CHAPTER 50

Hemolytic Uremic Syndrome

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OBJECTIVES

This chapter will:

1. Define and clinically characterize the hemolytic uremic syndrome.
2. Delineate the differences between the hemolytic uremic syndrome associated with infections by Shiga-like toxin-producing bacteria and the atypical form of the disease.
3. Describe hemolytic uremic syndrome as a disease of complement dysregulation.
4. Review treatment options for hemolytic uremic syndrome.

DEFINITION

Clinically defined by thrombocytopenia, nonimmune (Coombs negative) microangiopathic hemolytic anemia, and acute kidney failure, hemolytic uremic syndrome (HUS) is a microvascular occlusive disorder belonging to the spectrum of diseases known as thrombotic microangiopathies (TMAs).[1,2] The term TMA defines a histologic lesion found in the arterioles and capillaries and characterized by thickening of the vascular walls, prominent endothelial swelling and detachment, and subendothelial accumulation

of proteins and cell debris. In patients with TMA, the formation of fibrin and platelet-rich thrombi occurs in the microcirculation, obstructing vessel lumina, leading to end-organ ischemia and infarction. Thrombocytopenia is due partly to consumption in microthrombi. Hemolytic anemia likely is due to the fragmentation of erythrocytes as a consequence of the abnormally high levels of shear stress in obstructed vessels. In patients with HUS, organ dysfunction includes major involvement of the kidneys, although the heart, lungs, gastrointestinal tract, pancreas, and especially the brain also can be affected.[3]

HUS occurs most frequently in children younger than 5, in whom the incidence is five to six children/100,000/year, compared with an overall incidence of 0.5 to 1/100,000/year. Most cases (>90% of pediatric cases) are associated with infections by Shiga-like toxin- (Stx-) producing bacteria, such as enterohemorrhagic *Escherichia coli* (STEC) or *Shigella dysenteriae*. In these cases HUS is referred to more appropriately as STEC-HUS.[4] STEC-HUS is acquired as a foodborne illness or from a contaminated water supply and begins with a history of bloody diarrhea in most cases. It may be sporadic or occur as an outbreak. It affects predominantly children, except in epidemics, when it may occur in individuals with a wider range of ages.[5] In 2011 several European countries, particularly northern Germany, experienced one of the largest STEC-HUS outbreaks ever reported. About 4000 individuals suffered from *E. coli* O104:H4 infection, and more than 800 of them developed HUS. Almost 90% of affected patients were adults.

Approximately 5% of HUS cases in children result from infection by neuraminidase-producing *Streptococcus pneumoniae* (pneumococcal-HUS or neuraminidase-associated HUS).[6] Pneumococcal-associated HUS is a rare but potentially fatal disease that may complicate pneumonia or, less frequently, meningitis caused by *S. pneumoniae*.[7]

The term atypical HUS (aHUS) has been used to describe those rare cases (less than 10%) in which infections by Stx-producing bacteria or *S. pneumoniae* can be excluded. Atypical HUS is an extremely rare disease. The annual incidence is 0.6 to 2 per million.[8] Atypical HUS can occur at any age, from the neonatal period to adulthood.[9,10] Onset during childhood (≤18 years) appears to be slightly more frequent than during adulthood (approximately 60% and 40% of cases, respectively).[10,11] Seventy percent of children have the first episode before the age of 2 and approximately 25% before reaching 6 months of age.[9] Onset before the age of 6 months is strongly suggestive of aHUS, because less than 5% of STEC-HUS occurs in this age group.[12] Both sexes are equally affected in childhood,[9] whereas there is a female prevalence in adults.[13] Atypical HUS can be familial (approximately 20% of patients) or sporadic.[14] In the former case, the disease has either autosomal recessive or dominant patterns of inheritance.[1]

Over the last two decades, genetic or acquired defects leading to the dysregulation of the alternative pathway (AP) of the complement system (Fig. 50.1) have been discovered in about 50% to 60% of aHUS patients.[1] Many forms of aHUS are associated with a variety of conditions, oral contraceptives, calcineurin inhibitors, illicit drugs, cancer chemotherapy and ionizing radiation, malignant hypertension, bone marrow or solid organ transplantation, autoimmune disorders, malignancy, pregnancy, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome and, in children, methylmalonic aciduria with homocystinuria, cblC type, a rare, hereditary defect of the cobalamin metabolism.[15] These forms frequently are called *secondary* HUS. However, the term does not take into account the evidence that many of the above conditions often act as triggers of the disease in individuals with a genetic background, leading to complement dysregulation. For instance, a substantial proportion of aHUS cases that occur during pregnancy or postpartum have been found to

