critically ill cancer patient. Platelet dysfunction secondary to renal failure may cause significant bleeding. The pathophysiology of platelet dysfunction with uremia is multifactorial and includes dysfunctional vWF, increased levels of cyclic adenosine monophosphate and nitric oxide generated by platelets, uremic toxins, and anemia, which causes the platelets to be displaced from the vascular endothelium thereby decreasing their ability to adhere and aggregate in response to endothelial damage.\textsuperscript{44} Treatment is recommended for patients with active bleeding or for those undergoing an invasive procedure,
such as placement of a hemodialysis catheter. Patients usually respond to hemodialysis and administration of DDAVP at a dose of 0.3 μg/kg intravenous (IV); cryoprecipitate (10 units given IV over 30 minutes) and conjugated estrogens (0.6 mg/kg IV over 30–40 minutes once daily for 5 consecutive days) may occasionally be required. The time to onset of improvement with conjugated estrogens is as rapid as 6 hours, although peak effect occurs around 5 to 7 days after the start of treatment, and can be anticipated to last for up to 14 to 21 days. Erythropoietin-stimulating agents (ESA) such as recombinant human erythropoietin and darbepoetin have been shown to reduce and prevent bleeding in uremic patients, and have a more sustained effect than either DDAVP or conjugated estrogens. The effect of ESA on uremic bleeding occurs around 7 days after start of treatment, and is maximally effective once the hematocrit reaches normal level. The potential mechanisms for erythropoietin-mediated improvement include increased red cell volume pushing platelets closer to the endothelium thus decreasing the effective time to platelet-response to vascular injury, increase in reticular (metabolically most active) platelets, improved platelet aggregation and adherence to exposed subendothelium, increased platelet signaling via tyrosine phosphorylation, and the effect of increased hemoglobin as a nitric oxide scavenger.

**THROMBOCYTOSIS**

Cancer can cause both qualitative and quantitative changes in platelets. Significantly elevated platelet counts can occur with myeloproliferative disorders, mainly essential thrombocythemia (ET) and polycythemia vera (PV), and also in some solid tumors. The incidence of the recently described JAK2V617F mutation is found in virtually all patients with PV and approximately 50% of those with ET. Risk factors for thrombosis in both of these disorders include advanced age (>60 years) and prior history of thrombosis. Increased platelet turnover, TF, factor V and VIII activity, acquired activated protein C resistance, and decreased protein S have been shown to occur in patients with the JAK2 mutation and thrombosis.

For patients with critically high platelet counts (>1,000,000/μl) who are at risk for thrombosis or bleeding, secondary to abnormal platelet function of the majority of platelets, plateletpheresis may be considered along with cytoreductive therapy to treat the underlying myeloproliferative disorder in the acute setting. More long-term management once a patient has stabilized include interferon therapy, hydroxyurea, anagrelide, and JAK2 inhibitors, with limited side effects.

**BLEEDING ASSOCIATED WITH COAGULATION FACTOR ABNORMALITIES**

Critically ill cancer patients may develop various coagulation factor abnormalities as a result of vitamin K deficiency from malnutrition, diarrhea, liver disease, biliary obstruction, use of vitamin K antagonists, and antibiotic therapy. Patients with primary or metastatic hepatocellular carcinoma have deficiency of vitamin K-dependent factors (factors II, VII, IX, X, protein C, and protein S), similar to that seen with liver cirrhosis. These patients almost always have increased levels of fibrinogen, unlike patients with cirrhosis or acute liver failure who have decreased fibrinogen levels. Acquired inhibitors of coagulation factors are frequently seen in multiple myeloma and other plasma cell dyscrasias. Increased fibrinolysis is another cause of bleeding that may occur, especially in patients with acute promyelocytic leukemia where the leukemic cells overexpress annexin II, a t-PA cell surface receptor, which results in increased t-PA dependent plasmin generation. In addition to annexin II overexpression, patients may also develop increased fibrinolysis as a result of impaired TAFI.
activation by thrombin or deficiency in $\alpha_2$-antiplasmin or PAI-1 as a result of impaired synthetic function.56

**Acute Management of Coagulopathy**

The treatment of cancer patients with coagulation factor deficiencies, aside from the treatment of the underlying malignancy and localized control of hemostasis with direct application of pressure, topical agents such as thrombin powder or fibrin glue, or surgical repair of injured vessels, is generally supportive and consists of vitamin K, fresh frozen plasma (FFP), and cryoprecipitate. Oral vitamin K is the treatment of choice; its administration is predictably effective and has the advantages of safety and convenience over parenteral routes. However, in the critically ill cancer patient a rapid response is necessary, and may be achieved by administering a slow IV infusion of 10 mg vitamin K over 15 to 30 minutes to minimize the risk of anaphylactic reactions and fat embolism resulting from the lipid emulsion. Intravenous vitamin K doses can be repeated up to every 12 hours until international normalized ratio (INR) or PT is normalized.57

