Complement-mediated hemolytic uremic syndrome

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INTRODUCTION — Hemolytic uremic syndrome (HUS) is defined by the simultaneous occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury [1]. The most common cause of HUS is due to Shiga toxin-producing *Escherichia coli* (STEC). Research over the last 20 years has shown that complement dysregulation accounts for most of the non-STEC cases of HUS. This discovery has had a major impact on identifying the underlying cause of familial HUS, and on the management of these patients, who historically have had a poor prognosis.

The clinical manifestation, diagnosis, and management of complement-mediated HUS will be reviewed here. An overview of HUS and topics on the clinical manifestations, diagnosis, and management of STEC-HUS are found separately. (See "Overview of hemolytic uremic syndrome in children" and "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children" and "Treatment and prognosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children".)

CLASSIFICATION — Traditionally, HUS had been divided into diarrhea-positive and diarrhea-negative HUS. The former, also referred to as typical HUS, primarily resulted from Shiga toxin-producing *E. coli* (STEC) infections, and less frequently from *Shigella dysenteriae* type 1 infection. All other causes of HUS were referred to as atypical HUS or assigned to the diarrhea-negative HUS, even though some patients with non-STEC-HUS also presented with diarrhea.

The classification system used to describe the different etiologies of HUS has evolved as ongoing research has provided a better understanding of the underlying causes of HUS.

Currently, HUS is divided into [2]:

- Primary causes without coexisting disease, such as cases due to complement dysregulation (also referred to as atypical HUS) [3]:
  - Complement gene mutations
  - Antibodies to complement factor H (CFH)
- Secondary causes:
  - Infection:
    - STEC
    - *Streptococcus pneumoniae*
    - Human immunodeficiency viral (HIV) infection

- Drug toxicity, particularly in patients with cancer or solid organ transplant recipients
- Rarely seen in pregnancy or autoimmune disorders (eg, systemic lupus erythematous)

However, subsequent research has already demonstrated limitations of this schema with the identification of other genetic causes of atypical HUS, such as mutations in *DGKE*, which encodes the protein diacylglycerol kinase epsilon. (See 'Other genetic causes' below.)

EPIDEMIOLOGY — Complement-mediated HUS is a relatively rare disorder with an estimated prevalence of seven per one million children in Europe [4]. Most complement-mediated HUS cases are due to gene mutations of complement factors [5-7]. Antibodies to complement proteins have been implicated in the etiology of 6 to 10 percent of patients with complement-mediated HUS [8]. In addition, patients may have concurrent genetic mutations and antibodies to complement proteins [9].

Genetic complement disorders — Mutations in the following identified genes that encode complement proteins appear to account for at least 50 to 60 percent of non-Shiga toxin-producing *E. coli* (STEC) HUS cases [5,6,10-12]. The reported relative frequency of each affected gene for non-STEC-HUS cases is also listed:

- Complement factor H (*CFH*, 20 to 30 percent)
- *CD46*, previously known as membrane cofactor protein (5 to 15 percent)
- Complement factor I (*CFI*, 4 to 10 percent)
- Complement factor 3 (*C3*, 2 to 10 percent)
- Complement factor B (*CFB*, 1 to 4 percent)
- Thrombomodulin gene (*THBD,* 3 to 5 percent)

It is likely that the percent of noninfectious HUS cases due to a complement disorder will rise with ongoing research identifying new gene mutations. In addition, a significant number of patients with complement-mediated HUS have mutations of more than one complement protein [5,8,13,14]. It is important to stress that the penetrance of the disease is low, as less than half of family members carrying the same mutation as the patient with atypical HUS will be affected with the disease.

PATHOGENESIS — The complement proteins associated with complement-mediated HUS are components of the alternative complement pathway. HUS results from a loss-of-function mutation in a regulatory gene (*CFH*, *CFI*, or *CD46*) or a gain-of-function mutation in an effector gene (*CFB* or *C3*). The proposed mechanism for the development of HUS is a trigger event, such as infection or pregnancy, in a susceptible individual with a gene mutation(s) or antibodies to complement proteins, which leads to uninhibited continuous activation of the alternative pathway resulting in the formation of the membrane attack complex (MAC) [10,14]. This causes renal endothelium damage leading to activation of the coagulations cascade and thrombotic microangiopathy. (See "Complement pathways", section on 'Alternative pathway'.)

Data from an animal study suggest that *C5* activation is important in the pathogenesis of HUS, thus supporting the use of eculizumab, a humanized monoclonal antibody to *C5* [15]. (See 'Complement blockade: Eculizumab' below.)

GENETIC MUTATIONS

Factor H mutations — Mutations of the complement factor H (*CFH*) gene, which encodes a regulatory protein in the alternative complement pathway, and CFH-related proteins (CFHR) are the most frequently identified genetic abnormalities seen in patients with complement-mediated HUS [7,16]. CFH in conjunction with complement factor I (CFI) competes with complement factor B (CFB) for C3b binding and accelerates C3 convertase decay. Over 100 mutations of *CFH* have been reported, most of which are missense

mutations that do not affect the levels of CFH and C3. In these patients, mutations generally affect the C-terminal region, which is important for binding to C3b, glucosaminoglycans, heparin, and endothelial cells [17,18]. Other mutations are located throughout the gene and are associated with low levels of CFH antigen. Interestingly, renal survival is higher in patients with low CFH levels compared with those with normal levels of CFH.

CFH gene mutations have been associated with both autosomal recessive and dominant forms of HUS [19-25]. Patients with homozygous mutations have very low serum levels of CFH antigen, low serum C3 and CFB antigen levels, and a low CH50. However, most patients are heterozygous for the mutation and have normal or only slightly decreased serum CFH and/or *C3* levels. As a result, normal factor H and C3 levels do not exclude the presence of a *CFH* mutation. (See "Overview and clinical assessment of the complement system".)

Although several studies have reported that HUS associated with *CFH* mutations usually presents during infancy or early childhood [19-21,26-29], results from a French study showed that 25 of 59 patients with *CFH* mutations initially presented after 20 years of age [12]. The disease either may be sporadic or clearly associated with a family history of disease. Severe hypertension is frequently observed. Hemolytic anemia is marked at disease onset and during relapses, with haptoglobin levels remaining low during the course of the disease.

Patients with *CFH* mutations have the worst outcome of all the patients with complement-mediated HUS. The natural course of this disease results in 60 to 70 percent of patients progressing to end-stage renal disease (ESRD) or death within one year of presentation [16,30]. In addition, there is a high rate of recurrent disease in patients who undergo renal transplantation. (See 'Renal transplantation' below.)

CD46 mutations — Mutations of the complement regulatory protein CD46 gene, previously known as membrane cofactor protein (MCP) [31], have also been implicated in familial HUS [16,32-34]. CD46 is a cofactor of CFI in the degradation of C3b and C4b. The aberrant protein either results in decreased cell surface levels of CD46 (most common) or an impaired ability to control alternative pathway complement activation on host cells [35]. HUS associated with CD46 deficiency is characterized by onset in early childhood, a favorable renal outcome in most patients, frequent relapses, and a low rate of recurrence in the renal allograft.

