Management of hemolytic uremic syndrome

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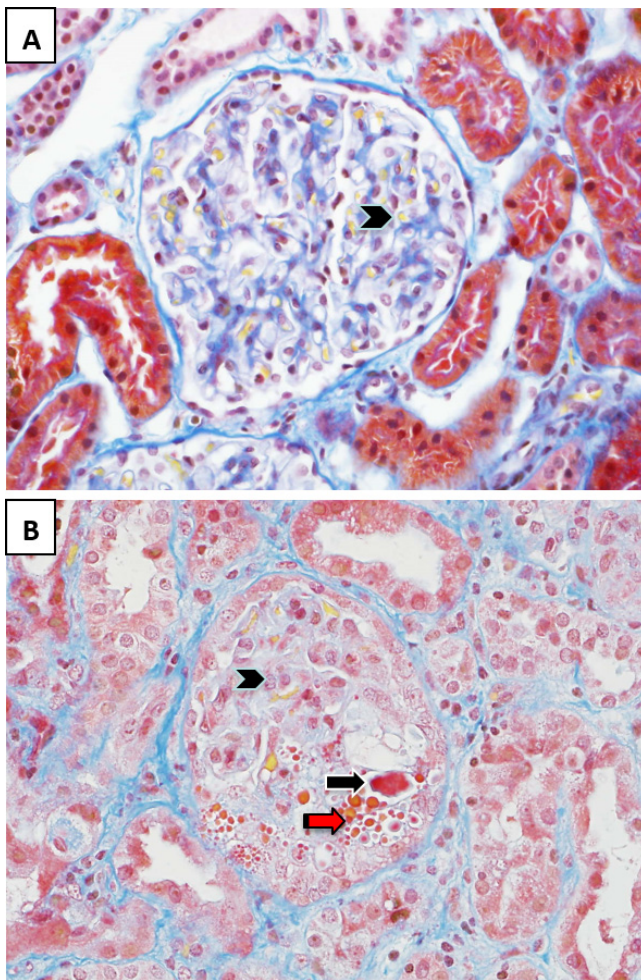
Abstract

Hemolytic uremic syndrome (HUS) is a disease characterized by hemolysis, thrombocytopenia, and acute kidney injury, although other organs may be involved. Most cases are due to infection with Shiga toxin-producing *Escherichia coli* (STEC). Early identification and initiation of best supportive care, with microbiological input to identify the pathogen, result in a favorable outcome in most patients. The remaining 10% of HUS cases are classed together as atypical HUS and have a diverse etiology. The majority are due to inherited or acquired abnormalities that lead to a failure to control complement activation. Atypical HUS occurring in other situations (for example, related to pregnancy or kidney transplantation) may also involve excessive complement activation. Plasma therapies can reverse defective complement control, and it is now possible to specifically target complement activation. This has led to improved outcomes in patients with atypical forms of HUS. We will review our current understanding of the pathogenesis of HUS and how this has led to advances in patient care.

Introduction

The thrombotic microangiopathies (TMAs) are a group of diseases that are characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and the occlusion of small vessels by thrombi (Figure 1). Endothelial injury and an inability to control coagulation are common features of all of these diseases. The clinical manifestations of a TMA depend on the site of vascular involvement and, on the basis of clinical presentation, were classically divided into two main types: HUS and thrombotic thrombocytopenic purpura (TTP). HUS typically affects the microvasculature of the kidney causing acute kidney injury (AKI), whereas in TTP neurological disease is more common. However, it is clear that disease classification based purely on clinical presentation can be misleading, as HUS can cause neurological disease (as well as affecting many other organs) and TTP can affect the kidney. In addition, it is clear that HUS does not represent a single disease with a common pathogenesis. Instead, HUS is a group of diseases that are due to different environmental or genetic factors and that have a similar clinical presentation.

As our understanding of the molecular basis of these diseases increases, it is now possible to classify HUS and TTP on the basis of etiology. Most cases of HUS follow infection with Shiga toxin-producing enteric pathogens or excessive activation of the complement system. TTP is due to diminished activity of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme responsible for the breakdown of multimeric von Willebrand factor, a pro-thrombotic protein produced by the endothelium, megakaryocytes, and vascular connective tissue [1]. It is evident that a disruption of endothelium function is common to all TMAs and therefore it is possible that there are links between the pathways that lead to specific diseases.