FFP is plasma isolated from whole blood that is frozen within 6 hours of donation, containing 0.7 to 1 unit/mL of clotting factor activity for each clotting factor and 1 to 2 mg of fibrinogen per unit of 200 to 280 mL volume. The appropriate milliliter dose of FFP is calculated by multiplying the estimated patient plasma volume by the percentage increase in factor VII desired divided by 100. Factor VII has the shortest half-life, and so redosing of FFP is based on repletion of this factor. In clinical practice the usual dose of FFP used is 10 to 15 mL/kg by IV infusion. FFP should be transfused when immediate correction of coagulation factor deficiencies is required because of bleeding or in patients undergoing an invasive procedure; the dose may be higher in patients with massive bleeding. The complete dose should be given at least every 6 hours until hemostasis is achieved and clotting parameters are normalized. The drawback to factor repletion with FFP is the large fluid volume that must be administered. In patients in whom volume status is of concern, the amount of fluid needed to fully and continuously reverse a coagulopathy may not be feasible. Furthermore, because of the low concentration of clotting factors, the relative increase in factor activity once more than 1 liter of FFP is given with respect to a patient’s total plasma volume will be minimal. In this circumstance, consideration of other blood products is necessary.58

Cryoprecipitate is the cryoglobulin fraction of plasma obtained by thawing a single donation of FFP. Cryoprecipitate is rich in factor VIII, von Willebrand factor, fibrinogen, fibronectin, and factor XIII; it is indicated for dysfibrinogenemia and hypofibrinogenemic states, and also for some patients with renal failure. Cryoprecipitate is generally administered at a dose of 1 unit of cryoprecipitate IV for every 5 kg of body weight.37 Generally, 10 bags of cryoprecipitate are given if the fibrinogen level is between 50 and 100 mg/dL and 20 bags if it is less than 50 mg/dL. A fibrinogen level measured at 30 to 60 minutes after completion of the transfusion should be used to determine the need for additional doses. The therapeutic goal is to keep the plasma fibrinogen level above 100 mg/dL.

In recent years, new clotting factor concentrates have been approved for use in bleeding diathesis. These agents include purified or recombinant single factors such as recombinant factor VII (rFVIIa), and products that are physiologically relevant complexes of coagulation factors such as activated prothrombin complex concentrates (aPCCs), including factor VIII inhibitor bypassing activity (FEIBA). The hemostatic effect of rFVIIa depends on binding to TF and activated platelets.

rFVIIa (NovoSeven) is administered in hemophilia patients with inhibitors at a dose of 90 μg/kg IV every 2 to 3 hours until the bleeding has stopped. When using rFVIIa, the
PT, fibrinogen, and D-dimer should be carefully monitored to minimize the risk of thrombosis and DIC. The dose of rFVIIa may also need to be titrated downward based on a patient’s underlying risk factors for thrombosis. rFVIIa has also been used to control bleeding in hematopoietic stem cell transplant patients with diffuse alveolar hemorrhage or hepatic veno-occlusive disease in whom acquired factor VII deficiency results from liver dysfunction, and for hemorrhagic cystitis secondary to chemotherapy or radiation. The main risk associated with rFVIIa use is thrombosis that has ranged from less than 1% to 7% depending on the underlying patient comorbidities. DIC, myocardial infarction, stroke, and allergic reactions have also been described.

Activated PCCs are used in the treatment of patients with factor IX deficiency and in those with inhibitors to factor VIII. FEIBA is a plasma-derived isolate of prothrombin (factor II), factor VII, factor VIIa, factor IX, and factor X that is designed to bypass factor VIII to generate factor Xa when dosed at 50 to 100 U/kg IV every 6 to 12 hours. FEIBA depends on the presence of platelet-derived factor V to localize and initiate coagulation. The action of FEIBA largely depends on its thrombin content, probably accounting for its relatively long half-life of thrombin generation, several hours longer than that of rFVIIa. In general, aPCCs must be used with caution as they can be associated with venous thromboembolism or DIC.

If a paraprotein is the suspected origin of a coagulopathy such as development of a factor VIII inhibitor or aVWD, additional treatment modalities such as IVIg at a dose of 1 g/kg daily for 2 doses and plasmapheresis should be considered. The main side effects of IVIg include allergic reaction, acute renal failure associated with the increased protein load and immune-complex formation, and hyperviscosity. IgA deficiency should be considered in patients with allergic reactions to IVIg.

