THROMBOTIC THROMBOCYTOPENIC PURPURA & HEMOLYTIC-UREMIC SYNDROME

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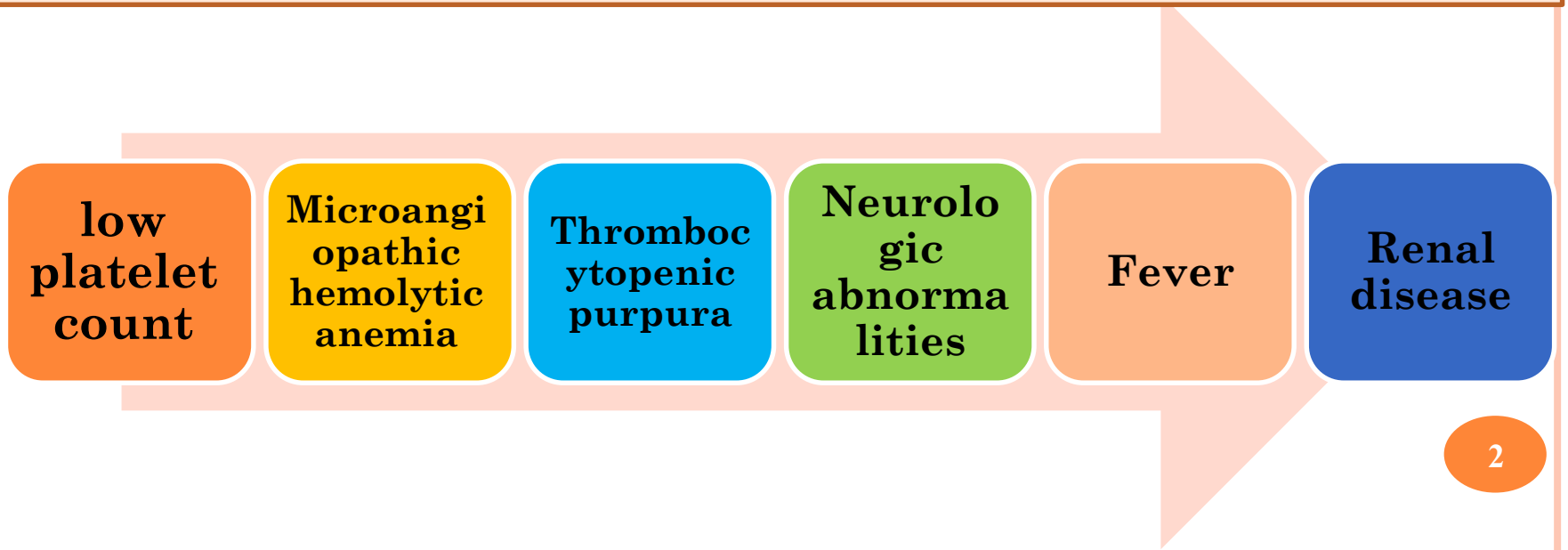