Factor I mutations — Mutations in *CFI*, the cofactor for CD46 and factor H, are also associated with HUS [30,36-38]. CFI is a serine protease, which cleaves C3b and C4b in the presence of CFH and CD46. Most patients have heterozygous *CFI* mutations, which result in either a quantitative or qualitative defect of the protein [36,37]. The prognosis of patients with HUS associated with *CFI* mutations is intermediate between those with HUS associated with *CD46* and those with *CFH* mutations. As an example, in two cohort studies, 50 to 60 percent of patients progressed to ESRD or died within two years of presentation [30,38], and in one of the studies, 30 percent of patients recovered from the initial presentation without disease recurrences [38]. Of note, in one of the cohort studies, 8 of 23 patients had an additional known genetic risk factor for HUS (ie, mutation of *CD46*, *CFH*, *C3*, or *CFB*) [38]. Recurrent HUS occurs in 45 to 80 percent of patients, resulting in graft loss.

C3 mutations — Heterozygous *C3* mutations resulting in persistently low C3 levels have been identified in patients with HUS [39-41]. These mutations are primarily located in the binding regions of C3b that interact with CFH, CD46, and complement receptor 1, and result in dysregulation of the alternative complement pathway [39]. Patients with *C3* mutations typically develop severe disease, with one-half to two-thirds of patients progressing to ESRD within the first year following presentation. Recurrent disease is common in patients following renal transplantation. In addition, there is an increase in the incidence of at-risk *CFH* and *CD46* haplotypes for HUS in these patients.

Factor B mutations — Gain of function mutations of *CFB*, which either enhances the formation or delays the inactivation of C3bBb convertase, have been reported in 1 to 3 percent of cases of complement-mediated

HUS [42,43]. Progression to ESRD occurs in 70 percent of patients. In the four reported cases of renal transplantation, all four reported graft failure because of HUS recurrence.

Thrombomodulin mutations — Thrombomodulin is a cofactor in the initiation of the protein C anticoagulant pathway, which accelerates the inactivation of C3b by factor I. In a study of 152 patients with atypical HUS (ie, non-Shiga toxin-producing *E. coli* [STEC]-HUS), seven patients had six different heterozygous mutations of the *THBD* gene [44]. In vitro studies demonstrated that the mutated *THBD* resulted in dysregulation of the complement system because it was less effective than normal thrombomodulin in converting C3b to its inactive form iC3b. (See "Overview of hemostasis", section on 'Activated protein C and protein S'.)

COMPLEMENT ANTIBODIES — Complement factor H (CFH) antibodies have been reported in about 8 to 10 percent of patients with atypical HUS (ie, non-Shiga toxin-producing *E. coli* [STEC]-HUS) [45-50]. The enzyme-linked immunosorbent assay (ELISA) technique for the detection and the quantification of anti-CFH has been standardized [51]. These antibodies interfere with the binding of CFH to the C3 convertase and are associated with a defective CFH-dependent cell protection. A study of 308 cases of atypical HUS (Newcastle cohort) reported the presence of CFH antibodies in 13 of 142 screened patients (9.2 percent) [49]. Most of these patients also had homozygous deletion of *CFHR1* and/or *CFHR3* genes, suggesting that this deletion has a pathogenetic role in the development of anti-CFH antibodies [45,47,49,52]. Mutations in other complement genes (*CFH*, complement factors I and B, *CD46*, and *C3*) also were identified in a minority of patients [49]. These findings suggest that in some patients, multiple "hits" to the complement system may be necessary for the clinical presentation of complement-mediated HUS [49,53].

Management approach

Medical management — The management of patients with CFH antibodies is challenging and evolving due to the reported beneficial effects of initial therapy with eculizumab, however limited data are based on small case series [50]. Prior to the introduction of eculizumab, the initial management of patients with CFH antibodies included supportive care with plasmapheresis or plasma exchange, followed by immunosuppressive therapy directed to inhibiting further production of antibodies and preventing relapses [54-56].

Based on the available evidence cited below, we begin treatment with plasma exchanges to rapidly remove circulating anti-CFH antibodies, followed by immunosuppressive therapy to ensure reduced production of anti-CFH antibodies. Immunosuppression ensures reduced production of anti-CFH antibodies and includes oral corticosteroids with or without the addition of intravenous (IV) cyclophosphamide, rituximab, or mycophenolate mofetil (MMF). Eculizumab is considered during the acute stage, particularly if plasma exchange is not available, if severe neurologic or cardiac illness is present, or if the patient does not respond to intensive plasma exchanges.

Alternatively, eculizumab may be considered as a first-line treatment with the possibility of adding corticosteroids and/or MMF in an attempt to reduce antibody titer. However, the safety efficacy profiles and cost-effectiveness of approaches combining few plasma exchanges and immunosuppressive therapy, or long-term eculizumab therapy, have to be determined.

Studies — Published immunosuppressive protocols following plasma exchange include:

- A regimen that consists of induction therapy of oral prednisone (1 mg/kg per day for four weeks and followed by alternate days for four weeks) with either two to five doses of IV cyclophosphamide or two doses of IV rituximab, and maintenance treatment with tapering doses of prednisone and mycophenolate mofetil or azathioprine for 18 to 24 months [54].

- Use of pulses of cyclophosphamide, oral prednisone, and plasma exchange resulted in sustain remission for three children. Rituximab was also used in one other patient to treat recurrent relapses [55,56]. In these four patients, sustained remission was achieved up to six years. Although anti-CFH Ab titer decreased, it remained detectable during remission.

Support for eculizumab therapy without immunosuppression is based on a case series of 17 children from the United Kingdom and Ireland, including seven patients with a coexisting rare genetic variant in a known HUS-associated gene [50]. Immunosuppressive therapy was not given, because of concerns over treatment-associated complications. The outcome varied based on management. All patients who received eculizumab recovered renal function and achieved sustained remission. Two patients treated only with supportive care developed end-stage renal disease (ESRD). Four of 11 patients treated with plasma exchange recovered renal function. The authors concluded that based on these results, their clinical practice is to initiate only eculizumab therapy for treatment of factor H autoantibody-mediated HUS and not include plasma exchange or immunosuppressive therapy.

Renal transplantation — Although data on the outcome of renal transplantation is limited in patients with CFH antibodies, one-quarter to one-third of patients have allograft loss due to recurrent disease [54]. The risk of recurrence increases with high antibody titers and if there is a concomitant mutation in genes encoding CFH, C3, or CFB. For patients at-risk for disease recurrence (antibody titers >1000 AU/mL and/or mutations in these specific complement protein), additional preventive measures (eg, eculizumab or plasma therapy) should be provided prior to transplantation. (See 'Preventive therapy' below.)

Outcome — Outcome of patients with CFH antibodies varies as demonstrated by the following case series:

- In one case series, outcome data at a mean follow-up of 39 months were available for 44 of the 45 patients [45]. Four patients died (unknown cause in two patients, one from pulmonary arterial hypertension, and one from cardiac disease), 25 patients had relapses, 17 developed chronic kidney disease (CKD) including 12 who went on to ESRD, and 11 patients had no sequelae.

- In the previously mentioned study from the United Kingdom and Ireland, six patients progressed to ESRD (two who received only supportive care and four who also received plasma exchange), and the others regained renal function, including six patients with sustained remission who were treated with eculizumab [50]. Five patients received renal transplants without specific factor H autoantibody-targeted treatment, and recurrence occurred in one patient who also had a functionally significant CFI mutation.