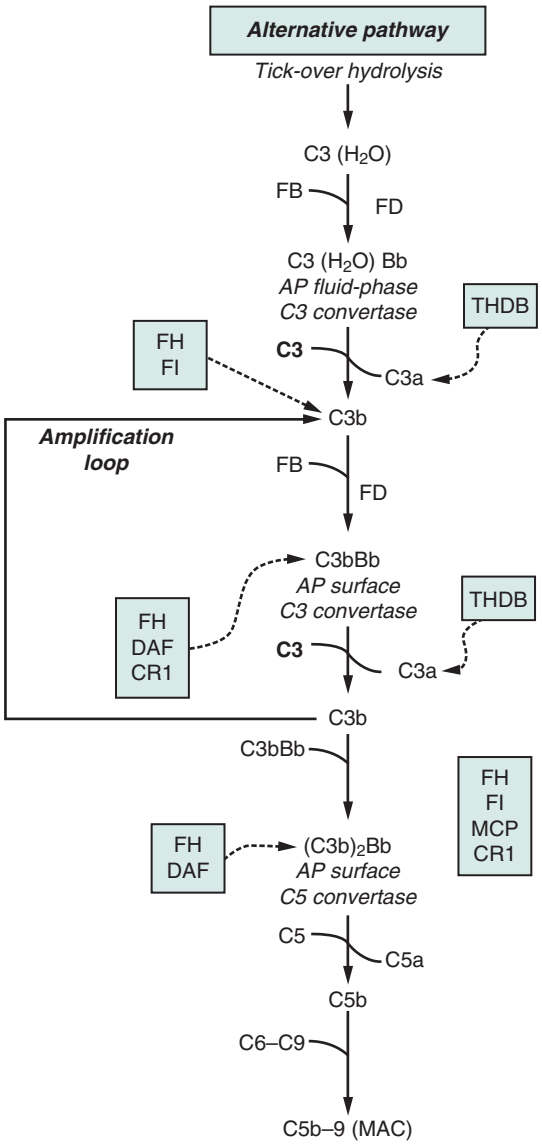


FIGURE 50.1 Schematic representation of the alternative pathway (AP) of the complement system. The AP is continuously activated in plasma by low-grade hydrolysis (tick-over hydrolysis) of C3 forming C3(H_2O). The latter binds to FB, which in turn is cleaved by factor D (FD) to form the AP fluid-phase C3 convertase, C3(H_2O)Bb. AP C3 convertases cleave C3 into C3a, an anaphylotoxin, and C3b, the main effector molecule of the complement system. Once formed, C3b contributes to the formation of the AP surface C3 convertase, C3bBb, that cleaves additional C3 molecules, resulting in an amplification loop. In addition, C3b contributes to the formation of the C5 convertases, $(C3b)_2Bb$ that cleave the complement component C5 producing the anaphylatoxin C5a, and C5b. C5b initiates the late events of complement activation leading to the formation of the membrane-attack complex (MAC or C5b-9 complex). Self-surfaces are protected from complement damage by protein regulators: FI, factor I, DAF (decay accelerating factor); MCP, membrane cofactor protein; CR1 (complement receptor 1); FH, factor H; THBD, thrombomodulin.

be associated with complement gene mutations.[16] Along with this, triggering/underlying clinical conditions have been reported in up to 70% of patients with complement gene mutations, showing that genetic predisposition and a precipitating event are required for the disease to develop.[10]

This chapter focuses on STEC-HUS and aHUS.

LABORATORY EXAMS

Microangiopathic hemolytic anemia and thrombocytopenia are the laboratory hallmarks of HUS.[1] Laboratory results indicate the presence of what is usually severe microangiopathic hemolytic anemia, highlighted by low hemoglobin levels (<10 g/dL in more than 90% of patients) and high serum levels of lactate dehydrogenase (LDH > 460 U/L), reflecting not only hemolysis but also diffuse tissue ischemia.[17] Other indicators of intravascular hemolysis include hyperbilirubinemia, uniformly elevated reticulocyte counts, and low or undetectable haptoglobin concentrations. The peripheral smear reveals increased schistocyte numbers, with polychromasia and often nucleated red blood cells. The detection of fragmented erythrocytes, together with a negative Coombs test, is crucial for confirming the microangiopathic nature of hemolytic anemia. The consumption of platelets in thrombi causes a remarkable reduction in platelet counts (platelets $\leq 150\times10^9$/L). In children with STEC-HUS, the duration of thrombocytopenia is variable and does not correlate with the course of renal disease.[18]

Evidence of kidney involvement is present in all patients with HUS (by definition). Elevated serum creatinine levels, low glomerular filtration rates (GFR), microscopic hematuria, and subnephrotic proteinuria are the most consistent findings.

STEC-HUS

Pathogenesis

Several strains of *E. coli* (O157:H7, O111:H8, O103:H2, O123, O26, O145, and O104:H4) isolated from human cases with diarrhea were found to produce Shiga-like toxins (Stxs).[19] After contaminated food or water is ingested, STEC colonizes the intestinal mucosa, where bacteria adhere closely to the epithelial cells, induce the destruction of brush border villi, and cause watery, or most often, bloody diarrhea. Once it has adhered to intestinal epithelial cells, STEC produces and releases Stxs into the gut lumen within a few days after bacterial colonization. It is assumed that Stxs reach the kidney and other target organs via the bloodstream after translocation across the intestinal epithelium. Free Stxs have not yet been detected in the sera of HUS patients, but it has been demonstrated that Stx binds to neutrophils.[20] It has been suggested that other circulating human blood cells, such as erythrocytes, platelets,[21] and monocytes,[22] serve as Stx carriers.