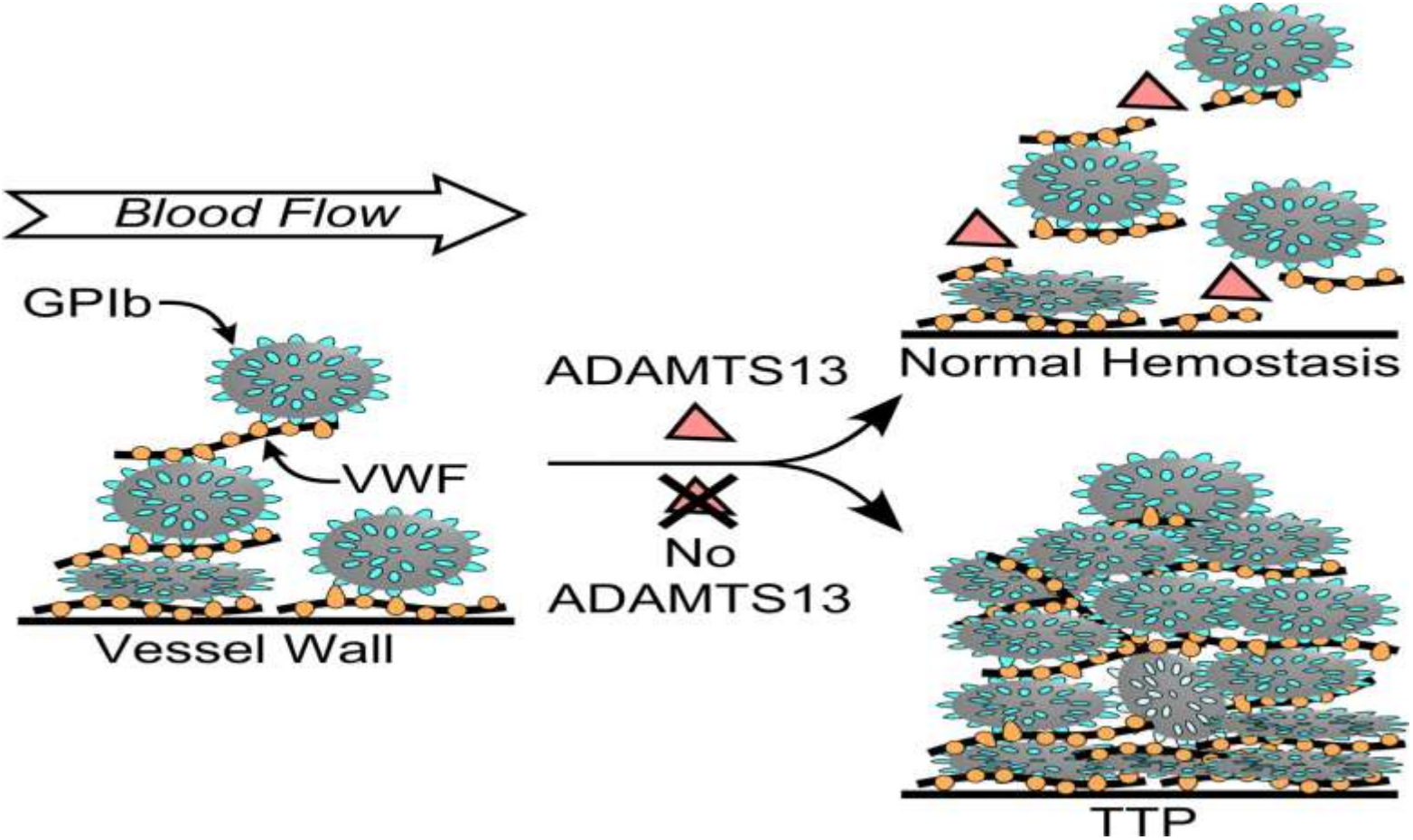
Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by clotting in small blood vessels of the body (thrombosis), resulting in:



CAUSE

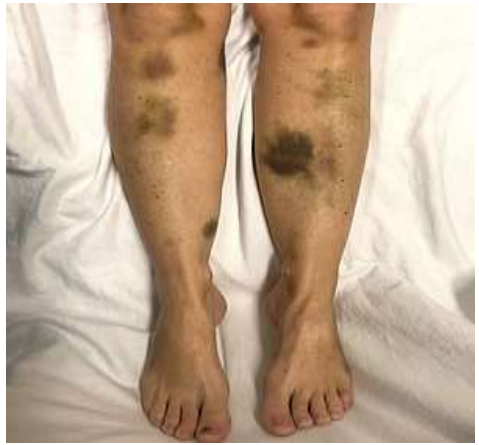
- **The exact etiology of TTP is unknown.**
- **Most sporadic cases of TTP appear to be associated with severe deficiency of ADAMTS13 activity due to autoantibodies against this protease.**
- **deficiency of a vWF-cleaving protease was associated with formation of platelet microthrombi in the small blood vessels.**
- **IgG antibodies directed against this enzyme caused TTP in a majority of non-familial cases.**

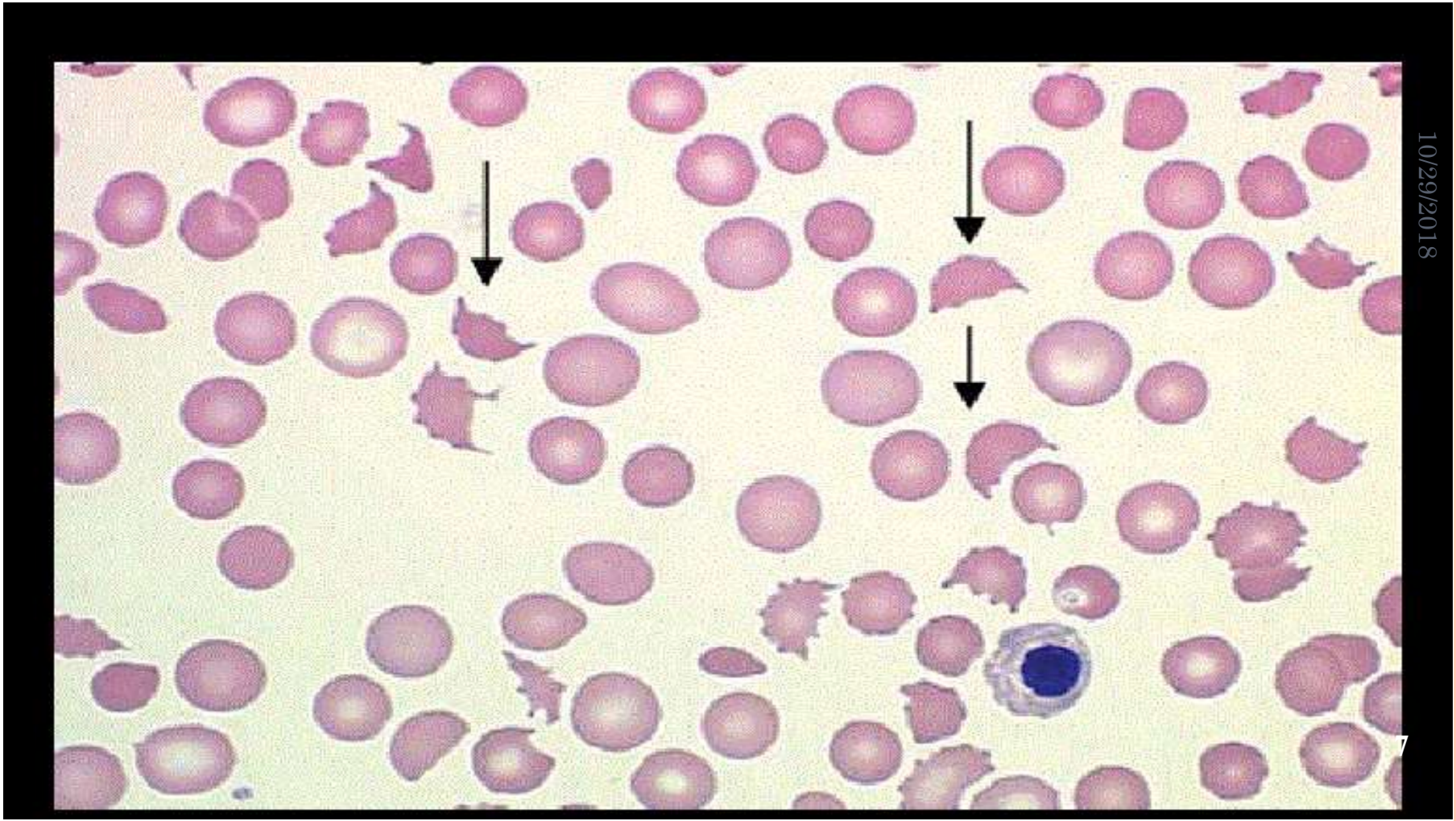

Blood Flow
GPIb
VWF
Vessel Wall
ADAMTS13
No
ADAMTS13
Normal Hemostasis
TTP

SIGNS AND SYMPTOMS

- **Acute or subacute onset of symptoms related to neurologic dysfunction, anemia, or thrombocytopenia.**
- **Neurologic manifestations include alteration in mental status, seizures, hemiplegia, paresthesias, visual disturbance, and aphasia.**
- **Fatigue due to anemia**
- **petechiae & large bruises & severe bleeding from thrombocytopenia is rare**
- **TTP can affect any organ system, but involvement of the peripheral blood, the central nervous system, and the kidneys causes the clinical manifestations**

- **Classic TTP patients (20-30%) present with:**
- **Microangiopathic hemolytic anemia (schistocytes, elevated LDH, and indirect hyperbilirubinemia).**
- **Thrombocytopenia**





DIAGNOSIS

- **Measuring ADAMTS13 activity level may aid in diagnosis.**
- **ADAMTS-13 activity is often severely deficient (<10% of normal)**

- **Laboratory studies:**
- **CBC, platelet count, blood smears, coagulation studies, BUN creatinine, and serum bilirubin and lactate dehydrogenase.**

- **Imaging studies and biopsies are not required for diagnosis.**

- Total white blood cell count is normal or slightly elevated
- Hemoglobin concentration is moderately depressed at 8-9 g/dL
- Platelet count generally ranges from 20,000-50,000/µL
- Peripheral blood smears reveal moderate-to-severe schistocytosis.
- Prothrombin time {(I N R) and APTT} results typically are normal in both TTP and in HUS).