- A large case series of 138 patients from India reported mean follow-up at 14.5 months for patients who mostly were treated with early plasma exchange therapy and/or immunosuppressive therapy [57]. Plasma exchange was performed in 105 patients and 87 received immunosuppressive therapy, which included oral prednisolone with or without additional agents such as intravenous cyclophosphamide (n = 49) and rituximab (n = 18). The following outcomes were noted:

    - 58 patients had normal renal function with hypertension and/or significant hematuria/proteinuria
    - 33 patients remained on dialysis
    - 20 deaths
    - 13 patients with normal renal function and normal urinalysis
    - 10 patients with impaired renal function, but not dialysis dependent
    - 3 patients underwent transplantation

OTHER GENETIC CAUSES — Other genetic defects that have been reported in patients with primary HUS include:

- *DGKE* mutations – Recessive mutations in *DGKE* (encoding diacylglycerol kinase epsilon) were identified in nine unrelated kindreds with atypical HUS [58]. The authors suggest loss of *DGKE* function results in a prothrombotic state as DGKE inactivates arachidonic acid-containing diacylglycerols (DAG), an activator of protein kinase C, which promotes thrombosis. In one consanguineous family with a novel truncating mutation in *DGKE* (p.K101X), patients showed significant complement activation and low C3

levels. Aggressive plasma infusion therapy controlled systemic symptoms and prevented renal failure [59]. Another study of four patients with *DGKE* mutations found that three of them also carried heterozygous mutations in thrombomodulin (*THBD*) or *C3* [60]. Plasma therapy was effective in two patients with *DGKE* and *THBD* mutations, while plasma infusions and eculizumab were effective in the patient with *DGKE* and *C3* mutations.

- *PLG* mutations – A comprehensive genetic analysis of complement and coagulation genes in patients with atypical HUS detected not only mutations in complement regulatory genes in over half of the patients, but also novel mutations in several genes in the coagulation system, particularly ones in the *PLG* gene, which encodes plasminogen [61]. Plasminogen deficiency results in a decreased degradation of thrombi, promoting thrombosis. The authors speculate that thrombi in small vessels cause mechanical damage to erythrocytes, releasing peptides (such as heme), or overexpression of other unidentified factors that activate the complement system resulting in endothelial cell damage and HUS.

CLINICAL MANIFESTATIONS — In all cases of HUS, clinical presentation includes the concurrent characteristic findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Data from clinical registries have provided additional clinical information for complement-mediated HUS [12,16,30,62]. However, data are often inconsistent as there is heterogeneity in the study population, and in the genes and coding sequences used for screening.

- Although earlier studies suggested that HUS due to genetic mutations of the complement proteins was primarily a pediatric disorder [16,30,62], a French cohort of 214 patients reported that more than half of their cohort presented as adults (58 percent) [12]. In this study, genetic mutations were demonstrated in 60 percent of the patients. However, in children with complement-mediated HUS, presentation typically occurred in young patients less than two years of age. Several studies also suggest that patients younger than six months who present with HUS are more likely to have complement-mediated disease than Shiga toxin-producing *E. coli* (STEC)-HUS.

  It remains unclear what effect, if any, specific mutations have on the age of presentation. As noted above, initial studies had reported that most patients with complement factor H (*CFH*) mutations present as infants or young children [19-21,26-29]. However, in the French study, 40 percent of patients with *CFH* mutations presented after 20 years of age [12]. It does appear that patients with *CD46* mutations (complement regulatory protein CD46) are more likely to present during childhood.

- A family history of HUS is obtained in about 20 to 30 percent of patients [1,12]. The penetrance of the disease is only about 50 percent, so that only half of the family members with the genetic mutation will manifest the disease. It has been shown that for the disease to manifest itself, other factors, such as a trigger (eg, infection) that activates complement, are typically present [6,16]. In other cases, multiple hits, such as the additional presence of antibodies to complement factor B or another genetic mutation, appear to increase the likelihood of disease expression.

- In most patients (70 to 80 percent), there is an antecedent trigger event that is thought to play a role in complement activation. In most patients, the trigger is an upper respiratory infection, however, a diarrheal prodrome has been observed in about one-quarter of patients. Pregnancy has also been reported as a trigger event in adolescents and adult women. (See 'Pathogenesis' above.)

- Previous episode of HUS.

- Severe hypertension.

- Patients with *C3* and factor B mutations and those with antibodies to factor H typically have low plasma C3 levels but normal C4 levels. In patients with other mutations (eg, mutations to factor H, *CD46*, and thrombomodulin [*THBD*]), levels of plasma C3 levels may be decreased or remain normal [2,14]. As a result, normal plasma levels of C3, C4, CFB, CFH, and CFI do not exclude the diagnosis of complement-mediated HUS.

Clinical course and outcome — The clinical course and outcome vary depending on the affected complement component [16,30]. For example, patients with mutations of the gene for CFH have a poor prognosis as most patients with this gene defect progress to end-stage renal disease (ESRD) or death within the first year of presentation. In contrast, few patients harboring mutations that affect CD46 progress to ESRD, although relapse is common [30]. (See 'Genetic mutations' above.)

DIAGNOSIS — The diagnosis of complement-mediated HUS is based on the clinical presentation of the classical triad findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, and demonstration of complement dysregulation, either due to gene mutations of complement proteins or antibodies to complement factors. The minimum set of genes that should be screened includes *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *THBD*, *CFHR1*, *CFHR5*, and *DGKE* [14]. Because of the frequent concurrence of genetic risk factors, screening should also include genotyping for the risk haplotypes *CFH-H3* and *MCP*.

Making the diagnosis is challenging because screening for mutations and antibodies to complement proteins is **not** widely available. Laboratories that offer complement genotyping for atypical HUS can be found from the National Center for Biotechnology Information website. Screening should be considered in patients with a positive family history, previous episode of HUS, who present within the first six to twelve months of age, or who present during pregnancy or postpartum [3]. In addition, complement genotyping may be indicated in patients with HUS in whom evaluation does not identify an underlying cause and who have a poor clinical course. (See "Overview of hemolytic uremic syndrome in children", section on 'Evaluation'.)

As noted above, although many patients with complement-mediated HUS will have low C3 or C4 levels, normal plasma levels of C3, C4, CFB, CFH, and CFI do not exclude the diagnosis of complement-mediated HUS. (See 'Clinical manifestations' above.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of complement-mediated HUS includes HUS due to other causes and conditions that also present concomitantly with anemia, thrombocytopenia, and acute kidney injury. Further evaluation including history and additional laboratory tests may differentiate complement-mediated HUS from these other disorders. (See "Overview of hemolytic uremic syndrome in children", section on 'Evaluation' and "Approach to the patient with suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

Other forms of HUS

- Shiga toxin-producing *E. coli* (STEC)-HUS accounts for 90 percent of pediatric cases of HUS. It is differentiated from complement-mediated HUS based on demonstrating a recent exposure to STEC. Screening for STEC-HUS is discussed separately. (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children", section on 'Evidence of STEC infection'.)

- Pneumococcal-associated HUS occurs in a patient with evidence of a pneumococcal infection (eg, pneumonia, sepsis, or meningitis), which is confirmed by a positive culture of blood and/or other pertinent tissues. (See "Overview of hemolytic uremic syndrome in children", section on 'Streptococcus pneumoniae'.)