If increased fibrinolysis is a contributing cause of bleeding, antifibrinolytic agents such as tranexamic acid or ε-aminocaproic acid (EACA) should be considered. Both are lysine analogues that effectively elute plasminogen from a fibrin clot by competing with the protease for binding to C-terminal lysine residues exposed during fibrin generation. EACA is dosed orally up to 50 mg/kg every 6 hours or IV starting with a slow 5 g IV bolus followed by a continuous infusion of 1 g/h. Tranexamic acid similarly is dosed orally at 25 mg/kg or 10 mg/kg IV every 8 hours. These agents should not be administered to patients with DIC or in those receiving other clotting factor replacement or all-trans retinoic acid (used in the treatment of acute promyelocytic leukemia [APL]), as this will increase the risk of thrombosis. In addition, the doses of these 2 antifibrinolytic agents should be continuously monitored and reduced with impaired renal function.

**THROMBOTIC MANIFESTATIONS**

Patients in the ICU are at high risk for venous thromboembolism (VTE), and the risk is higher if they have underlying cancer. VTE is a significant comorbidity for patients with cancer, identified in up to 15% of patients with cancer during their disease course, and in up to 35% to 50% of cancer patients in postmortem studies. Cancers with the highest incidence of VTE include pancreatic and gastrointestinal cancers, as well as lung, brain, prostate, breast, and ovary, and patients with acute promyelocytic leukemia and myeloproliferative disorders. Patients with cancer have a higher risk of VTE recurrence and a higher risk of bleeding diathesis compared with those without cancer. This finding highlights some of the difficulties that arise in treatment of cancer patients for VTE, including factors such as ongoing tumor activity, pharmacotherapy, end organ injury (especially hepatic and renal dysfunction), and malnutrition.
The pathogenesis of thrombotic complications in cancer patients is multifactorial. In addition to the common predisposing factors for thrombosis such as immobility, advanced age, history of previous thrombosis, venous stasis, sepsis, and the use of central venous catheters, tumor cells have unique prothrombotic characteristics. Transformed malignant cells can induce platelet abnormalities, abnormal activation of the coagulation cascade, decreased hepatic synthesis of anticoagulant and coagulant proteins, fibrinolytic abnormalities, acquired thrombophilias, and expression of inflammatory and angiogenic cytokines.\(^{17}\)

Thrombotic manifestations in cancer patients may present as one of the following: migratory thrombophlebitis or Trousseau syndrome, VTE including catheter-related thrombosis, thrombotic microangiopathy (TTP/HUS), arterial thrombosis, and DIC.

**Migratory Thrombophlebitis (Trousseau Syndrome)**

Trousseau syndrome is a classically described variant form of venous thrombosis characterized by a recurrent and migratory pattern preferentially involving superficial veins of the arms, chest, and neck.\(^{69}\) Trousseau syndrome is highly associated with mucin-producing adenocarcinomas.\(^{25}\) The clinical manifestations of Trousseau syndrome also include chronic DIC associated with microangiopathy, verrucous endocarditis, and arterial emboli in patients with cancer.

**Venous Thromboembolism**

VTE, as manifested by deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a leading cause of death in cancer patients.\(^{69}\) VTE often complicates the care of cancer patients undergoing major surgery and of patients receiving chemotherapy or hormonal therapy. The risk of developing thrombosis in cancer patients is influenced by the age and hormonal status of the patient. Postmenopausal women with advanced breast cancer receiving tamoxifen in addition to adjuvant chemotherapy have a higher risk for thrombotic events than do premenopausal women with breast cancer.\(^{70,71}\) Thromboembolic events have been also reported with angiogenesis inhibitors (thalidomide, lenalidomide, and bevacizumab).\(^{72-74}\) The pathogenic mechanisms of thromboembolic events associated with thalidomide are thought to be related to the development of acquired activated protein C resistance and a reduction in thrombomodulin level.\(^{72-74}\) Endothelial injury produced by the combination of thalidomide with chemotherapy and subsequent restoration of endothelial cell PAR-1 expression are probable factors that promote thrombosis.\(^{72-74}\) Cancer patients receiving erythropoiesis-stimulating agents for anemia have also been reported to have increased thrombotic risk.\(^{75}\)

