Ghosh et al., J Nephrol Ther 2016, 6:2
DOI: 10.4172/2161-0959.1000239

Journal of Nephrology & Therapeutics

Review Article Open Access

# Hemolytic Uremic Syndrome

**Jagabandhu Ghosh[1*], Dipankar Gupta[1] and Nibedita Chattopadhyay[2]**

[1]*Department of Paediatrics, I.P.G.M.E.R and S.S.K.M Hospital, Kolkata, West Bengal, India*
[2]*Department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India*

## Abstract

Hemolytic uremic syndrome (HUS), a common cause of acute renal failure (ARF) in children, consists of triad of microangiopathic haemolytic anemia (MAHA), thrombocytopenia, and ARF. The aim of the present article is to have a recent overview of HUS including its incidence, etiopathogenesis, clinical profile and management. It consists of two types a) Diarrhoea associated i.e. classical also called D+ HUS b) Non-diarrhoea associated i.e. atypical also called D- HUS. D+ HUS is caused mostly by *Escherichia coli* or occasionally by Shigella dysenteriae. The causes of HUS are infections, genetic defects, systemic diseases and drugs. The atypical form commonly presents with recurrent or chronic persistent attack. Thrombotic microangiopathy (TMA), the pathologic hallmark, includes HUS, atypical HUS (aHUS), thrombotic thrombocytopenic purpura (TTP) which is characterized by endothelial cell damage and microvascular injury. In the vast majority of aHUS susceptibility factors are familial and not acquired. In D+ HUS, following an attack of diarrhoea or dysentery the child abruptly develops pallor, irritability, swelling of body, oligoanuria, hematuria, and hypertension. Central nervous system disturbances like seizure, obtundation and encephalopathy may occur but less common than aHUS or TTP. Diagnosis of HUS is established by presence of MAHA in the peripherl blood smear i.e. schistocytes, burr cells, helmet cells etc. Thrombocytopenia is nearly always seen. ARF is reflected in elevated blood urea and creatinine level. Coagulation studies like prothrombin time (PT), activated partial thromboplastin time (APTT), will be normal unlike disseminated coagulopathy (DIC). D-dimer level will be raised in HUS similar to DIC. Interestingly, direct Coomb's test will be positive in Streptococcus pneumonia induced D- HUS. With excellent supportive care and often dialysis D+ HUS will show remarkable recovery whereas in addition plasmapheresis or plasma infusion outcome is poor in most of the D-HUS cases. Though incidence of gastroenteritis is very high in our country, only few patients may develop HUS, the reason of which remains unclear. The incidence of HUS as a cause for ARF in India may be reviewed further. Indiscriminate use of antimicrobials is to be avoided as far as possible to prevent HUS related mortality. Facilities for dialysis may be enhanced in most of the health care facilities in our country as a life saving measure to reduce HUS related mortality and morbidity.

**Keywords:** Microangiopathy; Thrombocytopenia; Haemolytic; Uremic; Acute renal failure

## Introduction

In1955 Gaser et al first reported Hemolytic uremic syndrome (HUS) in children who showed microangiopathic haemolytic anemia, thrombocytopenia, and acute renal failure [1]. HUS, recognised for more than 55 years, is one of the most common causes of acute renal failure in children [2]. It consists of the triad of microangiopathic haemolytic anemia, thrombocytopenia, and acute renal failure. The syndrome usually occurs in previously healthy children and often is preceded by an attack of diarrhoea or dysentery. HUS has several features which are common to thrombotic thrombocytopenic purpura (TTP). They share a common underlying pathologic process termed thrombotic microangiopathy (TMA), characterized by endothelial cell injury, intravascular platelet- fibrin thrombi, and vascular damage [3].

HUS can be divided into two types- a) Diarrhoea associated i.e., classical or typical which is most common, also called as d+ HUS b) non- diarrhoea-associated i.e. non classical or atypical which is infrequent but more severe in children, also called as D-HUS or atypical HUS (aHUS). These atypical cases can have worse prognosis with recurrent attacks [4,5]. Generally D+HUS is associated with gastrointestinal infection caused by Shiga-toxin producing *Escherichia coli* (STEC) or Shigella dysenteriae type 1 and some other organism [6].

