Atypical haemolytic uraemic syndrome

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The haemolytic uraemic syndrome (HUS) is characterized by the triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute renal failure. HUS may be classified as either diarrhoeal-associated or non-diarrhoeal/atypical (aHUS). aHUS has recently been shown to be a disease of complement dysregulation, with 50% of cases involving the complement regulatory genes, factor H (CFH), membrane cofactor protein (MCP; CD46), and factor I (IF). However, incomplete penetrance of mutations in each of these genes is reported. This suggests that a precipitating event or trigger is required to unmask the complement regulatory deficiency. The reported precipitating events predominantly cause endothelial injury. Discovery of these mutations has revealed important genotype–phenotype correlations. MCP-HUS has a better prognosis and a better outcome after transplantation than either CFH-HUS or IF-HUS.

Keywords: atypical haemolytic uraemic syndrome (aHUS); complement factor H (CFH); membrane cofactor protein (MCP; CD46); factor I (IF); renal transplantation; thrombotic thrombocytopenic purpura (TTP)
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**Table 1** Conditions predisposing to atypical haemolytic uraemic syndrome (aHUS)

<table>
<thead>
<tr>
<th>Complement regulatory defects</th>
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<tr>
<td>Factor H mutations</td>
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<tr>
<td>Factor I mutations</td>
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<td>MCP mutations</td>
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<tr>
<td>Autoantibodies to factor H</td>
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<tr>
<td>Bacterial</td>
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<tr>
<td><em>Streptococcus Pneumoniae</em></td>
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<tr>
<td>Viruses</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Chemotherapy (e.g. mitomycin C, gemcitabine, cisplatin, bleomycin)</td>
</tr>
<tr>
<td>Quinine</td>
</tr>
<tr>
<td>Immunosuppressive agents (cyclosporin, tacrolimus)</td>
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<tr>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>Illicit drugs [e.g. cocaine, heroin, 3,4-methyl-dioxymeth-amphetamine (ecstasy)]</td>
</tr>
<tr>
<td>Systemic disease</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Anti-phospholipid syndrome</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Hepatocellular adenocarcinoma</td>
</tr>
<tr>
<td>Prostatic adenocarcinoma</td>
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<tr>
<td>Gastric adenocarcinoma</td>
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<tr>
<td>Combined methylmalonic aciduria and homocystinuria</td>
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a thrombotic microangiopathy (TMA), a group of conditions characterized by endothelial cell injury and activation. The mechanisms by which the identified predisposing factors may lead to the onset of TMA in aHUS are discussed in this review. The importance of understanding the pathogenesis will be described in relation to the current recommendations for management and transplantation in aHUS.

**Pathology**

In aHUS, the predominant pathological abnormality is found in the renal arterioles and interlobular arteries. There is widespread endothelial swelling with retraction leading to exposure of the basement membrane. The vessel lumens are occluded by red cells and platelet fibrin thrombi. This pre-glomerular picture differs from D+ HUS where the pathology predominantly affects the glomerular capillaries [2].

**Differentiating aHUS from TTP**

Whilst differentiating D+ HUS from aHUS is relatively straightforward in the setting of a preceding diarrhoeal illness, discriminating aHUS
from thrombotic thrombocytopenic purpura (TTP), another TMA, can present a major diagnostic challenge. TTP is characteristically diagnosed when neurological features predominate, whilst aHUS is diagnosed when renal failure predominates. The historical literature reflects this uncertainty, the term HUS-TTP being widely used for situations in which the clinical symptoms did not fit clearly into either category.

Recent advances in molecular biology now better allow the two conditions to be distinguished on the basis of their pathogenesis. TTP is associated with either inherited mutations in a disintegrin and metalloprotease with eight thrombospondin-1-like domains (ADAMTS13) gene or with an acquired development of autoantibodies against ADAMTS13 [16] in around 80% of the cases. aHUS is predisposed to by mutations in the complement regulatory proteins, CFH [4–10] MCP [10–13] or IF [10, 12, 14, 15] or by autoantibodies to CFH [17].