Two major advances in the diagnosis of VTE include the development and validation of a standardized clinical model (Wells criteria) to determine the pretest probability of VTE, and the measurement of plasma D-dimer. The integration of these advances has resulted in the formulation of safe, diagnostic algorithms that decrease the need for serial or invasive testing.\(^{76}\) In a clinical trial for which the Wells clinical model was combined with compression ultrasonography, the need for venography and serial compression ultrasonography testing was decreased.\(^{77}\) D-dimer levels can be measured by enzyme-linked immunosorbent assay, latex agglutination assay, or by a rapid bedside whole blood assay. Of the 3 assays, the whole blood assay reportedly has the best predictive value, with sensitivity rates in symptomatic general medical patients ranging from 85% to 95% and specificity rates of 65% to 68%. The D-dimer test has a high negative predictive value (NPV) and sensitivity for PE in cancer patients and, if negative, can be used to exclude PE in this population.\(^{78}\)
The majority of DVT in cancer patients originates in the ileofemoral venous system. Diagnostic imaging modalities for DVT include ascending contrast venography, compression ultrasonography, and magnetic resonance venography. Ascending contrast venography remains the gold standard for diagnosing DVT, but this procedure is invasive and requires contrast material, which is frequently irritating and may result in complications. The finding of an intraluminal filling defect caused by thrombus surrounded by contrast is diagnostic for DVT. Noncompressibility of a proximal lower limb vein on compression ultrasonography has a diagnostic sensitivity rate of 97% and a specificity rate of 94%. Although compression ultrasonography is highly sensitive for detecting proximal DVT, it is not as accurate for diagnosing isolated calf DVT. Magnetic resonance venography, a relatively new imaging modality that does not use contrast, has sensitivity and specificity rates greater than 95% for proximal DVT. Magnetic resonance venography is potentially useful in diagnosing pelvic vein DVT, especially isolated iliac vein thrombosis, which is difficult to diagnose with compression ultrasonography.

Several studies conducted in cancer patients with suspected DVT have demonstrated that the combination of the following studies can reliably exclude DVT and decrease the need for invasive testing: a normal D-dimer level and a normal compression ultrasonogram, a low pretest probability and normal compression ultrasonogram, and a low pretest probability and a normal D-dimer level.

The standard treatment of VTE is to initiate anticoagulation with either intravenous or subcutaneous unfractionated heparin (UFH), or subcutaneous low molecular weight heparin (LMWH) or fondaparinux (an indirect factor Xa inhibitor) at therapeutic doses followed by oral warfarin therapy for a minimum of 3 months, to achieve an INR between 2.0 and 3.0. However, in patients with active cancer, continued anticoagulation is recommended following the first episode of VTE. Intravenous UFH is usually started with an initial bolus of 80 U/kg followed by a continuous IV infusion of 18 U/kg/h, adjusted to maintain the aPTT at 1.5 to 2.5 times the control value. Alternatively, low molecular weight heparins (LMWHs) can be administered in weight-adjusted, once- or twice-daily subcutaneous doses without the need for laboratory monitoring. LMWHs have several advantages over UFH, including improved bioavailability, more predictable dose response, and lesser incidence of heparin-induced thrombocytopenia (HIT). Currently approved LMWH agents in the United States are enoxaparin, dalteparin, and tinzaparin. However, in ICU patients who are morbidly obese or develop renal failure, dosing of LMWHs may be unpredictable and may lead to serious adverse consequences such as prolonged bleeding. In addition, ICU patients often have significant edema that may impair the absorption of LMWHs administered subcutaneously. Thus, monitoring of anti–factor Xa levels 4 h after injection of the LMWH should be considered in these settings. Target therapeutic range for anti–factor Xa is 0.5 to 1.0 U/mL for patients on twice daily LMWH dosing and 1.0 to 2.0 U/mL for patients dosed once daily. Although LMWHs have been demonstrated to be as effective and safe as UFH in clinical trials of acute PE, these trials excluded patients with hemodynamically significant PE and patients who developed PE in the ICU. Protamine sulfate is less efficacious in reversing LMWH-related bleeding and because of the longer half-life of LMWH, a second dose of protamine may be required. The dose is 1 mg protamine per 1 mg of enoxaparin or 100 U of dalteparin or tinzaparin. Fondaparinux, a novel anti–factor Xa inhibitor, has also been recently shown to be as effective and safe as intravenous UFH in hemodynamically stable patients with PE, and may also be used in patients with HIT. This agent, however, is limited in its use for ICU patients due to its long half-life (approximately 17 hours), and renal elimination precludes its use in patients with severe renal failure (CrCl <30 mL/min).
guidelines recommend the use of LMWH for the first 3 to 6 months as long-term treatment of VTE in cancer patients. The use of thrombolytic agents such as streptokinase and t-PA should be restricted to patients with massive iliofemoral DVT or massive PE and hemodynamic instability, because of the significant risks of bleeding associated with thrombolysis. Furthermore, despite the proven efficacy of thrombolytic agents in achieving more rapid resolution of radiologic and hemodynamic abnormalities, studies to date have not shown any survival benefit with thrombolysis. Catheter-directed thrombolysis for initial treatment of VTE should be confined to selected patients requiring limb salvage. In general, thrombolytic therapy is contraindicated in cancer patients with brain metastases who develop VTE because of their significant risk for intracranial bleeding. However, risk stratification may help to identify subgroups of patients at high risk of death that might benefit from systemic thrombolysis. Surgical thromboembolectomy is restricted to patients with massive PE who have contraindications to or who do not respond to thrombolysis, in centers that have the available resources. For cancer patients with VTE who have contraindications to anticoagulant therapy or those with recurrent VTE despite anticoagulation, placement of a retrievable or permanent inferior vena cava (IVC) filter is generally recommended. However, IVC filters are associated with undesirable side effects, such as debilitating leg symptoms caused by filter-related thrombosis. Wallace and colleagues reported that IVC filters were safe and highly effective in preventing PE-related deaths in cancer patients with VTE. In addition, patients with a history of DVT and bleeding or metastatic/disseminated stage of disease had the lowest survival after IVC filter placement.