- Other rare noninfectious secondary causes of HUS include drug toxicity, especially in patients with cancer or in bone marrow or solid organ transplant recipients, or are associated with pregnancy or autoimmune disease. It remains uncertain whether these clinical settings may act as triggers for activation of the complement pathway in susceptible individuals with genetic mutations in complement proteins. (See "Overview of hemolytic uremic syndrome in children", section on 'Non-infectious secondary causes'.)

- Inborn error of cobalamin C metabolism is a rare cause of HUS, especially in young infants (one to three months of age). The diagnosis is suggested by amino acid and organic acid chromatography findings of a marked increase of homocysteine and a low level of methionine in the plasma, and a very high urinary

excretion of homocysteine and methylmalonic acid. (See "Overview of hemolytic uremic syndrome in children", section on 'Non-infectious secondary causes'.)

Thrombotic thrombocytopenic purpura — Thrombotic thrombocytopenic purpura (TTP) is due to deficient activity of the Von Willebrand factor cleaving protease. Pediatric TTP is rare and is usually due to mutations of the *ADAMTS13* gene. Affected children usually present at birth with hemolytic anemia and thrombocytopenia. Renal involvement often occurs later in life and has a progressive course. TTP is distinguished from HUS by abnormally low ADAMTS13 activity. The mainstay of initial treatment for TTP is plasma exchange, as untreated patients progress to renal failure and further neurologic deterioration, and are at risk for cardiac ischemia and death. (See "Acquired TTP: Clinical manifestations and diagnosis", section on 'Reduced ADAMTS13 activity' and "Acquired TTP: Initial treatment", section on 'Initiation of PEX for a presumptive diagnosis of TTP' and "Hereditary thrombotic thrombocytopenic purpura (TTP)".)

Perhaps a further challenge in differentiating TTP from HUS is that partial ADAMTS13 deficiency may occur in patients with complement-mediated HUS. This was illustrated in a study of patients with atypical HUS based on clinical criteria that reported several of the 13 patients with mutation in complement genes also had mild to moderated reduction of ADAMTS13 activity due to single nucleotide polymorphism of the *ADAMTS13* gene [63]. The authors concluded that partial ADAMTS13 deficiency may occur in patients with complement-mediated HUS, and *ADAMTS13* activity should be evaluated in affected patients.

EVALUATION — The diagnostic evaluation that differentiates complement-mediated HUS from other conditions with similar presentations, such as other forms of HUS, thrombocytopenia thrombotic purpura (TTP), and inborn errors of vitamin B12, is discussed in detail elsewhere. (See "Overview of hemolytic uremic syndrome in children", section on 'Evaluation' and "Approach to the patient with suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

In summary, studies that may differentiate complement-mediated HUS from other disorders include [3]:

- Screening for Shiga toxin-producing *E. coli* (STEC) to differentiate complement-mediated disease from STEC-HUS includes testing for Shiga toxins (eg, enzyme-linked immunosorbent assays [ELISA]) in the stool, stool cultures, and serologic testing for immunoglobulin M (IgM) and anti-lipopolysaccharide antibodies against the most frequent STEC serotypes. In addition, polymerase chain reaction (PCR) testing for Shiga toxin genes can also be performed. (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children", section on 'Evidence of STEC infection'.)

- In the setting of concurrent serious infection, cultures of the blood, sputum, or cerebrospinal or pleural fluid may demonstrate an underlying serious pneumococcal infection, which is indicative of a diagnosis of pneumococcal-associated HUS rather than complement-mediated disease.

- In some patients, in whom the diagnosis is uncertain, a renal biopsy may be performed. Complement-mediated HUS is characterized by arteriolar thrombotic microangiopathy (image 1), perhaps accounting for the markedly increased blood pressure seen in some patients [64]. In contrast, most cases of STEC-HUS tend to have more glomerular than arteriolar involvement (image 2).

- Other studies that may be performed include assessing *ADAMTS13* function and screening for defective cobalamine metabolism. (See "Overview of hemolytic uremic syndrome in children", section on 'Differential diagnosis' and "Acquired TTP: Clinical manifestations and diagnosis", section on 'Reduced ADAMTS13 activity'.)

As noted above, indications for screening for complement dysregulation include [3] (see 'Diagnosis' above):

- Previous episode of HUS

- Family history of HUS

- Patient is less than one year of age and without evidence of a secondary cause (eg, pneumococcal or STEC infection)
- Episode of HUS during pregnancy or postpartum without evidence of a secondary cause

TREATMENT — The initial management of complement-mediated HUS is supportive and similar to the approach used for Shiga toxin-associated HUS. (See "Treatment and prognosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children", section on 'Supportive therapy'.)

In addition to supportive care measures, the management of complement-mediated HUS may include the following [14]:

- Plasma exchange or infusion
- Eculizumab, a monoclonal antibody to C5 that blocks the terminal complement cascade
- Renal or combination renal-hepatic transplantation

The following sections regarding the care of patients with atypical HUS are consistent with a published international consensus approach to the management of atypical HUS in children [3].

Supportive care — Supportive therapy includes [3]:

- Red blood cell transfusions for anemia when clinically indicated (eg, hemoglobin level in children is <6 g/dL or hematocrit <18 percent).
- Platelet transfusion for patients who have significant clinical bleeding or if an invasive procedure is required.
- Appropriate fluid and electrolyte management to maintain adequate intravascular volume and correct/avoid electrolyte abnormalities.
- Stopping nephrotoxic drugs or those that are implicated in the etiology of HUS.
- Initiation of dialysis therapy in patients with symptomatic uremia, azotemia (defined as a blood urea nitrogen >80 mg/dL [29 mmol/L]), severe fluid overload, or electrolyte abnormality that is refractory to medical therapy.
- Provision of adequate nutrition.

Complement blockade: Eculizumab — Patients with the diagnosis of atypical HUS should receive eculizumab as the first-line treatment. Several large case reports have demonstrated that eculizumab, a humanized monoclonal antibody to C5, is effective in the treatment of complement-mediated HUS due to genetic defects in complement proteins in native kidneys, or as rescue or preventive therapy in renal allografts [7,65-73]. It also appears to be beneficial in patients with complement-mediated HUS due to autoantibodies to complement factor H (CFH) [74,75].

Although data are observational [76], we recommend the initial use of eculizumab given its magnitude of effect in patients with severe complement-mediated HUS (eg, patients with *CFH* and complement factor I *[CFI]* mutations) who are at risk for end-stage renal disease (ESRD), mortality, or recurrence of disease after transplantation, despite its potential for adverse effects as discussed below. However, the cost of this treatment has been estimated to be in the range of USD $400,000 and EUR €300,000 per year for patients with paroxysmal nocturnal hemoglobinuria [77,78]. As a result, this therapy may not be available because of the prohibitive cost. If cost is an issue, plasma therapy remains a reasonable initial intervention for complement-mediated HUS. However, eculizumab should be considered in patients who fail to respond to plasma therapy.

The treatment with eculizumab should be started as soon as possible within the first 48 hours of admission. Testing for anti-CFH antibodies is the only urgent complement investigation required, as other treatment options are available for patients with HUS due to antibodies to CFH [54]. (See 'Complement antibodies' above and 'Plasma therapy' below.)

