



Hemolytic Uremic Syndrome

15

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Case Scenario

An 8-year-old presents to the emergency with increasing pallor and cola-colored urine since last 3 days. He has no significant past history of diarrhea or dysentery or fever. He has not passed urine since the last 12 h.

On clinical examination: He is pale, and puffy with pedal edema. His blood pressure is 130/80 mm Hg in right arm. He is conscious and alert. His systemic examination is unremarkable.

His laboratory evaluation shows:

Hemoglobin: 5 g/dl

Peripheral smear: schistocytes 5% with evidence of aniso-poikilocytosis, and reticulocytosis 7%

Total leucocyte count: 11,000

Platelet count: 20,000/mm³

Prothrombin time and APTT: normal

Blood urea: 200 mg/dl

Serum creatinine: 8 mg/dl

LDH 10,000 IU/ml

Venous blood gas: pH 7.2; bicarbonate 16 meq/L; base excess -8 mmol/L
C3 40 mg/dl; C4 20 mg/dl

He is being planned for dialysis. You have been called for planning the definitive care for the child.

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15.1 Introduction

There have been major advances in the understanding of pathogenesis and management of hemolytic uremic syndrome in the last decade. Since the consensus paper published in 2009 by the European Pediatric Study Group in 2009, there have been four prospective trials and multiple case reports on effective terminal blockade with Eculizumab, an international consensus on the diagnostic and therapeutic strategies for management has been published in 2015 [1–3].

15.2 Diagnosis

A classification based on etiology and pathogenesis has been proposed as follows in Fig. 15.1. This classification includes all thrombotic microangiopathies including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (HUS), and pregnancy-associated HUS. It is important to exclude Shiga toxin producing *Escherichia coli* (STEC) before defining Atypical HUS. Thrombotic thrombocytopenic purpura (TTP) either due to deficiency or antibodies to ADAM-TS 13 enzyme requires different definite therapy. Most consensus statements define aHUS as HUS without coexisting disease or infection [1–3].

Diagnosis of Hemolytic Uremic Syndrome should be suspected in the presence of all the following features:

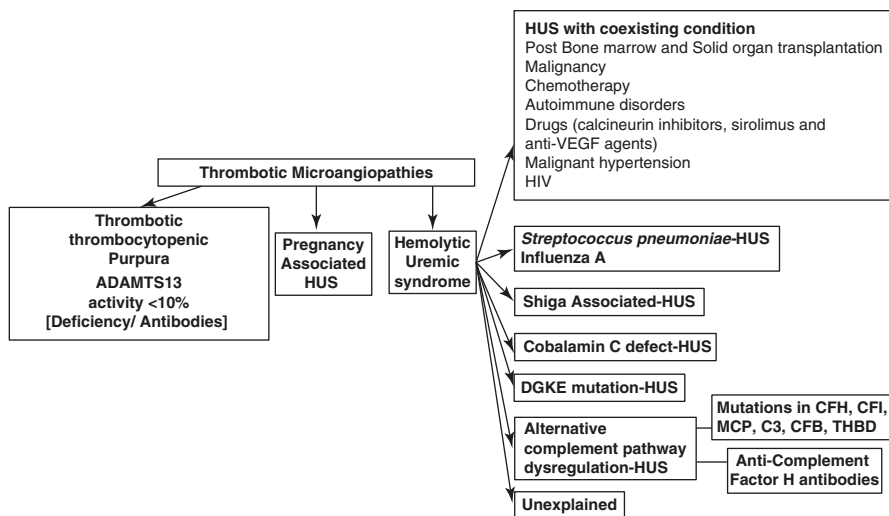


Fig. 15.1 An etiology-based classification of thrombotic microangiopathies. Adapted from Loirat et al. [3]

- Microangiopathic hemolytic anemia [hemoglobin <10 g/dl]; fragmented RBCs on peripheral smear (schistocytes >1%), and either elevated LDH or undetectable haptoglobin
- Acute kidney injury
- Thrombocytopenia [Platelets <150,000/ μ l]
- It is important to exclude disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP), especially in setting of sepsis and malignancy as per the clinical indication

15.2.1 Infection-Associated HUS

HUS is associated with various infections including Shiga or verotoxin producing *E. coli* or *Shigella dysenteriae* type 1, invasive pneumococcal infections, and other infections including influenza A, HIV, malaria, CMV, parvovirus B19, coxsackie virus, echovirus, Epstein–Barr, salmonella, campylobacter, bartonella, dengue, and rickettsia. Hence, these infections should be borne in mind when dealing with a case of hemolytic uremic syndrome [2–4].

A probable pneumococcal HUS should be suspected especially in children more than 2 years of age, with sepsis, pneumonia, or meningitis and a positive Coombs test without disseminated intravascular coagulation. Plasma infusions/exchanges should be avoided; washed blood products and platelets should be used only if necessary.