Differentiating between types of TMA on the basis of clinical parameters is a vital part of patient care. However, this is not always possible, and diagnostic accuracy requires identification of the underlying abnormality. Accurate and early diagnosis is increasingly

Figure 1. Glomerular pathology in hemolytic uremic syndrome

(A) In the normal glomerulus, patent capillary lumina containing erythrocytes stain yellow (arrowhead). (B) In hemolytic uremic syndrome, the glomerular capillary loops contain fibrin thrombi and microthrombi that stain bright red (black arrow). There is endothelial cell swelling with obliteration of some of the capillary lumina (arrowhead) and red cell fragmentation (red arrow). Stain: Martius scarlet blue trichrome; magnification: 400×.

important as new treatments become available that are specific for different types of TMA and with increasing evidence that early initiation of treatment improves patient outcomes. This review will discuss the pathogenic mechanisms that cause the different types of HUS, clinical and laboratory diagnosis of HUS, and the available treatment options.

Pathogenesis of hemolytic uremic syndrome

Although HUS is primarily a disease of the kidney, neurological involvement is common, potentially life-threatening, and an important determinant of mortality [2]. The incidence of HUS, usually as a consequence of infection, is higher in children; The overall incidence in the general population, including adults, is approximately 1 to 2 in 100,000 [3,4]. It can cause dialysis-requiring AKI, severe multi-organ failure, and death (<5%); however, in most cases, complete recovery occurs (75%), and the remaining patients have a reduced glomerular filtration rate, hypertension, or proteinuria [5]. Neurological involvement can present with irritability, confusion, focal deficit, seizures, or coma, and involvement of the heart, gastrointestinal tract, and pancreas has been described.

Most cases of HUS (90%) occur following infection with STEC, typically serotype O157. Other serotypes of *Escherichia coli* can produce toxin, and the largest recorded outbreak of STEC HUS occurred in Northern Europe in 2011 because of infection with serotype O104 [6]. Infection is acquired by ingestion of contaminated food and is followed about 3 days later, although not invariably [7], by abdominal pain and diarrhea that progresses to a colitic illness with bloody diarrhea (hence its previous name: diarrhea-positive HUS). Features of TMA and AKI develop over the following 3 to 4 days in 5% to 15% of patients with STEC infection [8]. Why only a small proportion of patients develop HUS following infection is not known. A genetic predisposition, perhaps involving genes associated with other forms of TMA, is possible, and complement gene mutations have been described in patients with STEC HUS and may predispose them to a poor outcome [9].

Pathogenic STEC strains express adhesins, which are thought to promote adherence to the intestinal epithelium following which there is translocation of toxin (usually Shiga toxin type 2) through the epithelium. It has been proposed that the toxin could then bind to circulating leukocytes [10–12], although the evidence for this is conflicting [13]. The Shiga toxin receptor is a glycosphingolipid: globotriaosylceramide (Gb3). When Shiga toxin binds Gb3, the complex is internalized and transported to the endoplasmic reticulum, where the complex is cleaved to release a protease into the cytoplasm. This protease inhibits ribosomal function and protein synthesis, leading to cell death. It can also activate signaling pathways, inducing an inflammatory response in affected cells [14]. Although Gb3 is found in other organs, the kidney is most susceptible to injury. This may be due to higher levels of Gb3 on renal cells, particularly the glomerular endothelium (but also podocytes, mesangial, and tubular epithelial cells [15]), the high blood flow to the kidney, or a greater susceptibility of renal cells to the effects of the toxin [16]. The expression of Gb3 at other sites (for example, within the central nervous system) explains the extra-renal manifestations of STEC HUS.

Atypical hemolytic uremic syndrome

Atypical HUS (aHUS) accounts for most of the remaining 10% of cases of HUS. With aHUS, as with STEC HUS, the kidneys are most frequently involved, but any organ can be affected. It is difficult to distinguish aHUS from STEC HUS or TTP on clinical grounds alone. A diagnosis of aHUS should be considered once STEC infection or reduced ADAMTS13 activity has been excluded. Although it is more common in childhood, aHUS can occur at any age and has a worse prognosis than STEC HUS, with a 3-year patient or kidney survival of 50% [17].