Despite this, the genotype–phenotype correlation is not absolute, with some individuals with ADAMTS13-associated TTP having renal involvement severe enough to cause ESRF. This has given rise to a debate on whether a severe deficiency of ADAMTS13 activity is sufficient to distinguish TTP from HUS [16, 18]. A genetic explanation for some of these phenotypic variations has been suggested by Noris et al [19]. They describe two sisters in a family who both had the same mutations in ADAMTS13 and TTP. In one sister, the disease was purely neurological while in the other sister there was also severe renal involvement leading to ESRF. In the sister with renal disease, a mutation in CFH was also discovered. The differences in phenotype seen in some individuals with TTP may therefore be explained by the inheritance of mutations in complement regulatory proteins in addition to mutations in ADAMTS13 [19].

**CFH**

Complement factor H is a 150-kDa serum glycoprotein predominantly synthesized by the liver but also by endothelial cells, platelets and fibroblasts. CFH is composed of 20 homologous units of approximately 60 amino acids, named complement control protein (CCP) modules (Fig. 1). CFH acts as an essential regulator of the alternative pathway (AP) of complement by

1. Functioning as a cofactor for IF-mediated proteolytic inactivation of C3b
2. Competing with factor B for C3b binding
3. Accelerating the decay of the C3 convertase into its components.
CFH is the most important fluid-phase regulator of the AP [3]. It can also down-regulate complement activation on host cells and exposed basement membranes by binding to glycosaminoglycans, e.g. heparan sulphate, through its C terminal domain (CCPs 19 and 20). The complement regulatory functions are located in CCPs 1–4 (Fig. 1).

Thompson and Winterborn first identified an association between CFH and aHUS in 1981 [20]. They reported two brothers with aHUS and low serum levels of CFH. In 1998, Warwicker et al.[4] established linkage in three families with aHUS to the regulators of complement activation (RCA) gene cluster, containing the CFH gene, on chromosome 1q32. This finding led directly to the discovery of the first mutations in CFH as a predisposing cause of aHUS [4]. Following this report, mutations in CFH have now been described in five large cohorts of aHUS patients and account for up to 30% of reported cases [5–10] (Fig. 1). The vast majority of CFH mutations are heterozygous and cause either premature stop codons or single amino acid changes. Incomplete penetrance of the reported mutations has been described in all series, suggesting that the mutants are predisposing factors for aHUS, requiring an additional trigger or endothelial cell insult to become manifest.
The C-terminal region of CFH is a hotspot for mutations in aHUS with 60% of mutations in either CCP 19 or 20. This is the region of CFH critical for binding to exposed basement membranes and endothelial cells. Human glomerular endothelial cells and kidney glomerular basement membranes are rich in polyanionic glycosaminoglycans that bind CFH, which in turn acts to prevent complement activation and endothelial cell damage.

Functional studies of CFH mutants associated with aHUS have been undertaken in a few cases (Table 2). These have demonstrated, for the most part, decreased binding of mutant CFH to glycosaminoglycans (using heparin as a marker molecule) and to endothelial cells. They have also shown a decreased binding capacity for the CFH ligand, C3b. These functional studies therefore suggest that mutations in CCPs 19 and 20 interfere with ligand binding and thus prevent CFH binding to host cell surfaces/basement membranes. This will prevent the control of AP amplification at these sites while fluid phase regulation remains unimpaired. This model is in keeping with recent renal biopsy data for an aHUS patient with a C-terminal mutant showing reduced CFH binding to renal endothelium compared with wild type CFH [21].