Shiga toxin-associated *Escherichia coli* (STEC)-associated HUS should be considered in children who present with a history of bloody diarrhea in the last 2–3 weeks, or HUS occurring during a known STEC-HUS outbreak in children more than 6 months of age. All probable cases should get a rectal swab or a stool specimen as soon as possible within 6 days of diarrhea. The infection should be confirmed by any of the following: real-time PCR on fecal specimen for *stx1* and *stx2* genes; positive stool culture on MacConkey Agar (0157:H7) or other media for non-0157 serotypes and positive stool PCR; immunological tests for fecal shiga toxin, or lipopolysaccharide (LPS); elevated antibodies by ELISA to LPS of prevalent serogroups of STEC. It is important to realize that patients can have STEC-HUS in the absence of diarrhea or dysentery. Moreover, the stool excretion may be short lasting; and the referral may have been delayed and may be post-administration of antibiotics. This may hamper the yield on the stool specimens [4].

There is an association between degree of dehydration and adverse outcomes in STEC infection. Hence, it is suggested that normal hydration should be maintained in these children by early use of isotonic fluids, starting from the onset of dysentery to including the day of onset of HUS. Patients with shigella dysentery should get prompt antibiotics to reduce mortality, complications, and fecal shedding of bacteria. Ciprofloxacin has been recommended as first-line therapy by the WHO for shigellosis; second agents being cefixime and azithromycin. There is now evidence that complement is activated in acute phase of STEC infection. Hence, complement

blockade with eculizumab may have a role in management of severe STEC dialysis-dependent HUS. While there is no clear benefit of routine use of eculizumab in large series from the German epidemic, few case series suggest that patients with neurological involvement may respond to timely initiation of eculizumab. Therapy with plasmapheresis or eculizumab may be considered in patients with severe neurological or cardiac manifestations, particularly STEC HUS patients with low levels of C3 or lack of recovery of renal function by 2 weeks [5–8].

15.2.2 Cobalamin [cblC] Deficiency HUS

Cobalamin deficiency-associated HUS deserves a special mention, since it may present at all ages and with different manifestations. Early recognition is important because this subset does not respond to plasma exchanges and requires specific therapy. These infants may present with failure to thrive, feeding difficulties, seizures, abnormal muscle tone, visual impairment and developmental delay, and megaloblastic anemia. Elevated blood levels of total homocysteine are characteristic of cblC deficiency. Free homocysteine levels are not required since even vitamin B12 and folate deficiency might also lead to elevated homocysteine levels. Plasma and urine methylmalonic acid (MMA) levels are usually elevated in cblC deficiency. Early treatment is recommended pending MMA levels and genetic sequencing [9].

15.2.3 Atypical HUS (aHUS)

Almost, 60–70% of children with aHUS have an identifiable mutation in the complement genes or antibodies to Factor H that leads to complement activation and thrombotic microangiopathy. Variations in six complement genes (*C3*, *CFH*, *CFI*, *CD46*, *CFB*, and *THBD*) and rearrangements of *CFHR1–5* and *CFH* are found in 19–52% of patients with aHUS. Almost all children with antibodies to complement factor H have a deficiency of complement factor H-related proteins (CFHR1 and CFHR3) due to homozygous deletions, hence MLPA should also be performed in all aHUS patients. It is important to remember that normal C3, C4, Complement Factor H and I plasma levels do not exclude a genetic defect of complement pathway, and moreover, C3 levels can be low in early phases of *Streptococcus pneumoniae* and STEC-HUS. C3 is low only in 30–40% of aHUS [10–12].

- *Recommended tests in aHUS:*
- The following are the recommended tests in all children with aHUS:
 - C3; C4; Complement Factor H; Complement Factor I; Complement Factor B
 - Anticomplement Factor H antibodies
 - MCP expression on polynuclear or mononuclear leucocytes
 - Screening for mutations using next-generation sequencing or direct sequencing Complement Factor's H; I; MCP; C3; Complement Factor B; Thrombomodulin, and DGKE

- Screening for Complement Factor H hybrid genes and copy number variations by Multiplex ligation-dependent probe amplification (MLPA)
- *Genetic Screening*: It is recommended that all children with first episode of aHUS, especially if they do not have a causative agent, or STEC infection, or ADAMS TS 13 deficiency, or hyperhomocysteinemia or methylmalonic aciduria should get genetic screening. All children with relapsing HUS, family history, de novo or recurrent post-transplant HUS should get a genetic evaluation. Genetic characterization confirms the diagnosis, helps in management, tells about the prognosis, helps in genetic counselling of the family, and helps in taking decisions regarding kidney transplantation and strategies required during transplant in these children [10–12].