Genetic or acquired defects in control of complement activation are commonly found in patients with aHUS. Complement is a complex system of enzymes, effector proteins, and inhibitors and forms part of the innate immune system. Low levels of circulating complement protein C3, suggestive of consumption, were first described in 1973 [18]. Twenty-five years later, loss-of-function mutations in the complement regulatory protein complement factor H (CFH) were described [19]. Since that first report, loss-of-function mutations in other complement regulators (complement factor I [20] and membrane cofactor protein (CD46) [21]) or gain-of-function mutations in complement activators (C3 [22] and complement factor B [23]), gene rearrangement in CFH and its related proteins [24], autoantibodies affecting regulator function [25–27], and "at risk" haplotypes [28,29] have been described in patients with aHUS. An abnormality in complement control can be identified in approximately 65% of patients with HUS and is also described in other glomerular [30–32] and non-renal [33] diseases. aHUS is usually inherited as an autosomal dominant trait, and there is incomplete penetrance with approximately 50% of people with a mutation developing disease [34]. The incomplete penetrance may be explained by the need for an environmental trigger, which can include pregnancy [35], infection (including a diarrheal illness which can occur in 23% of patients [36]), or drugs [37]. The presence of more than one mutation or susceptible haplotype may also increase the risk of disease [36]. Complement activation, primarily via the alternative pathway, leads to endothelial damage and activation, leading to small-vessel thrombosis in target organs (Figure 2).

Not all cases of aHUS are due to defects in proteins traditionally regarded as important in complement control. Genetic variants in thrombomodulin, a protein with anti-fibrinolytic and anti-inflammatory properties, have been associated with aHUS [38,39]. Thrombomodulin also accelerates the factor I-mediated cleavage of C3b, and loss of this effect may predispose to aHUS [38]. However, these variants can occur in the general population and may occur in combination with other disease-associated mutations [39,40]. In early childhood, recessive mutations in diacylglycerol kinase epsilon (DGKE) cause an HUS-like TMA that frequently progresses to renal failure [41,42]. How DGKE mutations cause TMA is not known, but defective DGKE signaling appears to promote a pro-thrombotic state.