## Etiology

The etiology of HUS may be classified broadly into 4 types (a) Infection associated (b) Systemic associated (c) Genetic (d) Drug induced.

Showing etiological classification of Hemolytic Uremic Syndrome.

**Infection associated:** Verotoxin or Shiga-like-toxin producing *Escherichia coli*, Shiga toxin-producing *Shigella dystenereiae*, Neuraminidase-producing *Streptococcus pneumonia*, Human immunodeficiency virus, other bacteria and viruses.

**Systemic disease associated:** Systemic lupus erythematosus, Antiphospholipid antibody syndrome, malignant hypertension, Bone marrow transplantation, HELP (haemolytic anemia, elevated liver enzymes, low platelet count) syndrome.

**Genetic:** Von Willebrand factor-cleaving protease (ADAMTS 13) deficiency, Complement factor H deficiency or mutation, Complement factor I deficiency or mutation, Membrane cofactor protein (MCP) mutation, Vitamin B12 metabolism defect, Familial autosomal recessive and dominant, Thrombomodulin mutations.

**Drug induced:** Chemotherapeutic cytotoxic agents like cisplatin, mitomycin C, Clopidrogel and ticlopidine, Calcineurin inhibitors e.g. tacrolimus, cyclosporine, Quinine the most common form of HUS i.e. D+ HUS is mostly caused by verotoxin producing *Escherichia coli* (VTEC) or STEC. Out of several serotypes producing verotoxin, the commonest serotype is O 157:H7. D+ HUS can occasionally be caused by Shiga toxin-producing *Shigella dysenteriae* type 1 (STPSD). VTEC is usually transmitted by undercooked meat, contaminated water, or unpasteurized milk. Other bacteria like *Campylobacter jejuni* and a variety of viruses have also been found to be responsible. On rare occasion *Streptococcus pneumoniae* typically presenting with manifestations of respiratory involvement like lobar pneumonia with or without empyema may lead to HUS. Untreated HIV has also been found to be responsible for HUS or TTP [2]. Some systemic diseases like

***Corresponding author:** Jagabandhu Ghosh MD, Consultant Paediatrician, Ex-Professor and HOD, I.P.G.M.E and R, Kolkata, Ushashi Housing Society, 245 Vivekananda Road, Kolkata-700006, India, Tel: 9434239336; E-mail: jbghosh@yahoo.com

**Received:** February 14, 2016; **Accepted:** March 04, 2016; **Published:** March 11, 2016

**Citation:** Ghosh J, Gupta D, Chattopadhyay N (2016) Hemolytic Uremic Syndrome. J Nephrol Ther 6: 239. doi:10.4172/2161-0959.1000239

systemic lupus erthematosus (SLE), antiphospholipid antibody (APLA) syndrome etc where TMA resulting in intravascular thrombosis may also be superimposed by HUS [2]. The aHUS which is the most important cause for recurrent or chronic presentation of this disease is commonly associated with genetic defect like inherited deficiency of Von Willebrand factor-cleaving protease (ADAMTS13) or complement factor H, I, or B. There are also familial cases like autosomal recessive and dominant HUS whose genetic defect is still unknown. Some drugs like calcineurin inhibitors, clopidrogel, ticlopidine, quinine may also occasionally lead to HUS.

## Pathogenesis

HUS is one of the TMA which includes a group of disorders like HUS, aHUS, and TTP. TMA is characterised by endothelial cell damage associated with microvascular injury. In the common, D+HUS enteropathogenic organism producing either Shiga toxin or Shiga-like verotoxin directly leads to endothelial damage. Endothelial damage leads to platelet adhesion, aggregation, and activation. The Shiga-toxin activated endothelial cells become thrombogenic by ill understood mechanism [7]. In the pneumococcal-associated HUS, neuraminidase cleaves sialic acid on the membranes of endothelial cells, RBCs and platelets to reveal underlying antigens which trigger microvascular injury [2]. In all forms of HUS, progressive damage to the endothelial cells of glomeruli leads to platelet aggregation and activation resulting in localised thrombosis particularly in the glomeruli in contrast to widespread generalised thrombosis seen in TTP. As a result of which renal insufficiency sets in. Mechanical damage of RBC membrane leads to fragmentation and microangiopathic haemolytic anemia (MAHA) as the RBCs pass through the damaged microvasculature. Platelets are also damaged in a similar way resulting in thrombocytopenia. Consumptive thrombocytopenia also occurs from progressive platelet aggregation in areas of endothelial injury.

