Injury to endothelial cells is the primary event in many microvascular diseases of the kidney, including thrombotic microangiopathies, radiation nephropathy, scleroderma, and the antiphospholipid syndrome. Moreover, physiologic conditions in the medulla predispose to erythrocyte deformation and occlusion of the microvasculature in patients with sickle cell disease, whereas in patients with atherosclerosis, small renal arteries and arterioles can be injured and occluded by cholesterol-containing emboli dislodged from atherosclerotic plaques lining the main arteries. Independent of the initiating events, diseases that occlude the renal microvasculature invariably impair kidney perfusion and function. Early diagnosis and effective interventions to restore the integrity of the kidney microvasculature are instrumental to prevent irreversible tissue damage and kidney failure.

**THROMBOTIC MICROANGIOPATHIES: HEMOLYTIC-UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA**

The term *thrombotic microangiopathy* (TMA) defines a lesion of arteriolar and capillary vessel wall thickening, with intraluminal platelet thrombosis and partial or complete obstruction of the vessel lumina. Depending on whether renal or brain lesions prevail, two pathologically indistinguishable, but somehow clinically different, entities have been described, the hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). In HUS and TTP, microvascular thrombosis is associated with thrombocytopenia, hemolytic anemia, and dysfunction of affected organs. Advances in our understanding of the molecular pathology have led to the recognition of three different diseases—typical HUS caused by Shiga toxin–producing *Escherichia coli* (Stx-HUS), atypical HUS (aHUS), associated with genetic or acquired disorders of regulatory components of the complement system, and TTP that results from a deficiency of ADAMTS13, a plasma metalloprotease that cleaves von Willebrand factor (Table 35.1). Complement hyperactivation appears to be a common pathogenetic effector that leads to endothelial damage and microvascular thrombosis in all three diseases. In Stx-HUS, the toxin triggers endothelial complement deposition through the upregulation of P-selectin and possibly interferes with the activity of complement regulatory molecules. In aHUS, mutations in the genes coding for complement components predispose to hyperactivation of the alternative pathway of complement. In TTP, severe ADAMTS13 deficiency leads to the generation of massive platelet thrombi, which might contribute to complement activation (Figure 35.1). More importantly, evidence is emerging that pharmacologic targeting of complement with the anti-C5 monoclonal antibody eculizumab can effectively treat not only aHUS for which it is indicated, but in some cases, also Stx-HUS and TTP (see Figure 35.1).
90% of cases is preceded by diarrhea, often bloody. Usually, incidence of 1 to 2 children/100,000/yr). Most cases (incidence, 6.1 children/100,000/yr compared to an overall occurs most frequently in children younger than 5 years Shiga toxin (Stx)–producing Hemolytic-Uremic Syndrome (HUS) Presentation Cause Clinical Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in patients with TMA lesions and reflect the consumption and pathologic hemolytic anemia, fever, and neurologic and renal dysfunction. Thrombotic Thrombocytopenic Purpura (TTP) Classification of Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura Table 35.1 *According to clinical presentation and underlying cause. 1No published data on frequency of complement gene mutations or anti-CFH autoantibodies; antiphospholipid syndrome, systemic lupus erythematosus, and other autoimmune diseases—depends on the specific primary disease. HSC, Hematopoietic stem cell transplantation; HELLP, hemolytic anemia, elevated liver enzymes, and low platelet count. fatal syndrome in children characterized by hemolytic anemia, thrombocytopenia, and severe renal failure. HUS occurs most frequently in children younger than 5 years (incidence, 6.1 children/100,000/yr compared to an overall incidence of 1 to 2 children/100,000/yr). Most cases (>90% of those in children) are associated with infection by Shiga toxin (Stx)–producing E. coli (Stx-HUS). Stx-HUS in 90% of cases is preceded by diarrhea, often bloody. Usually, patients are afebrile. Streptococcus pneumoniae causes a distinctive form of HUS, accounting for 40% of cases not associated with Stx-producing bacteria. Approximately 10% of HUS cases are classified as atypical, caused neither by Stx-producing bacteria nor by Streptococcus. Atypical HUS occurs at any age, can be familial or sporadic, and has a poor outcome; 50% progress to end-stage renal disease (ESRD), and 25% may die in the acute phase. Neurologic symptoms and fever can occur in 30% of patients. Pulmonary, cardiac, and gastrointestinal manifestations can also occur.

**Thrombotic Thrombocytopenic Purpura**

Thrombotic thrombocytopenic purpura is a rare disease, with an incidence of approximately two to four cases/1 million persons/yr. It is more common in women (female/male ratio, 3:2 to 5:2) and in whites (white/black ratio, 3:1). The peak incidence is in the third and fourth decades of life, but TTP can affect any age group. TTP typically presents with the pentad of thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and renal dysfunction. Thrombotic purpura is essential for the diagnosis; most patients present with a platelet count below 60,000/μL. Purpura is minor and can be absent. Retinal hemorrhages can be present, but bleeding is rare. Neurologic symptoms can be seen in over 90% of patients during the entire course of the disease. Central nervous system involvement mainly represents thromboocclusive disease of the grey matter, but can also include headache, cranial nerve palsy, confusion, stupor, and coma. These features are transient but recurrent. Up to 50% of patients who present with neurologic involvement may be left with sequelae. Renal insufficiency may occur. One group has reported 25% of patients to have creatinine clearance less than 40 mL/min. Low-grade fever is present in 25% of patients at diagnosis, but can often be seen as a consequence of plasma exchange. Less common manifestations include acute abdomen, pancreatitis, and sudden death.

**LABORATORY FINDINGS**

Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in patients with TMA lesions and reflect the consumption and disruption of platelets and erythrocytes in the microcirculation (Figure 35.2). Hemoglobin levels are low (<10 g/dL in >90% of patients). Reticulocyte counts are uniformly elevated. The peripheral smear reveals increased schistocyte numbers (see Figure 35.2), with polychromasia and, often, nucleated red blood cells. The latter may represent not only a compensatory response, but also damage to the bone marrow–blood barrier resulting from intramedullary vascular occlusion. Detection of fragmented erythrocytes is crucial to confirm the microangiopathic nature of the hemolytic anemia, provided heart valvular disease and other anatomic artery abnormalities that may cause erythrocyte fragmentation are excluded. Other indicators of intravascular hemolysis include elevated lactate dehydrogenase (LDH), increased indirect bilirubin, and low haptoglobin levels. The Coombs test is negative. Moderate leukocytosis may accompany the hemolytic anemia. Thrombocytopenia is uniformly present in HUS and TTP. It may be severe but is usually less so in patients with predominant renal
Figure 35.1 Pathways of thrombus formation in different forms of thrombotic microangiopathy. In diarrhea-associated HUS (dHUS), the microangiopathic process is initiated by endothelial exposure to Shiga toxin (Stx), with consequent up regulation of P-selectin expression and other adhesion molecules. In atypical HUS (aHUS), the process is mediated by genetic or acquired defects in different modulators of the complement system, with secondary uncontrolled complement activation, and in TTP by genetic or acquired defects in ADAMTS13 activity with abnormal von Willebrand factor (vWF) cleavage and persistency in the circulation of ultra-large vWF multimers. Independent of the initial event, microvascular occlusion by intravascular thrombi is the final event common to different forms of thrombotic microangiopathy.

Diagnosis of TMA:
- Low platelet count
- Increased serum LDH
- Fragmented erythrocytes in the peripheral smear

If no evidence of TTP or Stx HUS, screen for aHUS.

Figure 35.2 Diagnostic algorithm for TMA. A peripheral blood smear from a patient with thrombotic microangiopathy is shown (upper right). The presence of fragmented red blood cells that may assume the appearance of a helmet (fragmented erythrocytes with the shape of a helmet are identified by the black arrows) is pathognomonic for microangiopathic hemolysis in patients with no evidence of heart valvular disease.
PATHOLOGY

The diagnostic histologic lesions of TMA consist of widening of the subendothelial space and microvascular thrombosis (Figure 35.3). Electron microscopy best identifies the characteristic lesions of swelling and detachment of the endothelial cells from the basement membrane and the accumulation of fluffy material in the subendothelium (see Figure 35.3A), intraluminal platelet thrombi, and partial or complete obstruction of vessel lumina (see Figure 35.3B, D, and E). These lesions are similar to those seen in other renal diseases, such as scleroderma, malignant nephrosclerosis, chronic transplant rejection, and calcineurin inhibitor nephrotoxicity. In HUS, microthrombi are present primarily in the kidneys, whereas in TTP they mainly involve the brain, where thrombi may repeatedly form and resolve, producing intermittent neurologic deficits. In pediatric patients, particularly in those younger than 2 years and in those with HUS secondary to gastrointestinal infection with Stx-producing strains of *E. coli*, the glomerular injury is predominant. Thrombi and leukocyte infiltration are common in the early phases of the disease and usually resolve after 2 to 3 weeks. Patchy cortical necrosis may be present in severe cases; crescent formation is uncommon. In idiopathic and familial forms, and in adults, the injury...
mostly involves arteries and arterioles with thrombosis and intimal thickening (see Figure 35.3F), secondary glomerular ischemia, and retraction of the glomerular tuft (see Figure 35.3C). The prognosis is good in patients with predominant glomerular involvement, but is more severe in those with predominant preglomerular injury. Focal segmental glomerulosclerosis may be a long-term sequela of acute cases of HUS and is usually seen in children with long-lasting hypertension and progressive chronic renal function deterioration. 16-18

The typical pathologic changes of TTP are the thrombi that occlude capillaries and arterioles in many organs and tissues. These thrombi consist of fibrin and platelets, and their distribution is widespread. They are usually detected in kidneys, pancreas, heart, adrenals, and brain. Compared to HUS, pathologic changes of TTP are more extensively distributed, probably reflecting the more systemic nature of the disease. 16-18

**MECHANISMS, CLINICAL COURSE, AND THERAPY FOR DIFFERENT FORMS OF THROMBOTIC MICROANGIOPATHY**

**Hemolytic-Uremic Syndrome**

**Shiga Toxin–Associated Hemolytic-Uremic Syndrome**

*Mechanisms.* Stx-HUS may follow infection by certain strains of *E. coli* or *Shigella dysenteriae*, which produce a powerful exotoxin (Shiga toxin, or Stx). 9 The term *Shiga toxin* was initially used to describe the exotoxin produced by *Shigella dysenteriae* type 1. Then some strains of *E. coli* (mostly the serotype O157:H7, but also other serotypes—e.g., O111:H8, O103:H2, O123, and O26) isolated from human cases with diarrhea were found to produce a toxin similar to the one of *S. dysenteriae*. After food contaminated by Stx-producing *E. coli* or *S. dysenteriae* is ingested, the toxin is released in the gut and may cause watery or usually bloody diarrhea because of a direct effect on the intestinal mucosa. Stx-producing *E. coli* organisms adhere closely to the epithelial cells of the gastrointestinal mucosa, causing destruction of brush border villi. 19 These toxins are picked up by polarized gastrointestinal cells via transcellular pathways and translocate into the circulation, probably facilitated by the transmigration of neutrophils (PMN), which increase paracellular permeability. 20,21 Circulating human blood cells, such as erythrocytes platelets, and monocytes express Stx receptors on their surface and have been suggested to serve as Stx carriers from the intestine to the kidney and other target organs (Figure 35.4) 22-25.

Recently, evidence has been provided that Stx interacts with von Willebrand factor (vWF), a multimeric plasma glycoprotein that mediates platelet adhesion, activation, and aggregation. 25 In vitro experiments have shown that Stx binds to ultra-large vWF (UL-vWF) secreted from, and anchored to, stimulated human umbilical vein endothelial cells (HUVECs) and to immobilized vWF-rich HUVEC supernatant. This Stx binding reduces the rate of ADAMTS-13–mediated cleavage of vWF. The resulting delay in cleavage of endothelial cell–anchored UL-vWF multimers, by increasing the time available for platelet adhesion, activation, and aggregation, provides a possible explanation for thrombotic microangiopathy in diarrhea associated (D)+HUS.

Diagnosis rests on detection of *E. coli* 0157:H7 and other Stx-producing bacteria in sorbitol-MacConkey stool cultures. Serologic tests for antibodies to Stx and O157 lipopolysaccharide can be done in research laboratories, and tests are being developed for rapid detection of *E. coli* O157:H7 and Stx in stools.

Over the last decades, *E. coli* 0157:H7 and, less frequently, other Stx-producing *E. coli* strains, have been responsible for multiple outbreaks throughout the world, becoming a public health problem in developed and developing countries. Contaminated undercooked ground beef, meat patties, raw vegetables, fruit, milk, and recreational or drinking water have all been implicated in the transmission of *E. coli*.

A recent widespread outbreak associated with spinach in North America had dramatically higher than typical rates of hospitalization (52%) and HUS (16%) due to the emergence of a new variant of 0157:H7 serotype that had acquired several gene mutations, which likely contributed to more severe disease. 27

Secondary person-to-person contact is an important way of spread in institutional centers, particularly daycare...
centers and nursing homes. Infected patients should be excluded from daycare centers until two consecutive stool cultures are negative for Stx-producing E. coli to prevent further transmission. However, the most important preventive measure in childcare centers is supervised hand washing.

**Clinical Course.** Following exposure to Stx-E. coli, 38% to 61% of individuals develop hemorrhagic colitis and 3% to 9% (in sporadic infections) and up to 20% (in epidemic forms) progress to overt HUS.28,29 Stx-E. coli hemorrhagic colitis not complicated by HUS is self-limiting and is not associated with an increased long-term risk of high blood pressure or renal dysfunction, as shown by a 4-year follow-up study in 951 children who were exposed to a drinking water outbreak of E. coli O157:H7.30

Stx-HUS is characterized by prodromal diarrhea followed by acute renal failure. The average interval between E. coli exposure and illness is 3 days. Illness typically begins with abdominal cramps and nonbloody diarrhea; diarrhea may become hemorrhagic in 70% of cases, usually within 1 or 2 days.31 Vomiting occurs in 30% to 60% and fever in 30% of cases. The leukocyte count is usually elevated, and a barium enema may demonstrate thumbprinting, suggestive of edema and submucosal hemorrhage, especially in the region of the ascending and transverse colon. HUS is usually diagnosed 6 days after the onset of diarrhea.3 After infection, Stx-E. coli may be shed in the stools for several weeks after the symptoms are resolved, particularly in children younger than 5 years.5

Bloody diarrhea, fever, vomiting, elevated leukocyte count, extremes of age, and female gender, as well as the use of antimotility agents, have been associated with an increased risk of HUS following E. coli infection.28,32 Stx-HUS is not a benign disease. Of patients who develop HUS, 70% require red blood cell transfusions, 50% need dialysis, and 25% have neurologic involvement, including stroke, seizure, and coma.28,33,34 Although mortality for infants and young children in industrialized countries decreased when dialysis became available, and after the introduction of intensive care facilities, still 3% to 5% of patients die during the acute phase of Stx-HUS.33 A meta-analysis of 49 published studies (3476 patients; mean follow-up, 4.4 years) describing the long-term prognosis of patients who survived an episode of Stx-HUS, has reported death or permanent ESRD in 12% of patients and a glomerular filtration rate (GFR) below 80 mL/min/1.73 m² in 25%.34

Disease presentation and outcome were particularly severe during the Shiga toxin–producing Escherichia coli (STEC) O104:H4 German outbreak, in which 53 of 855 HUS patients died in Germany by its end.35 Compared to previous STEC epidemics, there was a higher incidence of dialysis-dependent kidney failure (20% vs. 6%) and death (6% vs. 1%).35 Almost 50% of patients presented with neurologic symptoms, and 20% of patients suffered seizures. The severe clinical phenotype was explained by lack of previous immunity to this novel STEC strain and also by its exceptional virulence.35 E. coli O104:H4 not only produces the same Stx as STEC enterohemorrhagic strains, but also has 93% of the genomic sequence of enteraggregative E. coli strains that form fimbriae, which facilitates adhesion to the intestinal wall. The evolution of E. coli O104:H4 is likely the result of the acquisition by an enteraggregative strain of E. coli of a Stx-encoding phage from a Stx-producing enterohemorrhagic strain of E. coli. The combination of these two virulence factors would lead to increased gut colonization and thus the release of increased quantities of toxin into the circulation. Moreover, although enterohemorrhagic E. coli are found in the gastrointestinal tract of ruminants, enteraggregative E. coli appear to have their reservoir in humans. This might explain why this strain has acquired new resistances to antibiotics most commonly used in human disease.

**Therapy.** Typical treatment of Stx-associated HUS of children is based on supportive management of anemia, renal failure, hypertension, and electrolyte and water imbalances. Intravenous isotonic volume expansion as soon as an E. coli O157:H7 infection is suspected—that is, within the first 4 days of illness, even before culture results are available—may limit the severity of kidney dysfunction and the need for renal replacement therapy.36 Bowel rest is important for the enterohemorrhagic colitis associated with Stx-HUS. Antimotility agents should be avoided because they may prolong the persistence of E. coli in the intestinal lumen and therefore increase the patient’s exposure to its toxin. The use of antibiotics should be restricted to the very limited number of patients presenting with bacteremia37 because, in children with gastroenteritis, they may increase the risk of HUS by 17-fold.38 A possible explanation is that antibiotic-induced injury to the bacterial membrane might favor the acute release of large amounts of preformed toxin. Alternatively, antibiotic therapy might give E. coli O157:H7 a selective advantage if these organisms are not as readily eliminated from the bowel as normal intestinal flora. Moreover, several antimicrobial drugs, particularly the quinolones, trimethoprim, and furazolidone, are potent inducers of the expression of the Stx2 gene and may increase the level of toxin in the intestine. Although the possibility of a cause-and-effect relationship between antibiotic therapy and increased risk of HUS has been challenged by a meta-analysis of 26 reports,39 there is no reason to prescribe antibiotics because they do not improve the outcome of colitis, and bacteremia is only exceptionally found in Stx-associated HUS. However, when hemorrhagic colitis is caused by S. dysenteriae type 1, early and empirical antibiotic treatment shortens the duration of diarrhea, decreases the incidence of complications, and reduces the risk of transmission by shortening the duration of bacterial shedding. Thus, in developing countries where S. dysenteriae is the most frequent cause of hemorrhagic colitis, antibiotic therapy should be started early, even before the involved pathogen is identified.