Perioperative cancer patients, particularly those with breast cancer undergoing chemotherapy or on selective estrogen receptor modulators, and patients with advanced cancers that are associated with high risk of VTE such as brain tumors, and colorectal, pancreatic, lung, renal cell, and ovarian adenocarcinomas, should receive antithrombotic prophylaxis with intermittent pneumatic compression devices or compression elastic stockings, and either subcutaneous UFH or LMWH. The recommended doses are low-dose UFH, 5000 U subcutaneous (SC) every 8 hours or LMWH, either dalteparin, 5000 U SC daily, or enoxaparin, 40 mg SC daily, or fondaparinux, 2.5 mg SC starting 8 to 12 hours postoperatively. Two perioperative cancer trials reported that continuation of LMWH prophylaxis for 3 weeks after hospital discharge reduced the risk of late venographic DVT by 60%.

Catheter-Related Thrombosis

Central venous catheters (CVCs) are frequently placed in ICU patients. The estimated thrombosis rate of CVCs ranges from 5% to 30%. Prophylaxis with low-dose warfarin (1 mg daily) or LMWH (dalteparin 2500 anti–factor Xa units daily) was previously shown to be efficacious in cancer patients with indwelling CVCs. It seems, however, that the incidence of catheter-related thrombosis in cancer patients is much lower than previously reported. Thus, routine prophylaxis with either warfarin, 1 mg daily or LMWH (dalteparin, 2500 IU SC once a day) is no longer recommended. Alteplase, a recombinant t-PA, at a dose of 1 to 2 mg per catheter lumen is effective in restoring flow to indwelling catheters occluded by thrombus.

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

TTP/HUS is a microangiopathic, hemolytic syndrome that is additionally characterized by thrombocytopenia, neurologic symptoms, renal dysfunction, and fever. Laboratory diagnosis of TTP is by examination of the peripheral smear for schistocytes and
verification of thrombocytopenia, measurement of lactate dehydrogenase (LDH), and absence of other clinical presentation that could otherwise explain the pathology. Patients receiving mitomycin-C, bleomycin, cisplatin, and tamoxifen as well as the post–bone marrow transplant population are at increased risk for cancer treatment-related TTP/HUS as are patients with breast, gastric, lung, and prostate cancer, and Hodgkin and non-Hodgkin lymphomas. The pathophysiology of cancer-associated TTP/HUS is postulated to be similar to that of usual primary TTP/HUS. The pathophysiology involves injury to vascular endothelium with release of ultralarge von Willebrand factor (VWF) multimers, due to a deficiency of a vWF-cleaving protease (ADAMTS-13) causing platelet aggregation. In cancer-related TTP, the activity of this enzyme seems to be decreased. ADAMTS-13 activity has also been correlated with the extent of tumor dissemination and development of TTP with malignant processes. The clinical manifestations of TTP/HUS in cancer patients are often not readily obvious because they tend to occur in complicated patients, often being treated with chemotherapy or radiation therapy with several comorbidities that may obscure the diagnosis. The microangiopathic hemolytic anemia and thrombocytopenia typically are severe, and reticulocytosis is usually present, with increased levels of LDH, reflecting intravascular hemolysis. The peripheral blood smear demonstrates numerous schistocytes. Renal failure and neurologic and pulmonary dysfunction are common. Neurologic signs and symptoms include headache, confusion, hemiplegia or hemiparesis, and coma. Severe acute respiratory distress syndrome rarely may occur late in the disease process and is usually fatal.

The cornerstone of TTP treatment is plasma exchange simultaneously to remove the ADAMTS-13 inhibitor and supply the patient with the active enzyme. If plasmapheresis is not immediately available, FFP at a dose of 30 mL/kg may be used as a temporizing measure. Other useful treatment modalities in refractory cases include vincristine, IVIg, rituximab, and splenectomy. Platelet transfusions are usually contraindicated because infused platelets may amplify the extent and severity of the formation of microvascular thrombi. However, recent evidence suggests that the potential harmful effect of platelet transfusion in TTP is uncertain. Regardless of treatment, the prognosis of cancer patients with TTP/HUS is generally poor.

