patients can start within the first weeks of life but in some instances may not present until the patient is several years of age. Both environmental and genetic factors are thought to influence the development of TTP. Plasma transfusion is an effective strategy for prevention and treatment.

Drug-induced TMA is a recognized complication of treatment with some chemotherapeutic agents, immunosuppressive agents, antiplatelet agents, and quinine. Two different mechanisms have been described. Endothelial damage (pathologically similar to that in HUS) is the main cause of the TMA that develops in association with chemotherapeutic agents (e.g., mitomycin C, gemcitabine) and immunosuppressive agents (cyclosporine, tacrolimus, and sirolimus). This process is usually dose-dependent. Alternatively, TMA may develop as a result of drug-induced autoantibodies. This form is less likely to be dose-dependent and can, in fact, occur after a single dose in patients with previous exposure. Ticlopidine produces TTP by inducing an autoantibody to ADAMTS13, but ADAMTS13 deficiency is found in fewer than half of patients with clopidogrel-associated TTP. Quinine appears to induce autoantibodies to granulocytes, lymphocytes, endothelial cells, and platelet glycoprotein IbB/IX or IIb/IIIa complexes, but not to ADAMTS13. Quinine-associated TTP is more common among women. TMA has been reported with drugs that inhibit vascular endothelial growth factor, such as bevacizumab; the mechanism is not completely understood.

TREATMENT HUS/TTP

Treatment should be based on pathophysiology. Autoantibody-mediated TTP and DEAP HUS respond to plasma exchange or plasmapheresis. In addition to removing the autoantibodies, plasma exchange with fresh-frozen plasma replaces ADAMTS13. Twice-daily plasma exchanges with administration of vincristine and rituximab may be effective in refractory cases. Plasma infusion is usually sufficient to replace the ADAMTS13 in Upshaw-Schülman syndrome. Plasma exchange should be considered if larger volumes are necessary. Drug-induced TMA secondary to endothelial damage typically does not respond to plasma exchange and is treated primarily by discontinuing use of the agent and providing supportive care. Similarly, STEC HUS should be treated with supportive measures. Plasma exchange has not been found to be effective. Antimotility agents and antibiotics increase the incidence of HUS among children, but azithromycin was recently found to decrease the duration of bacterial shedding by adults. Eculizumab is a monoclonal antibody to C5 that is approved for use in aHUS, for which ongoing therapy may be necessary. Plasma infusion/exchange may play a role in aHUS by replacing complement-regulatory proteins. Antibiotics and washed red cells should be given in neuraminidase-associated HUS, and plasmapheresis may be helpful. However, plasma and whole-blood transfusion should be avoided since these products contain IgM, which may exacerbate MAHA. Finally, combined factor H and ADAMTS13 deficiency have been reported. The affected patients are generally less responsive to plasma infusion, a result illustrating the complexity of the management of these cases.

HEMATOPOIETIC STEM CELL TRANSPLANTATION–ASSOCIATED THROMBOTIC MICROANGIOPATHY (HSCT-TMA)

HSCT-TMA develops after HSCT, with an incidence of 8.2%. Etiologic factors include conditioning regimens, immunosuppression, infections, and graft-versus-host disease. Other risk factors include female sex and human leukocyte antigen (HLA)–mismatched donor grafts. HSCT-TMA usually occurs within the first 100 days of HSCT. Table 341-1 lists definitions of HSCT-TMA currently used for clinical trials. Diagnosis may be difficult since thrombocytopenia, anemia, and renal insufficiency are common after HSCT. HSCT-TMA carries a high mortality rate (75% within 3 months). The majority of patients have >5% ADAMTS13 activity, and plasma exchange is beneficial in <50% of patients. Discontinuation of calcineurin inhibitors and substitution with daclizumab (antibody to the IL-2 receptor) are recommended. Treatment with rituximab and defibrotide may also be helpful.

TABLE 341-1 CRITERIA FOR ESTABLISHING MICROANGIOPATHIC KIDNEY INJURY ASSOCIATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

International Working Group	Blood and Marrow Transplant Clinical Trials Network Toxicity Committee
>4% schistocytes in the blood	RBC fragmentation and at least 2 schistocytes per high-power field
De novo, prolonged, or progressive thrombocytopenia	Concurrent increase in LDH concentration above baseline
A sudden and persistent increase in LDH concentration	Negative direct and indirect Coombs test
Decrease in hemoglobin level or increased RBC transfusion requirement	Concurrent renal and/or neurologic dysfunction without other explanations
Decrease in haptoglobin concentration	

Note: These features underscore the need to identify pathways of hemolysis and thrombocytopenia that accompany deterioration of kidney function.

Abbreviations: LDH, lactate dehydrogenase; RBC, red blood cell.

HIV-RELATED TMA

HIV-related TMA is a complication encountered mainly before widespread use of highly active antiretroviral therapy. It is seen in patients with advanced AIDS and low CD4+ T cell counts although it can be the first manifestation of HIV infection. The presence of MAHA, thrombocytopenia, and renal failure are suggestive, but renal biopsy is required for diagnosis since other renal diseases are also associated with HIV infection. Thrombocytopenia may prohibit renal biopsy in some patients. The mechanism of injury is unclear, although HIV can induce apoptosis in endothelial cells. ADAMTS13 activity is not reduced in these patients. Cytomegalovirus co-infection may also be a risk factor. Effective antiviral therapy is key, while plasma exchange should be limited to patients who have evidence of TTP.

RADIATION NEPHROPATHY

Either local or total body irradiation can produce microangiopathic injury. The kidney is one of the most radiosensitive organs, and injury can result with as little as 4–5 Gy. Such injury is characterized by renal insufficiency, proteinuria, and hypertension usually developing ≥6 months after radiation exposure. Renal biopsy reveals classic TMA with damage to glomerular, tubular, and vascular cells, but systemic evidence of MAHA is uncommon. Because of its high incidence after allogeneic HSCT, radiation nephropathy is often referred to as *bone marrow transplant nephropathy*. No specific therapy is available, although observational evidence supports renin-angiotensin system blockade.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Kidney involvement is common (up to 52%) in patients with widespread scleroderma, with 20% of cases resulting directly from scleroderma renal crisis. Other renal manifestations in scleroderma include transient (prerenal) or medication-related forms of acute kidney injury (e.g., associated with *D*-penicillamine, nonsteroidal anti-inflammatory drugs, or cyclosporine). Scleroderma renal crisis occurs in 12% of patients with diffuse systemic sclerosis but in only 2% of those with limited systemic sclerosis. Scleroderma renal crisis is the most severe manifestation of renal involvement, and is characterized by accelerated hypertension, a rapid decline in renal function, nephrotic proteinuria, and hematuria. Retinopathy and encephalopathy may accompany the hypertension. Salt and water retention with microvascular injury can lead to pulmonary edema. Cardiac manifestations, including myocarditis, pericarditis, and arrhythmias, denote an especially poor prognosis. Although MAHA is present in more half of patients, coagulopathy is rare.

The renal lesion in scleroderma renal crisis is characterized by arcuate artery intimal and medial proliferation with luminal narrowing.