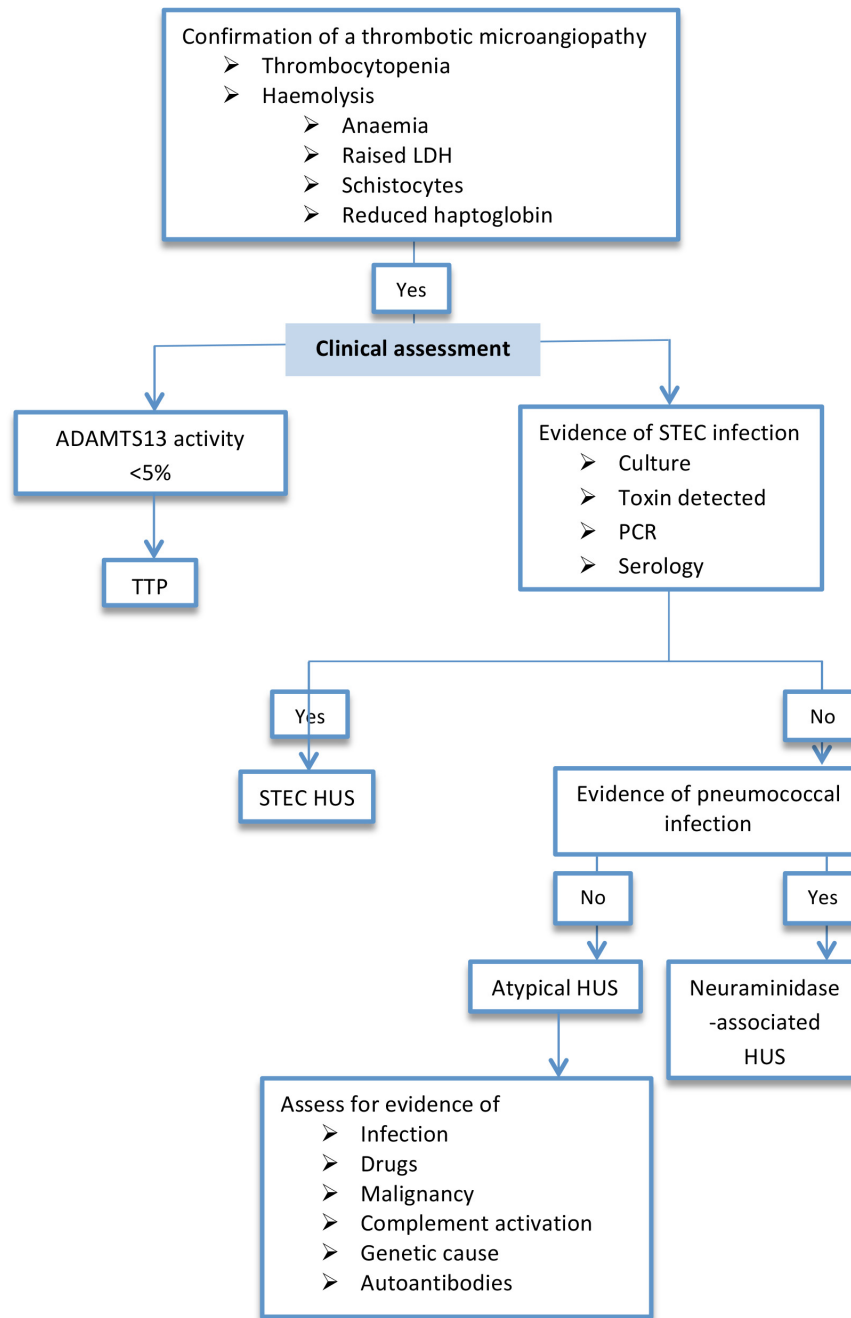## Other forms of hemolytic uremic syndrome

Thrombotic microangiopathic diseases with clinical, hematological, and histological features of HUS can occur in response to other triggers. Infection with neuraminidase-producing *Streptococcus pneumoniae* account for 5% of childhood HUS, inducing a severe TMA with high mortality [43]. One hypothesis for the link between infection and HUS is that neuraminidase strips N-acetylneuraminic acid from the glycocalyx of cells exposing epitopes on endothelial cells, erythrocytes, and platelets that are recognized by naturally occurring antibodies, leading to a pro-thrombotic state. Treatment is supportive with eradication of Streptococcal infection.

An autosomal recessive defect in vitamin B12 metabolism leads in early childhood to severe TMA, which can be controlled with daily vitamin B12 treatment [44,45]. The use of quinine is associated with a TMA [46,47] as are other drugs, in particular calcineurin inhibitors [48,49]. Infections (for example, HIV [50] and malignancy or its treatment [51]) are also associated with TMA and renal involvement. In some of these cases, particularly those related to pregnancy, the association may reflect a triggering event in patients carrying a genetic defect in complement control. In a series of patients with pregnancy-induced HUS, over 80% had a complement gene mutation [35].