In the kidney, Stx binds mainly to the glomerular endothelial cells through the receptor globotriaosylceramide (Gb3), although there is evidence that Stx can also bind to podocytes, mesangial cells, and proximal tubules.[23]

For many years it has been assumed that the only relevant biologic activity of Stxs was to induce cell death by modifying the ribosome and blocking protein synthesis. However, treating of endothelial cells with sublethal doses of Stxs exerts minimal influence on protein synthesis, leading instead to increased mRNA expression and protein levels of chemokines,[24,25] chemokine receptors,[25] and cell adhesion molecules.[26,27] By altering endothelial cell adhesion properties and metabolism, Stxs favor leukocyte-dependent inflammation and induce loss of thromboresistance in endothelial cells, leading to microvascular thrombosis.

Evidence is also emerging that complement system activation may contribute to microangiopathic lesions in STEC-HUS.[28] As early as in the 1970s, it was noticed that some STEC-HUS patients had low C3 plasma levels,[29] and more recent studies have confirmed C3 reduction in severe cases of STEC-HUS.[30,31] High plasma levels of complement activation products, Bb and sC5b-9, were found in children with STEC-HUS, indicating AP activation. Stxs may contribute directly to complement activation, as confirmed by C3 deposition on microvascular endothelial cell lines exposed to Stx and then perfused with human serum.[32] Complement deposition and loss of thromboresistance depended on Stx-induced upregulation of the membrane adhesion molecule P-selectin, which has been shown to bind C3b with high affinity,[32,33] thereby triggering the AP. In addition, FB-deficient mice treated with Stx and lipopolysaccharides (LPS) exhibited less thrombocytopenia and were protected against glomerular abnormalities and renal function impairment, indicating the involvement of AP activation in the glomerular thrombotic process.[32]

Clinical Manifestations

STEC infections cause a spectrum of clinical signs ranging from asymptomatic carriage to nonbloody diarrhea, hemorrhagic colitis, HUS, and death. The average interval between ingestion of STEC and illness manifestation is approximately 3 days, although this can vary between 2 and 12 days. Illness typically begins with severe abdominal cramping and nonbloody diarrhea, which becomes hemorrhagic in 70% of cases, usually within 1 or 2 days.[34] Vomiting occurs in 30% to 60% of cases, and fever is reported in up to 30% of patients during this initial phase of the disease. The percentage of cases that progressed to HUS ranged from 3% to 9% in sporadic infection to about 20% or more in some outbreaks.[34] The diagnosis of HUS usually is made 6 to 10 days after the onset of diarrhea, once kidney failure occurs.[2] Seventy percent of patients require red blood cell transfusions, and 40% to 50% need dialysis.[34,35] Although mortality in industrialized countries decreased with the introduction of dialysis, 1% to 2% of patients still die during the acute phase of the disease. More than 90% of childhood cases of STEC-HUS fully recover from the acute disease. However, a meta-analysis of 49 published studies describing the long-term prognosis of patients who survived an episode of STEC-HUS reported death or permanent end-stage renal disease (ESRD) in 12% of patients and a GFR below 80 mL/min/1.73 m^2 in 25%.[35] Extrarenal manifestations are an important cause of added morbidity and are the main cause of death. Central nervous system disturbances (stroke, seizure, and coma) are common and usually present early in the course of the illness.[34] Rare complications include pancreatitis, diabetes mellitus, cardiomyopathy, and myocarditis.

The diagnosis of STEC-HUS depends on the detection of *E. coli* O157:H7 and other Stx-producing bacteria and their products in stool cultures. Tests for *E. coli* O157 antigen can be done in research laboratories. The polymerase chain reaction is being used increasingly to detect Stx-encoding genes using DNA directly isolated from stool specimens, thus significantly shortening the turnaround time, providing

same-day results.[36] Convalescent-phase serum samples can be assayed for antibodies to O157 or to other specific strain-derived LPS, although this test is not commercially available.[34]

Treatment

Supportive Care

The typical management of STEC-HUS patients relies on correction of electrolyte and water imbalance, anemia, hypertension, and renal failure. Administering intravenous fluid and sodium as soon as a STEC infection is suspected appears to limit the severity of acute renal failure and the need for renal replacement therapy.[37] Up to 80% of patients receive packed red blood cells for symptomatic anemia.[38] Blood pressure control and renin-angiotensin system blockade may be particularly beneficial in the long-term for patients who have chronic kidney disease.[39] Bowel rest is important for the enterohemorrhagic colitis associated with STEC-HUS. Antimotility agents should not be administered, because they may prolong the persistence of *E. coli* in the intestinal lumen and therefore increase patient exposure to its toxin.

At present there is no indication to prescribe antibiotics. An interesting exception may be azithromycin, because its use appeared to have some benefit regarding the duration of bacterial shedding in adult patients in the German O104:H4 epidemic.[40] In contrast to STEC-HUS, hemorrhagic colitis and HUS caused by *S. dysenteriae* type 1 should be treated with antibiotics, because treatment shortens the duration of diarrhea, decreases the incidence of complications, and reduces the risk of transmission by shortening the duration of bacterial shedding.