Recent nuclear magnetic resonance (NMR) modelling data [22] would also seem to corroborate this. The generation of a 3-dimensional structure of CCPs 19 and 20 of CFH and the mapping of its glycosaminoglycan-binding site has demonstrated that nearly all the disease-associated mutations in this region either disrupt structure or congregate in the polyanion-binding site. Therefore, it appears that the mutations in CFH

### Table 2

<table>
<thead>
<tr>
<th>Mutant</th>
<th>CCP</th>
<th>C3b/d binding</th>
<th>Heparin binding</th>
<th>HUVEC binding</th>
<th>Sheep haemolysis assay</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>W1157R</td>
<td>19</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td>53</td>
</tr>
<tr>
<td>E1172X</td>
<td>20</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td></td>
<td>54, 55</td>
</tr>
<tr>
<td>W1183L</td>
<td>20</td>
<td>↓</td>
<td>↓**</td>
<td>↓</td>
<td></td>
<td>53, 56, 57</td>
</tr>
<tr>
<td>L1189R</td>
<td>20</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
<td>56</td>
</tr>
<tr>
<td>L1189F</td>
<td>20</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
<td>56</td>
</tr>
<tr>
<td>S1191W</td>
<td>20</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
<td>56</td>
</tr>
<tr>
<td>S1191L</td>
<td>20</td>
<td>ND</td>
<td>Normal</td>
<td>ND</td>
<td>↓</td>
<td>58</td>
</tr>
<tr>
<td>S1191L/V1197A</td>
<td>20</td>
<td>↓</td>
<td>Normal</td>
<td>ND</td>
<td>↓</td>
<td>58</td>
</tr>
<tr>
<td>V1197A</td>
<td>20</td>
<td>↓</td>
<td>↓**</td>
<td>↓</td>
<td></td>
<td>53, 56–58</td>
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<tr>
<td>E1198K</td>
<td>20</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>R1210C</td>
<td>20</td>
<td>↓</td>
<td>↓**</td>
<td>↓</td>
<td></td>
<td>53, 55–57</td>
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<tr>
<td>R1215G</td>
<td>20</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td></td>
<td>53, 55</td>
</tr>
<tr>
<td>P1226G</td>
<td>20</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>

ND, not done. CCP complement control protein module, HUVEC, human umbilical vein endothelial cell.
*Indicates contradictory results.
Plasma/serum from W1183L, V1197A and R1210C are reported to have normal affinity for heparin [57, 58]. Serum from R1210C patient showed reduced heparin binding in one study [55]. Studies examining these changes on a backbone of CCP-20 showed decreased heparin binding [53, 55].
in aHUS patients disrupt the normal binding of CFH to the renal microvasculature, allowing local uncontrolled activation of the AP and complement-mediated damage. This predisposes to the development of a TMA and consequently aHUS.

Factor H autoantibodies have also been reported as a mechanism for the development of sporadic aHUS. Dragon-Durey et al. [17] found anti-factor H autoantibodies in three patients (6% of cohort). In all cases, the antibodies were immunoglobulin G (IgG). Functional analysis of these antibodies revealed that they interfered with the complement regulatory decay accelerating activity.

**MCP, CD46**

Thus, mutations and autoantibodies to CFH account for 30–40% of patients with aHUS. In some families in whom no mutations were found in CFH, further linkage analysis on chromosome 1q32 suggested that other genes in the RCA cluster might be responsible. This work led to the discovery of mutations in MCP associated with aHUS in three families, by Richards et al. in 2003 [11].

MCP is a widely expressed membrane glycoprotein [23]. It is present on the surface of all human cells with the exception of erythrocytes. The extracellular portion of MCP consists of four CCPs, an alternatively spliced region rich in serine, threonine and proline (STP region) and a group of 12 amino acids of unknown function. It is followed by a transmembrane domain and an alternatively spliced cytoplasmic tail (Fig. 2).

MCP functions to protect host cells from complement attack by serving as a cofactor for IF. It is an intrinsic complement regulator, protecting the cell to which it is bound by the proteolytic inactivation of deposited C3b and C4b on host cells.

More than twenty mutations in MCP have been described in aHUS [10–13]. Mutations in MCP account for up to 13% of aHUS patients [10]. The majority of mutations cluster in the four CCP domains of MCP, which contains the region critical for complement regulation (Fig. 2). Mutations in MCP may be heterozygous, homozygous or compound heterozygous. The penetrance of MCP mutations was 54% in one recent series [10].