Arterial Thrombosis

Unlike venous thrombosis, arterial thrombosis is much less common in cancer patients. When it occurs, it is usually secondary to nonbacterial thrombotic endocarditis (NBTE) or associated with chemotherapeutic regimens containing cisplatin. NBTE represents a form of consumptive coagulopathy most commonly seen with lung and pancreatic adenocarcinomas. The diagnosis should be suspected in any cancer patient who presents with ischemic embolic events. Echocardiography is diagnostic with the finding of sterile thrombotic vegetations on cardiac valves. In addition to valvular vegetations, ventricular segmental wall motion abnormalities resulting from silent embolization to the coronary arteries has been reported in 18% of cancer patients with NBTE. Management is essentially supportive, and consists of treatment of the underlying cancer and anticoagulation therapy with unfractionated or LMWH.

Disseminated Intravascular Coagulation

DIC is a pathologic state in which nonspecific coagulation and secondary fibrinolysis are activated, resulting in consumption of clotting factors and natural anticoagulants. Although the initial phase of DIC is a thrombotic one, and all factors that predispose cancer patients to VTE are important in the initiation of DIC, eventually the systemic
depletion in clotting factors, fibrinogen, and platelets, as well as increased fibrinolytic activity, result in hemorrhage.\textsuperscript{16}

DIC is especially common in cancer patients with estimates of between 7\% and 20\% in those who develop overt DIC during their disease course.\textsuperscript{16,103} Some investigators have suggested that almost all cancer patients have subclinical DIC.\textsuperscript{16,104} Of note, cancer patients may experience both acute and chronic DIC. The thrombotic disorders associated with DIC include recurrent venous thrombosis, peripheral arterial thrombosis and cerebrovascular thrombosis, disseminated arterial disease with organ failure, peripheral limb ischemia, and gangrene. Chronic forms of DIC are characterized by less florid clinical findings and more subtle, but persistent, laboratory abnormalities. Metastatic cancer is a common cause of chronic DIC. Over time, approximately 25\% of patients with metastatic cancer develop a thrombotic event. Acute DIC occurs when a large concentration of TF is released from the tumor over a short period of time, and although it may occur with solid tumors including prostate and mucin-secreting adenocarcinomas of the pancreas, gastrointestinal track, ovary, thyroid, and gallbladder, it is most frequently seen in the hematological malignancies including APL, acute and chronic myelocytic leukemias, acute lymphocytic leukemia, and lymphomas. Acute DIC may occur in the presence of excessive tumor burden, or when treatment is initiated in instances of tumor lysis syndrome. In both cases, procoagulant intracellular factors are rapidly released into circulation as the tumor cells die, and initiate systemic coagulation. In acute DIC, although thrombosis occurs initially, the more profound clinical manifestations are those of bleeding.

In cancer patients, the diagnosis of DIC is made clinically and is corroborated by a constellation of laboratory abnormalities.\textsuperscript{105} There is no single laboratory test that can establish or exclude the diagnosis of DIC. In most cases, a combination of tests in a patient with a clinical condition that is associated with DIC can be used to diagnose the disorder with reasonable certainty. In the presence of an underlying disease associated with DIC, there is an initial platelet count of less than 100,000/mm\(^3\) or a rapid decline in the platelet count; prolongation of the PT and aPTT is seen in about 50\% to 60\% of cases of DIC; and fibrin(ogen) degradation products in plasma and D-dimers is present. Fibrinogen levels may remain in the normal range in the face of its consumption because of increased synthesis of this acute-phase reactant. A finding of hypofibrinogenemia is only useful diagnostically in very severe cases of DIC. The peripheral blood smear may also demonstrate the presence of red cell fragmentation or schistocytes, but rarely more than 10\% of the red cells. There seems to be no added value in measuring the natural anticoagulants protein C or antithrombin.\textsuperscript{106} The International Society of Thrombosis and Hemostasis (ISTH) scoring system for overt DIC\textsuperscript{106} has a sensitivity and specificity of 91\% and 97\%, respectively.\textsuperscript{107} It is important to repeat the tests to monitor the dynamically changing scenario based on the laboratory results and clinical manifestations.

In general, the treatment of DIC is directed against the underlying cancer, but supportive management for the bleeding or thrombotic manifestations is required. Cancer patients with DIC who are bleeding or at high risk for bleeding (patients undergoing surgery or invasive procedures) should receive platelet transfusions to maintain the platelet count above 50,000/µL and FFP (initial doses of 15 mL/kg, although a dose of 30 mL/kg produces a more complete correction of coagulation factor levels) if the PT or aPTT are prolonged. The administration of purified coagulation factor concentrates in DIC is not generally recommended unless patients are fluid overloaded and cannot receive FFP. Coagulation factor concentrates contain only specific factors, whereas in DIC there is a global deficiency in coagulation factors. Severe hypofibrinogenemia (<1 g/L) needs to be treated with cryoprecipitate or fibrinogen concentrates if
available. A dose of 3 g would raise plasma fibrinogen by 1 g/L; this can be given as 2 cryoprecipitate pools (10 donor units) or as a 3 g of a fibrinogen concentrate. The response to transfusion therapy should be monitored clinically and with laboratory tests.\textsuperscript{105} The bleeding associated with DIC in APL often responds dramatically to treatment with all-trans retinoic acid.\textsuperscript{108}