Careful blood pressure control and renin angiotensin aldosterone system (RAAS) blockade may be particularly beneficial in the long term for patients who suffer chronic renal disease after an episode of Stx-HUS. A study of 45 children with renal sequelae of HUS followed for 9 to 11 years has documented that early restriction of proteins and use of angiotensin-converting enzyme inhibitors (ACEIs) may have a beneficial effect on long-term renal outcome, as documented by a positive slope of 1/creatinine (1/Cr) values over time in treated patients.40 In another study, 8- to 15-year treatment with ACEIs after severe Stx-HUS normalized blood pressure, reduced proteinuria, and improved GFR.41
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35-7

HUS. 43, 44 These findings lead to the consideration of plasma infusion or exchange suitable for adult patients, in particular those with severe renal insufficiency and central nervous system involvement, such as patients involved in E. coli O104:H4 HUS outbreaks. 45 In this context, immunoglobulin G (IgG) depletion, through immunoadsorption rescue therapy added on to plasma exchange, has been reported to achieve complete neurologic recovery in 10 of 12 critically ill patients with delirium, epileptic seizures, or requirement for mechanical ventilation. 46

Kidney transplantation should be considered as an effective and safe treatment for children who progress to ESRD. Indeed, recurrence rates range from 0% to 10%, and graft survival at 10 years is even better than in control children with other diseases. 47-49 Importantly, genetic screening performed in a young woman with history of Stx-HUS and early graft failure, before planning a second transplantation, revealed a complement factor I (CFI) mutation. 50 This case indicates that screening of HUS-associated genes should be performed in patients on dialysis following severe episodes.

Table 35.2 Specific Therapies Used in Thrombotic Microangiopathy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosing</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Antiplatelet</td>
<td></td>
<td>Anecdotal efficacy in TTP</td>
</tr>
<tr>
<td>Aspirin</td>
<td>325-1300 mg/day</td>
<td>Anecdotal efficacy in HUS</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>400-600 mg/day</td>
<td>Not effective in preventing or treating Stx-associated HUS</td>
</tr>
<tr>
<td>Dextran 70</td>
<td>500 mg twice daily</td>
<td>Anecdotal efficacy in HUS</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>4-20 mg/kg/min</td>
<td>Anecdotal efficacy in HUS</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td></td>
<td>Anecdotal efficacy in HUS</td>
</tr>
<tr>
<td>Heparin</td>
<td>5000-U bolus followed by 750- to 1000-U/hr infusion</td>
<td>Not effective in addition to plasma exchange in patients with TTP and anti-ADAMST13 autoantibodies or in aHUS with antifactor H autoantibodies and in forms associated with autoimmune diseases; lack of evidence from controlled trials for immune-mediated HUS or TTP</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>250,000-U bolus followed by 100,000-U/hr infusion</td>
<td>Effective in treatment or prevention of TTP associated with immune-mediated ADAMTS13 deficiency resistant to, or relapsing after, immunosuppressive therapy</td>
</tr>
<tr>
<td>Shiga toxin–binding (Synsorb)</td>
<td>500 mg/kg/day for 7 days</td>
<td>First-line therapy for aHUS and TTP; unproven efficacy in childhood Stx-HUS</td>
</tr>
<tr>
<td>Antioxidant (vitamin E)</td>
<td>1000 mg/m³/day</td>
<td>To be considered if plasma exchange not available</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td></td>
<td>To replace whole plasma in case of plasma resistance or sensitization</td>
</tr>
<tr>
<td>Prednisone</td>
<td>200 mg tapered to 60 mg/day, then 5-mg reduction/wk</td>
<td>To limit the risk of infections</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>200 mg tapered to 60 mg/day, then 5-mg reduction/wk</td>
<td>To prevent FH-associated HUS recurrence posttransplantation; ~30% mortality risk</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>400 mg/kg/day</td>
<td>Reported efficacy in FH-associated HUS</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m³ followed by 1 mg every 4 days</td>
<td></td>
</tr>
<tr>
<td>CD20 cell depletion (rituximab)</td>
<td>375 mg/m³/wk up to CD20 depletion</td>
<td></td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>1-2 plasma volumes/day</td>
<td></td>
</tr>
<tr>
<td>Exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion</td>
<td>20-30 mL/kg followed by 10-20 mL/kg/day</td>
<td></td>
</tr>
<tr>
<td>Cryosupernatant</td>
<td>See plasma infusion, exchanges</td>
<td></td>
</tr>
<tr>
<td>Solvent detergent–treated plasma</td>
<td>See plasma infusion, exchanges</td>
<td></td>
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<tr>
<td>Liver-kidney transplantation</td>
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<tr>
<td>Complement inhibition (eculizumab)</td>
<td>600 mg/wk for first 4 wk; 900 mg every 14 days, up to 6 mo</td>
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FH, Factor H; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

An oral Stx-binding agent that may compete with endothelial and epithelial receptors for Stx in the gut (Synsorb PK) has been developed with the rationale of limiting target organ exposure to the toxin (Table 35.2). However, a prospective, randomized, double-blind, placebo-controlled clinical trial of 145 children with diarrhea-associated HUS failed to demonstrate any beneficial effect of treatment on disease outcome. 42

Heparin and antithrombotic agents may increase the risk of bleeding and should be avoided.

The efficacy of specific treatments in adult patients is difficult to evaluate because most information has been derived by uncontrolled series, which may include also atypical HUS cases. In particular, no prospective randomized trials are available to establish definitively whether plasma infusion or exchange may offer some specific benefit as compared to supportive treatment alone. However, comparative analyses of two large series of patients treated or not treated with plasma have suggested that plasma therapy may dramatically decrease overall mortality of Stx-E. coli O157:H7–associated HUS. 43, 44 These findings lead to the consideration of plasma infusion or exchange suitable for adult patients, in particular those with severe renal insufficiency and central nervous system involvement, such as patients involved in E. coli O104:H4 HUS outbreaks. 45 In this context, immunoglobulin G (IgG) depletion, through immunoadsorption rescue therapy added on to plasma exchange, has been reported to achieve complete neurologic recovery in 10 of 12 critically ill patients with delirium, epileptic seizures, or requirement for mechanical ventilation. 46

Kidney transplantation should be considered as an effective and safe treatment for children who progress to ESRD. Indeed, recurrence rates range from 0% to 10%, and graft survival at 10 years is even better than in control children with other diseases. 47-49 Importantly, genetic screening performed in a young woman with history of Stx-HUS and early graft failure, before planning a second transplantation, revealed a complement factor I (CFI) mutation. 50 This case indicates that screening of HUS-associated genes should be performed in patients on dialysis following severe episodes.
of Stx-HUS because they may be undiagnosed cases of HUS precipitated by STEC infection on a genetic background of impaired complement regulation.

Evidence that uncontrolled complement activation may contribute to microangiopathic lesions of STEC-HUS provided the background for complement inhibitor therapy in three children with severe STEC-HUS who fully recovered with the anti-C5 monoclonal antibody eculizumab. These encouraging results prompted nephrologists to use eculizumab therapy in HUS patients involved in the STEC O104:H4 outbreak in Germany (see Table 35.2). However, data are largely inconclusive because they were substantially biased by the retrospective and nonrandomized design of the studies. Although uncontrolled reports have suggested that eculizumab is associated with prompt and complete recovery, in particular if treatment is started early after disease onset, evidence from controlled studies—that disease outcome was similar between patients who received eculizumab together with plasma exchange and those who received plasma exchange alone—has strongly questioned the benefit of eculizumab added on as best available therapy, including plasma exchange. However, these findings are difficult to interpret because they were most likely biased by the preferential administration of eculizumab to patients with more severe disease. Thus, whether eculizumab is a useful adjunct to treating the most severe forms of STEC-HUS needs to be clarified by prospective, randomized, controlled trials.

**Streptococcus pneumoniae–Associated Hemolytic-Uremic Syndrome**

**Mechanisms.** This is a rare but potentially fatal disease that may complicate pneumonia or, less frequently, meningitis caused by *Streptococcus pneumoniae*. Neuraminidase produced by *S. pneumoniae*, by removing sialic acid from the cell membranes, exposes Thomsen-Friedenreich antigen (T-antigen). T-antigen exposure on red cells is detected using the lectin *Arachis hypogaea*. An immunoglobulin M cold antibody occurring naturally in human serum causes the polyaagglutination of red blood cells in vitro. This is why, unlike in other forms of HUS, there is a positive Coombs test result in neuraminidase-associated HUS. T–anti-T interaction on red cells, platelets, and endothelium was thought to explain the pathogenesis, whereas the pathogenic role of the anti-T cold antibody in vivo is uncertain.

Recently, a study investigating the complement system in five patients with *S. pneumoniae* HUS (SP-HUS) found a decrease in components of the classical and alternative pathways during the acute phase of the disease. This indicates early severe activation and consumption of complement, and most of these alterations normalized later in remission. In addition, three of the five SP-HUS patients carried mutations and/or risk haplotypes in genes previously reported to associate with complement-mediated aHUS—a previously described variant of factor I (PC50A) and two new mutations in factor H (R1149X) and thrombomodulin (T441). These observations suggest that severe complement dysregulation and consumption, in addition to neuraminidase action, accompany the progression of SP-HUS, and genetic variations of complement genes may contribute to the development of this complication in some affected patients.

**Clinical Course.** Patients, usually younger than 2 years, present with severe microangiopathic hemolytic anemia. The clinical picture is severe, with respiratory distress, neurologic involvement, and coma. The acute mortality is about 25%.

**Therapy.** The outcome is strongly dependent on the effectiveness of antibiotic therapy. In theory, plasma, infused or exchanged, is contraindicated, because adult plasma contains antibodies against the Thomsen-Friedenreich antigen that may accelerate polyaagglutination and hemolysis. Thus, patients should be treated only with antibiotics and washed red cells. In some cases, however, plasma therapy, occasionally in combination with steroids, has been associated with recovery. Evidence that complement activation plays a role in the pathogenesis of SP-HUS might provide a background for the possible benefits of complement inhibitor therapy in this context.

**Atypical Hemolytic-Uremic Syndrome.** Atypical HUS includes a number of associations and presentations. It can occur sporadically or within families. Research in the last 10 years has linked aHUS to uncontrolled activation of the complement system (Figure 35.5). Fewer than 20% of atypical HUS cases are familial. Reports date back to 1965, when Campbell and Carre described hemolytic anemia and azotemia in concordant monozygous twins. Since then, familial HUS has been reported in children and, less frequently, in adults. Although some cases were in siblings, suggesting autosomal recessive transmission, others were across two or three generations, suggesting an autosomal dominant mode. The prognosis is poor (cumulative incidence of death or ESRD, 50% to 80%).

Sporadic aHUS encompasses cases without a family history of the disease. Triggering conditions for sporadic aHUS include HIV infection, anticancer drugs (e.g., mitomycin, cisplatin, bleomycin, gemcitabine), immunotherapeutic agents (e.g., cyclosporine, tacrolimus, OKT3, interferon, quinidine), antiplatelet agents (e.g., ticlopidine, clopidogrel), malignancies, transplantation, and pregnancy.

De novo posttransplantation HUS has been reported in patients receiving renal transplants or other organs due to calcineurin inhibitors or humoral rejection. It has been reported in up to 5% to 15% of renal transplantation patients who receive cyclosporine and in approximately 1% of those who are given tacrolimus. Dose reduction or changing one calcineurin inhibitor for another sometimes results in recovery and suggests a causative role.

In 10% to 15% of female patients, aHUS manifests during pregnancy or postpartum. Atypical HUS may present at any time during pregnancy, but mostly in the last trimester and about the time of delivery. It is sometimes difficult to distinguish it from preeclampsia. The HELPP syndrome (hemolytic anemia, elevated liver enzymes, and low platelets) is a life-threatening disorder of the last trimester or parturition with severe thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and liver involvement. These forms are always an indication for prompt delivery, which is usually followed by complete remission. Postpartum HUS manifests within 3 months of delivery in most cases. The outcome is usually poor. About 50% of sporadic aHUS cases show no clear trigger (idiopathic HUS).
Classical pathway
- IgM, IgG immune complexes
- C1q, C1r, C1s
- C4, C2
- C4b2a

Lectin pathway
- MBL, MASP
- C3 convertase
- C3a
- C3b
- C4bC2aC3b

Alternative pathway
- Bacteria, viruses, activating surfaces
- C3
- C3 convertase
- C3a
- C3b
- (C3b)2BbP

Mechanisms.
Complement Abnormalities. Reduced serum levels of C3 with normal C4 in aHUS patients have been recognized since 1974. In cases of familial aHUS, serum C3 was low, even during remission, hinting to genetic defects. A low C3 reflected complement activation and consumption with high levels of activated products, C3b, C3c, and C3d. The complement system is part of innate immunity and consists of several plasma- and membrane-bound proteins protecting against invading organisms. Three activation pathways—classical, lectin, and alternative pathways—produce protease complexes, termed C3 and C5 convertases, that cleave C3 and C5, respectively, eventually leading to the membrane attack complex (MAC) lytic complex (Figure 35.5). The alternative pathway is initiated spontaneously in plasma by C3 hydrolysis responsible for the covalent deposition of a low amount of C3b onto almost all plasma-exposed surfaces (see Figure 35.5). On bacterial surfaces, C3b leads to opsonization for phagocytosis by neutrophils and macrophages. Without regulation, a small initiating stimulus is

![Figure 35.5](image_url)

The three activation pathways of complement. The classical pathway is initiated by the binding of the C1 complex to antibodies bound to an antigen on the surface of a bacterial cell, leading to the formation of a C4b2a enzyme complex, the C3 convertase of the classical pathway. The mannose-binding lectin pathway is initiated by binding of the complex of mannose-binding lectin (MBL) and the serine proteases mannose-binding, lectin-associated proteases 1 and 2 (MASP1 and MASP2) to mannose residues on the surface of a bacterial cell; this leads to the formation of the C3 convertase enzyme C4bC2a. The alternative pathway is initiated by the covalent binding of a small amount of C3b generated by spontaneous hydrolysis in plasma to hydroxyl groups on cell surface carbohydrates and proteins. This C3b binds factor B to form the alternative pathway C3 complex C3bBb. The C3 convertase enzymes cleave many molecules of C3 to form the anaphylatoxin C3a and C3b, which binds covalently around the site of complement activation. Some of this C3b binds to C4b and C3b in the convertase enzymes of the classical and alternative pathways, respectively, forming C5 convertase enzymes that cleave C5 to form the anaphylatoxin C5a and C5b, which initiates the formation of the membrane attack complex. The human complement system is highly regulated to prevent nonspecific damage to host cells and limit the deposition of complement to the surface of pathogens. This fine regulation occurs through a number of membrane-anchored and fluid phase regulators (in red) that inactivate complement products formed at various levels in the cascade and protect host tissues. CD59, Protectin (prevents the terminal polymerization of the membrane attack complex); CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein.
quickly amplified to a self-harming response until the consumption of complement components (see Figure 35.5). On host cells, such a dangerous cascade is controlled by membrane-anchored and fluid phase regulators (see Figure 35.5). They both favor the cleavage of C3b to inactive iC3b by the plasma serine-protease factor I (CFI, cofactor activity) and dissociate the multicomponent C3 and C5 convertases (decay acceleration activity). Foreign targets and injured cells that lack membrane-bound regulators or cannot bind soluble regulators are attacked by complement.

The C3 convertases of the classical and lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase requires cleavage of C3 only (see Figure 35.5). Thus, low serum C3 levels in aHUS with normal C4 indicate selective AP activation.22

Genetic Abnormalities. A variety of genetic abnormalities in members of the alternative pathway of complement have been described in aHUS, which account for about 60% of cases (see Table 35.1). Of note, different genetic abnormalities account for different patterns of dysfunction of the complement system with different outcomes, response to therapy, and risk of recurrence after kidney transplantation (Table 35.3).

Complement Factor H. Complement factor H (CFH) regulates the alternative pathway by competing with complement factor B (CFB) for C3b recognition by acting as a cofactor for CFI, and enhancing dissociation of C3 convertase.75 In 1998, Warwicker and coworkers demonstrated linkage of aHUS to the chromosome 1q32 locus, containing genes for CFH and other complement regulators.80 Since then, over 80 CFH mutations (interactive FH-HUS mutations database, http://www.FH-HUS.org) have been identified in aHUS patients (mutation frequency—40% to 45% familial forms, 10% to 20% sporadic forms).77-85 These mutations usually do not result in a quantitative CFH deficiency, but result in normal levels of a protein that is unable to bind to and regulate complement on endothelial cells and platelets.84 A high degree of sequence identity between CFH and the genes CFHR1-5 for five factor H–related proteins (CFHRs) located in tandem to CFH may predispose to nonallelic recombinations.85 In 3% to 5% of patients with aHUS, a heterozygous hybrid gene derived from an uneven crossover between CFH and CFHR1 contained the first 21 CFH exons and the last two CFHR1 exons, resulting in a gene product with decreased complement regulatory activity on endothelial surfaces.85 Additional forms of CFH and CFHR genes have been recently described.