Unlike the CFH mutants, most of the reported MCP mutants have been functionally characterized. Around 75% of the mutants described so far have reduced surface expression on peripheral blood mononuclear cells by FACS analysis (Fig. 2). These patients have between ~0 and 50% levels of MCP on cell surfaces and thus have a quantitative deficiency of complement regulation. However, for two other reported mutations (S206P; F208C), MCP expression was normal, but functional analysis showed reduced C3b binding and cofactor activity [10, 11].
A further mutant, E145Q showed reduced C4b cofactor activity, but the surface expression of this mutant was increased 3-fold, which may help offset its effect. Thus, like some of the reported CFH changes, these
mutants in MCP affect the ability of the protein to down-regulate complement activation on the renal endothelial cells.

In the two mutants (R69W; A304V), surface expression was normal and no functional abnormality could be found. It is possible that these two mutants represent rare genetic variants that do not contribute to the pathogenesis of aHUS. It illustrates the importance of modelling mutants in complement proteins before attributing functional significance and basing clinical decisions on reported genetic changes.

**IF**

More recently, mutations in IF have also been reported in patients with aHUS (Fig. 3) [10, 12, 14, 15]. IF is an 88-kDa serum glycoprotein predominantly synthesized in the liver. It is a specific serine protease that cleaves the $\alpha'$ chains of C3b and C4b in the presence of its cofactors. These cofactors are CFH for C3b; C4 binding protein (C4BP) for C4b.

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**Fig. 3** Mutations in factor I (IF) associated with atypical haemolytic uraemic syndrome (aHUS). The figure shows the structure of IF. The heavy and light chain are linked by a disulphide bond. Most mutations in IF are in the serine protease domain. Numbering of amino acid residues includes the 18 amino acid leader sequence. Mutations which are associated with reduced serum IF are marked with an asterisk.
and MCP and complement receptor 1 (CR1) for both. By inactivating these proteins and preventing the formation of the C3 and C5 convertases, IF acts to down-regulate both the alternative and the classical complement pathways. Unlike MCP and CFH, the IF gene does not reside in the RCA cluster on 1q32 but is located on chromosome 4q25.

IF is a heterodimer, and consists of a noncatalytic heavy chain, linked by a disulfide bond to a catalytic light chain. The modular structure of IF is in keeping with many complement proteins. The heavy chain contains two low-density lipoprotein receptor domains, a CD5 domain, and a module found only in FI and complement proteins C6 and C7. The light chain contains the serine protease domain (Fig. 3).

Mutations in IF appear to be a less common cause of aHUS than CFH or MCP mutations. Several studies report a frequency of around 3% [10, 12, 14] although the study by Fremeaux-Bacchi et al. reported 12% [15]. As in MCP- and CFH-associated HUS, mutations have been described in heterozygosity and incomplete penetrance is common. Around 40% of the IF mutants associated with aHUS result in low serum levels of IF. The remaining group are missense mutations. To date, there have been no functional evaluations or modelling experiments for these mutants.

**Other precipitating causes of aHUS**

Mutations in CFH, MCP and IF account for >50% of patients with aHUS. The mutations are thought to act as predisposing factors for the development of the disease. Many other precipitating causes of aHUS are recognized, these may act as the ‘initiating trigger’ for those who inherit a mutation in one of the complement regulators or cause de novo disease. Such conditions provide insight into other pathogenic mechanism(s) underlying abnormal endothelial cell activation and development of aHUS.

**Streptococcus Pneumoniae**

A recent study in the USA has shown S. Pneumoniae to be associated with around 40% of atypical HUS [24]. The incidence is greatest in children younger than 2 years [24]. S. Pneumoniae-associated HUS is most commonly seen in patients with parapneumonic empyema and also meningitis.

S. Pneumoniae produces the enzyme neuraminidase, which has been postulated to play a role in the development of disease. Neuraminidase cleaves sialic acid residues from the glycoproteins on the cell membrane
of erythrocytes, platelets, and glomeruli [25] exposing the normally hidden Thomsen-Freidenreich antigen (T-antigen). This then reacts with anti-T IgM antibodies, normally present in plasma. It has been hypothesized that binding of anti-T IgM to platelets and endothelial cells causes TMA by platelet aggregation and direct endothelial cell damage [25].