Mode of action — Eculizumab binds to complement protein C5, which blocks its cleavage, thereby preventing the production of the terminal complement components C5a and the membrane attack complex (MAC) C5b-9 [79]. This results in reduction of the terminal-complement activation that occurs in patients with complement-mediated HUS, thereby reducing endothelial damage and thrombosis, and subsequent renal injury. (See 'Pathogenesis' above.)

Efficacy — The initial efficacy of eculizumab was based on prospective open-label case series of patients who were treated with ongoing plasma therapy, which demonstrated improvement in renal function and hematological parameters while being able to discontinue plasma therapy in a majority of treated patients [71,76]. The US Food and Drug Administration (FDA) had granted accelerated approval for the use of eculizumab for the treatment of atypical HUS based on prior review of two of these studies [80]. Of note, in both case series, identification of complement gene mutations were not required, but patients with *ADAMTS13* activity below 5 percent of normal levels, evidence of STEC-HUS, and prior eculizumab treatment were excluded. A subsequent report has demonstrated that the earlier beneficial effects were maintained at a two-year follow-up [81].

The following findings were noted from these two case series:

- In the first case series of 17 pediatric and adult patients who were refractory to plasma therapy, four of five patients who required dialysis at baseline were able to discontinue dialysis therapy while receiving eculizumab and remained off dialysis over the two-year follow-up period. For 10 patients, there was an improvement in renal function with an increase of at least 15 mL/min per 1.73 m^2 in the estimated glomerular filtration rate (eGFR) that was sustained over the two-year follow-up period. Two patients, including one who discontinued eculizumab therapy, progressed to ESRD and began dialysis therapy.

  Normal platelet counts and lactate dehydrogenase levels, indicating thrombotic microangiopathy (TMA) event-free status, were observed in 14, 13, and 15 patients at 26 weeks, 1 year, and 2 years of follow-up, respectively. Thirteen patients were found to have complement mutations or antibodies to complement factor H. At the end of two years, 11 patients remained on eculizumab therapy.

- In the second prospective series of 20 patients who were maintained on plasma therapy, administration of eculizumab was associated with a discontinuation of plasma therapy in all patients, normalization of hematological parameters in 18 of the 20 patients that was maintained at two year follow-up, and improved renal function in three patients (increase of eGFR >15 mL/min per 1.73 m^2). For the two patients who were on dialysis at baseline, there was no improvement, as one remained on dialysis and the other remained on dialysis until undergoing renal transplantation. In addition, another patient required dialysis during a hospitalization for intestinal hemorrhage, and subsequently died. Fourteen patients were found to have complement mutations or antibodies to complement factor H. At the end of two years, 18 patients remained on eculizumab therapy.

- Serious adverse events were reported for all the patients in the first series and 12 of 20 patients in the second series. These complications included hypertension, influenza, peritonitis, asymptomatic bacteriuria, and venous sclerosis at the infusion site. There were no reported cases of meningococcal infection; however, all patients received meningococcal vaccination or prophylactic antibiotic therapy until two weeks after vaccination. (See 'Adverse effects' below.)

Subsequent studies continue to demonstrate the benefits of eculizumab in children and adults with atypical HUS [73,82,83]. Hematologic normalization and recovery of renal function has been observed in the vast majority of patients treated with eculizumab during their first episode and subsequent episodes of HUS including those who have undergone renal transplantation.

Dosing — Eculizumab is administered as an intravenous infusion. Induction dosing of eculizumab is based on patient body weight as follows [84]:

- 5 to <10 kg – 300 mg, one weekly dose
- 10 to <20 kg – 600 mg, one weekly dose
- 20 to <30 kg – 600 mg, two weekly doses
- 30 to <40 kg – 600 mg, two weekly doses
- ≥40 kg – 900 mg, four weekly doses

Maintenance dosing based on patient body weight as follows:

- 5 to <10 kg – 300 mg every three weeks, starting week two
- 10 to <20 kg – 300 mg every two weeks, starting week two
- 20 to <30 kg – 600 mg every two weeks, starting week three
- 30 to <40 kg – 900 mg every two weeks, starting week three
- ≥40 kg – 1200 mg every two weeks, starting week five

Of note, the doses for young children were calculated from a pharmacokinetic model derived from adult data because there are **no** data in children. In some children, the above dosing protocol has not completely blocked complement activation, and in these patients, dosing has been increased. If eculizumab is used in young children, complement activity should be assessed by measuring CH50. (See "Overview and clinical assessment of the complement system", section on 'CH50'.)

The use of functional complement testing has been used to monitor and modify eculizumab therapy [85,86].

Assessment of complement blockade — Monitoring of complement activity is required during eculizumab treatment and available tests include a CH50 and the Wieslab Complement System (an enzyme immunoassay for the qualitative determination of functional classical and alternative complement pathways) [14]. CH50 should be <10 percent for a complete suppression. Using the Wieslab assay in 18 patients, complement activity was completely suppressed one week, two weeks, and three weeks after eculizumab treatment and partially suppressed after four weeks, allowing in some patients to gradually extend the interval between doses up to four weeks based on strict clinical and laboratory control [86]. CH50 cannot be used for patients with complete CFH deficiency. Although not widely available, eculizumab blood levels appear to be the optimal way to monitor the treatment. Levels at 100 mg/mL or over 100 mg/mL markedly reduce CH50 activity while values less than 50 mg/mL do not [3].

Adverse effects — Treatment with eculizumab is associated with life-threatening and fatal meningococcal infections with a reported annual rate of 0.5 percent (see "Treatment and prognosis of paroxysmal nocturnal hemoglobinuria", section on 'Eculizumab'). In a report from the Centers for Disease Control and Prevention (CDC), 16 cases of meningococcal disease were identified in eculizumab recipients in the United States between 2008 and 2016, including patients who had received at least one dose of meningococcal vaccine [87]. (See "Epidemiology of Neisseria meningitidis infection", section on 'Use of eculizumab'.)

As a result, health care providers in the United States are required to enroll in a registration program, certify that they will counsel and provide educational materials to patients about the risks of eculizumab, and agree to promptly report cases of meningococcal infection. Enrollment and additional information are provided by the manufacturer (1-888-765-4747).

Patients should receive vaccinations for *Neisseria meningitis*, and for *S. pneumoniae* and *Haemophilus influenza type b*, as they are at risk of developing serious infections due to these bacterial species. However,

a review by Health Canada reported an increased risk of hemolytic anemia following receipt of the multicomponent meningococcal serogroup B vaccine (Bexsero, MenB-4C) among patients who were already being treated with eculizumab [88]. To minimize the risk of hemolysis, if possible, vaccination should be performed prior to the initiation of eculizumab therapy. In most patients with their initial presentation, this may not be possible. For those patients who are treated with eculizumab, the manufacturer of eculizumab recommends that vaccination should be administered when patients are stable and their disease is well controlled and it is assumed that the blood level of eculizumab is high. (See "Prevention of Haemophilus influenzae type b infection", section on 'Routine childhood immunization in the US' and "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children".)

In addition, prophylactic antibiotic coverage may be given to reduce the risk of Neisseria meningitis B infection, which is not covered by currently available neisserial vaccines. Prevention of meningococcal infection including vaccination and prophylactic antibiotics is discussed separately. (See "Treatment and prevention of meningococcal infection", section on 'Patients receiving eculizumab'.)