Although there are no clinical, randomized controlled trials demonstrating that the use of heparin in patients with DIC results in improved clinical outcome, unfractionated heparin may be used in cancer patients with DIC-associated thrombosis for stabilization while the cancer is being treated unless moderate to severe thrombocytopenia or bleeding is present. Monitoring aPTT may be complicated but monitoring for signs of bleeding is important. In critically ill, nonbleeding patients with DIC, pharmacologic thromboprophylaxis with either UFH or LMWH is recommended.\textsuperscript{105} In general, patients with DIC should not be treated with antifibrinolytic agents. However, in patients with DIC and bleeding secondary to primary fibrinolysis (eg, prostate cancer), the fibrinolytic inhibitor EACA can be administered with an initial loading dose of 4 to 6 g IV over 1 hour followed by an IV infusion of 1 g/h while monitoring the clinical response. The recommended oral dose of EACA is 50 to 60 mg/kg every 4 to 6 h.\textsuperscript{109} However, in those patients with a primary thrombotic presentation and secondary fibrinolysis, fibrinolytic inhibitors should be avoided until the thrombotic process is controlled.\textsuperscript{105}

The administration of purified coagulation factor concentrates in DIC is not generally recommended unless patients are fluid overloaded and cannot receive FFP. Coagulation factor concentrates contain only specific factors, whereas in DIC there is a global deficiency in coagulation factors. Severe hypofibrinogenemia (<1 g/L) needs to be treated with cryoprecipitate or fibrinogen concentrates if available. A dose of 3 g would raise plasma fibrinogen by 1 g/L. This dose can be given as 2 cryoprecipitate pools (10 donor units) or as 3 g of a fibrinogen concentrate.\textsuperscript{105} The bleeding associated with DIC in APL often responds dramatically to treatment with all-trans retinoic acid.\textsuperscript{108}

**HEPARIN-INDUCED THROMBOCYTOPENIA**

HIT is an immune-mediated thrombocytopenia that occurs in approximately 1% to 5% of patients receiving heparin.\textsuperscript{110} HIT occurs when a patient develops IgG antibodies against the complex formed between heparin and platelet factor 4 (PF4). The resulting antibodies activate platelets via their Fc\textsubscript{\gamma} IIa receptors, ultimately resulting in increased thrombin generation and development of a hypercoagulable state. The platelet count typically drops to a nadir of around 60,000/\mu L or 50% of the initial platelet count within 5 to 10 days of starting heparin therapy.\textsuperscript{111} This amount is in contrast to many drug- or malignancy-induced thrombocytopenias in which the platelet count decreases to an average of 10,000/\mu L.\textsuperscript{112} HIT may develop within 24 hours if there has been exposure to heparin during the preceding 3 months. On occasion the platelet count starts to decrease only after heparin has been stopped (delayed-onset HIT). The thrombocytopenia of HIT is in part related to platelet consumption, and most patients with HIT develop concurrent thrombosis.\textsuperscript{113} Major risk factors that predispose to the development of HIT include gender\textsuperscript{114} (women have an increased incidence), type of heparin preparation (bovine UFH>porcine UFH>LMWH), the exposed patient population (postoperative>medical>pregnancy),\textsuperscript{110} and duration of heparin use.\textsuperscript{113} Venous or arterial thromboses including DVT, PE, limb artery thrombosis, thrombotic stroke, and myocardial infarction can occur. A clinical pretest probability score known as the 4 Ts (degree of thrombocytopenia, timing of thrombocytopenia, other etiologies of thrombocytopenia and thrombosis) is useful in clinical practice. HIT should be
suspected and treatment rapidly instituted in a patient with an intermediate or high test probability. \(^{115}\)

The “gold standard” test for laboratory diagnosis is the platelet serotonin release assay; however, this test is cumbersome and is performed only in a few specialized coagulation laboratories. In clinical practice, the laboratory diagnosis of HIT is made with a positive platelet factor 4-dependent immunoassay. Management consists of discontinuing all forms of heparin and using direct thrombin inhibitors (DTIs) such as lepirudin or argatroban, which do not have any cross-reactivity to HIT antibodies. Lepirudin is excreted by the kidney and should not be used in patients with severe renal failure (creatinine clearance <20 mL/min). The recommended doses are 0.4 mg/kg bolus followed by 0.15 mg/kg/h in HIT with thrombosis and 0.10 mg/kg/h without a bolus in HIT without thrombosis. Argatroban is metabolized by the liver, and the dose should be reduced in patients with hepatic impairment. The usual dose is 2 \(\mu\)g/kg/min to maintain the aPTT at 1.5 to 3 times baseline. The starting dose should be reduced by 75% in a patient with significant liver dysfunction. In countries where danaparoid (a heparanoid) is available, this agent may also be used for the prevention and treatment of HIT complicated by thrombosis.\(^{110}\) Warfarin should be avoided during the acute HIT episode because it decreases the level of protein C and predisposes to microvascular thrombosis, including warfarin-induced venous limb gangrene and skin necrosis syndromes. For patients receiving warfarin at the time of diagnosis of HIT, reversal of warfarin anticoagulation with vitamin K is recommended.