**Pregnancy**

While pregnancy-associated HUS is rare, it occurs in association with pregnancy or the postpartum in 13% of women with HUS or TTP [26]. Although HUS can present early in pregnancy, most acute episodes occur near term or postpartum.

Physiological changes in pregnancy may be responsible for precipitating HUS and TTP. Specifically, pregnancy increases concentrations of pro-coagulant factors, decreases fibrinolytic activity, reduces endothelial thrombomodulin, and decreases activity of ADAMTS13 [26], predisposing to the development of TMA. In some individuals with mutations in the complement regulatory proteins *CFH* [5, 10] and *IF* [10, 14], pregnancy has precipitated acute attacks of aHUS. Patients should be followed, as HUS recurs in about 50% of patients regardless of the presence of complement regulatory protein mutations [27].

**Drugs**

Many drugs have been reported to cause aHUS [28] although it is difficult to determine whether aHUS is drug induced or a consequence of the condition for which the drug was administered. Drugs cause aHUS by two main mechanisms: immune-mediated damage and direct toxicity.

Quinine, used in the treatment of malaria and leg cramps, causes an immune-mediated aHUS. It occurs because of the development of autoantibodies reactive with either platelet glycoprotein Ib/IX or IIb/IIIa complexes or both [29]. Antibodies against granulocytes, lymphocytes and endothelial cells have also been described. Quinine-associated HUS is not dose-related and recurs if quinine is reingested [29].

Mitomycin C, an alkylating agent used to treat a variety of malignancies, is thought to cause aHUS by a direct toxic effect on endothelium. When mitomycin was perfused into the kidneys of rats, a pathological picture resembling HUS resulted, with fibrin deposition and endothelial proliferation [30]. In patients receiving it as part of combination chemotherapy, the incidence of HUS is 4–15% [31]. Mitomycin-induced HUS develops in a dose-dependent manner [31], patients seldom developing HUS until a cumulative dose of >30 mg/m² has been given.
As with most precipitating causes of aHUS, drugs have been shown to unmask latent complement regulatory defects [10].

Transplantation

Both *de novo* aHUS and recurrent aHUS are seen post-renal transplantation. Cyclosporin and Tacrolimus are thought to precipitate aHUS by direct endothelial cell injury [32, 33]. Other risk factors include acute rejection and CMV infection. aHUS is also seen in association with other types of transplant, especially hematopoietic cell transplantation (HCT). The TMA frequently occurs months after HCT has been performed. There is a great variation in the incidence following allogeneic HCT with rates reported from 0 to 63.6% with a median of 7.9% [34]. The aetiopathogenic cause of HUS following HCT is not clear, however, the conditioning regime—especially the irradiation—is thought to be the primary cause of renal endothelial damage, with post-HCT factors such as graft versus host disease, infections (aspergillus species and cytomegalovirus) and medications (e.g. calcineurin inhibitors, cyclophosphamide, sirolimus and anti-thymocyte globulin) playing a modulatory role. The dose of radiotherapy is thought to be important [35] with renal shielding during total body irradiation protective. The reported mortality in a systemic review of 379 patients was 61%.

HIV infection

Human immunodeficiency virus (HIV)-related HUS (HIV-HUS) is now less frequent with the use of highly active antiretroviral therapy [36]. It is associated with advanced HIV disease, opportunistic infections, AIDS-related tumours and the drugs used to treat complications of AIDS and has a very poor prognosis [36]. The pathogenesis of HIV-HUS remains poorly understood, but as in other forms of aHUS, endothelial damage and development of a procoagulant phenotype are thought to be primary pathogenic events.