Other reported serious adverse events in patients with complement-mediated HUS treated with eculizumab include hypertension, asymptomatic bacteremia, influenza, peritonitis, and venous sclerosis at the infusion site [81].

Discontinuation — Based on observational studies, it appears that eculizumab therapy can be discontinued in some patients who have had a favorable response to therapy. The following data suggest eculizumab therapy can be discontinued in patients who are in complete remission. However, some patients may relapse, so ongoing close monitoring is required so eculizumab therapy can be reinitiated as relapsed patients respond to resumption of therapy.

- In a study of 10 patients in whom eculizumab therapy was discontinued, three patients relapsed within six weeks of stopping treatment [89]. Therapy was resumed immediately, and all three patients fully recovered. The other seven patients remained in remission with no sign of acute disease. In this case series, patients were monitored at home for hemoglobinuria by urine dipstick.

- In the French atypical HUS registry database, eculizumab was discontinued in 38 (9 children and 29 adults) of the 108 patients treated with eculizumab (median treatment duration of 17.5 months) [90]. After a median follow-up of 22 months, 12 patients (31 percent) experienced relapse. In relapsing patients, early reintroduction of eculizumab (within 48 hours) led to rapid hematologic remission and a return of serum creatinine to baseline (median time of 26 days). At last follow-up, renal function remained unchanged in nonrelapsing and relapsing patients compared with baseline values before eculizumab discontinuation. Of note, in this cohort, patients who relapsed after eculizumab discontinuation were more likely to have novel or rare complement gene variants, including *CFH* and *CD46* (membrane cofactor protein) variants.

- In another retrospective study from a single center, eculizumab therapy was discontinued in 15 of 17 adult patients in remission with atypical HUS (mean treatment duration of eculizumab 90.5 days) [91]. Three patients experienced relapse and resumption of therapy in two patients resulted in remission with platelet count and renal function returning to pre-cessation values. The other patients did not have evidence of recurrent disease at the time of last follow-up (median of 309 days). In the original cohort, there were two deaths; one while on eculizumab therapy, and the other after cessation of eculizumab due to malignant hypertension.

- One single case report showed successful discontinuation of eculizumab for a patient with anti-CFH disease [88].

These results are informative in guiding decisions regarding discontinuation of eculizumab. They suggest that discontinuation of eculizumab is possible in many patients who are in complete remission after eculizumab therapy. It appears that the risk of relapse after eculizumab withdrawal differs based on the underlying genetic mutation with higher relapse rates seen in patients with *CFH* and *CD46* mutation [90]. However,

these data also highlight the need for ongoing monitoring so that eculizumab therapy can be reinstituted if there is any evidence of relapse.

Further studies are needed to further define the optimal timing of withdrawal of eculizumab therapy and the patient population in whom therapy can be safely discontinued. Until that data are available, the decision to withdraw eculizumab therapy should be made in conjunction with a clinician with expertise in managing patients with complement-mediated HUS.

Plasma therapy — Plasma therapy was the first-line therapy for patients during the acute episode of atypical HUS before eculizumab was introduced. Although there are no supportive data from clinical trials, most experts in the field advocate plasma exchange (plasmapheresis) rather than plasma infusion as a means to both remove defective mutant proteins and antibodies to CFH, and restore normal functioning complement proteins [7,54]. In addition, plasma exchange avoids the risk of volume overload and hypertension in patients with acute kidney injury.

Empiric plasma therapy was started as soon as possible in any patient in whom noninfectious HUS was suspected while awaiting the results of complement testing and genotyping, as irreversible renal lesions may develop within a few days [4,92,93]. Plasma therapy was continued for a few weeks or even months as it may take a while for completion of complement genotyping. However, only about half of the patients with complement-mediated HUS will respond to plasma therapy with both renal (normal or improved renal function) and complete hematologic recovery (ie, no evidence of hemolysis and a normal platelet count) [6].

In patients who fail to respond, but also in those who have responded to an initial treatment with plasma infusions or plasma exchange, it is recommended to switch to eculizumab. This strategy offers the best chance of complete renal recovery. However, patients who are in full remission and have normal renal function under plasma therapy without catheter complications nor plasma intolerance may remain on this therapy [3].

The response to plasma treatment varies depending upon the affected complement component [7,16].

- Complement factor H (*CFH*) mutations – In patients with *CFH* mutations, plasma therapy results in complete or partial remission in about two-thirds of patients. This has improved outcome with a decrease in mortality, and if initiated early in the course of the disease, preservation of renal function over months and years [94-97]. Those who fail to respond generally progress to ESRD. In addition, resistance to long-term plasma therapy has been reported in patients [98]. Maintenance plasma therapy appears to be superior to intermittent plasma therapy given only during acute episodes of recurrent disease. However, the overall rate of complete renal recovery is only five percent. Because long-term plasmapheresis is expensive and requires central venous access, efforts are underway to develop a purified human plasma-derived CFH concentrate, which can be given in a small volume.

- Antibodies to complement factor H (CFH) – Although data are limited, plasma exchange plus immunosuppressive therapy have been successful measures in some patients with CFH antibodies [45-47,49,55,99]. In contrast, treatment with intravenous immune globulin (IVIG) does not appear to be beneficial [45].

- Complement factor I (*CFI*) mutations – The response to plasma therapy is often inadequate, with only about one-quarter of patients with *CFI* mutations achieving remission.

- CD46 deficiency – Plasma therapy provides no additional benefit in patients with CD46 deficiency, as CD46 is a transmembrane protein, and most of these patients recover fully without plasma therapy [6,30].

- Limited data suggest a positive benefit of plasma therapy in patients with gene mutations of *C3* and thrombomodulin (*THBD*). However, data are insufficient to determine whether plasma therapy is beneficial in patients with gene mutations of complement factor B (*CFB*).

Complications of plasma exchanges include hypotension, catheter-related complications (infection, thrombosis), and anaphylactic reactions to plasma. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Complications".)

Transplantation

Renal transplantation — Patients with mutations in genes for *CFH*, *CFI*, or *C3* who fail to respond to plasma therapy, and/or have relapsing disease are likely to progress to ESRD [16]. In these patients, the outcome of renal transplantation is poor because recurrence of disease occurs in 50 percent of the transplanted kidneys, and graft failure occurs in 90 percent of those with recurrent disease [7,16,100-102].

In contrast, limited data suggest a favorable outcome of renal transplantation in patients with mutations of *CD46* or in those with disease due to antibodies to factor H, provided the autoantibodies to CFH are absent at the time of transplantation [33,34,99,100].

The variable prognosis emphasizes that all patients with HUS prior to transplantation should undergo complement genotyping to determine whether or not there is an underlying gene mutation. The above data suggest that renal transplantation alone without preventive therapy (eg, eculizumab therapy) is not an option for patients with HUS due to mutations of *CFH*, *CFI*, or *C3* [7]. In particular, living-related donor transplantation is not recommended unless genetic testing has been performed to ensure that the same mutation is not present in the potential living donor [103,104]. In our practice, a living-related transplantation is only performed if both the donor and the recipient have given informed consent, if the recipient has a mutation with a high risk of recurrence that is absent in the donor, and if eculizumab therapy is administered to the recipient at the time of and after transplantation to reduce the risk of disease recurrence.