Diagnosis and treatment of patients with STEC hemolytic uremic syndrome

A diagnosis of STEC HUS should be considered in any patient developing a TMA, particularly if it follows a diarrheal illness and is associated with AKI. However, atypical forms of HUS also may be associated with diarrhea and therefore STEC infection should be confirmed (Figure 3). Stool samples should be sent for STEC culture, but this may be negative, particularly if sample collection is delayed [52]. Diarrhea may have stopped by the time of presentation, but STEC can still be cultured from feces or rectal swab. Samples should also be assessed for the presence of Shiga toxin [53]. Shiga toxin can be detected directly from feces, but the results are variable [54], and this is best performed after overnight culture. Polymerase chain reaction-based assays can be used to detect STEC Shiga toxin genes [55]. Serology can also be useful indicator of STEC infection [56].
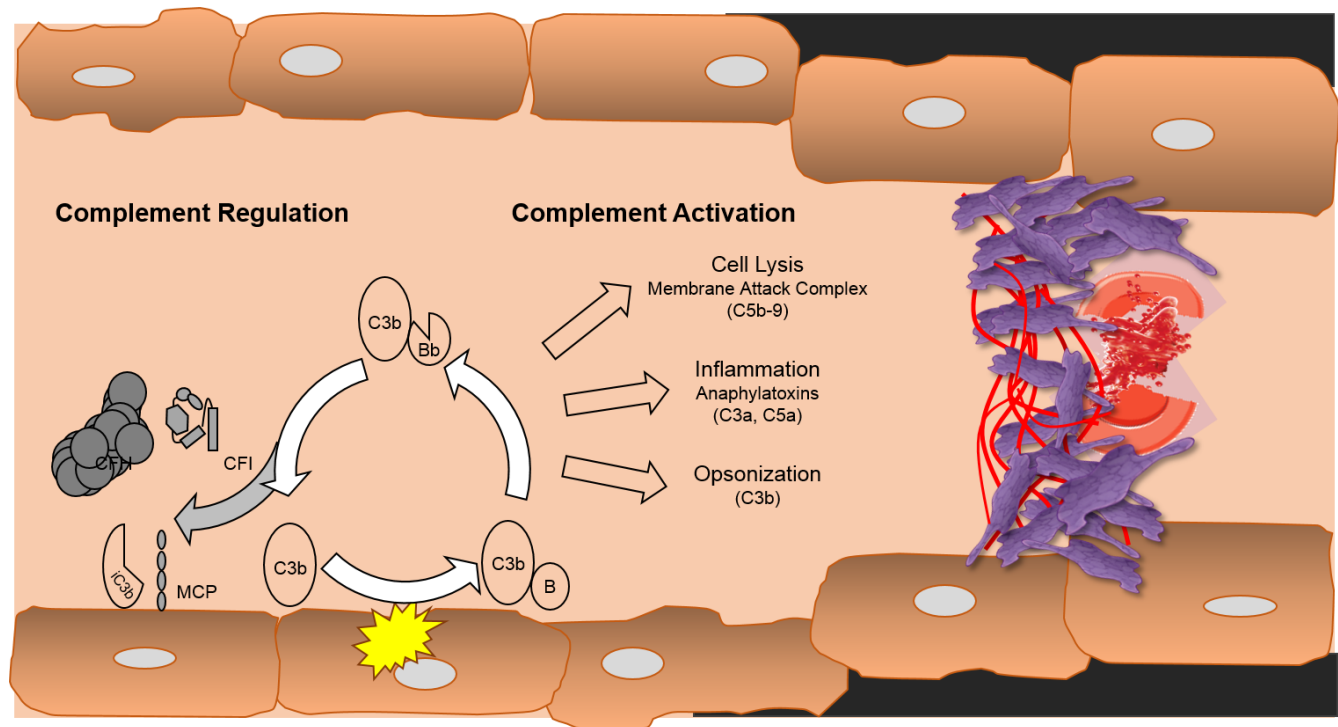
Figure 2. Algorithm for the diagnosis of the main types of thrombotic microangiopathy

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; STEC, Shiga toxin-producing *Escherichia coli*; TTP, thrombotic thrombocytopenic purpura.

Best supportive care (BSC), with particular attention to fluid replacement, renal support, and treatment of neurological manifestations of the disease, is the mainstay of treatment for patients with HUS [57,58]. The improved survival in patients with STEC HUS in recent years probably reflects better supportive care. Evidence for the addition of plasma-based therapy to BSC for the treatment for STEC HUS is limited and it probably has no role [59,60]. There was a report from the 1990s suggesting a reduced mortality in older patients treated

Figure 3. Complement activation in atypical hemolytic uremic syndrome

The complement system, through the alternative pathway, is in a state of continuous low-level activation with generation of a fluid phase C3 convertase (C3H$_2$OBb). This generates the fragment of C3, C3b, which can bind to cell membranes, which leads to cell-bound C3 convertase. If unchecked, this process leads to rapid amplification of complement activation and generation of the effector proteins of the system: C5b-9, C3a, C5a, and more C3b. To prevent this, there are cell surface (or membrane co-factor protein [MCP]) and fluid phase—complement factor H and complement factor I (CFI)—inhibitors of complement activation. Failure to adequately control activation leads to endothelial injury, with thrombus formation, red cell fragmentation, and platelet consumption.

with plasma exchange [61]. However, several studies have found no benefit or worse outcomes following treatment with plasma therapies [59,60], including a prospective study of 619 children [62] and analysis of outcomes from the German outbreak [63,64].