Combined methylmalonic aciduria and homocystinuria

Combined methylmalonic aciduria and homocystinuria (cblC) is a rare hereditary cause of aHUS [37]. It is a disorder of cobalamin (vitamin B12) metabolism characterized by neurological, metabolic and developmental symptoms. The pathophysiologic mechanism of HUS in the cblC defect is obscure. The generalized nature of the endothelial abnormalities on kidney biopsies [38] is striking and suggests that endothelial cell
dysfunction may be the precipitating event. CblC is a heterogeneous disorder and only a proportion of patients get aHUS, and even in these cases, the severity of renal disease can vary greatly. Guigonis et al. [39] provide an explanation for some of the variability in a description of a family with cblC and TMA. Two sisters with cblC had evidence of a TMA but in only one sister did severe renal failure requiring renal replacement therapy result. This sister was shown to have a mutation in CFH in addition to cblC [39].

**Penetrance of aHUS**

Thus, it can be seen that the majority of precipitating causes of aHUS have direct or indirect endothelial cell injury as a common mechanism. However, aHUS occurs in only a small percentage of those exposed to the stimulus. Similarly, incomplete penetrance of the mutations in CFH, MCP and IF is well recognized. The penetrance of the disease phenotype is approximately 50%. One explanation for this is that other genetic factors act as modifiers of disease penetrance. Caprioli et al. [40] showed an association between CFH single nucleotide polymorphisms (SNPs) and aHUS. This has recently been extended to include SNPs in MCP in three aHUS cohorts [12, 41]. These findings suggest that the complement regulatory genes in the RCA cluster may work together to prevent host cell damage. Only when an unfavourable network of complement regulatory genes is present in the face of endothelial injury will aHUS develop. This is most elegantly illustrated by the independent segregation of three complement risk factors in aHUS [42]. Only when three independent risk factors were present, did aHUS result. Even here, the onset of aHUS was not until middle age, suggesting that a precipitating cause is needed to unmask the complement regulatory defects. In a recent series of patients with mutations in MCP, aHUS was precipitated in all cases by infection [10]. In CFH-HUS, 70% of the cases were preceded by infection while pregnancy and drugs both accounted for 4% [10]. In IF-HUS, 40% were preceded by pregnancy while 60% were precipitated by infection [10].

**Outcome of aHUS**

Overall, aHUS has a much poorer outcome than D+ HUS with 50% developing ERSF and up to 25% dying in the acute phase [2]. However, within aHUS itself differences in outcome are also seen, with some patients having very mild disease; others very severe disease. When patients are stratified
According to mutation, an important ‘genotype-phenotype’ correlation is observed. Patients with mutations in \textit{CFH} have more severe disease compared with those with mutations in \textit{MCP} \cite{10}. Seventy percent of those with CFH-HUS develop ESRF or die while over 80\% with MCP-HUS remain dialysis-independent \cite{10}. For IF-HUS, numbers are small, but to date, >60\% develop ESRF. While MCP-HUS is usually associated with a better prognosis than CFH-HUS, there are exceptions. It is likely that these will be due to different genetic and environmental modifiers of disease expression.

\section*{Treatment of aHUS}

Plasma exchange and plasma infusion are the first line therapy in treating aHUS, but debate still exists about their efficacy as there are no prospective randomized controlled trials. However, overall, following the introduction of plasma exchange and plasma infusion, the mortality rate has dropped from 50 to 25\% \cite{2}.

It has been suggested that plasma exchange may be relatively more effective than plasma infusion alone. It has been postulated that this is due to the removal of toxic substances, but may merely represent the larger amount of plasma that is able to be given with plasma exchange. Certainly, in situations which limit the amount of plasma that can be given, such as renal failure or heart failure, we would recommend plasma exchange as the treatment of choice. Treatment should be started as soon as possible after diagnosis. The suggested dosing for plasma infusion is 30–40 ml/kg initially and 20 ml/kg per day thereafter \cite{43, 44}. For plasma exchange one plasma volume (40 mg/kg) is exchanged per session. Treatment should continue for a minimum of 2 days after complete remission is obtained \cite{2}.