Acquired defects of CFH function are also seen in the form of inhibitory antibodies that are reported in 5% to 10% of aHUS patients.86 Analogous to the genetic defect seen in CFH, these autoantibodies also predominantly target the C-terminal end of the protein, thereby impairing complement regulation on host cell surfaces. The development of CFH autoantibodies in aHUS has a genetic predisposition, being strongly associated with a deletion of the CFHR1 and CFHR3 genes.

Membrane Cofactor Protein. Membrane cofactor protein (MCP) is pivotal against C3 activation on glomerular endothelium. Anti-MCP antibody completely blocked cofactor activity in cell extracts.87 In 2003, two groups described mutations in MCP encoding the widely expressed transmembrane regulator, membrane cofactor protein, in affected individuals of four families. MCP serves as a cofactor for CFI to cleave C3b and C4b on cell surfaces.88,89 MCP mutations account for 10% to 15% of aHUS cases.89 Most are heterozygous, about 25% are homozygous or compound.

### Table 35.3 Outcomes of Atypical Hemolytic-Uremic Syndrome (aHUS)*

<table>
<thead>
<tr>
<th>Affected Gene(s)</th>
<th>Affected Protein and Main Effect</th>
<th>Frequency in aHUS (%)</th>
<th>Rate of Remission With Plasma Exchange†</th>
<th>5- to 10-yr Rate of Death or ESRD (%)</th>
<th>Rate of Recurrence after Kidney Transplantation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H (no binding to endothelium)</td>
<td>20-30 (dose- and timing-dependent)</td>
<td>60</td>
<td>70-80</td>
<td>80-90†</td>
</tr>
<tr>
<td>CFHL1, CFHL3 MCP</td>
<td>Factor HR1, R3 (anti-factor H antibodies)</td>
<td>6</td>
<td>70-80 (combined with immunosuppression)</td>
<td>No indication for plasma exchange</td>
<td>30-40</td>
</tr>
<tr>
<td></td>
<td>Membrane cofactor protein (no surface expression)</td>
<td>10-15</td>
<td>&lt;20</td>
<td>15-20†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor I (low levels, low cofactor act)</td>
<td>4-10</td>
<td>30-40</td>
<td>60-70</td>
<td>70-80</td>
</tr>
<tr>
<td></td>
<td>Factor B (C3 convertase stabilization)</td>
<td>1-2</td>
<td>30</td>
<td>70</td>
<td>One case reported</td>
</tr>
<tr>
<td></td>
<td>Complement C3 (resistance to C3b inactivation)</td>
<td>5-10</td>
<td>40-50</td>
<td>6%</td>
<td>40-50</td>
</tr>
<tr>
<td></td>
<td>Thrombomodulin (reduced C3b inactivation)</td>
<td>5</td>
<td>60</td>
<td>60</td>
<td>One case reported</td>
</tr>
</tbody>
</table>

*According to the associated genetic abnormality.
†Complete remission or hematologic remission with renal sequelae.
‡Kidney or combined liver and kidney transplantation.
§Single kidney transplantation.
heterozygous (http://www.FH-HUS.org). Most cluster in critical extracellular modules for regulation. Expression on blood leukocytes was reduced for about 75% of mutants, causing quantitative defects. Conversely, others have low C3b-binding capability and decreased cofactor activity.\textsuperscript{81,94}

**Complement Factor I.** CFI is a plasma serine protease that regulates the three complement pathways by cleaving C3b and C4b in the presence of cofactor proteins. CFI mutations affect 4% to 10% of aHUS patients.\textsuperscript{81,92,94} All mutations are heterozygous; 80% cluster in the serine-protease domain. Approximately 50% of mutations result in low CFI levels. Others disrupt C3b and C4b cleavage.\textsuperscript{81,92,94}

**Complement Factors B and C3.** Gain-of-function mutations can affect genes encoding the alternative pathway C3 convertase components, CFB and C3.\textsuperscript{93,95} CFB mutations are rare in aHUS (1% to 2%).\textsuperscript{96} Patients have chronic alternative pathway activation, with low C3 and, usually, normal C4.\textsuperscript{96} CFB mutants have excess C3b affinity and form a hyperactive C3 convertase resistant to dissociation. C3b formation is thereby enhanced in vivo.\textsuperscript{96}

About 4% to 10% of aHUS patients have heterozygous mutations in C3, usually with low C3 levels. Most mutations reduce C3b binding to CFH and MCP, severely impairing degradation of mutant C3b.\textsuperscript{96}

**Thrombomodulin.** Mutations in the \textit{THBD} gene encoding thrombomodulin, a membrane-bound glycoprotein with anticoagulant properties that modulates complement activation on cell surfaces, have been associated with aHUS.\textsuperscript{97} About 5% of aHUS patients carry heterozygous \textit{THBD} mutations. Cells expressing these variants inactivate C3b less efficiently than cells expressing wild-type thrombomodulin.\textsuperscript{97} These data document a functional link between complement and coagulation, opening new perspectives for candidate gene research in aHUS.

**Diacylglycerol Kinase-ε.** Homozygous or compound heterozygous mutations in diacylglycerol kinase-ε (DGK-ε) were recently reported in nine unrelated children with aHUS and autosomal recessive inheritance.\textsuperscript{98} Mutation carriers presented with aHUS before the age of 1 year, had persistent hypertension, hematuria, and proteinuria, and developed chronic kidney disease as they got older. DGK-ε encodes diacylglycerol kinase-ε, which is expressed in endothelium, platelets, and podocytes. Diacylglycerol kinase-ε is apparently unrelated to the complement cascade, and the mechanism whereby DGK-ε mutations cause aHUS remains to be elucidated.

**Determinants of Disease Penetrance.** Two other factors are thought to determine the development of aHUS. First, in most patients, there is a trigger. Infection and pregnancy are the most frequently described triggers.\textsuperscript{99} Second, a further genetic variant (modifier) can increase the risk of developing the disease. This can be in the form of an additional mutation in one of the aforementioned genes and/or the presence of a common at-risk genetic variant. It is now recognized that about 10% of aHUS patients will have mutations in more than one gene.\textsuperscript{98} Common at-risk genetic variants (single-nucleotide polymorphisms [SNPs] and haplotype blocks) in \textit{CFH}, \textit{CD46}, and \textit{CFHR1} have been shown to act as susceptibility factors for development of the disease.\textsuperscript{50}

**Clinical Course.** Of aHUS patients, irrespective of mutation type, 67% are affected during childhood, and almost all patients with anti-CFH antibodies develop the disease before 16 years.\textsuperscript{81,100} Acute episodes manifest with severe hemolytic anemia, thrombocytopenia, and acute renal failure. Extra-renal involvement (central nervous system or multisystem) occurs in 20% of cases.\textsuperscript{5,81,100}

Short- and long-term outcomes vary according to the underlying complement abnormality (see Table 35.3). About 60% to 70% of patients with \textit{CFH}, \textit{CFI}, and \textit{C3} mutations and one third of children with anti-CFH autoantibodies lose renal function, die during the presenting episode, or develop ESRD following relapses.\textsuperscript{5,81,100} \textit{CFB} mutations are associated with poor renal outcome (renal function loss in seven of eight patients).\textsuperscript{96}

Chronic complement dysregulation may lead to atheroma-like lesions. About 20% of patients with \textit{CFH} mutations have cardiovascular complications (e.g., coronary or cerebrovascular disease, myocardial infarction) and excess mortality. Long-term survival is worse in patients with \textit{CFH} mutations (50% at 10 years) than in those with \textit{CFI} and \textit{C3} mutations or anti-CFH autoantibodies (80% to 90% at 10 years).\textsuperscript{5,81,100}

\textit{MCP} mutation carriers have a good prognosis (complete remission, 80% to 90%). Recurrences are frequent but the long-term outcome is good, and 80% of patients remain dialysis free.\textsuperscript{5,81,100} However, rare patients with \textit{MCP} mutations have severe disease, immediate ESRD, intractable hypertension, and coma, possibly because of concurrent genetic abnormalities.\textsuperscript{81}

**Therapy. Fresh-Frozen Plasma.** Guidelines suggest that plasma therapy (plasma exchange, one or two plasma volumes/day; plasma infusion, 20 to 30 mL/kg/day) should be started within 24 hours of diagnosis.\textsuperscript{5} Plasma exchange allows supplying larger amounts of plasma than would be possible with infusion while avoiding fluid overload (see Table 35.2). Trials of plasma therapy in HUS are scanty and not current. The only two published trials in HUS comparing supportive therapy alone with supportive therapy plus plasma infusion did not demonstrate significant benefit for plasma in inducing remission.\textsuperscript{102,103} However, neither trial examined outcomes separately for Stx-HUS versus aHUS, which invariably weakened the potential benefits of plasma for aHUS.\textsuperscript{104,105} Because CFH is a plasma protein, plasma infusion or exchange provides normal CFH to patients carrying \textit{CFH} mutations.\textsuperscript{81,100,106,107} Long-term treatment, however, may fail due to the development of plasma resistance.\textsuperscript{108} Heterozygous \textit{CFH} mutation carriers usually have normal levels of CFH, half of which is dysfunctional. The beneficial effect of plasma is strongly dependent on amount, frequency, and modality of administration, with plasma exchange being superior to plasma infusion for remission and prevention of recurrences by removal of mutant CFH that could antagonize the normal protein.\textsuperscript{109,110} Overall, published data in patients with \textit{CFH} mutations show complete or partial (hematologic normalization with renal sequelae) remission of 60% of plasma-treated episodes (see Table 35.3).\textsuperscript{5,81,100} Plasma exchange is used to remove anti-CFH antibodies, but the effect is usually transient.\textsuperscript{86,100} Immunosuppressants (corticosteroids and azathioprine or mycophenolate mofetil) and rituximab, an anti-CD20 antibody, combined with plasma exchange allows long-term, dialysis-free survival in 60% to 70% of patients.\textsuperscript{86,101,111,112}

Patients with \textit{CFI} mutations show only a partial response, with remission in about 30% to 40% of plasma-treated
episodes. Because MCP is a cell-associated protein, effects of plasma are unlikely in patients with MCP mutations. Indeed, 80% to 90% of patients undergo remission independently of plasma treatment (see Table 35.3). Thirtysix percent of patients with CFB mutations and 50% of those with C3 mutations respond to plasma infusion or exchange. Possibly, these patients need abundant and frequent plasma exchanges to clear the hyperfunctional mutants CFB and C3. 

Transplantation. Whether kidney transplantation is appropriate for aHUS patients with ESRD has been long debated. Disease recurred in about 50% of transplant patients with CFH, CFI, CFB, and C3 mutations, and graft failure occurred in 80% to 90% of them. Living related donation is contraindicated by a high risk of recurrence and may be risky to donors. A man with a heterozygous CFH mutation developed de novo HUS after donating a kidney to his child.

Intensive chronic plasma prophylaxis prevented recurrence in one patient with a CFH mutation but failed in another patient. Simultaneous kidney and liver transplantation was performed in two children with aHUS and CFH mutations, with the rationale of correcting the genetic defect and preventing recurrences. However, both cases were complicated by premature liver failure. The first child recovered after a second liver transplantation. The child had no symptoms of HUS for 3 years but died from sequelae of hepatic encephalopathy. This case offered the proof of concept that transplantation could cure HUS associated with CFH mutations by correcting the genetic defect. The second case was also complicated by liver failure, with widespread microvascular thrombosis and complement deposition. It was reasoned that the surgical stress with ischemia and reperfusion induced complement activation in the liver that could not be regulated because of functional CFH deficiency. A modified approach to the combined transplantation was applied to eight cases, including extensive plasma exchange before surgery to provide a timely enough normal CFH until the liver graft recovered synthetic function. This procedure was successful in seven patients. However, another child developed severe hepatic thrombosis and fatal encephalopathy. The risks of kidney and liver transplantation require a careful assessment of benefits for candidate patients.

The outcome of kidney transplantation is favorable in patients with MCP mutations. More than 80% did not experience HUS recurrence, with long-term graft survival comparable to that of patients transplanted for other causes. The theoretical rationale is strong. MCP is a transmembrane protein that is highly expressed in the kidney. Not surprisingly, a kidney graft corrects the defect of MCP-mutated recipients. Screening for mutations should allow patients and clinicians to make informed decisions regarding listing for transplantation based on the risk of recurrence (Figure 35.6). Algorithms have been developed to optimize the cost-effectiveness of screening programs for genetic defects in patients with aHUS (see Figure 35.6). A position paper has defined the groups of patients in whom isolated kidney transplantation is extremely risky, where a combined kidney-liver transplantation is recommended, and those eligible to isolated kidney transplantation.
Figure 35.6  Flow diagram of the steps suggested to optimize the cost-effectiveness of screening for genetic defects in patients with aHUS and suspected genetically determined abnormalities in complement regulatory proteins. A preliminary screen for serum CFH and CFI levels by enzyme-linked immunosorbent assay (ELISA) or radial immunodiffusion (RID), and for MCP expression in peripheral blood leukocytes by flow cytometry (FACS), is recommended to identify which is the candidate gene to evaluate. If no abnormalities are detected, we suggest screening for anti-CFH autoantibodies and then, if none are detected, to look for mutations of candidate genes starting with the CFH gene; this is more frequently affected by pathogenic mutations, followed by MCP1 and CFI genes, respectively. Within each gene, the exons where the mutations tend to localize more frequently should be studied first. CFH, Complement factor H; CFI, complement factor I; MCP, membrane cofactor protein.
prevent and treat aHUS recurrence after solitary kidney transplantation.157 This approach is safe and effective as long as treatment is continued. In some cases, eculizumab might have the additional benefit of reducing the risk of antibody-mediated rejection.158 On the other hand, the risk of sensitization associated with chronic drug exposure and the enormous costs that could be unbearable in resource-limited settings suggest that careful treatment tapering up to withdrawal, whenever possible, should be attempted in most cases under tight control of disease and complement activity. In this context, a successful liver transplantation might allow safely withdrawing eculizumab therapy by restoring the bioavailability of liver-produced complement modulators such as factor H or factor I. On the other hand, perioperative eculizumab therapy might protect the liver from thrombotic microangiopathy and protect against early failure by preventing uncontrolled complement activation precipitated by surgical stress and revascularization damage. Thus, liver transplantation, under the umbrella of perioperative eculizumab therapy, might be a valuable option when chronic eculizumab therapy is unfeasible because of safety concerns or resource restriction.159

Hemolytic-Uremic Syndrome Associated with Inborn Abnormal Cobalamin Metabolism

Mechanisms. This is a rare autosomal recessive form of HUS associated with an inborn abnormality of cobalamin C metabolism.130 The biochemical features of cobalamin C deficiency are hyperhomocysteinemia and methylmalonic aciduria.

Clinical Course. Patients with cobalamin C deficiency usually present in the early days and months of life with failure to thrive, poor feeding, and vomiting.65,130 Rapid deterioration occurs due to metabolic acidosis, gastrointestinal bleeding, hemolytic anemia, thrombocytopenia, severe respiratory and hepatic failure, and renal insufficiency. Children may present neurologic symptoms of fatigue, delirium, psychosis, and seizures. In cases with early onset, the disease has a fulminant evolution and occasionally involves the pulmonary vasculature, but when it ensues later in childhood it may follow a more chronic course. The hallmarks of defective cobalamin C metabolism are hyperhomocysteinemia and methylmalonic aciduria, and the extremely high homocysteine levels (up to tenfold higher than normal) have been suggested to have a role in the pathogenesis of the vascular lesions. Without treatment, the disease is fatal, and some children likely die undiagnosed.

Therapy. Daily intramuscular administrations of hydroxycobalamin may reduce homocysteine levels and methylmalonic aciduria, whereas oral hydroxycobalamin and cyanocobalamin are ineffective. Oral betaine helps reduce serum homocysteine levels further by activating betaine homocysteine methyltransferase. Folic acid supplementation to avoid folate deficiency induced by methyltetrahydrofolate trapping and L-carnitine to increase propionyl carnitine excretion have been suggested, but their role in improving disease outcome is unclear.131

Despite treatment, most children with early-onset disease die or have severe neurologic sequelae. Intensified treatment in older children with less acute disease may achieve remission of the microangiopathic process and amelioration of the other clinical manifestations of the metabolic disorder. Whether plasma therapy has a role in improving disease outcome is unknown.

Thrombotic Thrombocytopenic Purpura

In the microvasculature of patients with TTP, systemic platelet thrombi are developed, mainly formed by platelets and vWF. This protein plays a major role in primary hemostasis by forming platelet plugs at the sites of vascular injury under high shear stress. vWF is a large glycoprotein synthesized in vascular endothelial cells and megakaryocytes. On stimulation, vWF is secreted by endothelial cells as ultra-large multimers that form stringlike structures attached to the endothelial cells, possibly through interaction with P-selectin.152 Under fluid shear stress, the UL-vWF strings are cleaved to generate the range of vWF multimer sizes that normally circulate in the blood, from approximately 500 kDa to 20 million Da.153 The proteolytic cleavage of vWF multimers appears to be critical to prevent thrombosis in the microvasculature (Figure 35.7, right upper panel).