The use of antibiotics is controversial. It is recommended not to use antibiotics to treat STEC infection (*E. coli* O157) because of either no benefit or potential increase in the risk of developing HUS [65–68]. There is evidence that antibiotic use leads to an increase in toxin production [69] or release [70]. A study from Japan reported a lower rate of HUS in patients with STEC infection treated with fosfomycin [71]. However, this was evident only on subgroup analysis of the fosfomycin-treated cohort, and patients in the control cohort may have received other antibiotics. A beneficial effect of fosfomycin is therefore unproven. A subsequent meta-analysis failed to show a harmful or beneficial effect of antibiotics but included the subgroup analysis from the Japanese study [72,73]. Data from the 2011 German outbreak with *E. coli* O104 support the use of antibiotics in patients with established STEC

HUS, with a reduction in seizures, deaths, and requirement for abdominal surgery when combined antibiotics were used [63]. Antibiotics also eliminate STEC from the gut more rapidly [74] but will have no effect on the individual patient. It may be that the results from the German outbreak due to *E. coli* O104 may not be generalizable to infections with other serotypes as *E. coli* O104, in contrast to O157, does not release increased quantities of Shiga toxin in response to therapeutic concentrations of antibiotics [75].

There is evidence from a pre-clinical rodent model of Shiga toxin-mediated injury that complement activation may augment the effects of the toxin on cells [76,77], although no evidence of complement activation was seen in a primate model [78]. There is also evidence of complement activation in the circulation of patients with STEC HUS [79], and a report of three children with severe neurological involvement suggested a response to treatment with the anti-C5 monoclonal antibody, eculizumab [80]. Eculizumab was used extensively during the German outbreak with no reported benefit

in an analysis of 67 patients [63]. The rate of resolution of disease was equivalent in eculizumab-treated and untreated case controls. A report in 2014 of nine cases of STEC O104 HUS in France suggested a benefit with eculizumab. However, in that report, unlike the report from Germany, there were no control cases [81]. The use of eculizumab in STEC HUS requires further evaluation before its use can be recommended.

Several other treatments for STEC HUS, including oral administration of Shiga toxin-binding agents [82], corticosteroids, anti-platelet agents, and heparin, have been suggested but have not proven beneficial [58]. Although other treatments have been associated with good outcomes, it is difficult to assess their benefit in a disease that in most cases is self-limiting. These treatments include immunoadsorption to treat an immunoglobulin-mediated component of the neurological disease [83] and recombinant thrombomodulin [84,85].

Diagnosis and treatment of patients with atypical hemolytic uremic syndrome

aHUS should be considered in any patient presenting with a TMA, particularly if the preceding history does not suggest STEC infection. Clinical features may suggest a diagnosis of aHUS but alone are insufficient to confidently diagnose aHUS. Evidence of STEC infection should be sought, and reduced ADAMTS13 activity should be excluded [86]. Serum levels of C3, C4, factor H, and factor I should be measured before plasma exchange is started. Low C3 concentrations suggest but are not diagnostic of aHUS [87]. Genetic screening and testing for autoantibodies should be performed on all suspected cases. Though important to elucidate the cause of aHUS, these tests take time and do not form part of the initial diagnostic algorithm.

Plasma exchange (PE) until recently has been considered the most effective treatment [88,89]. PE replaces functionally defective proteins and removes overactive proteins. It is also the treatment for TTP and therefore is appropriate while laboratory investigations are being performed to differentiate between aHUS and TTP. PE should be started as soon as the diagnosis is suspected, replacing 1 to 2 plasma volumes in adults and 50 to 100 mL/kg in children with each treatment. The volume exchanged and the frequency of treatments should be increased until the TMA is controlled. In those patients who respond, PE can be gradually withdrawn, although a significant proportion will require continued PE to maintain remission.