In the vast majority of aHUS, susceptibility factors are familial, not acquired. They are genetic defects in complements and complement regulatory proteins or related factors, which permit uncontrolled amplification of the alternate complement pathway. This potentiates platelet activation, aggregation, and complement-mediated endothelial injury throughout the microvasculature [8-10].

Von Willebrand Factor (VWF), a glycoprotein that carries factor viii in the circulation, is required for platelet adhesion and aggregation [11]. ADAMTS 13, a metalloproteinase enzyme, produced in the liver, acts on VWF as a cleaving protease. It acts on VWF to degrade large multimeric into smaller ones i.e. dimers. In its absence ultralarge multimeric VWF (ULVWF) levels are increased in circulating plasma which leads to preferential binding of platelets to ULVWF than the smaller ones. Finally platelet aggregation leads to thrombi formation, thereby, tissue ischemia.

The aHUS can be caused by complement dysregulation. The genetic mutation related to complement factor H, factor I, factor B, membrane co-factor protein (MCP), leads to activation of complement through alternative pathway, thereby, accumulation of activated complement on the surface of bacteria or damaged tissue e.g. apoptosed or inflamed renal tissue [12,13]. ST2 otherwise known as suppression of tumorigenicity 2 and, a member of the interleukin-1 (IL-1) receptor family, consists of a trans-membrane ligand (ST2L) and a soluble form (sST2). ST2 is released while cardiomyocytes are undergoing biochemical strain [14]. sST2 is a blood protein confirmed to act as a decoy receptor for interleukin-33 (IL-33). Assessment of plasma level of sST2 has been considered as a novel marker of cardiovascular events related to heart failure and ischemic heart diseases [15]. The ST2/IL-33 pathway is involved in the pathophysiology of myocardial dysfunction by attenuating the cardioprotective effects of IL-33 [16]. It may be postulated that endothelial damage in HUS might cause similarly sST2 level in serum which might predict ensuing HUS.

## Pathology

HUS is characterized by widespread TMA in renal glomeruli, the gastrointestinal tract, brain and the pancreas [17]. TMA shows evidence of vessel wall thickness with endothelial swelling, accumulation of amorphous material in the subendothelial space, intraluminal thrombosis and partial or complete obstruction of the vessel lumen leading to organ dysfunction. Endothelial cell damage is the key factor of TMA found in HUS. Fibrin thrombi are predominantly formed within small vessels followed by ischemic damage. Glomerular endothelial cell swelling, thrombotic occlusions of capillary lumen, tubular epithelial cell damage, mesangial expansion and mesangolysis have been observed [18].

## Clinical features

HUS is commonly seen in young children less than 5 years though it may affect adolescent as well. In developing countries like India, gastroenteritis being a very common illness in children it is found to be the major cause of acute renal failure (ARF) in children. But in author's personal experience D+ HUS is not so common as a cause of ARF in contrast to other causes like gastroenteritis with shock leading to prerenal renal failure, acute poststreptococcal glomerulonephritis, snake bite, acute on chronic renal failure, are major causes (Unpublished personal observation). In D+HUS manifestations of HUS starts after an interval of few days of onset of gastroenteritis which presents with fever, vomiting, abdominal pain, and frequent passage of loose stool which after 1-2 days interval may be changed to stool mixed with blood and mucus. Following the gastrointestinal episode child abruptly develops pallor, irritability, oligoanuria, lethargy, swelling of body, hypertension, hematuria. During this phase of ARF loose motions might abate or still continue showing evidence of dehydration. In HUS patients can show features of dehydration or volume overload depending on whether the enteritis or renal insufficiency predominates [2]. CNS disturbances like seizures, obtundation, irritability, and encephalopathy may occur but less common than TTP, aHUS. Thrombocytopenia which is quite commonly seen usually does not lead to cutaneous or mucosal bleeds. Extrarenal manifestations like pancreatitis, intestinal necrosis, jaundice, may also rarely occur. Apart from severe pallor child may show evidence of hepatosplenomegaly, elevated reticulocyte count, serum unconjugated bilirubin and lactate dehydrogenase (LDH).