Plasma Therapy

The efficacy of specific treatments in adult patients is difficult to evaluate because most information is derived from uncontrolled reports that also may include aHUS cases. In particular, no prospective, randomized trials are available to definitively establish whether plasma infusion (PI) or plasma exchange (PE) offers specific benefits compared with supportive treatment alone. However, comparative analyses of two large series of patients treated[41] or not treated[42] with plasma suggest that plasma therapy may decrease the overall mortality of STEC-HUS.

Eculizumab

Evidence that uncontrolled complement activation may contribute to microangiopathic lesions of STEC-HUS[32,43] provided the background for treatment with the anti-C5 monoclonal antibody eculizumab in three children with severe STEC-HUS who recovered fully with this treatment.[31] No significant difference in treatment efficacy was observed between HUS patients who received eculizumab together with PE and those who received PE alone in the STEC O104:H4 outbreak in Germany.[44] Notably, patients with more severe disease received more intensive treatment with PE and eculizumab. Thus similar outcomes between sicker patients receiving PE and eculizumab and patients with less-severe disease treated with conservative therapy alone may reflect the superior benefit of PE and eculizumab. However, the data from the study are inconclusive; they were collected retrospectively from a nonrandomized study. Whether eculizumab is a useful adjunct for the treatment of the most severe forms of STEC-HUS should be clarified by prospective, controlled trials.

Kidney Transplantation

Kidney transplant is effective and safe, and graft survival at 10 years is even better than in control children with other diseases.[45] Recurrence rates range from 0 to 10% because of potential genetic complement abnormalities. Genetic screening therefore should be performed before kidney transplantation in all patients who developed ESRD after STEC-HUS because they may be undiagnosed cases of aHUS and at risk of posttransplant recurrence.

ATYPICAL HUS

Pathogenesis

Atypical HUS is linked to uncontrolled activation of the AP of complement (Fig. 50.2). One or more genetic or acquired abnormalities in the complement system have been documented in nearly 50% to 60% of patients with aHUS.[10]

Complement Factor H Mutations, Complement Factor H–Hybrid Genes and Anti-FH Autoantibodies

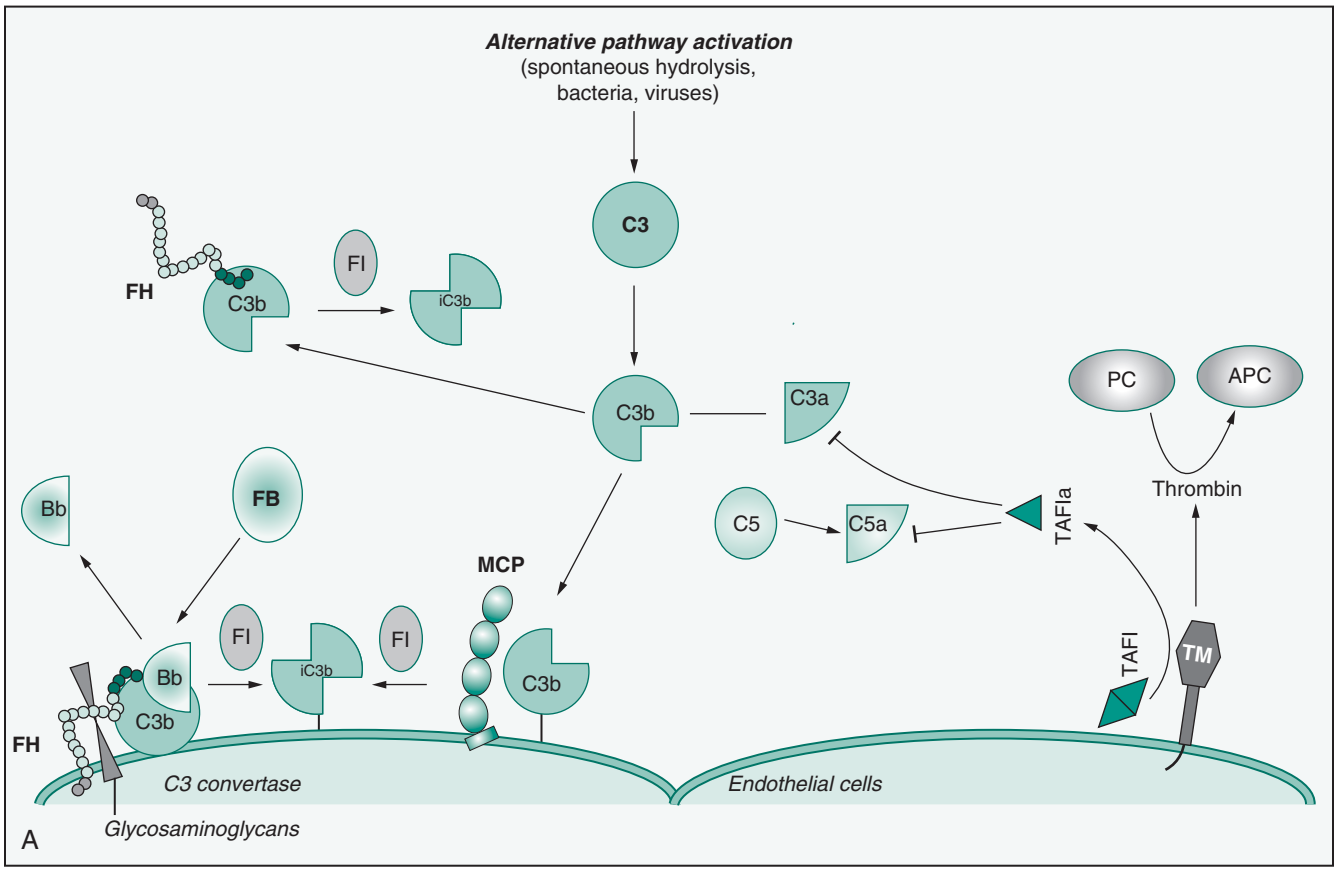
Mutations in complement factor H *(CFH)* are the most frequent genetic abnormality in aHUS patients, accounting for 20% to 30% of cases.[10,46,47] More than 100 *CFH* mutations[47a] have been identified in adults and children with sporadic or familial aHUS. Some patients had homozygous mutations, but most were heterozygous. Some mutations are associated with a quantitative FH deficit, whereas most are associated with normal levels of FH and result in a mutant protein that is unable to bind to and regulate complement on endothelial cells and platelets.