Preventive therapy — Preventive therapy to reduce the risk of recurrent disease includes eculizumab and plasma therapy. (See "Recurrent and de novo HUS after renal transplantation", section on 'Prevention of recurrent HUS'.)

Patients with a low risk of recurrence do not need a preventive treatment. These include those with isolated membrane cofactor protein or *DGKE* mutations and patients with anti-complement factor H antibodies in whom the level of antibodies decreased to a negative level long-term. (See 'Complement antibodies' above.)

Eculizumab — Eculizumab therapy is our preferred intervention to prevent recurrent disease in renal transplant recipients with an identified mutation in *CFH*, *CFI*, *C3*, or *CFB*, or in those with a previous post-transplant episode of recurrent disease [67,82,103,105-107]. Eculizumab may also be an option for patients with a moderate risk of recurrence. However, as noted above, this therapy may not be available in some settings because of the prohibitive cost of eculizumab. Another alternative in patients with complement autoantibodies is the addition of rituximab therapy to the immunosuppressive regimen, which was used successfully in one case report of a patient with CFH antibodies and deletion of *CFHR1* and *CFHR3* genes [108]. The optimal duration of eculizumab therapy remains unknown, but in our practice we continue long-term eculizumab therapy in high-risk patients for disease recurrence throughout the lifespan of the allograft unless combined liver-kidney transplantation is undertaken. (See 'Combined liver-renal transplantation' below.)

Plasma therapy — If plasma therapy is used to prevent recurrent disease, the first exchange is performed a few hours prior to transplantation. After transplantation, plasma therapy is initially performed daily followed by decreasing frequency [109]. However, prophylactic plasma therapy may fail to prevent recurrence and may mask clinical signs of recurrence [102].

Recurrent disease — Eculizumab has been shown to be beneficial in patients with post-transplant recurrent disease [66,70,71,82,103,110-112]. In contrast, plasma therapy has failed to improve graft survival in renal transplant recipients with recurrent disease. (See "Recurrent and de novo HUS after renal transplantation", section on 'Treatment'.)

Combined liver-renal transplantation — Liver transplantation may be a curative intervention for severe complement-mediated HUS for patients with mutations of *CFH*, *CFI*, *CFB*, and *C3*, which are proteins that are synthesized in the liver. In addition, combined liver-renal transplantations have been proposed in patients with ESRD in whom there is a high likelihood of recurrent disease [109]. However, data are limited regarding patient outcome. A 2014 review reported 25 patients with complement-mediated HUS underwent combined liver-renal transplantation [113]. All five children who did not have a preparative regimen for complement regulation (eg, plasma therapy or eculizumab) suffered fatal complications, presumably due to uncontrolled complement activation. In the remaining 20 cases that were performed with either or both plasma therapy or eculizumab administration, transplantation was successful in 16 patients. There were three deaths, and in one patient, liver transplantation was successful, but the renal transplant never gained function. Of this group of 20 patients, 16 had *CFH* mutations (14 successful outcomes), 1 with *CFB* mutation (successful), 1 with *C3* mutation (unsuccessful), and 2 with *CFH*/*CFHR1* hybrid mutations (one successful).

The decision of combined liver-renal transplantation to definitively cure the disease is based on an evaluation that carefully weighs the risks and benefits for the individual patient. It should only be performed in pediatric centers with expertise in solid combined organ transplantation and with provision of preparative measures to control complement activation. The decision to perform combined liver-renal transplantation should be taken on a case-by-case basis, after discussion with the patient and families, taking into account the benefits and risks of each option and the cost of the long-term eculizumab treatment. In patients with high risk of recurrence and preserved renal function, isolated liver transplantation may be an option.

SUMMARY AND RECOMMENDATIONS — Hemolytic uremic syndrome (HUS) is defined by the concurrent characteristic triad of HUS: microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. The most common cause of HUS is due to Shiga toxin-producing *Escherichia coli* (STEC). Complement-mediated HUS accounts for most of the non-STEC-HUS.

- Complement-mediated HUS is a relatively rare disorder, with an estimated prevalence of seven per one million children in Europe. Most complement-mediated HUS cases are due to gene mutations of complement factors, although acquired complement dysregulation due to antibodies to complement proteins occurs in 6 to 10 percent of patients with complement-mediated HUS. (See 'Epidemiology' above.)

- The complement proteins associated with complement-mediated HUS are components of the alternative complement pathway. They include complement factors H, I, and B (CFH, CFI, and CFB), C3, CD46 (previously known as membrane cofactor protein [MCP]), and thrombomodulin (THBD). (See 'Genetic complement disorders' above and 'Genetic mutations' above and 'Complement antibodies' above.)

- The proposed pathogenesis of complement-mediated HUS is that a trigger (eg, infection) causes uninhibited continuous activation of the alternative complement pathway in a susceptible individual with either gene mutations or antibodies to complement proteins. This results in renal endothelial damage leading to thrombotic microangiopathy. (See 'Pathogenesis' above.)

- In addition to the clinical triad of HUS (microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury), patients with complement-mediated HUS typically will have a history of a triggering antecedent event (eg, upper respiratory infection or diarrheal illness). There is often a positive family history, and/or a history of a previous episode. Severe hypertension is a common clinical finding. (See 'Clinical manifestations' above.)

- The clinical course and outcome vary depending on the affected complement component. (See 'Clinical course and outcome' above.)

    - Patients with *CFH* mutations generally have a poor prognosis with most patients progressing to end-stage renal disease (ESRD) or death within the first year of presentation. (See 'Factor H mutations' above.)

- In contrast, patients with mutations of *CD46* do not usually progress to ESRD, although relapse is common. (See 'CD46 mutations' above.)

- Patients with *CFI* mutations have an intermediate course between those with *CFH* and *CD46* mutations, with one-half of patients progressing to ESRD or death within two years of presentation. (See 'Factor I mutations' above.)

- The diagnosis of complement-mediated HUS is based on the clinical presentation of the classical triad findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, and demonstration of complement dysregulation, either due to gene mutations of complement proteins or antibodies to complement factors. Laboratories that offer complement genotyping for atypical HUS can be found from the National Center for Biotechnology Information website. (See 'Diagnosis' above.)

- The differential diagnosis of complement-mediated HUS includes other forms of HUS (eg, STEC-HUS), thrombotic thrombocytopenic purpura (TTP), and inborn errors of vitamin B12. (See 'Differential diagnosis' above.)

- The diagnostic evaluation consists of laboratory studies that differentiate complement-mediated HUS from other conditions that have similar presentations. This includes screening for STEC, cultures of blood and other pertinent bodily fluids (eg, cerebral spinal fluid, urine, or sputum), *ADAMTS13* function, or renal biopsy. (See 'Evaluation' above and "Overview of hemolytic uremic syndrome in children", section on 'Evaluation' and "Approach to the patient with suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

- The initial management of atypical HUS is supportive and similar to the approach used for STEC-HUS. (See 'Supportive care' above and "Treatment and prognosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children", section on 'Supportive therapy'.)

- We recommend the use of eculizumab, a humanized monoclonal antibody to C5, in patients with severe complement-mediated HUS who are at risk for death or ESRD (eg, patients with *CFH* mutations) (**Grade 1B**). However, eculizumab therapy is expensive and may not be available to patients because of its prohibitive cost. In these patients with severe disease, we suggest plasma therapy as an alternative option (**Grade 2B**). (See 'Complement blockade: Eculizumab' above and 'Plasma therapy' above.)