Patients showing clinical features of pneumonia or empyema caused by *S. pneumoniae* may develop aHUS. Genetic or familial forms of HUS are usually protracted and unremitting or may have recurrent episodes which are frequently precipitated by various infections. Classical HUS commonly presents clinically with renal involvement in contrast to other types of TMA like aHUS, TTP more commonly having multiple systemic involvement e.g. CNS, lung, liver, pancreas, gastrointestinal tract etc. Intestinal complication can include intususception, bowel perforation and gangrene, ischemic enteritis, hemorrhagic colitis. Extrarenal involvement is common in aHUS and may even be the cause of death or sequelae in these patients [19,20].

## Diagnosis

Peripheral blood smear establishes the presence of MAHA by schistocytes, burr cells, helmet cells etc. The passage of RBC through

the narrow glomerular capillary lumen results in fragmentation of RBC, thereby, producing hemolysis and moderate to severe degree haemoglobin reduction. Thrombocytopenia is always seen though its degree is rarely severe. Polymorphoneuclear leucocytosis is usually seen. The degree of leucocytosis has been related to a poor prognosis [21]. Excess hemolysis leads to elevation of serum unconjugated bilirubin, lactate dehydrogenase. Intravascular hemolysis leads to reduction of haptoglobin due to its binding with released haemoglobin. Urine routine analysis reveals hemoglobinuria, hematuria, and mild protinuria [22,23]. The degree of renal insufficiency, which is nearly always presents, varies and is determined by evidence of raised serum urea, creatinine, phosphate and potassium. Coagulation studies like prothrombin and partial thromboplastin time are commonly normal in contrast to disseminated intravascular coagulation (DIC). The direct Coombs test is usually negative with the exception of pneumococcal induced HUS where it is positive in over 90% of cases [24]. In patients with D+HUS , etiological establishment of diagnosis by identification of pathogenic EHEC or Shigella on stool culture is very poor because the organisms that cause HUS following diarrhoea rapidly is cleared from stool. Evaluation for genetic forms should be done when prodromal history of diarrhea or pneumococcal infection is not available specially when the episodes are recurrent, chronic and associated with positive family history.

In D- HUS patients assay of specific complement factors (FH, FI, MCP) and ADAMTS13, levels of which are reduced, and antibody levels against FH, ADAMTS13, may be done. Genetic studies may also be considered for mutation analysis of complement factors, cobalamin and ADAMTS13 gene for confirmation of diagnosis. All the coagulation studies for exclusion of DIC show normal results in HUS except D-Dimer showing elevation. Aminoacidogram of serum and urine showing homocystinuria, hyperhomocystinemia and methyl malonic aciduria with low serum levels of methionine highlights cobalamine metabolism defects [25]. Apart from DIC other causes of acute renal failure associated with MAHA and thrombocytopenia like SLE, malignant hypertension, APLA syndrome should be considered in the appropriate clinical setting and excluded by relevant laboratory studies like antinuclear antibody (ANA), anti-double stranded DNA (anti-ds DNA),APLA,C3, C4, etc. Human immunodeficiency virus serology may be indicated in certain situations [26].

Renal biopsy is generally not required to diagnose D+HUS. The pathological changes described above under pathology are seen similarly in all the three types of TMA. In classical D+HUS predominantly fibrin thrombi are found in glomerular capillaries. In contrast, in aHUS the thrombi are made of fibrin, platelet and VWF clumps that involve larger renal and interlobular arterioles, thus causing ischemia and inflammation of larger volume of renal parenchyma [27]. Biopsy is indicated to determine the degree chronic injury and, therefore, long term prognosis, also in situations where diagnosis is in doubt. But sometimes thrombocytopenia may preclude renal biopsy.