ADAMTS13 is the protease, predominantly expressed by the liver, that cleaves vWF; it is deficient in most patients with TTP, leading to the accumulation of UL-vWF multimers that are highly reactive with platelets (see Figure 35.7, right lower panel).134,135 Two mechanisms for the deficiency of ADAMTS13 activity have been identified in patients with idiopathic TTP—an acquired deficiency caused by the formation of anti-ADAMTS13 autoantibodies (acquired TTP) and a genetic deficiency due to homozygous or compound heterozygous mutations in the ADAMTS13 gene (congenital TTP; see Table 35.1).

Immune-Mediated Deficiency of ADAMTS13 Associated with Thrombotic Thrombocytopenic Purpura

Mechanisms. This is an immune-mediated, nonfamilial form of TTP that most likely accounts for most cases (from 60% to 90%) so far reported as acute idiopathic or sporadic TTP (see Table 35.2). The disease is characterized by a severe deficiency of ADAMTS13; its activity is inhibited by specific autoantibodies that develop transiently and tend to disappear during remission.8,134,135,137,138 These inhibitory anti-ADAMTS13 antibodies are mainly IgG, although IgM and IgA anti-ADAMTS13 antibodies have also been described.134,135,136

Patients with TTP secondary to hematopoietic stem cell transplantation, malignancies, or HIV infection rarely have severe ADAMTS13 deficiency and inhibitory IgG antibodies.160-167 TTP associated with ticlopidine and clopidogrel (thienopyridine drugs that inhibit platelet aggregation) represent interesting exceptions of secondary TTP consistent with a drug-induced autoimmune disorder. Severe ADAMTS13 deficiency and ADAMTS13 inhibitory antibodies were detected in 80% to 90% of patients with ticlopidine-associated TTP and in two patients with clopidogrel-induced TTP.168 The deficiency resolved after the drugs were discontinued.

Evidence of the pathogenic role of TTP-associated, anti-ADAMTS13 autoantibodies has been derived by the finding that they usually disappear from the circulation when remission is achieved by effective treatment; this occurs in parallel with the normalization of ADAMTS13 activity. In patients with acquired ADAMTS13 deficiency, a risk as high as 50% to develop a relapse has been reported, and undetectable
90% of cases. The rationale of combined treatment is that plasma exchange will have only a temporary effect on the presumed autoimmune basis of the disease, and additional immunosuppressive treatment may cause a more durable response. Of 108 patients with TTP or HUS, 30 were reported to have recovered after treatment with corticosteroids alone. All of them, however, had mild forms, and none of them were tested for ADAMTS13 activity.

Some prospective studies have successfully and safely used rituximab in patients who had failed to respond to standard daily plasma exchange and methylprednisolone and in patients with relapsed acute TTP who had previously demonstrated antibodies to ADAMTS13 (see Table 35.2). Treatment was associated with clinical remission in all patients, disappearance of anti-ADAMTS13 antibodies, and an increase of ADAMTS13 activity to levels higher than 10%. Rituximab has been also used electively to prevent relapses in patients with autoantibodies and recurrent disease. In one study, five patients with persistent undetectable ADAMTS13 activity and high autoantibody titers were treated with rituximab preemptively during remission. ADAMTS13 activity ranging from 15% to 75% and the disappearance of inhibitors were achieved after 3 months in all patients, and activity was still more than 20% at 6 months. Three patients maintained a disease-free status after 29, 24, and 6 months, respectively. Relapses were documented at 13 and 51 months in the remaining two patients during follow-up. Longitudinal evaluation of ADAMTS13 activity and autoantibody levels may help monitor patient response to treatment. Retreatment with rituximab should be considered to prevent a relapse when

**Clinical Course.** Patients with anti-ADAMTS13 antibodies experience a more severe manifestation of the disease and have a higher mortality rate than patients without these antibodies. Neurologic symptoms usually dominate the clinical picture and may be fleeting and fluctuating, probably because of continuous thrombus formation and dispersion in the brain microcirculation. Coma and seizures complicate the most severe forms. The detection of high titers of anti-ADAMTS13 antibodies correlates with relapsing disease and poor prognosis.

TTP has been reported in 1 in 1600 to 5000 patients treated with ticlopidine. Eleven cases have been reported during treatment with clopidogrel, a new antiaggregating agent that has achieved widespread clinical use for its safety profile. Most patients had neurologic involvement. The overall survival rate is 67% and is improved by early treatment withdrawal and plasma therapy.

**Therapy.** Plasma manipulation is a cornerstone in the therapy of the acute episode (see Table 35.2). Plasma may serve to induce remission of the disease by replacing defective protease activity. In theory, as compared to infusion, exchange may offer the advantage of also rapidly removing anti-ADAMTS13 antibodies but this needs to be proven in controlled trials. Corticosteroids might be of benefit in autoimmune forms of TTP by inhibiting the synthesis of anti-ADAMTS13 autoantibodies. In a series of 33 patients with undetectable ADAMTS13 activity and anti-ADAMTS13 antibodies, combined treatment with plasma exchange and prednisone was associated with disease remission in about 90% of cases. The rationale of combined treatment is that plasma exchange will have only a temporary effect on the presumed autoimmune basis of the disease, and additional immunosuppressive treatment may cause a more durable response. Of 108 patients with TTP or HUS, 30 were reported to have recovered after treatment with corticosteroids alone. All of them, however, had mild forms, and none of them were tested for ADAMTS13 activity.

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ADAMTS13 activity decreases and inhibitors reappear into the circulation (see Table 35.2).

**Congenital Deficiency of ADAMTS13 Thrombotic Thrombocytopenic Purpura**

**Mechanisms.** This rare form is associated with a genetic defect of ADAMTS13 and accounts for about 5% of all cases of TTP (see Table 35.2). Emerging data also indicate that patients with a clinical diagnosis of HUS may have a complete lack of ADAMTS13 activity, albeit less frequently. Thus, on clinical grounds, a possible congenital defect of ADAMTS13 cannot be excluded only on the basis of predominantly renal localization of disease manifestations. TTP associated with congenital ADAMTS13 deficiency has been found in families or patients with no familial history of the disease. In both cases the disease is inherited as a recessive trait, as documented by studies have revealed that the mutation causes a severe defect of ADAMTS13 and accounts for about 5% of all cases of TTP (see Table 35.2). Environmental factors may contribute to induce full-blown manifestation of the disease. According to this two-hit model, deficiency of ADAMTS13 predisposes to microvascular thrombosis, and thrombotic microangiopathy supervenes after a triggering event that activates microvascular endothelial cells and causes the secretion of UL-vWF multimers and P-selectin expression. Potential triggers of these phenomena are infections and pregnancy. Six women with congenital ADAMTS13 deficiency developed late-onset TTP during pregnancy. Also, genetic modifiers may be implicated in the susceptibility to develop thrombotic microangiopathy in a condition of ADAMTS13 deficiency, which may include genes encoding proteins involved in the regulation of the coagulation cascade, vWF, or platelet function, components of the endothelial vessel surface or of the complement cascade.

**Therapy.** When a critically ill patient is admitted because of severe anemia and thrombocytopenia with renal failure and/or neurologic signs, and the microangiopathic nature of the anemia is confirmed by detection of fragmented erythrocytes in the peripheral blood smear in association with increased serum LDH levels (see Figure 35.2), therapy with plasma exchange should be immediately started. If the clinical history, screening for Stx-producing *E. coli* infection, and evaluation of ADAMTS13 activity allow reasonably excluding Stx HUS and TTP, eculizumab should be started as soon as possible on the basis of the assumption that the patient could be affected by aHUS (see Figure 35.2). In most cases, eculizumab will achieve prompt remission of signs and symptoms of the microangiopathic process, and plasma exchange will no longer be required. However, should more exchange sessions be indicated, additional eculizumab doses should be administered shortly after each procedure because the drug is fully cleared from the circulation during the exchange.

If less than 10% ADAMTS13 activity orients the diagnosis toward TTP, plasma exchange should be continued to restore ADAMTS13 bioavailability and to remove anti-ADAMTS13 autoantibodies in patients with immune-mediated disease. Fresh-frozen plasma, 1 or 2 L, should be exchanged daily until complete and sustained remission of the microangiopathic process has been obtained (see Table 35.2). Plasma cryosupernatant—plasma without the cryoprecipitate—may supply the same amount of ADAMTS13 as fresh-frozen plasma, with a reduced risk of acute infusion reactions. Moreover, at least according to some uncontrolled reports, it also appears to be effective in patients who failed to respond to exchange with fresh-frozen plasma. These findings could be explained by less vWF content and less ADAMTS13 in complex with larger vWF multimers, which might translate into increased ADAMTS13 bioavailability as compared to that of fresh-frozen plasma.

In immune-mediated cases, add-on therapy with steroids or other immunosuppressants is indicated to inhibit the production of anti-ADAMTS13 autoantibodies. Prospective studies have successfully and safely used rituximab (see Table 35.2), an anti-CD20 monoclonal antibody depleting B lymphocytes, in patients who had failed to respond to
standard daily plasma exchange and methylprednisolone and in patients with relapsed acute TTP who had previously demonstrated antibodies to ADAMTS13. Treatment was associated with clinical remission in all patients, disappearance of anti-ADAMTS13 antibodies, and an increase of ADAMTS13 activity to levels higher than 10%. Of the approximately 100 rituximab-treated patients reported in the literature so far, normalization of platelets and LDH have been noted in about 95% of cases, but time to remission has been variable, from 1 to 4 weeks after the first dose. The duration of remission has ranged from 9 months to 4 years, with relapses reported in approximately 10%. Rituximab has been also used electively to prevent relapses in patients with autoantibodies and recurrent disease. Longitudinal evaluation of ADAMTS13 activity and autoantibody levels may help monitor response to treatment. Retreatment with rituximab should be considered when ADAMTS13 activity decreases and inhibitors reappear in the circulation to prevent a relapse.

After plasma exchange has effectively restored a stable clinical and laboratory state in patients suffering from TTP associated with congenital ADAMTS13 deficiency, disease remission might be maintained by plasma infusion alone. Providing sufficient ADAMTS13 to achieve 5% normal enzymatic activity is sufficient to degrade large vWF multimers, which translates into induced remission of the microangiopathic process, and this effect is sustained over time. Infused ADAMTS13 has a plasma half-life of 2 or 3 days in vivo and, although plasma levels fall below 5% within 3 to 7 days after plasma administration, the effect of plasma on the platelet count and clinical parameters may last up to 3 weeks, suggesting that ADAMTS13 remains available (e.g., on platelets and endothelial cells). Patients with congenital ADAMTS13 deficiency tend to relapse. Patients with frequent relapses, a severe clinical course with neurologic sequelae, renal insufficiency, and patients who have siblings who have died of TTP, should be put on regular prophylactic plasma infusions every 2 to 3 weeks, a regimen that has been shown to be effective in preventing acute TTP bouts and maintaining the patient in good health for years.

Although complement activation appears to play a role also in the pathogenesis of TTP, at this stage there is no controlled evidence in support of eculizumab therapy in this context.

AHEROEMBOLIC RENAL DISEASE

Atheroembolic renal disease (ARD) is part of a systemic syndrome of cholesterol crystal embolization. Renal damage results from the embolization of cholesterol crystals from atherosclerotic plaques present in large arteries, such as the aorta (see Figure 35.3), to small arteries in the renal vasculature. The prevalence appears to depend on sampling bias; it has ranged from 0.8% in a series of 2126 autopsies in patients older than 60 years to 36% in a cohort of patients undergoing surgical revascularization for atherosclerotic renal artery stenosis. In two large renal biopsy studies, a 1% prevalence was reported. However, in people older than 60 years, the prevalence was 4.0% to 6.5%. In clinical practice, Mayo and Swartz have estimated that 5% to 10% of all cases of acute renal failure could be due to atheroembolism.

CLINICAL FEATURES

The disease may ensue suddenly, few days after a precipitating factor, or insidiously, over weeks or months. General systemic manifestations occur in fewer than 50% of patients and include fever, myalgias, headaches, and weight loss. The rate of cutaneous manifestations such as livedo reticularis, purple toes, and toe gangrene varies widely, from 35% to 90%, in parallel with the heterogeneous accuracy of data reporting. Cutaneous symptoms constitute the most common extrarenal findings and may herald renal involvement, but other regions, such as the eyes, musculoskeletal system, nervous system, and abdominal organs, can be affected. An autopsy review of 121 cases of ARD noted the kidney to be the most commonly involved internal organ, with 75% of patients showing evidence of renal cholesterol emboli. In other series, the kidneys were affected in approximately 50% of patients. Almost 50% of patients manifest with mild or accelerated, and occasionally malignant, hypertension. Renal function loss is usually progressive but, in a few cases, renal failure can be acute and oliguric. The clinical course of renal failure can be variable. Dialysis is needed in 28% to 61% of patients with acute or subacute disease, with 20% to 30% recovering some kidney function after a variable period of dialytic support. Renal infarction is rare.

The differential diagnosis includes systemic vasculitis, subacute bacterial endocarditis, polymyositis, myoglobinuric renal failure, drug-induced interstitial nephritis, and renal artery thrombosis or thromboembolism. The time course of renal dysfunction may help differentiate atheroembolic renal disease that manifests over 3 to 8 weeks after angiographic procedures from radiocontrast-induced nephropathy, which manifests earlier and often resolves within 2 to 3 weeks after appropriate intervention. Definitive diagnosis is based on the histologic demonstration of cholesterol crystals in small arteries and arterioles of target organs.

Atheroembolic renal disease can also occur in renal allografts, with a frequency ranging from 0.39% to 0.47%. Atheroemboli causing injury to the renal allograft can arise from the donor or recipient vessels. Two distinct clinical presentations have been described. The first is an early atheroembolic renal disease, with emboli frequently released from the donor’s arteries before or during organ harvesting. More rarely, early embolization originates from the recipient’s atheromatous vessels during the anastomosis. The early form is usually associated with primary nonfunction, and the embolic disease is confined to the allograft. The second form is a late clinical presentation, which can arise years after transplantation in stable grafts. In these cases, emboli originate from the recipient’s vessels. The disease is usually associated with precipitating factors, and in some cases shows features of a systemic disorder.

Outcomes differ significantly. Early presentation is frequently associated with poor prognosis, whereas late manifestations generally have a more benign course. This difference could be attributable to extensive embolization in an atherosclerotic donor during organ procurement. Because the use of donors and recipients older than 60 years and of marginal donors with advanced atherosclerosis has increased, atheroembolic renal disease in renal allografts...
which represent the cholesterol crystals that are dissolved during tissue processing. These crystals are usually small and may not completely occlude the vessel lumen; however, they frequently induce an endothelial inflammatory response, which leads to complete obstruction of the vessel within weeks or months (Figure 35.8). Cholesterol crystals are birefringent under polarized light. The subsequent intravascular inflammatory reaction has been studied in experimental models of atheroembolism and in human biopsy and autopsy samples. \(^\text{181}\) The early phase is characterized by a variable polymorphonuclear (PMN) and eosinophil infiltrate, followed by the appearance of macrophages and multinucleated giant cells in the lumens of affected vessels within 24 to 48 hours after atheroembolism. In the chronic phase, tissue ischemia is perpetuated by marked endothelial proliferation, intimal thickening, concentric fibrosis of the vessel wall, and persistence of cholesterol crystals and giant cells in the lumens of affected arteries. Hyalinization of glomeruli, atrophy of renal tubules, and multiple wedge-shaped infarcts in the kidney result in reduced kidney size. \(^\text{181}\)

**MECHANISMS**

Male gender, older age, hypertension, and diabetes mellitus are important predisposing factors. \(^\text{192,193}\) Patients with cholesterol embolization syndrome often have a history of ischemic cardiovascular disease, aortic aneurysm, cerebrovascular disease, congestive heart failure, or renal insufficiency. \(^\text{182,192}\) A significant association between renal artery stenosis and atheroembolic renal disease has also been reported. \(^\text{181,192}\) At least one of the precipitating factors, which include vascular surgery, arteriography, angioplasty, anticoagulation, and thrombolytic therapy, can be identified in most patients. \(^\text{187,192,196}\) Arteriographic procedures constitute the most common intervention reported to incite cholesterol embolization. \(^\text{182}\) The most common is coronary

**LABORATORY FINDINGS**

Laboratory test findings are nonspecific, such as anemia, leukocytosis, thrombocytopenia, and raised concentrations of inflammatory markers (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein). Hypocomplementemia has also been reported but is not a consistent finding. \(^\text{184,181,192}\) At diagnosis, as many as 25% of patients have a serum creatinine level higher than 5 mg/dL, and in about 80% it is higher than 2 mg/dL. \(^\text{182}\) Changes in the urinary sediment are frequent but nonspecific. \(^\text{181}\) Granular and hyaline casts occur in approximately 40% of cases, whereas microscopic hematuria or pyuria are observed in fewer than 30%. \(^\text{182}\) Eosinophiluria was observed in one third of patients with renal biopsy–proven atheroembolic renal disease. Proteinuria is present in more than 50% of patients and may occasionally be in the nephrotic range. \(^\text{181,182}\) Eosinophilia is reported in up to 60% to 80% of patients and is usually transient. \(^\text{181,182,184,186}\) An increased ESR, leukocytosis, and anemia are frequent, but usually transient. Antineutrophilic cytoplasmic antibodies (ANCAs) have been found in a few cases, but not in large series, and their relevance is uncertain. \(^\text{181,195}\) A few studies have reported cholesterolemia in patients with atheroembolic renal disease, with total cholesterol levels higher than 5.2 mmol/L, ranging from 23% to 64%. \(^\text{180,194}\)

**PATHOLOGY**

The histologic hallmark of the disease is the presence of elongated, biconvex, transparent needle-shaped clefts, which represent the cholesterol crystals that are dissolved during tissue processing. These crystals are usually small and may not completely occlude the vessel lumen; however, they frequently induce an endothelial inflammatory response, which leads to complete obstruction of the vessel within weeks or months (Figure 35.8). Cholesterol crystals are birefringent under polarized light. The subsequent intravascular inflammatory reaction has been studied in experimental models of atheroembolism and in human biopsy and autopsy samples. \(^\text{181}\) The early phase is characterized by a variable polymorphonuclear (PMN) and eosinophil infiltrate, followed by the appearance of macrophages and multinucleated giant cells in the lumens of affected vessels within 24 to 48 hours after atheroembolism. In the chronic phase, tissue ischemia is perpetuated by marked endothelial proliferation, intimal thickening, concentric fibrosis of the vessel wall, and persistence of cholesterol crystals and giant cells in the lumens of affected arteries. Hyalinization of glomeruli, atrophy of renal tubules, and multiple wedge-shaped infarcts in the kidney result in reduced kidney size. \(^\text{181}\)
angiography, which has a rate of cholesterol embolism of 0.1% to 1.4%. An estimated 15% of patients with atheroembolism do not have any of the known risk factors.