The effective use of eculizumab in aHUS was first described in 2009 [90], and since then there have been many reports of its use [91–94]. Two trials of eculizumab

in adolescents and adults with plasma therapy-resistant or -dependent aHUS have recently been reported. In total, 37 patients were treated in these open-label, uncontrolled trials. Eculizumab was effective in more than 80% of patients, controlling hemolysis, improving renal function, and allowing the withdrawal of plasma therapy [95]. Treatment of aHUS should be started early (as soon as other causes of TMA have been excluded on the basis of clinical and laboratory assessment) since early treatment is associated with a better renal outcome [96]. There are still unanswered questions about eculizumab treatment of aHUS, in particular how long to continue treatment. Withdrawal of eculizumab is associated with relapse, but it can be withdrawn in some patients, with a recent report describing successful withdrawal in 7 out of 10 patients [97]. Because of the risk of *Neisseria meningitides* infection, all patients receiving eculizumab should be vaccinated and long-term antibiotics should be considered [98].

The rationale for anti-complement treatment in patients without a defined defect in complement control or with a non-complement mutation is less clear. Nevertheless, patients without an identified mutation responded similarly to treatment with eculizumab [95], which may reflect a role for complement in the development of aHUS, even if the causative mutation lies outside the complement system. There are also links between thrombomodulin and complement activation. The exception is patients with DGKE mutations who appear resistant to treatment targeting complement activation [41].

Transplantation in patients with hemolytic uremic syndrome

Although STEC frequently causes AKI, recovery of renal function usually occurs. Recovery of function may not be complete, and in some cases maintenance dialysis is required. In these cases, transplantation is possible provided that there is no coexisting defect in complement control [9]. In contrast, aHUS frequently recurs after transplantation. Overall, 60% of patients develop recurrent disease after transplantation, 90% of whom will lose their graft [99]. The risk of recurrence depends on the underlying abnormality, with high risk in patients with factor H, C3, and B mutations but lower risk with CD46 mutations or if no abnormality is detected [99–101]. Recurrent disease after transplantation can be treated successfully with eculizumab, and 40% of patients in the recent trails developed disease in a transplanted kidney [95,102]. Eculizumab can also be used prophylactically to prevent recurrence in patients at high risk of recurrence who are undergoing transplantation [96].

As most complement proteins are synthesized in the liver (with the exception of CD46), combined liver and kidney

transplantation reverses the complement abnormality, controls disease, and allows successful kidney transplantation [103,104]. Initial outcomes of combined transplantation were poor [105]. Aggressive plasma exchange or eculizumab to correct the complement abnormality prior to transplantation allows successful transplantation and this option should be discussed with patients [106].

If the predisposing mutation occurs in other pathways, aHUS can recur after transplantation. Recurrence after transplantation has been reported in patients with thrombomodulin mutations [38,107]. Transplantation has been performed in patients with aHUS due to DGKE mutations without evidence of recurrent aHUS [41].

The etiology of *de novo* HUS after transplantation is complex, and ischemia reperfusion, drugs, and humoral immunity are potential precipitants. Complement may also be involved. Thirty percent of patients who develop *de novo* HUS have a complement mutation [108], and even in the absence of a mutation eculizumab can be effective [109].

Conclusions

Most commonly, HUS is due to STEC infection. This can be a severe, life-threatening disease but in most cases is self-limiting and will resolve completely. Treatment is with BSC, and although other treatments, including plasma therapy, eculizumab, and toxin binders, have been proposed, there is very little evidence to support their use outside of clinical trials. aHUS is, in most cases, due to impaired control of complement activation. It can be treated effectively with complement inhibition, but this may not be successful if treatment is started late or the disease is caused by a problem in another pathway.

Undoubtedly, progress has been made in the treatment of HUS. However, there are very few high-quality clinical trials to guide treatment. HUS is a rare, etiologically heterogeneous disease and there is a need for multi-center collaborative studies to test the efficacy of new treatments and inform best practice in the treatment of this disease.

Abbreviations

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; BSC, best supportive care; CFH, complement factor H; DGKE, diacylglycerol kinase epsilon; Gb3, globotriaosyl-ceramide; HUS, hemolytic uremic syndrome; PE, plasma exchange; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Disclosures

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