- In patients with ESRD, we recommend renal transplantation from a nonrelated donor (**Grade 2B**). Prior to transplantation, patients should undergo complement genotyping to determine whether or not there is an underlying gene mutation. Living-related donor transplantation is not recommended **unless** genetic testing has been performed to ensure that the same mutation is not present in the potential living donor. (See 'Renal transplantation' above.)

- We recommend prophylactic administration of eculizumab to prevent recurrent disease in the allograft for renal transplant recipients who are at risk for recurrent disease in the allograft (**Grade 1B**). These include patients with an identified mutation in *CFH*, *CFI*, *C3*, or *CFB*, those with high titers of CFH antibodies, or in those with a previous post-transplant episode of recurrent disease. However, eculizumab therapy is expensive and may not be available to patients because of its prohibitive cost. In these patients at risk allograft failure due to recurrent disease, we suggest plasma therapy as an alternative option (**Grade 2B**).

- Combined liver-renal transplantation provides a definitive cure for complement-mediated HUS with mutations of *CFH*, *CFI*, *CFB*, and *C3*. However, this procedure carries a significant risk of death in the postoperative period. It should only be performed in pediatric centers with expertise in solid combined organ transplantation and after careful consideration of the risks and benefits for the individual patient. (See 'Combined liver-renal transplantation' above.)

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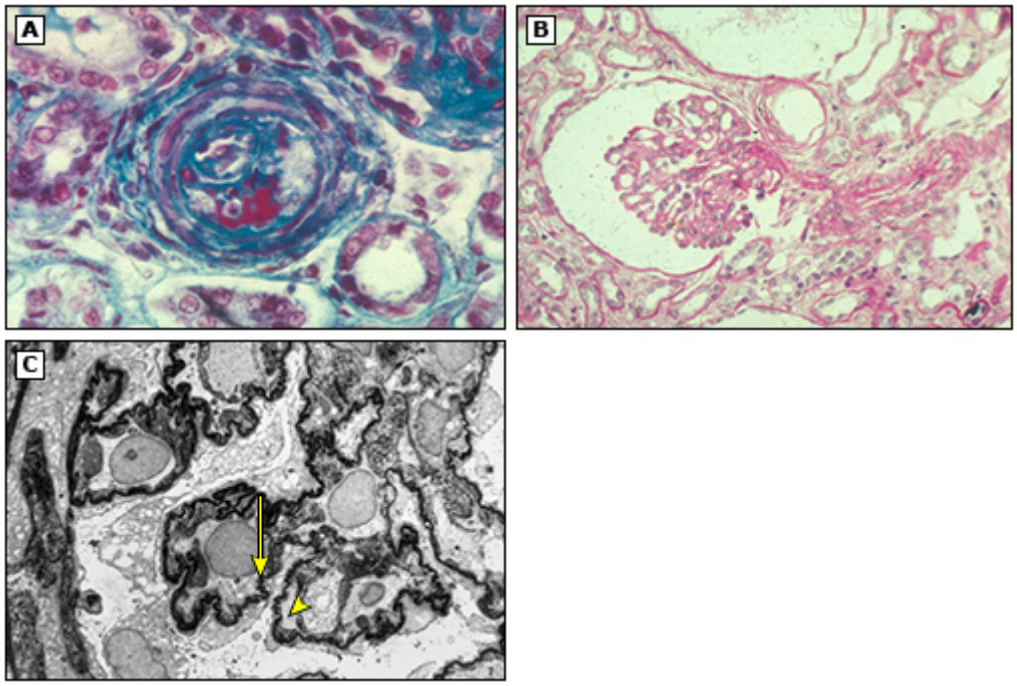
Topic 6084 Version 54.0

GRAPHICS

Arterial thrombotic microangiopathy in hemolytic uremic syndrome



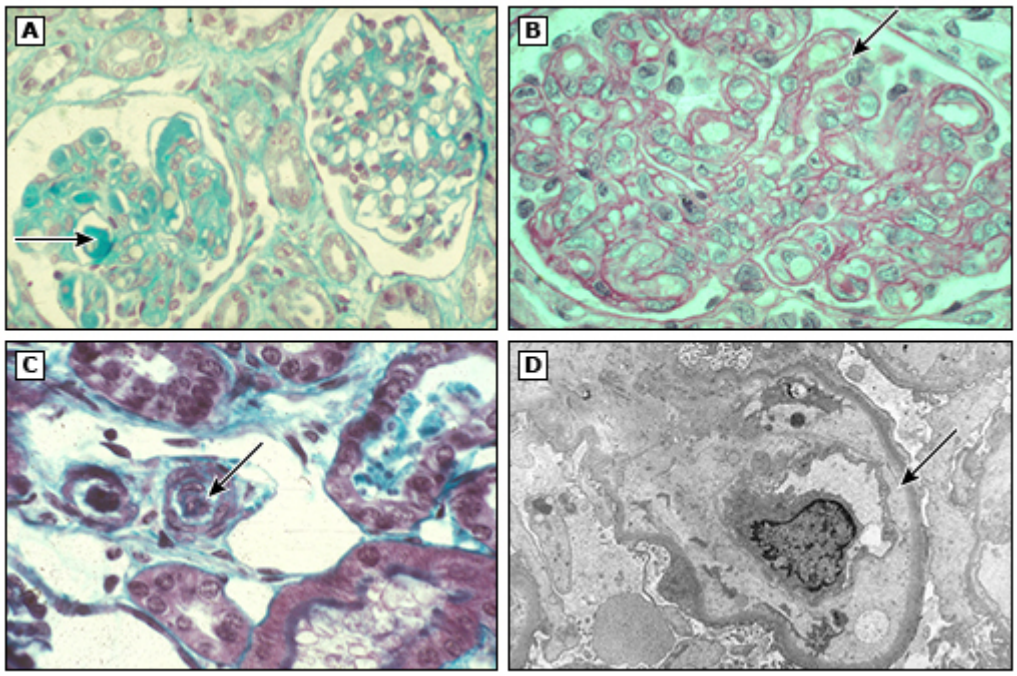
Panel A shows endothelial swelling, narrowing of the lumen, and intraluminal thrombus of an afferent arteriole. Panel B demonstrates shrunken and ischemic glomeruli. Panel C is an electron micrograph showing splitting of the capillary wall (arrowhead) and wrinkling of the glomerular basement membrane (arrow).

HUS: hemolytic uremic syndrome.

Courtesy of MC Gubler, MD.

Graphic 90803 Version 1.0

Glomerular thrombotic microangiopathy in hemolytic uremic syndrome



Histopathology of a patient with hemolytic uremic syndrome. Panel A demonstrates fibrin deposition in the glomerular capillaries (arrow). Panel B shows narrowing of the glomerular arteriole due to widening of the subendothelial space (arrow). Panel C demonstrates double contour appearance of glomerular capillary wall and widening of the subendothelial space (arrow). Panel D is an electron micrograph showing swollen endothelial cells.

HUS: hemolytic uremic syndrome.

Courtesy of MC Gubler, MD.

Graphic 90801 Version 1.0

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