Stool studies should also be performed for patients without diarrhea because *E. coli* O157:H7 may rarely cause HUS in the absence of intestinal symptoms. If *E. coli* O157:H7 is not detected, culture for other Shiga-toxigenic organisms should be pursued.

The pathologic renal lesions of HUS include vessel wall thickening with endothelial cell swelling and intraglomerular thrombosis with platelet- and fibrin-rich thrombi. Fragmentation of red blood cells may be seen in the renal vasculature and within the vessel wall.

Treatment of D+ HUS is supportive, including adequate volume repletion with isotonic intravenous fluids, transfusion for severe anemia, and avoidance of other nephrotoxic agents (e.g., nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, iodinated contrast). Platelet transfusion is not recommended because it may worsen the ongoing microvascular thrombosis. Antibiotic treatment of patients with bloody diarrhea is not recommended because it is not effective in reducing the incidence of HUS and may increase the risk. Corticosteroids, anticoagulation (e.g., aspirin, heparin), thrombolytic agents, and plasma administration have proved ineffective for the treatment of HUS.

With supportive care alone, most patients with D+ HUS recover with normalization of renal function or only mild residual CKD, although about 25% may develop advanced CKD or ESRD over the next 1 to 2 decades of life. Risk for CKD is increased with cortical necrosis and involvement of more than 50% of glomeruli identified on renal biopsy. The risk for complications and death increases with age, with the mortality rate increasing from about 5% to 10% for children to about 30% for adults.

D− HUS (atypical HUS) accounts for about 5% of cases and has a higher likelihood of recurrence, ESRD, or death. Many cases are caused by genetic defects in the complement pathway (e.g., C3, C5, complement H, factor I, CD46). Testing for ADAMTS13 levels, which are normal in D− HUS, can be useful in differentiating atypical HUS from TTP. Specialty laboratories can test for complement cascade abnormalities. Eculizumab is a humanized monoclonal antibody that binds with high affinity to complement protein C5 and prevents the generation of C5a, C5b, and the terminal complement complex C5b-9. In patients with atypical HUS, eculizumab inhibits complement-mediated thrombotic microangiopathy.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid antibodies (APAs) refer to autoantibodies such as lupus anticoagulants or IgG or immunoglobulin M (IgM) anticardiolipin antibodies that interfere with phospholipid-binding proteins and in vitro phospholipid-dependent clotting assays such as the partial thromboplastin time. Because not all lupus anticoagulants cause prolongation of the partial thromboplastin time, other tests of the coagulation system, such as the dilute Russell viper venom time, may need to be obtained. The diagnosis of antiphospholipid antibody syndrome (APS) is based on the occurrence of arterial or venous clotting events or fetal loss during pregnancy after 10 or more weeks' gestation in the setting of laboratory detection of an APA. Lupus anticoagulant and anticardiolipin antibodies are detectable in up to 10% of healthy populations, and their presence alone is insufficient for a diagnosis of APS. Apolipoprotein H (apo H, formerly β_2-glycoprotein 1) is the main antigenic target of anticardiolipin antibodies.

In the absence of an underlying autoimmune disease, the syndrome is referred to as primary APS. Secondary APS occurs when associated with other diseases such as systemic lupus erythematosus (SLE). APAs are detectable in 30% to 50% of patients with SLE, and renal involvement is often observed in this setting.

The procoagulant effect of APAs may result from interference with the anticoagulant apo H, inhibition of fibrinolysis, direct endothelial injury, accelerated atherosclerosis, and activation of platelet, monocyte, and endothelial cells. Renal involvement occurs in about 25% of patients with primary APS and can occur in patients with SLE or other causes of APS. Thrombosis may occur throughout the renal vasculature, including main or branch renal arteries, arterioles, glomeruli, and veins. These findings resemble those found in other diseases associated with a thrombotic microangiopathy. Focal atrophy of the cortex in association with interstitial fibrosis may be observed due to resulting ischemia.

The RENAL manifestations of APS vary. Some patients have mild proteinuria with preserved kidney function, and others develop severe hypertension, nephrotic-range proteinuria, and AKI or CKD. Renal arterial thrombosis can cause infarction, acute onset of flank pain, hematuria, and decreased kidney function. Renal vein thrombosis may be silent or, if acute and complete, may manifest with sudden flank pain and reduced kidney function. Pathologic changes seen on renal biopsy of patients with primary APS are small vessel vaso-occlusive disease with fibrous intimal hyperplasia of interlobular arteries, recanalizing thrombi in arteries and arterioles, focal cortical atrophy, and thrombotic microangiopathy. Other manifestations of APS include thrombocytopenia, hemolytic anemia, and a prolonged activated partial thromboplastin time in the absence of heparin therapy.

Long-term warfarin anticoagulation with a target international normalized ratio (INR) between 2 and 3 is indicated for patients with primary or secondary APS and prior deep vein thrombosis, arterial thrombosis, or recurrent spontaneous abortion. Because warfarin is contraindicated during pregnancy, heparin with or without low-dose aspirin (81 mg) is necessary until the end of pregnancy.

Treatment of APA-positive patients in the absence of prior clinical events is controversial because of the high false-positive rate for the tests. Aspirin therapy for primary prevention in patients persistently positive for APAs has been advocated but not proved. Plasmapheresis, prednisone, and hydroxychloroquine have been advocated for the treatment of thrombotic microangiopathy due to APS and should be considered in severe cases.

RENAL VEIN THROMBOSIS

Renal vein thrombosis (RVT) is uncommon, occurring mostly in association with malignancy, but it also is a consequence of nephrotic syndrome, abdominal surgery or trauma, pancreatitis, and genetic or acquired hypercoagulable states. Most malignancy-associated RVT is caused by renal cell carcinoma with venous