15.3 Treatment Options

- *Plasma therapies*: European Pediatric Study Group for HUS published a guideline suggesting early (within 24 h of onset) intensive plasmapheresis [2]. However, later audits showed catheter-related complications and risk of sensitization [2, 3]. Moreover, early plasmapheresis though may lead to early renal and hematological remission, these children have a poor long-term outcome in terms of proportion reaching end-stage renal disease (48% children and 67% adults reaching end-stage disease at 3 years after onset) [4]. The benefit of plasma therapy in children with DGKE mutations is uncertain.
- However in areas where Eculizumab is not available, or not affordable, the 2009 guidelines may be followed as follows:
 - Initiation of plasmapheresis 1.5 plasma volume (60–75 ml/kg) per session initiated within 24 h of diagnosis. Replace the fresh frozen plasma or Octoplas.
 - Plasmapheresis should be done daily for 5 days, then five times a week for 2 weeks, and then three times a week for another 2 weeks.
- *Eculizumab*: Eculizumab is a monoclonal humanized anti-C5 antibody. It prevents the cleavage of C5 and blocks the pro-inflammatory C5a and pro-thrombotic complement activation of C5b-9. It has been approved for aHUS in the European Union and the USA. It has been following excellent results of four prospective, open-label, single arm trials done by the Alexion Pharmaceuticals. The four trials included adults/adolescents with progressive thrombotic microangiopathy despite plasma exchanges and plasma infusion, adults/adolescents with long disease duration and chronic kidney disease under long-term plasma exchanges and plasma infusions, children with early initiation, and adults with early initiation.

Recommended dosing duration is indicated in Table 15.1.

For children who present with clinical diagnosis of aHUS, eculizumab should be initiated without any delay within 24–48 h of onset. It also avoids the needs of central venous double-lumen catheter and plasma-related complications. In the absence

Table 15.1 Recommended eculizumab dosing regimen for patients with atypical HUS (aHUS)

Patient body weight	Induction regimen	Maintenance regimen
40 kg and over	900 mg weekly × 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly × 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly × 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 3 weeks

of availability of eculizumab, plasma exchanges should be initiated as highlighted above. There are also reports on early switch from plasma therapy to eculizumab that may help in full renal recovery.

Confirmation of a complement mutation is not required for initiation of therapy. Anticomplement factor H antibody titer should also be sent at onset, since positive titer will require immunosuppressive therapy initiation.

It is mandatory to administer meningococcal vaccine and antibiotic prophylaxis before eculizumab therapy. Tetravalent vaccine against serotypes A, C, W135, and Y is available; however, it does not protect against serotype B. Methylpenicillin, given twice daily, remains the drug of choice for antibiotic prophylaxis. Macrolides may be given in cases of penicillin allergy. Antibiotic prophylaxis should be given during 2 weeks after the vaccination in patients receiving eculizumab. However, most of the clinicians believe in giving continuous antibiotic prophylaxis. It is important for clinicians to educate the parents regarding early recognition and treatment of meningococcal infections [10–12].

15.4 Anticomplement Factor H Antibodies aHUS

Antibodies to Factor H-related HUS appear to an important subset of patients since these patients have excellent results with a combination of plasmapheresis and immunosuppression. American Society of Apheresis assigns level I category for plasmapheresis for this subset, implying the efficacy of the plasmapheresis to remove these antibodies well. The international consensus recommends to give eculizumab along with the combination therapy since it may help in acute complement blockage, especially in severe acute injury of vital organs, e.g., heart and brain.

The anti-factor H-associated HUS is strongly associated with a polymorphism: an 84-kb homozygous deletion of the CFHR1 gene in around 90% patients. Multiplex ligation-dependent probe amplification (MLPA) or end-point PCR is useful in confirming the CFHR1 deletion. It is suggested to evaluate for copy number variation/hybrid genes in CFH and CFHR1–5 region by multiplex

ligation-dependent probe amplification (MLPA) or detection of CFHR1 deletion in these patients [10–13].

The international consensus recommends the following induction regimen:

- Anti-factor H antibodies with mild or no extra renal manifestations: Two approaches can be followed:
 - Consider eculizumab, along with adding steroids and mycophenolate as immunosuppression.
 - Switch these patients to maintenance plasmapheresis with monthly cyclophosphamide pulses (total 5–6) or rituximab with steroids.
- Anti-factor H antibodies with severe extra renal manifestations: Combining eculizumab, plasmapheresis with immunosuppression of cyclophosphamide pulses or rituximab and steroids.

Plasmapheresis or eculizumab can be stopped once the titer reaches less than 1000 AU/ml. Maintenance immunosuppression is recommended to consist of prednisolone in tapering doses and mycophenolate mofetil. It can be stopped after 1 year in stable patients with hematological remission and titer less than 1000 AU/ml and normal C3. Antibodies to factor H titer should be monitored closely, at weekly intervals in the first month, and then preferably at 3–6 months thereafter during the first 12–24 months of illness [10–13].

15.5 Conclusions

With better understanding, there are now better available drugs targeting complement in these patients, with better outcomes. However, there is a lot of geographical disparity in availability and affordability of these drugs, and there is a need for more trials especially looking at newer blockers, and also safe withdrawal of treatment in these patients.

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