The molecular mechanisms of crystal-induced inflammation have been only rather recently identified and involve crystal uptake by tubular cells into intracellular lysosomes and, eventually, lysosomal leakage. Crystal uptake activates the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome and triggers caspase-1–dependent interleukin-1β (IL-1β) and IL-18 secretion. These events induce a general inflammatory response, including the recruitment of neutrophils and macrophages to the site of crystal formation. Although these enhance local inflammation, macrophages may also contribute to crystal clearance or progressive scarring, respectively.

TREATMENT

Various treatments have been suggested to improve the outcome of atheroembolic renal disease, but none has been found to be appreciably effective, with probably the only exception being chronic therapy with cholesterol-lowering agents. A plausible explanation is that statins have a plaque-stabilizing effect, perhaps as a result of their cholesterol-lowering effect, as well as their antiinflammatory and immunomodulatory properties. The use of steroids is controversial and, in some series, does not appear to be beneficial, whereas in other series it has been associated with improved outcomes, independent of the doses administered. The therapeutic efficacy of low-density lipoprotein (LDL) apheresis is also uncertain, whereas antiplatelet agents should be avoided because of the risk of precipitating more atheroembolization. Surgical excision of atheromatous plaques in the suprarenal region of the aorta is not advocated because of significant postoperative mortality, worsening renal function, and lower limb loss.

Altogether, improved outcomes that have been observed appear to be largely explained by better supportive therapy, including immediate withdrawal of anticoagulants, postponement of aortic procedures, reduction of blood pressure to less than 140/80 mm Hg, careful treatment of heart failure, dialysis therapy, and adequate nutritional support. On the other hand, lack of effective specific treatments that can appreciably improve the outcome of the disease are thought to emphasize the importance of preventive measures aimed at limiting the risk of arterial thromboembolism—in particular, during angiographic studies. Also, the brachial approach for aortography or coronary angiography appears to be burdened by less morbidity than the femoral approach. Interest has arisen about the use of distal protection devices (DPDs) to prevent embolization of material during interventional procedures. They have been most widely used in the coronary and carotid vascular beds, where they have demonstrated the capacity to trap embolic materials and, in some cases, reduce complications. Early experience with DPDs in the renal arteries in patients with suitable anatomy has suggested retrieval of embolic materials in approximately 70% of cases and renal function improvement or stabilization in 98%; the combination of platelet inhibition and a DPD may provide even greater benefit.

There are isolated reports of successful therapy in small numbers of patients given iloprost, pentoxifylline, and LDL apheresis. However, these approaches have yet to be tested in controlled studies.

RADIATION NEPHROPATHY

Following the original description in 1904 by Baerman and Linser, a great number of studies have indicated that external kidney radiation causes progressive tissue injury, resulting in organ dysfunction and fibrosis. This process is an example of tissue response to radiation that may affect any organ exposed to therapeutic irradiation. Because kidney inflammation is minimal or absent on radiation exposure, the term radiation nephritis originally introduced to describe this clinical entity has been progressively replaced with the more appropriate term, radiation nephropathy. This is the terminology we will use throughout this review.

CLINICAL FEATURES

Typically, exposure of the kidneys to x-rays or gamma rays in a dose higher than 2000 cGy (rad) is required to cause radiation nephropathy. However, a 10-Gy, single-fraction dose is sufficient to cause chronic renal failure after bone marrow transplantation (BMT), and with many years of follow-up, a 1-Gy, single-fraction dose is associated with the development of chronic kidney disease. Although these effects are not immediate, as is the case for radiation injury to the bone marrow or gastrointestinal tract, kidney injury at these doses indicates that the kidneys are quite radiosensitive.

Modern radiation therapy is sharply focused on the area to be treated; therefore, it is very unlikely that the kidneys would be irradiated in a case of irradiation for uterine cervical cancer or prostate cancer. In patients who have undergone BMT, partial renal shielding reduces, but does not abolish, the risk of BMT nephropathy.

TYPES

Acute Radiation Nephropathy

Radiation nephropathy may ensue abruptly 6 to 12 months after exposure to ionizing radiation with headache, vomiting, fatigue, hypertension, and edema. Patients manifest arteriovenous nicking on funduscopic examination, normochromic normocytic anemia, microscopic hematuria, proteinuria, and urinary casts. Worsening of renal function may accompany these symptoms. The outcome may range from complete or partial recovery of renal function to terminal kidney failure and can be complicated by malignant hypertension.

Acute BMT nephropathy (BMTN) is one of the most frequent forms of acute radiation nephropathy and may follow total-body irradiation of candidates for bone marrow transplantation. Acute BMTN presents with an HUS-like picture, with severe hypertension, peripheral edema, microangiopathic hemolytic anemia, and thrombocytopenia. Renal function decreases progressively, with significant proteinuria and microscopic hematuria, with or without casts. In a retrospective analysis of 363 recipients of allogeneic, myeloablative BMT, the incidence of severe renal failure (grades 2 and 3 combined) was approximated 50%. In this study, acute renal failure did not appear to affect patient survival, but in another study it was associated with increased mortality.
**Chronic Radiation Nephropathy**

Occasionally, the disease manifests with hypertension, proteinuria, and gradual loss of renal function, with a latency period that from 18 months to years after the initial exposure. Hypertension, isolated or occasionally associated with proteinuria, and isolated low-level proteinuria may ensue 2 to 5 and 5 to 19 years after exposure, respectively. These are expressions of a mild disease, with a benign outcome in most cases.

Chronic BMTN presents with mild to moderate hypertension and mild hemolytic anemia. Kidney function decreases slowly, with a biphasic pattern in most patients, with persistent decline in the first 12 to 24 months, followed by a period of stabilization. Also present is proteinuria higher than 1 g/day and microscopic hematuria, with or without casts. A period of 8 years is generally necessary for chronic renal failure to occur. In a long-term study of 105 adult survivors of BMT, Lawton and colleagues reported late renal dysfunction in 14 patients. All of them had received 1400 rad prior to transplantation, whereas none of the patients receiving lower doses of irradiation developed late hypertension or decreased GFR.

**Late Malignant Hypertension**

This condition arises 18 months to 11 years after irradiation in patients with chronic radiation nephropathy or benign hypertension. High-renin hypertension resulting from irradiation of one kidney and recovery after removal of the affected kidney have been described. Irradiation to one kidney and the ipsilateral renal artery may produce renovascular hypertension, mostly in infants and children.

**PATHOLOGY**

Early changes following renal irradiation include atypia, endothelial microvascular damage, as observed on light microscopy, with mild endothelial cell swelling, and basement membrane splitting in the glomerular capillaries. With scanning (e.g., computed tomography [CT], magnetic resonance imaging [MRI]), marked subendothelial expansion, with deposition of basement membrane-like material adjacent to the endothelial cells, is evident. The endothelial cell lining may be absent in some capillary loops. Immunofluorescence studies do not show specific staining patterns. Similar glomerular endothelial injury was observed in kidney biopsy specimens from patients who developed renal insufficiency and hypertension after total body irradiation (TBI) and BMT. Some patients also showed arteriolar intimal thickening and tubular atrophy. Glomerular capillary endothelial cell loss and mesangiolysis are observed within weeks after irradiation. After initial injury, the endothelial injury resolves, but mesangial lesions progress. Late changes include reduction in total renal mass, with prominent and sclerosed interlobar and arcuate arteries, glomerular capillary loop occlusion and hyalinization, with progressive tubular atrophy, increased mesangial matrix, mesangial sclerosis and, finally, glomerulosclerosis.

**MECHANISMS**

Renal tissue damage and dysfunction are a direct consequence of ionized radiation. The effect of radiation is dose-dependent, and pathogenic doses exceed by at least 1000-fold the dose to which a patient can be exposed for a radiologic examination, such as a standard abdominal CT scan. Irradiation for neoplastic diseases of the pelvis, in particular for the treatment of malignant seminomas, has historically been the major cause of radiation nephropathy. This explains why, in parallel with the progressive replacement of irradiation with pharmacologic therapy for this disease, the incidence of radiation nephropathy has been progressively declining over time. In more recent years, however, the incidence of the disease again began to increase, along with the rapidly increasing use of total body irradiation of candidates for bone marrow transplantation. It has been suggested that chemotherapy administered as part of the preparative regimen could potentiate the effects of irradiation on the kidneys. Actinomycin enhances the effects of irradiation on many tissues (e.g., gut, lung, skin). Whether this also applies to the kidney is controversial. Cisplatin and carmustine (BCNU) are toxic, mainly when radiation precedes platinum administration.

Most of the theories proposed to explain the pathogenesis of radiation nephropathy are based on murine studies. These studies have consistently shown that endothelial, mesangial, and tubular cells are the major targets of radiation injury and that double-stranded DNA breaks are the initial cause of radiation-induced cell apoptosis and death. Damage to the endothelial cell may impair the physiologic thromboresistance of the capillary vascular wall, which, in more severe cases, may cause intravascular clotting, with pathologic patterns typical of thrombotic microangiopathy. Impaired generation of prostacyclin by endothelial cells and increased production of plasminogen-activator inhibitor mRNA have been suggested to explain the microangiopathic processes that often complicate radiation nephropathy. On the other hand, mesangial cells might acquire a myofibroblast phenotype, which may further contribute to progressive fibrosis and scarring of the kidney tissue. Diffuse apoptosis and lysis of tubular cells, with different degrees of proliferation of the residual cells, is another characteristic pattern of radiation nephropathy. Apoptosis early after 5-Gy, single-dose, total body irradiation has been demonstrated in rats, followed by a late proliferative response. The net balance between cell death and replication will eventually determine the extent of residual tubular atrophy and loss.

Activation of RAAS may also contribute to sustain and amplify the initial injury induced by radiation exposure. Angiotensin II infusion from 4 to 8 weeks after total body irradiation causes more azotemia than irradiation alone. This effect was associated with the induction of arteriolar fibrinoid necrosis, which, in combination with increased transforming growth factor-β (TGF-β) production and enhanced oxidative stress, may contribute to progressive tissue fibrosis and scarring. Finding that this sequence of events is attenuated by concomitant treatment with an inhibitor of RAAS has provided additional evidence for the central role of angiotensin II in the pathogenesis and progression of renal damage in radiation injury.

**THERAPY**

No specific therapies are available for radiation nephropathy, and the disease is often progressive, independent of
CHAPTER 35 — MICROVASCULAR AND MACROVASCULAR DISEASES OF THE KIDNEY

35-21

Clinical Features

The pattern of presentation may range from limited to diffuse cutaneous involvement. In limited cutaneous scleroderma, fibrosis is mainly restricted to the hands, arms, and face. Raynaud’s phenomenon affects approximately 95% of patients and usually is the first manifestation of the disease. Diffuse cutaneous scleroderma is a rapidly progressing disease that in addition to affecting a large area of the skin, compromises one or more internal organs. The kidneys, along with the esophagus, heart, and lungs, are the most frequent targets (Figure 35.9), although any internal organ can be involved. In rare cases, skin can be spared by scleroderma. Systemic lupus erythematosus, rheumatoid arthritis, polymyositis, or Sjögren’s syndrome may accompany scleroderma in the context of an overlap syndrome. 228

Renal Involvement

Renal involvement typically manifests with malignant hypertension and acute renal failure (scleroderma renal crisis). The crisis may occur de novo or may complicate a preexisting chronic kidney involvement. Less frequently, renal involvement manifests with slowly progressing kidney dysfunction and occasionally as rapidly progressive kidney disease. 228-230

Renal Crisis. The prevalence of renal crises is decreasing, perhaps related to early therapy with ACEIs. However, in the United States, renal crisis affects approximately 10% of patients with diffuse scleroderma and 2% of patients with limited disease. 231 Studies from the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database have suggested a lower prevalence (5% of diffuse scleroderma and 2% of limited), and a retrospective cohort study from Japan has reported a

RENAL INVOLVEMENT IN SYSTEMIC DISEASES: SCLERODERMA, SICKLE CELL DISEASE, AND THE ANTIPHOSPHOLIPID SYNDROME

SCLERODERMA

Scleroderma is a complex disease of extensive fibrosis, vascular changes, and autoantibodies against various cellular antigens. The reported incidence ranges from 2.3 to 22.8 cases/million population with a 3 to 14 times higher incidence in women than men. 226,227

Figure 35.9 Latex injection of postmortem normal kidney (left) and kidney from a patient with scleroderma renal crisis (right). Note obstruction to flow at the level of the medium-sized interlobular arteries.
prevalence of 3.2%. Geographic differences in autoantibody profiles, particularly anti-RNA polymerase III antibodies, likely contribute to these prevalence variations.

The renal crisis resembles a Raynaud-like phenomenon in the kidney. Severe vasospasm leads to cortical ischemia and enhanced production of renin and angiotensin II, which in turn sustain renal vasoconstriction. Hormonal changes (e.g., pregnancy), physical and emotional stress, or cold temperature may trigger the Raynaud-like arterial vasospasm. The role of the RAAS in perpetuating renal ischemia is underscored by the significant benefit of ACEIs in treating this potentially fatal complication.

Affected patients typically present with severe hypertension and acute renal impairment. Hypertension, however, is not universal and normotensive crises, usually with poor outcome, have been described. Nonnephrotic proteinuria and hematuria, often with granular casts, are common findings. Oliguria is an ominous sign, but is unusual in patients diagnosed and treated appropriately. Other clinical features include hypertensive retinopathy and encephalopathy. Evidence that retinal and central nervous system involvement may also affect patients with seemingly mild hypertension or even normal blood pressure confirms that endothelial dysfunction may play a central role in the pathogenesis of vascular lesions of scleroderma, independently of blood pressure levels. Microangiopathic hemolytic anemia is common, although significant coagulopathy is rare. Pericarditis, myocarditis, and arrhythmias may supervene and are associated with a poorer prognosis.

**Chronic Kidney Disease.** Kidney function can be decreased in patients with scleroderma, even without renal crisis. In these cases, a decreased GFR reflects a chronic kidney disease that may also reflect chronic kidney hypoperfusion due to concomitant cardiac and pulmonary arterial involvement or concomitant treatment with nephrotoxic drugs; it is normally characterized by a benign prognosis.

**Laboratory Findings**

Detection of autoantibodies against topoisomerase (Scl-70), centromere-associated proteins, and nucleolar antigens is crucial for the diagnosis of the disease and may help predict clinical manifestations and prognosis. Antibodies against centromeres are associated with limited cutaneous involvement and risk for pulmonary hypertension, whereas those targeting topoisomerase I are associated with diffuse progressive disease and severe interstitial lung disease. Patients with anti-Th/To antibodies normally have limited skin involvement but are at high risk for lung fibrosis and pulmonary artery hypertension, with severe involvement of kidneys and other internal organs, whereas those with anti-RNA polymerase I/III antibodies have an almost selective renal involvement.

**Pathology**

**Renal Crisis.** Biopsy samples from patients with scleroderma crisis show intimal and medial vessel proliferation, with luminal narrowing that typically occurs in arcuate arteries and are indistinguishable from changes of accelerated or malignant hypertension (Figure 35.10). Fibrinoid necrosis and thrombosis are also common. A study of 58 biopsies has shown that acute vascular changes, including mucoid intimal thickening and thrombosis, invariably predict a poor outcome, with 50% of affected subjects progressing to terminal kidney failure compared to only 13% of those with predominantly chronic changes.

**Chronic Kidney Disease.** As in other affected organs, the histologic pattern of chronic kidney involvement is
CHAPTER 35 — MICROVASCULAR AND MACROVASCULAR DISEASES OF THE KIDNEY

Mechanisms
The pathogenesis of scleroderma is still unclear, with multiple cells and mediators taking part in the different phases of the microangiopathic process. Microvascular injury is an early event most likely initiated by endothelial cell damage, with secondary proliferation of basal lamina layers. Entrapment of peripheral blood mononuclear cells in the vessel wall, as well as perivascular mononuclear cell infiltrates, are occasionally observed. Activated endothelial cells, in turn, release endothelin-1, which induces chemotaxis, proliferation, extracellular matrix production, and the release of cytokines and growth factors that amplify the inflammatory focus. The next phase is characterized by fibrosis, organ architecture disruption, rarefaction of blood vessels, and eventually, hypoxia, which fuels fibrosis.