An exception to the use of plasma infusion or exchange is for patients with \textit{S. pneumoniae}-induced HUS because plasma contains anti-T IgM which may exacerbate the disease \cite{24}. Treatment here is of the underlying infection with appropriate antibiotics. For HUS following HCT, there is no convincing data to support the efficacy of plasma infusion or exchange \cite{34} and prevention is the major goal, by shielding the kidneys \cite{35}. Long-term management of cblC disease is with intramuscular hydroxycobalamin, oral folic acid and betaine \cite{39}.

No conclusive benefits for steroids, aspirin, heparin or antioxidants in the treatment of aHUS have been shown. Severe hypertension is common because of overexpansion of intravascular volume and ischemia-induced activation of the renin-angiotensin system \cite{45}. Correction of the fluid status and multi-drug therapy is often required for control of blood pressure.
Transplantation in aHUS

Overall, renal transplantation is complicated by recurrence of aHUS in the allograft in approximately 50% of patients. However, when genetic factors are examined separately, two distinct groups emerge: those with mutations in serum complement regulators (CFH/IF) and those with membrane-bound complement regulator mutations (MCP) [46].

To date, about 80% of patients with CFH mutations who have been transplanted have had recurrent disease [46]. Similarly, all six renal transplants in patients with IF mutations have had recurrent disease [10, 14, 15, 46]. In contrast, in patients with MCP mutations, the recurrence rate is significantly lower [10, 11, 46]. This would be expected as MCP is a transmembrane regulator, and allografts will therefore be protected by wild-type MCP from the donor. Of the 10 patients with MCP mutations, there has only been one recurrence in the allograft. In this case, the patient had low serum C3 and factor B levels suggesting alternate pathway activation but analysis of the MCP mutant in vitro showed only a defect in classical pathway regulation. This suggests that this patient has a yet undiscovered mutation in another complement regulator.

Thus, even allowing for this complex case, the recurrence rate for those with MCP-HUS is only 10% compared with 80% for CFH-HUS and 100% for IF-HUS. Screening for mutations in these genes should therefore allow patients and clinicians to make informed decisions regarding listing for transplantation, based on the risk of recurrence and its not inconsiderable consequent morbidity and mortality.

Live donor renal transplantation is associated with an equally poor outcome. Furthermore, in four reported cases, the donors themselves have gone on to develop HUS within a year of donation [47]. Because of the risk of recurrence in the recipient and of de novo disease in the donor, many centres do not recommend live-related transplantation. If live donation is considered, it is essential that the donor and recipient undergo CFH, MCP and IF genotyping to identify hitherto unsuspected carriers, given the high reported rates of incomplete penetrance for mutations in all three genes. This will not, however, prevent the risk for the donor in those with an unknown genetic basis.

Because CFH and IF are both synthesized in the liver, combined liver and renal transplantation has been attempted and would appear a logical form of treatment. Unfortunately, none of the three initial reports [48–50] describing this for CFH-HUS had a favourable outcome, with 2 out of 3 patients dying (Table 3). A more recent report using plasma exchange preoperatively was successful [51]. It is likely that local complement activation within the donor organ occurs immediately after transplantation. Unless functioning factor H is
already present in the recipient, this complement activation will result in failure of the graft [51].

**Summary**

aHUS is a disease precipitated by endothelial damage. Recent advances have identified defects in complement regulatory proteins as a predisposing factor in over 50% of cases. In this setting, we hypothesize that excessive complement activation following endothelial damage will result in the generation of a procoagulant state and aHUS. The discovery of mutations in CFH, MCP and IF and the characterization of specific phenotypes related to mutations demonstrate the importance of identifying the causes of aHUS. MCP-HUS has a better prognosis with or without plasma infusion/exchange and a better outcome after transplantation than either CFH-HUS or IF-HUS.

**Acknowledgements**

We gratefully acknowledge the help and support of John Atkinson. We thank Rebecca Saunders and Stephen Perkins for helpful discussion.

This work was supported by the Northern Counties Kidney Research Fund, The Peel Medical Research Trust, Kidney Research UK, The Robin Davies Trust, The Foundation for Children with atypical HUS and Newcastle Healthcare Charity. DK is a Kidney Research UK Training Fellow. AR is a 2005/2006 Fulbright Distinguished Scholar.
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