**NOVEL DRUGS FOR TREATMENT OF BLEEDING AND THROMBOTIC DISORDERS**

**Recombinant Factor VIIa**

The expanding use of rFVIIa in the acute care setting in recent years merits brief further discussion. rFVIIa has been used in the acute management of life-threatening intracerebral bleeding, uncontrolled surgical bleeding (cardiac and hepatic surgery), trauma-related bleeding, and for reversal of anticoagulation-related bleeding due to LMWH and DTIs. The use of rFVIIa in nonapproved settings should be critically evaluated, given the high costs and significant risk of thrombosis associated with its use. It is likely that recommendations about the use of rFVIIa will change rapidly in the coming years as the results of clinical trials become available.

**Novel Thrombopoietic Agents**

IL-11 (oprelvekin) is a Food and Drug Administration approved cytokine molecule that promotes megakaryocyte differentiation, and may be used in solid tumor and lymphoma treatment associated thrombocytopenia, but not for thrombocytopenia associated with myeloid lineage malignancies.\(^{116}\)

Cloning of Mpl (TPO-receptor) ligands have offered novel agents directed toward stimulating thrombopoiesis. The first generation of Mpl agonists showed initial promise, with dose-dependent improvement in chemotherapy-associated thrombocytopenia as well with poor platelet production associated with MDS. However, reports of autoantibody development against TPO with these agents resulting in severe thrombocytopenia have curtailed their further use.\(^{117}\) Two second-generation TPO mimetics, romiplostim and eltrombopag, have been recently approved for the treatment of refractory chronic immune thrombocytopenia, and are also being evaluated for the treatment of chemotherapy-induced thrombocytopenia.

Of importance is that these novel thrombopoietic agents are not recommended for use in the acute management of critically low platelet counts with associated bleeding events, as they increase megakaryocyte differentiation over the course of weeks to
months. Although some patients may have a durable improvement in platelet counts with these agents, in many patients the platelet counts rapidly decrease with attendant bleeding risks when these agents are withdrawn, especially if the underlying cause for thrombocytopenia is unresolved.

**Novel Anticoagulants**

Oral direct factor Xa inhibitors such as rivaroxaban and apixaban, and oral DTIs such as dabigatran, are completing clinical trials for the prevention and treatment of VTE. These oral agents can be given in fixed doses without routine monitoring. Rivaroxaban has a half-life of 9 hours and is eliminated by the renal and intestinal routes. Apixaban has a half-life of 12 hours and is cleared by the fecal and renal routes. Phase 2 trials of apixaban in cancer patients are currently ongoing. Dabigatran etexilate is a prodrug that, once absorbed, is converted to its active metabolite dabigatran. Peak plasma level occurs at 2 hours, and its half-life is 8 hours after a single dose administration and 17 hours after multiple doses. As 80% of dabigatran is excreted by the kidney, this agent is contraindicated in patients with renal failure. Idraparinux is an indirect factor Xa inhibitor that binds with high affinity to antithrombin and has a plasma half-life of 80 hours, allowing for subcutaneous administration once a week. Idraparinux can cause excessive bleeding; therefore a biotinylated form of idraparinux has been developed that has the same pharmacokinetics and pharmacodynamic properties as idraparinux, but can be neutralized by avidin. Avidin binds biotin with high affinity, and the complex is cleared renally. To the authors’ knowledge, there are no clinical trials using these novel antithrombotic agents in critically ill patients.

**SUMMARY**

Cancer affects multiple organ systems, nearly all of which can severely impact the delicate balance of thrombosis and hemostasis. Although much progress has been made in the diagnosis and management of many types of cancers, a significant number of cancer patients still develop life-threatening bleeding and thrombotic complications requiring ICU admission. Cancer- and chemotherapy-related malnutrition, renal failure, and hepatic dysfunction all directly increase a patient’s risk of developing thrombosis, significant bleeding, or both as occurs with DIC. Furthermore, the malignancy and its treatment may make diagnosis of these processes more complicated, for example, differentiating TTP-associated thrombocytopenia from a complication of chemotherapy. Fortunately, there is an ever-increasing assortment of diagnostic and therapeutic tools available for management of hemostatic complications in cancer patients that one hopes will allow for improved survival of these patients.

**REFERENCES**