Microvascular Injury. Patients with scleroderma often display early signs of vasculopathy, with many experiencing Raynaud’s phenomenon, often for many years before developing overt signs of skin fibrosis. Consistent with this, morphologic changes in capillaries are detectable before or at disease onset, which can be used for early diagnosis using nail fold capillaroscopy. Endothelial injury, whether caused by immunologic stimuli, ischemiareperfusion injury, or other factors results in increased production of endothelin. Endothelin 1 (ET-1) is involved in the regulation of vascular function under normal physiologic conditions and plays a key role in vascular disease by promoting hypertrophy of the vascular smooth muscle cells, vascular permeability, and activating leukocytes through the induction of cytokine and adhesion molecule expression. The effects of endothelin are transmitted on binding to two cognate receptors, endothelin type A (ET-A) and endothelin type B (ET-B), which are mainly expressed on endothelial cells, smooth muscle cells, and fibroblasts. Endothelial dysfunction has been found to be ameliorated by therapy with the ET-1 antagonist bosentan, which provides additional, although indirect, evidence of the pathogenic role of the ET system in the vascular damage of scleroderma.

Increased Collagen Production. Fibroblast secretion of collagen, the main extracellular matrix component of connective tissue, is markedly increased in scleroderma.

Cytokines and growth factors, such as TGF-β, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and ET-1, secreted in the skin and lungs, activate resident fibroblasts, promoting the accumulation of collagen, proteoglycans, fibronectin, tenasin, and elastin. Furthermore, TGF-β induces the differentiation of fibroblasts into smooth muscle cell-like myofibroblasts in situ. Myofibroblasts elaborate matrix molecules and profibrotic cytokines that increase the stiffness of the extracellular matrix (ECM). Moreover, they are relatively resistant to apoptosis and accumulate and persist in affected tissues, where they contribute to further progression of the fibrosis.

Bone marrow–derived mesenchymal progenitor cells fuel expansion of the fibroblast population in affected tissue, which then further contributes to connective tissue accumulation. The signals inducing the bone marrow to mobilize progenitor cells and govern their homing and engraftment in lesional tissue remain unknown. Intriguingly, patients with scleroderma have circulating antibodies directed against the PDGF receptor that activates fibroblasts. Once collagen is secreted into the extracellular space, it undergoes cross-linking and maturation, resulting in a highly stable matrix that accounts for the stiffness of fibrotic skin and other tissues. The stiff matrix may itself serve as a strong stimulus for integrin-mediated TGF-β activation and increasing fibrosis.

Immunologic Mediators. A wide spectrum of autoantibodies have been recently discovered that may have a major role in the pathogenesis of the disease—such as autoantibodies against extracellular matrix components such as metalloproteinases and fibrillin-1, fibroblasts and endothelial cells, and the PDGF receptor—and have been associated with different clinical manifestations and outcomes. Thus, a careful evaluation of circulating autoantibodies is instrumental to predict individual risk and guide treatment. Thus, patients with anticientromere antibodies (ACAs) have limited cutaneous involvement and good outcome, provided pulmonary hypertension is detected early and treated adequately.

Cytokines. In addition to autoantibodies, immune injury is sustained by the release of cytokines such as IL-1, IL-2, IL-8, tumor necrosis factor-α (TNF-α), PDGF, TGF-β, interferon-γ (IFN-γ), and endothelin. Moreover, intercellular adhesion molecules and soluble IL-2 receptors have been demonstrated in patients. Skin fibroblasts from patients with scleroderma produce much higher levels of IL-6 than normal fibroblasts and may contribute to T cell activation. IL-6 and PDGF-A were shown to be elevated through the action of endogenous IL-1α in fibroblasts from patients with scleroderma.

Therapy
Although there is no evidence for any effective strategy to prevent renal crises, it is common practice to advise patients and physicians of the risk of renal crisis to expedite rapid diagnosis and therapy. A major advancement in the treatment of scleroderma renal crises has been achieved with the introduction of ACEIs in clinical practice. In the pre-ACEI era, the 1-year survival rate did not exceed 10%, whereas with the use of ACEIs, up to 65% of patients survive the crisis. A prospective cohort study evaluating short-term and long-term outcomes of 154 patients with renal crises treated with ACEIs found that 61% were free from chronic dialysis, and 80% to 85% were alive at 8 years after the event, a survival rate similar to that of patients with diffuse scleroderma without renal crises. Angiotensin II receptor blockers are less effective than ACEIs and can be considered as add-on therapy when full-dose ACEI therapy is not sufficient to control blood pressure. α-Blockers and calcium antagonists are also helpful for refractory hypertension, whereas diuretics are best avoided because of their ability to stimulate renin...
Table 35.4 Therapies Used for Scleroderma

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites: Methotrexate</td>
<td>10-25 mg/wk</td>
<td>Disappointing results, with only mild effect on skin disease</td>
</tr>
<tr>
<td>Antioxidants*</td>
<td>1 tablet/day</td>
<td>Not effective</td>
</tr>
<tr>
<td>Corticosteroids: Dexamethasone</td>
<td>100 mg/mo for 6 mo</td>
<td>Improvement in skin scores</td>
</tr>
<tr>
<td>Endothelin receptor antagonists:</td>
<td>62.5 mg for 4 wk, then 125 mg for 12 wk</td>
<td>Improvement in pulmonary function</td>
</tr>
<tr>
<td>Bosantan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormones: Relaxin</td>
<td>25/100 μg/kg/day (IV)</td>
<td>Improvement in skin scores</td>
</tr>
<tr>
<td>Immunosuppressives: Cyclophosphamide</td>
<td>600 mg/m²</td>
<td>Significant, albeit modest, improvement in lung function</td>
</tr>
<tr>
<td>Interferons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-2α</td>
<td>13.5 × 10⁶ units/wk</td>
<td>Disappointing results with interferon-α, improved organ involvement with interferon-γ</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>300 mg/wk</td>
<td>Improved renal and patient survival in renal crisis, slowed progression in chronic renal involvement</td>
</tr>
<tr>
<td>RAAS inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclin analogue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iloprost</td>
<td>960 ng/kg/day (IV)</td>
<td>Improvement in pulmonary function</td>
</tr>
<tr>
<td>Beraprost</td>
<td>60 μg three times daily</td>
<td></td>
</tr>
<tr>
<td>Nonpharmacologic treatment—photopheresis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Selenium, beta-carotene, vitamin E, vitamin C, and methionine.

ACE, Angiotensin-converting enzyme; RAAS, renin angiotensin aldosterone system.


Plasma exchange is also indicated when the renal crisis is accompanied by a microangiopathc process. With this therapy, it is estimated that approximately two thirds of patients with renal crisis presenting to an experienced center will require renal replacement therapy. However, about 50% of them will eventually recover sufficiently to discontinue dialysis and be maintained on conservative therapy and remain dialysis free. Patients treated appropriately when experiencing a scleroderma renal crisis (SRC) may recover renal function for up to 2 years. This should be taken into consideration before including patients on a waiting list for kidney transplantation. Renal transplant recipients who have progressed to ESRD because of renal crises have a lower graft and patient survival rate as compared to those with diabetic renal disease. One of the causes of premature graft or patient loss is the recurrence of the disease in the transplanted kidney, in particular in those with more aggressive disease process before transplantation. In a cohort of 260 patients with scleroderma renal crisis who developed ESRD and underwent kidney transplantation, the overall 5-year graft survival rate was 56.7%. Among those, the recurrence of disease after transplantation was 6.7% in a report of the United Network of Organ Sharing (UNOS). Based on the finding that cyclosporine A (CsA) may be responsible for acute renal failure in patients with scleroderma and systemic sclerosis (SSc), calcineurin inhibitors are not generally recommended as immunosuppressants after kidney transplantation. The use of high-dose steroids should be also limited as much as possible due to studies supporting an association between doses higher than 15 to 30 mg/day and the onset of renal crisis. Several groups have tested continuous low doses of prostacyclin, with no strong beneficial evidence. Plasma exchange or immunosuppressive drugs have shown no beneficial effect in the treatment of SRC. As noted, because of their deleterious effects, corticosteroids are contraindicated in SRC.

Endothelin receptor blockers have been proposed as first-line therapy in addition to ACEIs. In a small open-label trial, six patients within 6 weeks of confirmed SRC received bosentan, 62.5 mg for 1 month, and then 125 mg twice daily for 5 months. Bosentan seemed safe and well-tolerated when combined with ACEI therapy for SRC, with no difference in mortality and dialysis rates between the two study groups. This evidence formed the basis for a larger prospective study testing the effect of bosentan on renal crisis (NCT01241383; see Table 35.4).

Sickle cell disease

Sickle cell anemia, and occasionally the heterozygous forms of sickle cell disease, can lead to multiple renal abnormalities, which include hematuria, proteinuria, tubular dysfunction, or a combination of these, eventually resulting in renal function impairment.

Clinical Features

Hematuria and Renal Papillary Necrosis. Gross and often painless hematuria is one of the most frequent features of sickle cell anemia, sickle cell trait (HbSA) disease, and HbSC disease. Hematuria in sickle cell disease can occur at any age and is reported most often with HbSA. A total of 15% to 36% of patients with sickle cell disease develop renal papillary necrosis, which could manifest as an episode of gross hematuria or as a silent finding. Papillary necrosis
occurs in both the homozygous and the heterozygous forms of sickle cell disease and is best diagnosed by intravenous pyelography (Figure 35.11). Microscopic hematuria is present in most patients with sickle cell anemia. The origin of blood is usually the left kidney, but either kidney may be involved.

Proteinuria. Proteinuria occurs in 20% to 30% of patients with sickle cell disease, more commonly in homozygous HbSS than in heterozygous HbSA, with HbSC in between. Proteinuria can be in the nephrotic or nonnephrotic range. Nephrotic patients have a poorer prognosis and tend to progress to renal failure.

Tubular Dysfunction. Patients with homozygous and heterozygous forms of sickle cell disease fail to concentrate the urine maximally because of erythrocyte sickling in the medullary microcirculation, with secondary medullary ischemia and dysfunction. This abnormality is reversible with multiple transfusions for children younger than 15 years, but becomes irreversible later in life. Patients with sickle cell anemia are capable of diluting their urine normally. Another renal defect seen in patients with sickle cell disease, particularly those with the HbSS or HbSC phenotype, is an incomplete form of distal renal tubule acidosis characterized by the inability to achieve minimal urinary pH during acid loading because of impairment of titratable acid excretion. This defect, however, is not severe enough to cause systemic acidosis. Patients with sickle cell trait (HbSA) do not have evidence of impaired urinary acidification. Other tubular defects in sickle cell anemia (SCA) include mild impairment of K⁺ excretion that does not lead to clinical hyperkalemia. Fractional excretion of creatinine is increased, which necessitates the use of inulin clearance to measure the GFR accurately. However, Herrera and colleagues have demonstrated an impaired tubular secretion of creatinine in SCA patients with a normal GFR. In addition, there is increased phosphorus reabsorption in the proximal tubule, which could account for the hyperphosphatemia observed in SCA patients.

Pathology

In 1923, Sydenstricker and colleagues described enlarged glomeruli distended with blood in the kidneys of patients with sickle cell disease. Necrosis and pigmentation of tubular cells were also observed. Medullary lesions are the most prominent finding in the kidneys of these patients. Edema, focal scarring, interstitial fibrosis, and tubule atrophy are observed. Cortical infarction has also been reported in patients with sickle cell disease or sickle cell trait. In Hb-SS patients without renal insufficiency, renal pathology includes glomerular hypertrophy characterized by open, dilated, glomerular capillary loops. Enlarged glomeruli are most commonly found in the juxtamedullary region of the kidney. In patients with proteinuria and mild renal insufficiency, Falk and coworkers reported glomerular hypertrophy and focal segmental glomerulosclerosis (FSGS). FSGS is thought to be the most common cause of renal failure in sickle cell disease. In a study of 240 adult patients with sickle cell anemia and the nephrotic syndrome, Bakir and associates reported the presence of mesangial expansion and glomerular basement membrane duplication by electron microscopy, as well as effacement of epithelial cell foot processes. These changes suggest hyperfiltration injury and often are referred to in these patients as sickle cell glomerulopathy. Membranoproliferative pathology was observed in some sickle cell anemia patients, most of whom had no immune deposits.

Mechanisms

The underlying biologic defect in sickle cell disease is a single amino acid substitution of valine for glutamic acid at the sixth position in the hemoglobin β-chain. This alteration leads to the aggregation of deoxygenated sickle cell hemoglobin (HbSS) molecules, resulting in a deformation of the shape and decreased flexibility of red blood cells. HbSS polymerization is promoted by higher degrees of deoxygenation, increased intracellular hemoglobin concentration, and the absence of hemoglobin F. As red blood cells from sickle cell patients flow through arterioles and capillaries, HbSS polymerization may occur, increasing the adherence of Hb-SS erythrocytes to the vascular endothelium. Gee and Platt have found that sickle reticulocytes adhere to the endothelium via vascular cell adhesion molecule-1 (VCAM-1). Kumar and coworkers have reported that increased sickle erythrocyte adherence to the endothelium involves αvβ₃ integrin receptors. Integrins on the cell surface of red blood cells (RBCs) bind to fibronectin and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells. This is induced by the presence of inflammatory cytokines such as TNF-α.

Platelet activation has also been suggested to play a role in sickle cell–mediated vasoocclusion. Thrombospondin from activated platelets promotes sickle erythrocyte adherence to the microvascular endothelium. Increased concentration of intracellular sickle hemoglobin may promote polymerization and trigger the sickling process.

The pathogenesis of medullary renal lesions in sickle cell disease is the result of microvascular occlusion by
erythrocytes that carry the mutant hemoglobin β-chain. Erythrocytes passing through the vessels of the inner renal medulla and renal papillae are most vulnerable to sickling because of the high osmolality of the blood, which leads to cell shrinkage and increased hemoglobin concentration.

The pathogenesis of sickle cell glomerulopathy is generally attributed to hyperfiltration, which is common in children affected by the disease. Later in life, the GFR often declines, despite persistently high renal blood flow rates. G
guasch and associates have described a distinct pattern of glomerular dysfunction in patients with sickle cell anemia that consists of a generalized increase in permeability to dextrans secondary to an increased pore radius in the glomerular basement membrane. With progression to chronic renal failure, the number of pores is reduced and a size-selective defect occurs. This abnormality may account for the proteinuria observed in patients with sickle cell glomerulopathy. Schmitt and colleagues found that in early dysfunction, the ultrafiltration coefficient is increased.

Hypoxia and decreased blood flow, with a secondary increase in ET-1 secretion, have been suggested in the pathogenesis of sickle nephropathy. In addition, the roles of nitric oxide (NO) and the activation of NO synthase have been studied in the mechanism of glomerular hyperfiltration, and in ischemia-reperfusion–mediated apoptosis of cells.

Therapy
The management of patients with sickle cell disease is targeted at limiting sickle cell crises and end-organ damage. Factors that trigger sickling, such as infection and dehydration, should be treated aggressively. Exposure to hypoxia, cold, or medications that may induce sickle cell crisis should be avoided. Treatment options include transfusion therapy and, more recently, BMT. Interestingly, multiple transfusions may restore the urine-concentrating capacity in very young children with sickle cell anemia.

A conservative approach for hematuria is suggested, considering its generally benign course. Maintaining high urinary flow through adequate fluid intake and the use of diuretics is helpful in clearing clots from the bladder. Alternative approaches targeting pathogenic mechanisms have been proposed. The use of hydroxyurea in patients with sickle cell anemia aims at increasing the formation of HbF instead of HbS. Studies in adults and children have shown a reduction in the incidence of acute sickling episodes, and this allows normal growth and development in children.

In some reports, the use of ACEIs significantly reduced proteinuria, and combined therapy with ACEIs and hydroxyurea may prevent progression from microalbuminuria to frank proteinuria.

Patients with sickle cell disease who reach ESRD have a 60% survival rate at 2 years after the administration of renal replacement therapy. Dialysis is the most common form of renal replacement therapy used. Kidney transplantation as a possible alternative to dialysis has been attempted, with reported success. One study demonstrated a 1-year survival rate adjusted for age in kidney transplant recipients that was similar between groups, with or without sickle cell disease. However, graft loss increased significantly with the duration of follow-up in transplanted patients with sickle cell disease compared to patients without sickle cell disease. Scheinman analyzed U.S. Renal Data System (USRDS) data up to the year 2000. A total of 237 transplant patients with sickle cell disease had a survival rate of 56%, whereas 1419 sickle cell disease patients on dialysis had a survival rate of 14%. As such, we believe that the best option for renal replacement therapy in patients with ESRD is kidney transplantation, although a greater frequency of posttransplantation crises has been described in correlation with anemia correction. Moreover, sickle cell nephropathy can recur in the graft, even within 3.5 years, although graft loss due to this cause is rare. Hydroxyurea has been suggested to prevent recurrence. There is no place for the use of nonsteroidal antiinflammatory drugs (NSAIDs) or steroids in the management or prevention of sickle cell nephropathy. Because of the high rate of hyperimmune individuals among sickle cell disease patients, identification of novel immunosuppressive strategies able to control the anti-HLA humoral response will be instrumental in improving the prognosis of kidney transplant recipients with sickle cell disease.