## Treatment

In all HUS patients supportive care, early recognition of the disease and its complication with proper monitoring are the cornerstone of primary approach. If there is fluid deficit, fluid supplementation is of paramount importance. In volume overloaded condition fluid restriction, correction of electrolyte derangement, control of hypertension, and early initiation of dialysis if the patient is grossly oligoanuric, are essential. In the presence of significant anemia fresh packed red cell transfusions are given very carefully. Platelet transfusions are generally not required in view of absence of profound bleeding and also not given because transfused platelets are rapidly consumed by the active intravascular coagulation as well as excess destruction. Platelet transfusions are only considered prior to invasive procedure or where there is uncontrolled severe active bleeding.

There is no evidence that antimicrobial therapy directed against organism causing D+ HUS to arrest the cause provides benefit, but sometimes it may worsen the situation also. Several reports showed a worse outcome with antibiotic use; however a meta-analysis did not support any effect of antibiotics on the occurrence of HUS [28,6]. The use of antimotility drugs like loperamide inhibits expulsion of offending organism from gut and thus, invites the risk of HUS. Antibiotic therapy to remove the offending toxigenic organism can lead to excess production, thereby, worsening the disease process. Antibiotics may be indicated for the management of shigellosis with its complication. Prompt treatment of pneumococcal infection in pneumococcal HUS is most essential.

Plasma infusion (PI) or plasmapheresisis (PP) may be indicated in severe degree classical HUS especially with CNS involvement, although, no controlled data regarding its efficacy is available. There is definite role of replacement of deficient complement factors like factor H, I, and ADAMTS13 by PI in aHUS. PP is a useful treatment for removal of autoantibodies, VWF multimers, cytokines in aHUS.

## Prognosis

The immediate outcome of classical HUS is relatively good than in any other type of HUS. The classical D+ HUS has less than 5% mortality with good supportive care in most medical centres. Although the long term outcome is also better in these patients than other form of HUS, up to 10-30% patients develop chronic kidney disease and nearly 5-10% of these patients develop end stage renal disease (ESRD) in the next 10 years [27,22]. The prognosis for D- HUS is worse. Pneumococci-associated HUS, whose prognosis depends on severity of co-existent infection, causes increased morbidity, with mortality as high as 20%. In non- infection related HUS, up to 25% patients die in the acute phase, 50% progress to end stage renal failure [29]. The outcome of HUS due to ADAMTS 13 deficiency has improved with the advent of plasma therapy with mortality figures dropping from 80-90% to 10- 20% [30].

## Conclusion

The incidence of HUS as a cause of ARF in our country may be reviewed by further studies. Though the incidence of gastroenteritis in our country is very high in children only limited number of them suffers from HUS. Its reason is ill understood. This warrants future study to find out the cause. Indiscriminate use of antimicrobial in D+HUS is to be avoided as far as possible to reduce the incidence of mortality of HUS. Facilities for dialysis may be enhanced in most of the health care facilities in our country as a life saving measure to reduce HUS related mortality and morbidity. This review suggests future research work towards study of estimation of sST2 level in HUS patient which might help its early detection.

### Conflict of interest

None

### References

1. Gasser C, Gautier E, Steck A, Siebenmann RE, Oechstin R (1955) Hemolytic-uremic syndrome : bilateral necrosis of the renal cortex in acute acquired haemolytic anemia. Schweiz Med Wochenschr 85: 905-909.

2. Scot K, Why Van, Avner ED (2011) Hemolytic-Uremic Syndrome. In: Kliegman RM, Bonita, Stanton, St. Geme J, Schor N, Behrman RE (eds.) Nelson Textbook

of Pediatrics, (19thedtn), Saunders Elsevier, Philadelphia, pp: 1791-194.

