fibrin accumulation extending into the glomeruli, often with ischemic collapse, but without features of glomerulonephritis.

Activation of the renin-angiotensin-aldosterone system appears to play an important role in the progression of the disease. Before the advent of ACE inhibitors and hemodialysis, scleroderma renal crisis was fatal in about 75% of patients at 1 year. ACE inhibitor therapy has reduced this 1-year mortality rate to less than 15%. Captopril is often recommended as the ACE inhibitor of choice due to its short half-life and ease of dose titration. If the diagnosis of scleroderma renal crisis is made before advanced renal failure is established, ACE inhibition may halt or reverse the decline in renal function. Some experts recommend continuing ACE inhibitors even if kidney function declines and temporary dialysis is necessary, citing an increased chance of renal recovery. ACE inhibitors are not useful for prevention of scleroderma renal crisis, and their use in this setting has been associated with a poorer outcome, including greater risk of requiring permanent dialysis if renal crisis occurs. Use of ACE inhibitors rather than ARBs is recommended because of the long track record of success with ACE inhibitors in this disease.

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC-UREMIC SYNDROME

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) manifest with microangiopathic hemolytic anemia (MAHA) and organ dysfunction due to microvascular thrombosis, but each syndrome has distinct clinical, pathophysiologic, and epidemiologic features (Table 30-3).

Although many processes cause microvascular endothelial injury (Table 30-4), renal involvement from these disorders affect the vasculature at different levels. Renal involvement by HUS and TTP primarily affects the glomeruli, whereas scleroderma often extends to the interlobular arteries, and malignant hypertension more often affects the afferent arterioles. However, there is significant overlap and similar histologic features among these diseases, making careful clinical evaluation essential for accurate determination of the cause.

Thrombotic Thrombocytopenic Purpura

TTP is characterized by MAHA and thrombocytopenia. Patients may also have fever, AKI, and neurologic impairment. Purpura is only rarely observed, and it is not necessary to make the diagnosis. TTP occurs with a female-to-male ratio of 3 : 2 and a peak incidence in the third and fourth decades of life. MAHA and thrombocytopenia manifesting similar to TTP may occur in response to some drugs (e.g., ticlopidine, cyclosporine, tacrolimus), after stem cell transplantation, in association with human immunodeficiency virus (HIV) infection, and in patients with malignant hypertension, sepsis, disseminated intravascular coagulation, or advanced cancers.

TTP may be caused by a deficiency or reduced activity of ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin-1–like domains). ADAMTS13 is a plasma protease that normally cleaves von Willebrand factor (vWF) and limits the extent of intravascular thrombosis (Fig. 30-4). Microthrombi composed primarily of platelets and vWF accumulate in the vascular bed of multiple organs, leading to a MAHA. Deficiency in ADAMTS13 may be acquired, caused by

TABLE 30-3 DIFFERENTIATION OF SHIGA TOXIN–RELATED HEMOLYTIC-UREMIC SYNDROME FROM THROMBOTIC THROMBOCYTOPENIC PURPURA

FEATURE	SHIGA TOXIN–RELATED HUS	TTP
Epidemiology	Endemic areas (commonly but not exclusively)	Endemic regions not reported
Similar cases in family	If yes, synchronous	If yes, separated in time and space
Recurrences	Rare	Common
Gastrointestinal prodrome	Painful diarrhea, frequently bloody	Nondiarrheal abdominal symptoms predominate, but not as prodrome
von Willebrand factor profile	Increased degradation to smaller multimers	Ultra-large forms (assay not universally available); depletion of large and ultra-large forms in advanced stage
ADAMTS13 expression	Normal or slightly decreased	Deficient (<0.1 U/mL)
Characteristics of intravascular thrombi	Fibrin predominates	von Willebrand factor predominates
Endothelial cell appearance	Swollen	Not swollen
Response to plasma therapy	Not demonstrated	Yes
Diagnosis	Isolation of STEC; antibody response to *Escherichia coli* O157:H7 LPS antigen	ADAMTS13 activity; inhibitors of ADAMTS13 activity; genetic analysis for mutations of *ADAMTS13* gene

Data from Tarr PI, Gordon CA, Chandler WL: Shiga toxin-producing Escherichia coli and haemolytic uraemic syndrome, Lancet 365:1073–1086, 2005.

ADAMTS3, A disintegrin and metalloproteinase with thrombospondin-1–like domains; HUS, hemolytic-uremic syndrome; LPS, lipopolysaccharide; STEC, Shiga-toxigenic *E. coli*; TTP, thrombotic thrombocytopenic purpura.

TABLE 30-4 DISORDERS ASSOCIATED WITH THROMBOTIC MICROANGIOPATHY

CONDITIONS	EXAMPLES
TTP	ADAMTS13 protease deficiency, acquired (autoantibody), genetic
HUS	Shiga toxin-associated (*E. coli*, others); D+ (typical HUS)
	Complement dysregulation; D– (atypical HUS)
Pregnancy	Preeclampsia, HELLP syndrome
Medications	Cyclosporine, tacrolimus, VEGF inhibitors, chemotherapeutic agents (e.g., mitomycin C), quinine, cocaine, ticlopidine (with anti-ADAMTS13 antibodies), muromonab-CD3 (OKT3), clopidogrel
Transplantation	Allogeneic bone marrow and stem cell transplants, solid organ
Neoplastic diseases	Metastatic cancers
Prothrombotic disorders	Antiphospholipid antibody syndrome
Infectious diseases	Rocky Mountain spotted fever, anthrax, HIV
Other conditions	Malignant hypertension, SLE, scleroderma renal crisis, radiation therapy, DIC, cardiovascular surgery

Data from Tsai HM: Advances in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura. J Am Soc Nephrol 14:1072–1081, 2003.

D+, Positive for diarrhea; D–, negative for diarrhea; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; HELLP, hemolysis, elevated liver enzyme levels, and a low platelet count; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.