ANTIPHOSPHOLIPID SYNDROME
The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by hypercoagulability, arterial and venous thromboses, and pregnancy morbidity. The diagnosis rests on the detection of lupus anticoagulant (LA), anticardiolipin (aCL), or anti-β2-glycoprotein I antibodies persisting in the circulation for a minimum of 12 weeks. The syndrome can be an isolated idiopathic entity or is found in subjects with other immune diseases, in particular systemic lupus erythematosus (SLE). When APS is associated with SLE, morbidity and mortality are remarkably increased. Antiphospholipid antibodies can also be found in otherwise healthy subjects, with a prevalence of less than 1% in the general population and up to 5% of older subjects. In those with SLE, the prevalence is much higher, and IgG aCL, IgM aCL, and LA have been observed in 24%, 13%, and 15% of patients, respectively. Notably, subjects with persistently moderate-to-high aCL levels and/or LA who had previous thrombotic events are at higher risk of future events.

Clinical Features
The most common manifestations of APS include deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, and renal macrovascular and microvascular thrombosis. Livedo reticularis is a hallmark of the disease that almost invariably predicts a severe outcome. Hypertension is frequent. It affects more than 90% of those with renal involvement and is often associated with vascular lesions, including arteriosclerosis, fibrous intimal hyperplasia, arterial and arteriolar fibrous and fibrocellular occlusions, and TMA. Poorly controlled hypertension often reflects renal artery stenosis, a disease that may affect up to 26% of hypertensive patients with antiphospholipid antibodies as compared to only 8% of young patients attending a hypertension clinic and 3% of living related renal donors with stenosis. The stenotic lesions are generally smooth noncritical stenoses in the midportion of the renal artery, quite distinct from fibromuscular dysplasia or atherosclerosis.

Thrombotic Microangiopathy. This is one of the more serious manifestations of the syndrome. It can be isolated or may be a component of catastrophic APS, a rare but
devastating disease that manifests in approximately 1% of patients with AP antibodies, in most cases following a triggering event such as infection, trauma, or surgery. Hypertension and proteinuria are almost invariable findings often associated with renal impairment, even in the early phases of the disease. Proteinuria is mild, and the sudden onset of nephrotic-range proteinuria may reflect a concomitant thrombosis of the renal veins and inferior vena cava. Outcome is poor, in particular in the context of lupus nephritis and catastrophic APS. In catastrophic APS, three or more target organs are involved, multiorgan failure is frequent, and the mortality rate approximates 50%.306

Pathology

Kidney biopsy samples from patients with APS-associated thrombotic microangiopathy show focal or diffuse microangiopathic changes affecting the whole intrarenal vascular tree and glomerular tufts, with fresh or old recanalizing thrombi.307 Ultrastructure findings pathognomonic for APS nephropathy include a combination of glomerular basement membrane wrinkling and reduplication and redundant wrinkled segments of basement membrane, with straighter thin basement membrane sections adjacent to the endothelium.307 Small arterioles can also be affected by a noninflammatory and frequently thrombotic vasculopathy. These changes, however, are less specific because they can be observed in a wide variety of conditions, including TTP, HUS, scleroderma renal crisis, malignant hypertension, pre-eclampsia, postpartum renal failure, cyclosporine or chemotherapy toxicity, and renal transplant rejection.299,307

Mechanisms

A two-hit hypothesis has been suggested to explain the clinical observation that thrombotic events occur only occasionally, in spite of the persistent presence of antiphospholipid antibodies.308 According to this principle, the antibody (representing the first hit) induces a thrombophilic state, but clotting takes place only in the presence of another thrombophilic condition (the second hit).309 Providing support for this mechanism, the administration of a small amount of lipopolysaccharide (LPS) was required for human β2-glycoprotein I (β2-GPI)–specific antiphospholipid antibody IgG to produce a thrombogenic effect in rat mesenteric microcirculation.310 In line with this observation, it has been suggested that infectious processes might constitute the second hit because they frequently precede full-blown APS and might be the initiator of the catastrophic subtype.311 This hypothesis fits well with the potential involvement of pattern recognition receptors (e.g., Toll-like receptors [TLRs]) in sensing microbes and triggering an inflammatory response. Because TLR2 and TLR4 have been reported to contribute to endothelial cell and monocyte activation by β2-GPI–dependent antiphospholipid antibodies, one can speculate that the combination of the effect of infection plus the perturbation of TLR function mediated by the autoantibodies overcomes the threshold for triggering thrombosis,312,313 Alternatively, infections or inflammation might increase expression of the antiphospholipid antibodies’ target antigen or the expression of antigenic epitopes that are hidden in resting conditions.314 Accordingly, preliminary data have shown that LPS can upregulate β2-GPI expression in mice.315

Therapy

Risk factors for atherosclerosis and cardiovascular disease, including obesity, smoking, hypertension, diabetes, and hyperlipidemia, should be addressed with lifestyle measures and appropriate pharmacologic therapy. Oral contraceptives and estrogen replacement therapy are absolutely contraindicated, given their association with thromboembolic complications. Aspirin, heparin, warfarin, and immunosuppressive drugs are key elements of the pharmacologic therapy of APS. Effective anticoagulation may help prevent worsening of hypertension, stent re-occlusions, and progressive renal impairment and should be considered, even in the absence of previous thrombotic events.316 Treatment with rituximab, an anti-CD20 monoclonal antibody, achieved persistent disappearance of AP antibodies from the circulation in isolated case reports.317 However, whether this may translate into improvements in clinical outcomes remains to be addressed in adequately designed trials.318 TMA is an indication for plasmapheresis with fresh-frozen plasma. In secondary forms of APS, treatment will also be aimed at the underlying renal disease. Thus, steroids and immunosuppressants, including cyclophosphamides, may be indicated for patients with SLE and renal involvement.299

Case reports have documented the use of the C5 inhibitor eculizumab to prevent APS-associated thrombotic microangiopathy that complicates renal transplantation and to treat patients with acute catastrophic antiphospholipid syndrome.319,320 In vivo murine studies implicating the activation of the classical complement pathway in thrombosis associated with APS were the basis for the use of eculizumab in these case reports.320,321 Activation of complement by antiphospholipid autoantibodies generates C5a, which binds and activates neutrophils, leading to tissue factor expression.322 On the basis of murine studies, C3 and C5 have been proposed as possible therapeutic targets for treating obstetric APS.323,324

MACROVASCULAR DISEASES

Macrovascular diseases of the kidney include acute occlusion, aneurysms, and dissecting aneurysms of the renal artery and thrombosis of the renal artery. Stenosis of the renal artery is discussed in Chapter 47.

OCCLUSION OF THE RENAL ARTERY

THROMBOEMBOLISM OF THE RENAL ARTERY

Different conditions may predispose to artery thrombus formation, including atherosclerosis, renal artery aneurysm, fibrioid dysplasia, and aortic dissection, as well as the presence of endothelial injury secondary to the use of substances such as cocaine.325-326 Infectious and inflammatory states are also known to predispose to renal artery thrombosis, with cases reported in patients with polycystic kidney disease, Takayasu’s arteritis, and Behçet’s disease.327-329

Although inherited hypercoagulable states are typically associated with venous rather than arterial thrombosis, acquired hypercoagulable states can lead to arterial thrombosis, including APS, factor V Leiden
mutation, antithrombin, methylenetetrahydrofolate reductase (NAD(P)H) (MTHFR), hyperhomocysteinemia, and nephrotic syndrome. 350-355  

Clinical Features  
The clinical presentation of renal artery thromboembolism is variable and depends on the extent of renal injury and overall clinical picture. 336 Although anuria is characteristic of bilateral renal artery and solitary kidney renal artery involvement, it has been reported in unilateral renal artery thromboembolism, probably because of reflex vasospasm of the contralateral kidney. 337 Patients usually present with unexplained abdominal pain, gross hematuria, abdominal or flank tenderness, fever, and hypertension. 338 There may be signs of involvement of other end-organs by thromboembolic or recent cardiac events, such as atrial fibrillation or myocardial infarction. Most patients have an elevated serum LDH level and hematuria, and leukocytosis is common. 339 Doppler ultrasound with contrast agents may represent the first-line investigation, although it is operator dependent and is burdened by the possibility of false-negative results. 340,341 In case of high clinical suspicion (despite negative Doppler), a contrast-enhanced CT scan readily demonstrates the absence of enhancement in the affected renal tissue although there is concern about further damage to the kidney with the use of iodinated contrast material. 342 Contrast-enhanced three-dimensional magnetic resonance angiography (MRA) displays sharp images of the renal arteries and perfusion abnormalities. 343 Isotopic flow scans show absent or markedly reduced perfusion of the affected kidney. 344 Although angiography is considered the gold standard for diagnosis, its use is reserved for situations in which intervention is contemplated.  

Mechanisms  
The heart is the main source of peripheral thromboemboli, including those to the renal arteries. 338 Men and women with atrial fibrillation have a fourfold and almost sevenfold risk, respectively, of developing peripheral thromboemboli compared to those without atrial fibrillation, but only 2% of peripheral emboli secondary to atrial fibrillation target the kidney. 344 Myocardial infarction and heart failure may predispose to the formation of thromboemboli. Valvular heart disease, bacterial endocarditis, heart tumors, and dilated cardiomyopathy are other predisposing factors. The aorta can be a source of renal artery thromboemboli, especially following endovascular repair of aortic aneurysms. 345 The incidence of renal infarcts after such a procedure is about 9%. 345 Endovascular revascularization of renal artery stenosis may also be complicated by distal emboli. 346 However, the use of angioplasty and stenting with distal protection baskets may decrease the rate of complications. 346  

Therapy  
The human kidney is believed to tolerate the absence of blood flow for 60 to 90 minutes. 347 The presence of adequate collateral circulation from lumbar, suprarenal, or ureteral vessels may allow the kidney a longer ischemia time. 348 The duration and extent of ischemia are major determinants of the prognosis of an ischemic kidney. 349  

Treatment options for an acutely occluded renal artery are surgical embolectomy, percutaneous interventional techniques, and intraarterial thrombolysis. 350 Despite the restoration of kidney function in up to 64% of patients with surgical intervention, the mortality rate ranges between 15% and 20%. 349 The outcome of surgical embolectomy has been reported to be worse regarding kidney function. 350 The use of intraarterial thrombolytic agents has been associated with a high rate of renal artery recanalization, but the success of the procedure does not always translate into recovery of renal function. 351 Patients who sustain a complete occlusion or receive delayed treatment have a generally worse prognosis. Nevertheless, there are several case reports that describe favorable outcomes with intraarterial thrombolysis, even in cases of prolonged ischemia (20 to 72 hours) and in renal transplantation patients. 340 Successful results have also been reported with the use of systemic thrombolysis. Percutaneous aspiration thromboembolotomy and rheolytic thrombectomy have been performed, with some success. 349  

TRAUMATIC THROMBOSIS OF THE RENAL ARTERY  
Renal artery thrombosis is an uncommon sequela of blunt abdominal trauma. Motor vehicle accidents are the main cause of this injury. 352 Renal vessels can be affected by stretch injury, contusion, or avulsion, all of which may lead to thrombosis. 352 The left renal artery is slightly more affected than the right, but bilateral injury may be present as well. 352 Patients with traumatic renal artery thrombosis are usually critically ill and have other associated injuries, usually abdominal. The prognosis is poor, with the mortality rate reaching 44%. 353  

Clinical Features  
Patients present with a history of major trauma and have flank and abdominal pain, nausea, vomiting, and fever. They may develop severe hypertension. Patients with bilateral renal artery thrombosis or thrombosis of a solitary functioning kidney develop anuria. 340 Hematuria is present in the majority, but may be absent in about 25% of patients. Mild proteinuria is often present. Blood analyses show elevation of serum lactate dehydrogenase, creatinine phosphokinase, serum transaminase, and alkaline phosphatase levels. 340 CT is the preferred diagnostic modality in patients with suspected renal artery thrombosis. It has the advantage of speed, accuracy, and the ability to detect other associated injuries. 352 Patients with renal artery thrombosis usually have absent parenchymal enhancement in the affected kidney. There is also abrupt termination of the renal artery just beyond its origin. 340 There might be enhancement of the cortex due to perfusion from peripheral and collateral arteries; this is referred to as the rim sign on CT. 354 The gold standard for the diagnosis of renal artery injury is renal artery angiography, which shows intimal flaps with partial stenosis or complete occlusion. 352 Angiography has the advantage of detecting the location of the injury with high accuracy; however, angiography is not usually necessary for confirmation if the CT scan is diagnostic and is associated with an increased risk of contrast-induced nephropathy. 342 Ultrasonography is unreliable. 355  

Therapy  
Ischemia time is a major determinant of the outcome of revascularization in patients with traumatic renal artery thrombosis; 80% of renal artery revascularizations
performed within 12 hours are successful. The success rate decreases with time, reaching zero for revascularizations performed after more than 18 hours.\(^{356}\) However, there are case reports of late successful revascularizations.\(^{357}\) Other determinants of the outcome are the extent of renal injury, presence of collateral circulation, technical difficulties of the surgical procedure, and injury to other organs.\(^{340}\)

A significant number of patients who have had successful surgical revascularization develop hypertension. Many of them eventually require nephrectomy.\(^{358}\) The outcome of surgical revascularization in patients with unilateral traumatic renal artery thrombosis may be no better than observation and medical management.\(^{360}\) Nevertheless, revascularization is indicated for patients with bilateral renal artery thrombosis and patients with a solitary kidney.\(^{358}\) Late revascularization may be considered if the kidney size is normal on imaging studies and if preserved glomerular architecture is noted on renal biopsy.\(^{359}\)

Several surgical procedures can be performed for the repair of a renal pedicle injury, including thrombectomy, resection of the injured arterial segment and replacement with a venous or graft bypass, and autotransplantation with ex vivo repair of the vascular lesions.\(^{340}\) Endovascular stent placements for traumatic intimal tears have been described.\(^{360}\) Nephrectomy is required at times to control renal hemorrhage.\(^{340}\)

**ANEURYSMS OF THE RENAL ARTERY**

Large autopsy studies have suggested that the incidence of renal artery aneurysms (RAAs) is 0.01% in the general population, but in patients undergoing renal arteriography primarily for the evaluation of renovascular hypertension, RAAs are observed in 1%.\(^{340}\) Many RAAs remain asymptomatic. However, the clinical concerns of RAAs are their potential to rupture, thrombose (causing distal embolization), or lead to renovascular hypertension. Intrarenal aneurysms may erode into adjacent veins to produce arteriovenous fistulae.\(^{340}\)

**Clinical Features**

Renal artery aneurysms are classified as saccular, fusiform, dissecting, or intrarenal. They may be located anywhere along the vascular tree, but most of them are found at the bifurcation of the renal artery or in the first-order branch arteries.\(^{361}\) Saccular aneurysms, the most common type, constitute 60% to 90%. They are diagnosed typically at about 50 years of age, but can be seen in those from 13 to 78 years of age. In approximately 20% of cases, RAAs are bilateral. Renal artery stenosis may be associated.

Renal artery aneurysms are frequently asymptomatic and are diagnosed as part of a workup for renovascular hypertension. Occasionally, patients may complain of flank pain, which should raise the concern of an expanding aneurysm, rupture and hemorrhage, thrombosis, thromboemboli with impending renal infarction, or dissection.\(^{340}\) Rupture of an RAA, a potentially catastrophic event, may present with vascular collapse and hemorrhagic shock. Aneurysm size is a factor in the potential for rupture. The incidence of rupture of RAAs smaller than 2.0 cm in diameter is low. Large aneurysms, especially those larger than 4.0 cm in diameter, have a greater tendency to rupture and usually require surgical intervention.\(^{350}\) Pregnant women constitute a disproportionate number of cases of RAA rupture. In a review of 43 cases of rupture, 18 (42%) occurred in pregnant women.\(^{362}\) Most of these occurred during the last trimester of pregnancy, but rupture and hemorrhage also occurred earlier in pregnancy and during the postpartum period.\(^{361}\) Pathogenic factors include increased renal blood flow, particularly during the last trimester, the effect of female hormones on the vasculature, and increased intraabdominal pressure.\(^{340}\) Emergency nephrectomy is usually required in this setting to control the hemorrhage. Maternal mortality decreased to 6% and fetal mortality to 25% if the pregnancy reached the third trimester.\(^{363}\) If rupture occurs before the third trimester, fetal mortality approaches 100%.

Rupture of an RAA manifests with flank pain, vascular collapse, and shock. Abdominal distention or a flank mass may be detected. Hematuria may be a helpful finding in some patients, but its absence does not exclude the diagnosis. Renal angiography and MRA will diagnose RAAs, and CT and radionuclide scanning may be useful screening techniques.

**Mechanisms**

Renal artery aneurysms are sometimes attributed to atherosclerosis, but marked atherosclerotic changes are found in only 16% of patients and may be secondary.\(^{361}\) Fusiform aneurysms are often seen in medial fibromuscular dysplasia and usually arise distal to a focal stenotic segment, giving the appearance of a poststenotic dilation.\(^{364}\) Occasionally, several small aneurysms in sequence give the string of beads appearance seen in fibromuscular dysplasia. Fusiform aneurysms are typically found in young hypertensive patients who undergo renal angiography for the evaluation of renovascular hypertension. As with fibromuscular dysplasia, fusiform aneurysms are more common in women. Renal artery aneurysms have been described in polyarteritis nodosa, Takayasu’s arteritis, Behçet’s disease, Ehlers-Danlos syndrome, and mycotic aneurysms.\(^{329,363-367}\) Intraparenchymal renal aneurysms make up 10% to 15% of RAAs and are frequently multiple. They may be congenital, posttraumatic (e.g., after renal biopsy), or associated with polyarteritis nodosa.