The *CFH* gene is in close proximity to the *CFHR1-5* genes encoding five FH-related proteins. *CFH* and *CFHRs* share a high degree of sequence identity. This homology predisposes to gene conversions and genomic rearrangements. Hybrid genes resulting in gene products with decreased complement regulatory activity on endothelial surfaces have been reported in 3% to 5% of aHUS patients.[3]

An acquired FH defect resulting from anti-FH IgG autoantibodies[48] accounts for 5% to 10% of patients[10,49,50] and around 25% to 50% of pediatric cases.[51,52] These antibodies reduce FH binding to C3b[53,54] and other C3 fragments,[53] perturb FH-mediated cell surface protection,[53,54] and in some individuals also impair cofactor activity[53] or decay accelerating activity.[48] The development of anti-FH antibodies has a genetic predisposition, being strongly associated with the deletion of the *CFHR1* and *CFHR3* genes, a polymorphism also observed at a frequency of 4% in healthy Caucasians who do not develop anti-FH antibodies.

Membrane Cofactor Protein Mutations

More than 40 different membrane cofactor protein *(MCP)* mutations have been identified so far in aHUS patients, accounting for 10% to 15% of cases, and most are heterozygous[47a]. Most patients (~75%) have decreased MCP


Alternative pathway activation
(spontaneous hydrolysis,
bacteria, viruses)
C3
FH
C3b
FI
iC3b
C3b
C3a
PC
APC
Thrombin
Bb
FB
C5
C5a
TAFIa
MCP
FI
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FH
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Endothelial cells
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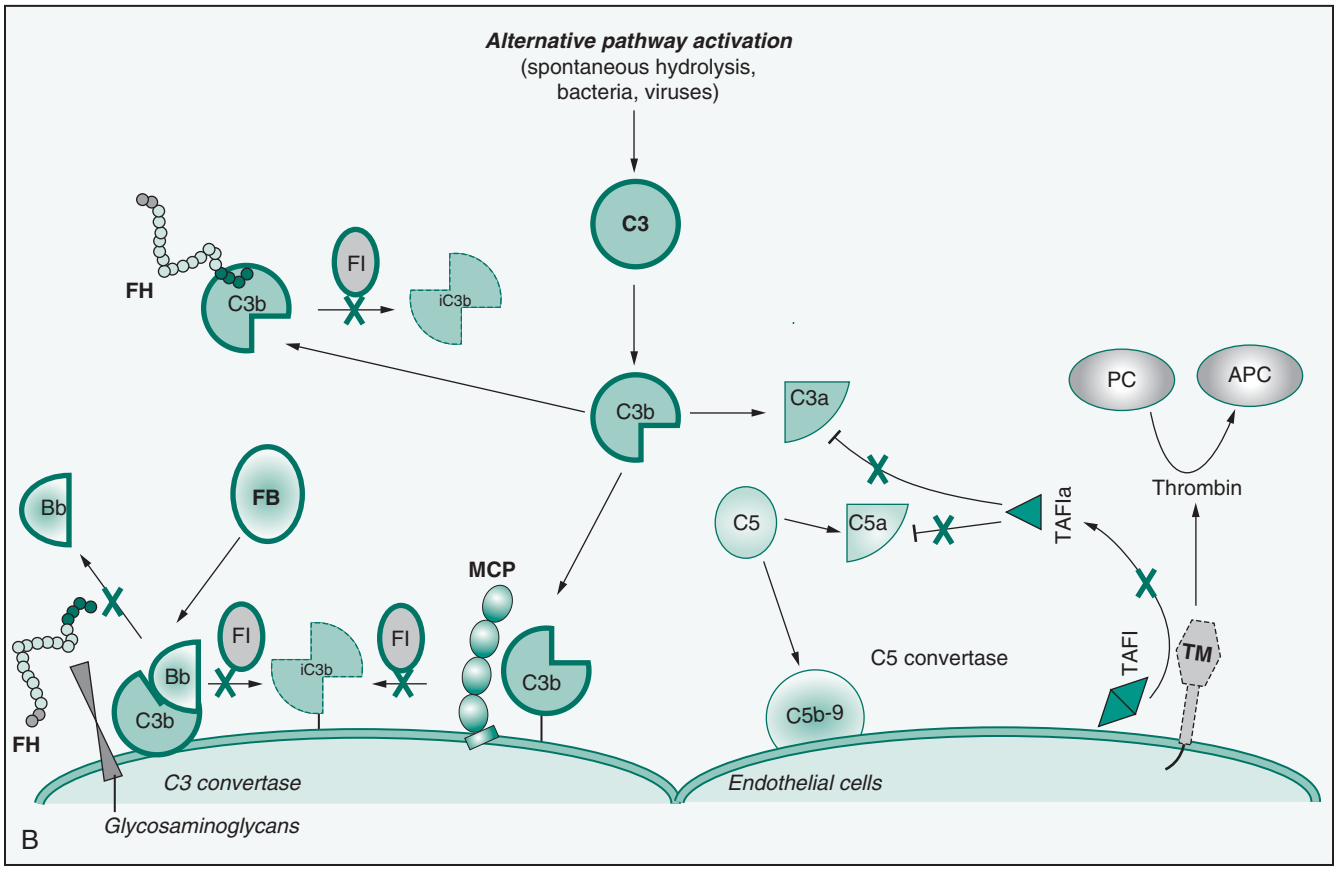
Alternative pathway activation
(spontaneous hydrolysis,
bacteria, viruses)
C3
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FI
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C3b
C3a
PC
APC
Thrombin
Bb
FB
C5
C5a
TAFIa
MCP
FI
FI
iC3b
Bb
C3b
C3b
C5 convertase
C5b-9
TAFI
TM
FH
C3 convertase
Endothelial cells
Glycosaminoglycans
B