3. Kaplan B, Levin M, De Chadrevian JP (1992) The haemolytic uremic syndrome. In: Edelman C Jr (ed.) Pediatrc kidney disease, (2ndedn) Little Brown, Bonston, pp: 1383-1405.
4. Fitzpatrick MM, Dillon MJ (1991) Current views on aetiology and management of haemolytic uraemic syndrome. Postgrad Med J 67: 707-709.
5. Kaplan BS, Meyers KE, Schulman SL (1998) The pathogenesis and treatment of hemolytic uremic syndrome. J Am Soc Nephrol 9: 1126-1133.
6. Scheiring J, Andreoli SP, Zimmerhackl LB (2008) Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). Pediatr Nephrol 23: 1749-1760.
7. Zoza C, Buelli S, Morigi M (2010) Shiga toxin-associated haemolytic uremic syndrome: pathophysology of endothelial dysfunction. Pediatr Nephrol 25: 2231-2240.
8. Noris M, Remuzzi G (2009) Atypical hemolytic-uremic syndrome. N Engl J Med 361: 1676-1687.
9. Skerka C, Józsi M, Zipfel PF, Dragon-Durey MA, Fremeaux-Bacchi V (2009) Autoantibodies in haemolytic uraemic syndrome (HUS). Thromb Haemost 101: 227-232.
10. Roumenina LT, Jablonski M, Hue C, Blouin J, Dimitrov JD, et al. (2009) Hyperfunctional C3 convertase leads to complement deposition on endothelial cells and contributes to atypical hemolytic uremic syndrome. Blood 114: 2837-2845.
11. Furlan M (1996) Von Willebrand factor: molecular size and functional activity. Ann Hematol 72: 341-348.
12. Kavanagh D, Richards A, Atkinson J (2008) Complement regulatory genes and hemolytic uremic syndromes. Annu Rev Med 59: 293-309.
13. Atkinson JP, Goodship TH (2007) Complement factor H and the hemolytic uremic syndrome. J Exp Med 204: 1245-1248.
14. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, et al. (2007) IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 117: 1538-1549.
15. Ky B, French B, Levy WC, Sweitzer NK, Fang JC, et al. (2012) Multiple biomarkers for risk prediction in chronic heart failure. Circ Heart Fail 5: 183-190.
16. Ciccone MM, Cortese F, Gesualdo M, Riccardi R, Di Nunzio D, et al. (2013) A novel cardiac bio-marker: ST2: a review. Molecules 18: 15314-15328.
17. Ruggenenti P, Noris M, Remuzzi G (2001) Thrombotic microangiopathy, haemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int 60: 831-846.
18. Habib R (1992) Pathology of the haemolytic uremic syndrome. In: Kaplan BS, Trompeter RS, Moake JL (eds.) Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic purpura. Marcel Dekker, Newyork, pp: 315-353.
19. Upadhyaya K, Barwick K, Fishaut M, Kashgarian M, Siegel NJ (1980) The importance of nonrenal involvement in hemolytic-uremic syndrome. Pediatrics 65: 115-120.
20. Siegler RL (1994) Spectrum of extrarenal involvement in postdiarrheal hemolytic-uremic syndrome. J Pediatr 125: 511-518.
21. Exeni RA, Fernandez GC, Palermo MS (2007) Role of polymorphonuclear leucocytes in the pathophysiology of typical haemolytic uremic syndrome. Scientific world J 7: 1155-1164.
22. Ray PE, Liu XH (2001) Pathogenesis of Shiga toxin-induced hemolytic uremic syndrome. Pediatr Nephrol 16: 823-839.
23. Sadler JE, Moake JL, Miyata T, George JN (2004) Recent advances in thrombotic thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program.
24. Copelovitch L, Kaplan BS (2008) Streptococcus pneumonia- associated haemolytic uremic syndrome. Pediatr nephrol 23: 1951-1956.
25. Sharma AP, Greenberg CR, Prasad AN, Prasad C (2007) Hemolytic uremic syndrome (HUS) secondary to cobalamin C (cblC) disorder. Pediatr Nephrol 22: 2097-2103.
26. Copelovitch L, Kaplan BS (2008) The thrombotic microangiopathies. Pediatr Nephrol 23: 1761-1767.
27. Blackall DP, Marques MB (2004) Hemolytic uremic syndrome revisited: Shiga toxin, factor H, and fibrin generation. Am J Clin Pathol 121 Suppl: S81-88.
28. Safdar N, Said A, Gangnon RE, Maki DG (2002) Risk of hemolytic uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 enteritis: a meta-analysis. JAMA 288: 996-1001.
29. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, et al. (2006) Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood 108: 1267-1279.
30. Loirat C, Girma JP, Desconclois C, Coppo P, Veyradier A (2009) Thrombotic thrombocytopenic purpura related to severe ADAMTS13 deficiency in children. Pediatr Nephrol 24: 19-29.