**Therapy**

Various authors have attempted to provide criteria for elective surgical intervention for RAAs.\(^{340}\) Most agree that an aneurysm larger than 4.0 cm in diameter should be resected, and one smaller than 2.0 cm in diameter can be safely followed with periodic imaging studies. There is uncertainty about the mid-sized aneurysms, those between 2.1 and 4.0 cm. It may be prudent to recommend repair of RAAs larger than 3.0 cm in diameter in patients with surgical risks if there is reasonable certainty that nephrectomy will not be required.\(^{340}\) In addition to large size of the aneurysm, other factors are considered in the choice for elective surgical intervention, including the presence of lobulations, expansion over time, presence of signs and symptoms, women of childbearing age, localization in a solitary kidney with the potential for embolization or dissection, or secondary renovascular hypertension.\(^{340}\)

Several surgical techniques for the treatment of RAAs have been described, but the most commonly used approach is in situ aneurysmectomy and revascularization. When
carefully done, this surgery carries the least risk of damage to the kidney and ureter. However, even at experienced centers, almost 5% of patients eventually undergo an unplanned nephrectomy because of technical complications encountered during the attempted revascularization.361

DISSECTING ANEURYSMS OF THE RENAL ARTERY

Dissecting aneurysms of the renal artery are rare but severe disorders of the renal artery. Acute dissections may manifest in an explosive manner, with malignant hypertension, flank pain, and renal infarction. Chronic dissection usually manifests as renovascular hypertension.364 Acute dissection can occur spontaneously and can be precipitated by strenuous physical activity or trauma.508 Fibromuscular dysplasia and atherosclerosis are common predisposing factors that lead to intimal tears, medial necrosis of the artery wall, and dissection. Iatrogenic dissection due to angiographic procedures may occur from trauma induced by guidewires, catheters, or angioplasty balloons.540 Dissections have also been found as incidental autopsy findings, apparently without clinical symptoms during life.540 Renal artery dissections are about three times more common in men, and there is a predilection toward involvement of the right side. Approximately 20% to 30% are bilateral. Dissection is most common in 40- to 60-year-olds, although younger patients with fibromuscular dysplasia may be affected.

Patients with acute dissection may present with new-onset, accelerated, or worsening hypertension.360 Flank pain is frequent, and headache may occur, perhaps as a result of hypertension. In some cases, especially with lesions that develop from an angiographic procedure, the patient may be asymptomatic except for worsening hypertension. Selective angiography is necessary for the diagnosis.340 The clinical course is variable. Some patients have persistent, severe renovascular hypertension that may be resistant to medical therapy. These patients may benefit from revascularization or nephrectomy if they suffered renal infarction, and many show improvement or complete resolution of hypertension after these procedures.362 Endovascular interventions have also been reported.570 Appropriate therapy depends on the severity of the hypertension and its response to therapy. Edwards and colleagues have noted adequate responses to medical management in most patients.568 Dissecting aneurysms can be managed with open surgery, endovascular repair, or a combination of both.371

ACUTE RENAL VEIN THROMBOSIS

An acute presentation is usually seen in young patients with a short history of nephrotic syndrome. RVT manifests with acute flank pain, macroscopic hematuria, and loss of renal function and may mimic a renal colic or acute pyelonephritis.372,577 The physician should have a high index of suspicion, especially in patients with predisposing risk factors for hypercoagulability. In these cases, imaging reveals an enlarged kidney and pyelocalyceal irregularities.372

CHRONIC RENAL VEIN THROMBOSIS

A chronic presentation is usually seen in older patients with the nephrotic syndrome who have little or no accompanying symptoms except for peripheral edema, increase in proteinuria, and gradual decline in renal function.376 They also have a greater incidence of pulmonary emboli and other thromboembolic events.372

DIAGNOSTIC PROCEDURES

Doppler ultrasonography can visualize the actual venous flow, increased blood velocity, and turbulence in a narrowed vein or complete cessation of flow if the lumen is totally occluded. Ultrasonography with Doppler color flow should be the initial noninvasive diagnostic study. However, sonography is highly operator dependent and has a low specificity (56%), despite a high sensitivity (85%) in experienced hands.377

A characteristic radiographic finding of RVT is notching of the ureter, which usually occurs when collateral veins in close relation to the ureters become tortuous as they dilate to form an alternative drainage route. Originally, the notching of the ureters was interpreted as representing mucosal edema; however, more detailed radiographic studies have shown indentation of the ureters by the collateral venous circulation. Notching of the ureter is a very infrequent finding in nephrotic patients with RVT and usually occurs only in a minority of patients with chronic rather than acute RVT.578 Retrograde pyelography may demonstrate a rectangular, linear mucosal pattern, with irregular renal pelvic outlines.

 Inferior venacavography with selective catheterization of the renal vein establishes the diagnosis of RVT. If the inferior vena cava is patent and free of filling defects, and if a good streaming of unopacified renal blood is demonstrated to wash out contrast from the vena cava, a diagnosis of RVT is unlikely. The Valsalva maneuver is useful during venacavography; when the intraabdominal pressure is increased, the transit of contrast agent and blood from the inferior vena cava is slowed, the proximal part of the main renal vein may be opacified, and the patency of the lumen or even the outline of the thrombus may be demonstrated.579

 Often, the inferior venacavogram is not diagnostic, and selective catheterization of the renal vein must be performed. A normal renal venogram demonstrates the entire intralobar venous system to the level of the arcuate vein. In general, the use of epinephrine for better visualization of the smaller vessels is not necessary. However, in the presence of normal renal blood flow, all contrast material is washed out of the renal vein within 3 seconds or less, and occasionally only the main renal vein and major branches are visualized. In this situation, there may be uncertainty about thrombi in major or smaller branches. Then the use of intrarenal arterial epinephrine, by decreasing blood flow,
that can increase the risk of RVT (Figure 35.12); these abnormalities vary in intensity in proportion to the degree of albuminuria and hypoalbuminemia. The underlying mechanisms of the so-called thrombophilia of the nephrotic syndrome are essentially related to an imbalance of prothrombotic factors (e.g., increased fibrinogen levels, increased factor VIII levels, increased platelet adhesiveness) and antithrombotic factors (e.g., reduced antithrombin III levels, reduced protein C and S levels or activity) and impaired thrombolytic activity (e.g., decreased plasminogen levels, elevated plasminogen activator inhibitor-1 levels, or albumin deficiency-related impairment of the interaction of plasminogen and fibrin). An additional mechanism sustaining the procoagulant state is thrombocytosis, which has been found in a number of nephrotic adults and children. Moreover, platelets of nephrotic patients seem to display a tendency to hyperaggregability. Hypoalbuminemia results in a higher availability of arachidonic acid for the synthesis of the proaggregant thromboxane A2 within platelets. Platelet activation may also be enhanced by high levels of cholesterol, fibrinogen, and vWF and by thrombin and immune complexes. Volume depletion, diuretic and/or steroid therapy, venous stasis, immobilization, or immune complex activation of the clotting cascade may also participate in the thrombophilia of the nephrotic syndrome. It remains a mystery why only certain conditions have such a strong (but

Figure 35.12 Pathogenic factors predisposing to renal vein thrombosis in patients with the nephrotic syndrome. An imbalanced bioavailability of prothrombotic and antithrombotic factors in favor of prothrombotic factors predisposes to intravascular clotting. Impaired thrombolysis and concomitant factors such as volume depletion, hypoalbuminemia, impaired venous blood flow, and immobilization may contribute to precipitate renal vein thrombosis.

Mechanisms

Nephrotic Syndrome. Multiple hemostatic abnormalities have been described in patients with nephrotic syndrome

<table>
<thead>
<tr>
<th>Prothrombotic factors</th>
<th>Antithrombotic factors</th>
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<tr>
<td>Increased fibrinogen and factor VII levels</td>
<td>Reduced antithrombin III levels</td>
</tr>
<tr>
<td>Increased platelet adhesiveness</td>
<td>Reduced protein C and S levels or activity</td>
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Impaired thrombolytic activity

- Decreased plasminogen levels
- Elevated plasminogen activator inhibitor-1
- Impaired plasminogen-fibrin interaction due to albumin deficiency
- Anti-enolase antibodies in MN patients (possibly interfering with fibrinolysis)

Concomitant factors

- Blood volume depletion (Hypoalbuminemia, diuretic therapy)
- Immobilization
- Slowed venous blood flow

Enhances retrograde venous filling and allows later visualization of the smaller intrarenal veins. An abnormal renal venogram usually demonstrates a thrombus within the lumen as a filling defect surrounded by contrast material. In the presence of partial thrombosis, extensive collateral circulation can be demonstrated. The presence of such collaterals usually reflects the chronicity of the RVT and may explain the lack of renal functional deterioration.

Both contrast-enhanced CT and MRI have been used for the diagnosis of RVT. Both are less invasive than venography; CT uses ionizing radiation and iodinated contrast agent, so MRI has significant advantages over CT. Because MRI produces highly contrasting images of flowing blood, vascular walls, and surrounding tissues, vascular patency may be best determined by this technique. However, a low signal from the renal veins and pseudofilling defects due to slow flow, mimicking a thrombus, makes interpretation of the image difficult. Gadolinium-enhanced MRI can overcome the limitation of poor signal from the renal vessels and, by performing a delayed second scan, the venous anatomy is well demonstrated, and an occult renal artery stenosis can also be disclosed.

Mechanisms

Nephrotic Syndrome. Multiple hemostatic abnormalities have been described in patients with nephrotic syndrome

That can increase the risk of RVT (Figure 35.12); these abnormalities vary in intensity in proportion to the degree of albuminuria and hypoalbuminemia. The underlying mechanisms of the so-called thrombophilia of the nephrotic syndrome are essentially related to an imbalance of prothrombotic factors (e.g., increased fibrinogen levels, increased factor VIII levels, increased platelet adhesiveness) and antithrombotic factors (e.g., reduced antithrombin III levels, reduced protein C and S levels or activity) and impaired thrombolytic activity (e.g., decreased plasminogen levels, elevated plasminogen activator inhibitor-1 levels, or albumin deficiency-related impairment of the interaction of plasminogen and fibrin). An additional mechanism sustaining the procoagulant state is thrombocytosis, which has been found in a number of nephrotic adults and children. Moreover, platelets of nephrotic patients seem to display a tendency to hyperaggregability. Hypoalbuminemia results in a higher availability of arachidonic acid for the synthesis of the proaggregant thromboxane A2 within platelets. Platelet activation may also be enhanced by high levels of cholesterol, fibrinogen, and vWF and by thrombin and immune complexes. Volume depletion, diuretic and/or steroid therapy, venous stasis, immobilization, or immune complex activation of the clotting cascade may also participate in the thrombophilia of the nephrotic syndrome. It remains a mystery why only certain conditions have such a strong (but
variable) association with RVT. The discovery of the association of antienolase autoantibodies with membranous nephropathy offers a tantalizing clue, because these autoantibodies could interfere with fibrinolysis.\textsuperscript{381} The coexistence of another thrombophilic state with nephrotic syndrome, such as hereditary resistance to the activation of protein C (Leiden trait), could be another factor involved in the generation of thrombotic events in selected patients.\textsuperscript{379,382}

**Other Predisposing Factors.** In addition to the hemostatic abnormalities associated with the nephrotic syndrome, other causative factors include amyloidosis, oral contraceptives, steroid administration, and genetic procoagulant defects.\textsuperscript{373} Thrombosis can occur secondary to trauma (e.g., blunt, surgical), neoplasms (e.g., hypernephroma, Wilms’ tumor), extrinsic compression (e.g., retroperitoneal tumors, pregnancy, lymphoma), arterial diagnostic puncture, placement of central catheters, and functional states of hypoperfusion, such as congestive heart failure.\textsuperscript{376} Hypovolemia, a cause of RVT in neonates, has also been reported in adults. Morrissey and associates have reported a case of bilateral RVT in a previously healthy 22-year-old man that resulted in a moderate proteinuria without underlying glomerular pathology and with a normal coagulation profile.\textsuperscript{376} The RVT was preceded by a 3-day history of nausea and vomiting as the only precipitating event. Treatment with fibrinolytics followed by heparin was successful.\textsuperscript{376}

Renal vein thrombosis triggered by hypovolemia has also been suggested in other studies.\textsuperscript{380} Steroids aggravate hypercoagulable states by increasing factor VIII and other serum protein levels and by decreasing fibrinolytic activity.\textsuperscript{383} Historically, the advent of steroid therapy coincided with an increase in thromboembolic complications.\textsuperscript{384} The use of oral contraceptives has been implicated as an additional cause of RVT and may unmask underlying hypercoagulable disorder.\textsuperscript{375}

Acute RVT has been noted with increasing frequency in the transplanted kidney, which, unlike the native kidney, has a single drainage system.\textsuperscript{385} In this setting, RVT may be accompanied by thrombosis of extrarenal sites.\textsuperscript{335} RVT usually leads to permanent damage of the graft within hours. Predisposing factors are muromonab-CD3 (OKT3) and cyclosporine therapy.\textsuperscript{385} Neonatal RVT accounts for 15% to 20% of systemic thromboembolic events in neonates and results in significant long-term morbidity.\textsuperscript{386} Maternal and patient risk factors for RVT are presented in Table 35.5.

**Therapy: Treatment of Overt Thrombotic or Embolic Events**

Treatment of established renal vein thrombosis can be divided into measures targeting the specific cause of the occlusion (primary renal disease, tumors, systemic disease) and those aimed at the thrombus itself and/or its complications. The latter includes volume resuscitation, dialysis as necessary, but first and primarily anticoagulation. Current management of renal vein thrombosis has shifted from surgical to medical treatment.\textsuperscript{387}

**Anticoagulation and Thrombolysis.** Anticoagulation is the mainstay of therapy, and is intended to prevent further propagation of the thrombus and thromboembolic complications while permitting recanalization of occluded vessels.\textsuperscript{372,375} Thrombolytics provide the possibility of more rapid and complete resolution than anticoagulants but at the expense of a higher risk of bleeding.\textsuperscript{372} The relative efficacy of anticoagulation versus fibrinolytics in the treatment of RVT is not well defined.\textsuperscript{372} Thrombolytic therapy is likely warranted in patients with bilateral RVT, extension into inferior vena cava, pulmonary embolism, acute kidney injury (AKI), acute renal failure (ARF), or severe flank pain.\textsuperscript{372}

Choice of systemic versus local administration depends on the evaluation of risk-benefit factors. Systemic administration is safe and effective if no obvious contraindications exist and avoids the need for invasive procedures.\textsuperscript{388} Anticoagulation is indicated for nephrotic patients who experience a thromboembolic event. Heparin should be given, although its effect may be attenuated in the presence of low antithrombin III (ATIII) levels. ATIII deficiency in nephrotic patients rarely causes heparin resistance.\textsuperscript{385} If ATIII levels are extremely low, fresh-frozen plasma or ATIII concentrates can be administered.\textsuperscript{389}

Following heparin, oral vitamin K antagonists should be used. The optimal duration of warfarin therapy is unknown, but given the risk of recurrence, it is reasonable to maintain anticoagulation as long as the patient is nephrotic and has significant hypoalbuminemia. Treatment with heparin warrants monitoring of the anticoagulation response and is associated with some complications, such as thrombocytoopenia and osteoporosis.\textsuperscript{356} Low-molecular-weight heparin (LMWH) has been suggested as an alternative for the treatment of RVT.\textsuperscript{390}

**Prophylactic Anticoagulation of Asymptomatic Patients with Nephrotic Syndrome.** No randomized controlled trials have been conducted to assess the risk-benefit profile of anticoagulation therapy in patients with nephrotic syndrome. However, a Markov-based decision analysis model has found that the number of fatal emboli prevented by prophylactic anticoagulation exceeds that of fatal bleeding in nephrotic patients with idiopathic membranous nephropathy.\textsuperscript{391}

![Table 35.5 Maternal and Patient Risk Factors for Renal Vein Thrombosis](image-url)
However, before formal evidence from a properly designed randomized trial is available, indications for anticoagulant therapy should be decided on an individual basis. Patients who have severe nephrotic syndrome, regardless of underlying cause, and a history of a thromboembolic event (DVT or pulmonary embolus) should be offered prophylactic anticoagulants if no contraindications exist. Patients with severe nephrotic syndrome (serum albumin level <2.0 to 2.5 g/dL) should also be considered candidates for prophylactic anticoagulation if they have other risk factors for thrombosis (e.g., congestive heart failure, prolonged immobilization, morbid obesity, abdominal, orthopedic, or gynecologic surgery). Patients with a family history of thrombophilia might also be considered for prophylactic therapy.

An alternative therapeutic approach is represented by low-dose aspirin, considering the increased platelet function in nephrotic patients. A retrospective study to assess the influence of low-dose aspirin on the incidence of RVT in deceased and living related renal transplant recipients receiving cyclosporine-based triple immunosuppression has shown that although not abolished, the incidence of RVT decreases significantly with the addition of low-dose aspirin.

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KEY REFERENCES