expression on peripheral leucocytes. Less frequently, MCP expression is normal, but the protein is dysfunctional.[3]

Complement Factor I Mutations

Complement factor I *(CFI)* mutations account for 4% to 10% of patients. Eighty percent of them cluster in the serine-protease domain. Approximately 50% of mutations induce a default of protein secretion; some are secreted but have proteolytic activity disrupted.[55,56]

Mutations in the AP C3 Convertase Components

Heterozygous gain-of-function mutations can affect genes encoding the AP C3 convertase components, complement component C3 *(C3),* and complement Factor B *(CFB).*[57,58] *C3* mutations account for 2% to 10% of aHUS patients,[10,46,58] whereas mutations in *CFB* are rarer, accounting for only 1% to 4% of aHUS patients.[10,46,47,59,60]

Thrombomodulin Mutations

Heterozygous mutations in thrombomodulin *(THBD)* have been found in 3% to 4% of patients with aHUS,[10,46,61] documenting a functional link between complement and coagulation.

Combined Complement Abnormalities

There are reports of patients (3.4%) with mutations in more than one complement gene or mutations in one complement gene in addition to anti-FH autoantibodies.[10,46,47,55,62] Notably, only 8% to 10% of patients with *CFH*, *C3,* or *CFB* mutations carried abnormalities in other genes, suggesting that mutations in *CFH*, *C3*, or *CFB* alone may be sufficient to cause aHUS. In contrast, approximately 25% of patients with a mutation in *MCP* or *CFI* had a second or third mutation in other complement genes.

Diacylglycerol Kinase Epsilon Mutations

Very recently, homozygous or compound heterozygous mutations in diacylglycerol kinase epsilon *(DGKE)* cosegregated with aHUS in nine unrelated kindreds.[63] Mutation carriers presented with aHUS before 1 year of age, had persistent hypertension, hematuria, and proteinuria, and developed chronic kidney disease with age. DGKE apparently is unrelated to the complement cascade, and the mechanism by which *DGKE* mutations cause aHUS remains to be elucidated.

Incomplete Penetrance and Triggering Factors

Mutations in complement genes can be found in healthy family members. Incomplete penetrance has been reported in approximately 50% of individuals carrying mutations in *CFH*, *CFI, MCP*, *CFB*, and *C3*.[10,11] Thus it can be inferred that the genetic alterations are important but are not sufficient for the development of aHUS. As discussed above, patients may carry mutations in more than one gene or mutations combined with autoantibodies; otherwise, they may carry a mutation in combination with common at-risk genetic variants (single nucleotide polymorphisms and haplotype blocks) in *CFH*[10,64–67] or *MCP*[64,66] or *CFHR1*.[68] It has been observed that penetrance increases as the number of alterations in a patient increase. Even in a situation in which a patient has multiple genetic/acquired risk factors, aHUS may not occur until middle age, suggesting that a triggering stimulus is required for the disease to manifest (multiple hits theory).[65]

Precipitating events, most commonly upper respiratory tract infections or gastroenteritis, have been reported in more than half of patients.[9,10] Although the association with diarrhea is well established with STEC-HUS, diarrhea also preceded aHUS in up to 24% of patients.[10] However, it remains unclear whether the diarrheal episode acted as a trigger or was a consequence of the diffuse character of the TMA. Other infectious triggers such as varicella,[69] H1N1 influenza[70] and, interestingly, STEC-diarrhea[9,10,49,71] have been reported in aHUS patients. Pregnancy is a frequent

