Chronic DIC Low-grade, compensated DIC can occur in clinical situations including giant hemangioma, metastatic carcinoma, or the dead fetus syndrome. Plasma levels of FDP or D-dimers are elevated. aPTT, PT, and fibrinogen values are within the normal range or high. Mild thrombocytopenia or normal platelet counts are also common findings. Red cell fragmentation is often detected but at a lower degree than in acute DIC.

Differential Diagnosis The differential diagnosis between DIC and severe liver disease is challenging and requires serial measurements of the laboratory parameters of DIC. Patients with severe liver disease are at risk for bleeding and manifest laboratory features including thrombocytopenia (due to platelet sequestration, portal hypertension, or hypersplenism), decreased synthesis of coagulation factors and natural anticoagulants, and elevated levels of FDP due to reduced hepatic clearance. However, in contrast to DIC, these laboratory parameters in liver disease do not change rapidly. Other important differential findings include the presence of portal hypertension or other clinical or laboratory evidence of an underlying liver disease.

Microangiopathic disorders such as thrombotic thrombocytopenic purpura present an acute clinical onset of illness accompanied by thrombocytopenia, red cell fragmentation, and multiorgan failure. However, there is no consumption of clotting factors or hyperfibrinolysis.

Over the last few years, several clinical trials on immune therapies for neoplasias using monoclonal antibodies or gene-modified T cells targeting tumor-specific antigens showed unwanted inflammatory responses with increased cytokine release. These complications are sometimes associated with increased D-dimers and decreased fibrinogen levels, cytopenias, and liver dysfunction; thus, careful screening tests for DIC are indicated.

TREATMENT DISSEMINATED INTRAVASCULAR COAGULATION

The morbidity and mortality associated with DIC are primarily related to the underlying disease rather than the complications of the DIC. The control or elimination of the underlying cause should therefore be the primary concern. Patients with severe DIC require control of hemodynamic parameters, respiratory support, and sometimes invasive surgical procedures. Attempts to treat DIC without accompanying treatment of the causative disease are likely to fail.

MANAGEMENT OF HEMORRHAGIC SYMPTOMS

Administration of FFP and/or platelet concentrates is indicated for patients with active bleeding or at high risk of bleeding, such as in preparation for invasive procedures or after chemotherapy. The control of bleeding in DIC patients with marked thrombocytopenia (platelet counts <10,000–20,000/μL) and low levels of coagulation factors will require replacement therapy. The PT (>1.5 times the normal) provides a good indicator of the severity of the clotting factor consumption. Replacement with FFP is indicated (1 unit of FFP increases most coagulation factors by 30% in an adult without DIC). Low levels of fibrinogen (<100 mg/dL) or brisk hyperfibrinolysis will require infusion of cryoprecipitate (plasma fraction enriched for fibrinogen, FVIII, and VWF). The replacement of 10 U of cryoprecipitate for every 2–3 U of FFP is sufficient to correct the hemostasis. The transfusion scheme must be adjusted according to the patient's clinical and laboratory evolution. Platelet concentrates at a dose of 1–2 U/10 kg body weight are sufficient for most DIC patients with severe thrombocytopenia. Clotting factor concentrates are not recommended for control of bleeding in DIC because of the limited efficacy afforded by replacement of single factors (FVIII or FIX concentrates) and the high risk of products containing traces of aPCCs that further aggravate the disease.

REPLACEMENT OF COAGULATION OR FIBRINOLYSIS INHIBITORS

Drugs to control coagulation such as heparin, antithrombin III (ATIII) concentrates, or antifibrinolytic drugs have all been tried in the treatment of DIC. Low doses of continuous-infusion heparin (5–10 U/kg per h) may be effective in patients with low-grade DIC associated with solid tumor, acute promyelocytic leukemia, or in a setting with recognized thrombosis. Heparin is also indicated for the treatment of purpura fulminans during the surgical resection of giant hemangiomas and during removal of a dead fetus. In acute DIC, the use of heparin is likely to aggravate bleeding. To date, the use of heparin in patients with severe DIC has no proven survival benefit. The use of antifibrinolytic drugs, EACA, or tranexamic acid to prevent fibrin degradation by plasmin may reduce bleeding episodes in patients with DIC and confirmed hyperfibrinolysis. However, these drugs can increase the risk of thrombosis, and concomitant use of heparin is indicated. Patients with acute promyelocytic leukemia or those with chronic DIC associated with giant hemangiomas are among the few patients who may benefit from this therapy. The use of protein C concentrates to treat purpura fulminans associated with acquired protein C deficiency or meningococcemia has been proven efficacious. The results from the replacement of ATIII in early-phase studies are promising but require further study.

Guidance for diagnosis and treatment of DIC had been proposed by the International Society of Thrombosis and Haemostasis. This initiative will permit more detailed clinical data on diagnosis and treatment of DIC. The clinical utility of these scoring systems and therapeutic recommendations contained in these guidelines is not yet known.

VITAMIN K DEFICIENCY Vitamin K–dependent proteins are a heterogenous group, including clotting factor proteins and also proteins found in bone, lung, kidney, and placenta. Vitamin K mediates posttranslational modification of glutamate residues to γ-carboxylglutamate, a critical step for the activity of vitamin K–dependent proteins for calcium binding and proper assembly to phospholipid membranes (Fig. 141-2). Inherited deficiency of the functional activity of the enzymes involved in vitamin K metabolism, notably the GGCX or VKORC1 (see above), results in bleeding disorders. The amount of vitamin K in the diet is often limiting for the carboxylation reaction; thus recycling of the vitamin K is essential to maintain normal levels of vitamin K–dependent proteins. In adults, low dietary intake alone is seldom reason for severe vitamin K deficiency but may become common in association with the use of broad-spectrum antibiotics. Disease or surgical interventions that affect the ability of the intestinal tract to absorb vitamin K, either through anatomic alterations or by changing the fat content of bile salts and pancreatic juices in the proximal small bowel, can result in significant reduction of vitamin K levels. Chronic liver diseases such as primary biliary cirrhosis also deplete vitamin K stores. Neonatal vitamin K deficiency and the resulting hemorrhagic disease of the newborn have been almost entirely eliminated by routine administration of vitamin K to all neonates. Prolongation of PT values is the most common and earliest finding in vitamin K–deficient patients due to reduction in prothrombin, FVII, FIX, and FX levels. FVII has the shortest half-life among these factors that can prolong the PT before changes in the aPTT. Parenteral administration of vitamin K at a total dose of 10 mg is sufficient to restore normal levels of clotting factor within 8–10 h. In the presence of ongoing bleeding or a need for immediate correction before an invasive procedure, replacement with FFP or PCC is required. The latter should be avoided in patients with severe underlying liver disorders due to high risk of thrombosis. The reversal of excessive anticoagulant therapy with warfarin or warfarin-like drugs can be achieved by minimal doses of vitamin K (1 mg orally or by intravenous injection) for asymptomatic patients. This strategy can diminish the risk of bleeding while maintaining therapeutic anticoagulation for an underlying prothrombotic state.

In patients with life-threatening bleeds, the use of recombinant factor VIIa in nonhemophilia patients on anticoagulant therapy has been shown to be effective at restoring hemostasis rapidly, allowing emergency surgical intervention. However, patients with underlying vascular disease, vascular trauma and other comorbidities are at risk for thromboembolic complications that affect both arterial and venous