FIGURE 50.2 *(Shown on previous page.)* Schematic representation of the consequences of complement mutations in HUS patients. (A) After viral or bacterial infection or spontaneous hydrolysis, complement is activated and C3b is formed. FH binds fluid-phase C3b and favors its degradation by FI. FH competes with FB for C3b binding and accelerates the C3 convertase decay. In addition, FH protects host surfaces by binding to polyanions. MCP is a surface-bound complement regulatory protein acting as a cofactor for the FI-mediated cleavage of deposited C3b. THBD facilitates the activation of protein C by thrombin and enhances thrombin-mediated activation of plasma procarboxypeptidase B (TAFI), an inhibitor of fibrinolysis that also inactivates complement-derived C3a and C5a. THBD also has been shown to down-regulate the AP by accelerating FI-mediated inactivation of C3b in the presence of cofactors (not shown). (B) Mutant FH has a normal cofactor activity in fluid phase. However, most HUS-associated mutations affect the polyanion interaction site at the C-terminal region of the protein so that FH shows reduced bind to proteoglycans, resulting in more C3b reaching the cell surface. In addition, deposited C3b is not degraded and forms the surface AP C3 convertase that further cleaves C3 to C3b. MCP mutations result in a reduced surface expression of the protein or in a reduced capability of MCP to bind C3b or have low cofactor activity. In all cases, membrane-bound C3b is not efficiently inactivated, leading to undesirable amplification of C3b formation and deposition on endothelial cell through the formation of C3 convertase. Most C3 mutations induce a defect on the ability of complement regulators to bind to C3b and lead to severe impairment of mutant C3b degradation. Others lead to mutant C3 that bind to FB with higher affinity, resulting in increased C3 convertase formation. *CFB* mutations induces an increased stability and activity of the AP C3 convertase, resistant to decay by FH, with enhanced formation of C5b-9 complexes and deposition of C3-fragments at cell surfaces. Cells expressing THBD mutants inactivate C3b less efficiently than cells expressing wild-type protein (not shown).

triggering event in women[1,10,16]: as many as 20% of women with aHUS experience the disease during pregnancy, 80% of them during the postpartum period.[16] Thus it is likely that aHUS is the result of an otherwise innocuous stimulus that triggers the AP and sets off a self-amplifying cycle that cannot be controlled appropriately in genetically susceptible individuals.

Clinical Manifestations

Symptoms are characterized by the presence of the complete triad of HUS in most patients.[72] Arterial hypertension is frequent and often severe. Approximately 20% of patients have progressive onset with subclinical anemia and fluctuating thrombocytopenia for weeks or months, and normal renal function at diagnosis. Some patients have no anemia or thrombocytopenia, and the only manifestation of an active renal TMA is hypertension and proteinuria and a progressive increase of serum creatinine.

Although TMA, by definition, affects predominantly renal vessels in aHUS, the lesion can involve the microvasculature of other organs (heart, intestines, pancreas, lungs, and especially the brain) in about 20% of patients.[9,10] The most frequent (~10%) extrarenal symptoms are neurologic, although myocardial infarction, cardiomyopathy, heart failure, and peripheral ischemic heart disease have been observed.[47,49] The failure of different organs, as well as death, can occur unpredictably at any time, either very quickly or after prolonged symptomatic or asymptomatic disease progression.[1,9,10,47]

In contrast with STEC-HUS, which tends to occur as a single event, aHUS is a chronic condition and involves a poorer prognosis.[9–11] Half of the children and the majority of adults need dialysis at admission and until very recently, when eculizumab was introduced,[73] about 50% of patients never recover renal function. After the first episode, mortality has been reported to be higher in children than in adults, but progression to ESRD is more frequent in adults.[74] Three to five years after onset, 36% to 48%[10,75] of children and 64% to 67%[10,75] of adults die or reach ESRD.

Outcomes vary according to the underlying complement alteration.[9,10,75] Individuals with mutations in *CFH*, *CFI*, *C3, CFB,* or *THBD* have a poor prognosis: 50% to 70% of patients lose renal function, die during the presenting episode, or develop ESRD after relapses.[1,10,11] In patients with anti-FH–associated HUS, 35%[49] to 60%[10] of individuals die or reach ESRD within 3 years of follow-up. In patients with *MCP* mutations, long-term outcome is good with 80% of patients dialysis free.[1,10,11] In individuals with *MCP* mutations combined with a mutation in another complement gene, the prognosis is worse than in patients with an *MCP* mutation alone.[62]

Treatment

Plasma Therapy

Plasma therapy in the form of PE or PI has been the gold standard of aHUS therapy since the 1980s and was essentially the only therapy available until 2011. The efficacy of plasma therapy is presumed to be related to its ability to deliver normal levels of complement proteins and, when plasma is exchanged by apheresis, to remove mutant regulators, anti-FH antibodies, and hyperfunctional complement components.[76] However, the efficacy of plasma therapy for treating aHUS never has been studied formally.

Consensus-based guidelines recommended that empiric plasma therapy should be started within 24 hours of diagnosis of aHUS and then continued until there are signs of TMA resolution, or a declaration of nonresponse.[77,78] In the case of aHUS resulting from anti-FH antibodies, PE is recommended strongly, mainly in association with immunosuppressants (corticosteroids and azathioprine or mycophenolate mofetil).[49] Data on the effect of rituximab, an anti-CD20 antibody, under such circumstances are scanty and inconsistent.[49]

In those patients who respond, plasma therapy can be withdrawn slowly, although individuals with genetic defects in the complement system are frequently plasma dependent and require long-term plasma therapy to maintain remission.[79]

Eculizumab

Eculizumab was approved in 2011 for the treatment of aHUS after successful trials in adults and adolescents.[73] Eculizumab has been shown to induce remission of acute episodes of aHUS refractory to plasma therapy and is now used widely as a first-line therapy, provided that other causes of TMA (STEC infection or TMA associated with ADAMTS13 deficiency) are excluded.[3] It is not clear, however, how long eculizumab therapy should be extended and what the ideal treatment regimen is. This issue is also relevant because of the high cost of the drug. Chronic, lifetime treatment with eculizumab at doses that can persistently block the complement cascade conceivably could be indicated to prevent disease recurrence in occasional patients with the most severe genetic forms. However, whether and to what extent this applies to all patients with aHUS associated with complement genetic abnormalities is unknown. In addition, the risk of sensitization associated with chronic eculizumab exposure or with its deposition in tissues, and the recent report of hepatotoxicity associated with the use of eculizumab in pediatric patients,[80] suggest that careful treatment tapering up to withdrawal whenever possible should be attempted under control of disease and complement activity. Levels of serum C3 and plasma sC5b-9, as well as C5 activity (CH50), are not suitable markers of complement activation in aHUS, because in aHUS complement dysregulation is restricted on cell surfaces.[72,81] A recently reported ex vivo assay specifically detected complement deposits at endothelial level in aHUS patients. Ex vivo complement deposits normalized after eculizumab, and guided drug dosing and timing, thus representing a future tool to specifically monitor complement activity in patients undergoing eculizumab tapering or discontinuation.[81]

One concern with eculizumab treatment is the risk of infection with encapsulated bacterial organisms, particularly *Neisseria meningitis,* as a result of terminal complement blockade.[82] Therefore patients must receive meningococcal vaccination before being treated with eculizumab at least 1 week before treatment. Antibiotic prophylaxis is recommended highly because not all serotypes are covered by vaccination. In pediatric patients, vaccination against *Haemophilus influenzae* and pneumococci is also necessary.[83]

Organ Transplantation

The outcome of kidney transplantation in aHUS was considered poor and much depending on the underlying genetic alteration,[84] despite the fact that robust enough data are admittedly not available yet. Disease recurred in 65% to

80% of transplanted patients with mutations in complement circulating proteins (FH, FI, and C3). Conversely, the lowest incidence of recurrence was observed in patients with *MCP* and *DGKE* mutations[10,63]; this can be explained by the fact that *MCP* and *DGKE* are highly expressed primarily in the kidney, and a graft that brings normal proteins corrects the defect.

Eculizumab was used efficiently as prophylaxis to prevent posttransplant aHUS recurrence in 10 patients,[83,85–88] in whom a high recurrence risk was predicted from identified genetic abnormalities. Whether aHUS transplanted patients should continue lifelong eculizumab prophylaxis or whether it can be stopped at any time and used as rescue therapy if clinical signs of relapse occur remains to be established in controlled trials.

In patients with *CFH* mutations, combined liver-kidney transplant may be a treatment option with the rationale of correcting the genetic complement defect, thus preventing disease recurrence in the transplanted kidney.[89,90] Liver transplantation, in contrast to eculizumab therapy, cures aHUS definitively without the need of specific therapies other than standard immunosuppression to prevent graft rejection. More than 80% of patients who received liver transplantation have had excellent long-term outcomes.[91] The short-term mortality risk associated with acute complement activation in the liver graft observed in initial attempts has been reduced substantially with prophylactic plasmapheresis and perioperative eculizumab. However, the risks of kidney and liver transplantation have limited widespread diffusion of this option and ask for a careful assessment of benefits in candidate patients. When compared with kidney-liver transplant, eculizumab has the lower short-term risk and more effectiveness in preventing recurrences; however, the disadvantages are the need of chronic treatment, the potential long-term effects of C5 inhibition on the already heavily immunosuppressed transplant recipients, and the extremely high costs. In low-income and poor countries, the high costs prevent eculizumab use, and such limitation applies to the large majority of patients worldwide.

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Key Points

1. Hemolytic uremic syndrome is a thrombotic microangiopathy with manifestations of nonimmune microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.
2. Hemolytic uremic syndrome most commonly is triggered by Shiga-like toxin-producing *Escherichia coli* and manifests with diarrhea, often bloody.
3. Atypical hemolytic uremic syndrome is significantly less common than STEC-associated hemolytic uremic syndrome and accounts for less than 10% of all cases of the disease.
4. Gene alterations in complement proteins have been shown to predispose persons to the development of hemolytic uremic syndrome.
5. Complement inhibition by eculizumab administration leads to a rapid and sustained normalization of hematologic parameters with improvement in long-term renal function.

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A complete reference list can be found online at ExpertConsult.com.

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