- D-dimers are indicative of fibrinolysis and thrombin activation, which usually is normal or mildly elevated in patients with TTP
- Fibrinogen typically is in the high to high-normal range

- **Evaluation of renal function**

- **LDH level in the 1000 IU/L range (normal, < 200 IU/L) is not unusual.**
- **Moderate degree of hyperbilirubinemia (2.5-4 mg/dL) is present, with the indirect form predominating.**
- **The direct Coombs test determines the presence of antibodies on red cells.**
- **Antibodies, if present, are more consistent with autoimmune hemolytic anemia.**
- **Because of the association of TTP/HUS with HIV infection, serologic evaluation for HIV infection should be obtained.**
- **Measurement of von Willebrand factor–cleaving protease (ADAMTS13) activity holds the promise of helping diagnose TTP.**

Management

- The therapy of choice for TTP is plasma exchange with fresh frozen plasma.

- **Usually, at least five plasma exchanges are performed in the first 10 days.**
- **it is to exchange 1.5 plasma volumes with each exchange for five consecutive days.**
- **If no response to exchange is observed, a second course of five exchanges can be performed.**
- **Others have used a course of at least seven exchanges during the first nine days of therapy.**
- **The vast majority of responses were seen within the first 10 plasma exchanges.**
- **In few some patients took up to 15 exchanges to respond**

- **Plasma exchange generally is well tolerated.**

- **COMPLICATION**
- **intravenous access problems**
- **hypotension**
- **reactions to plasma.**

- **Hypotension can result from the necessary extracorporeal volume in the apheresis device.**

Complete response criteria

- Resolution of neurologic symptoms
- Normalization of hemoglobin, platelet count, LDH, and bilirubin
- Normalization of creatinine

ADEQUATE INITIAL RESPONSE IS FULFILLED

- if neurologic signs and symptoms disappear
- Platelet count climbs to greater than 50,000/µL
- LDH level declines.

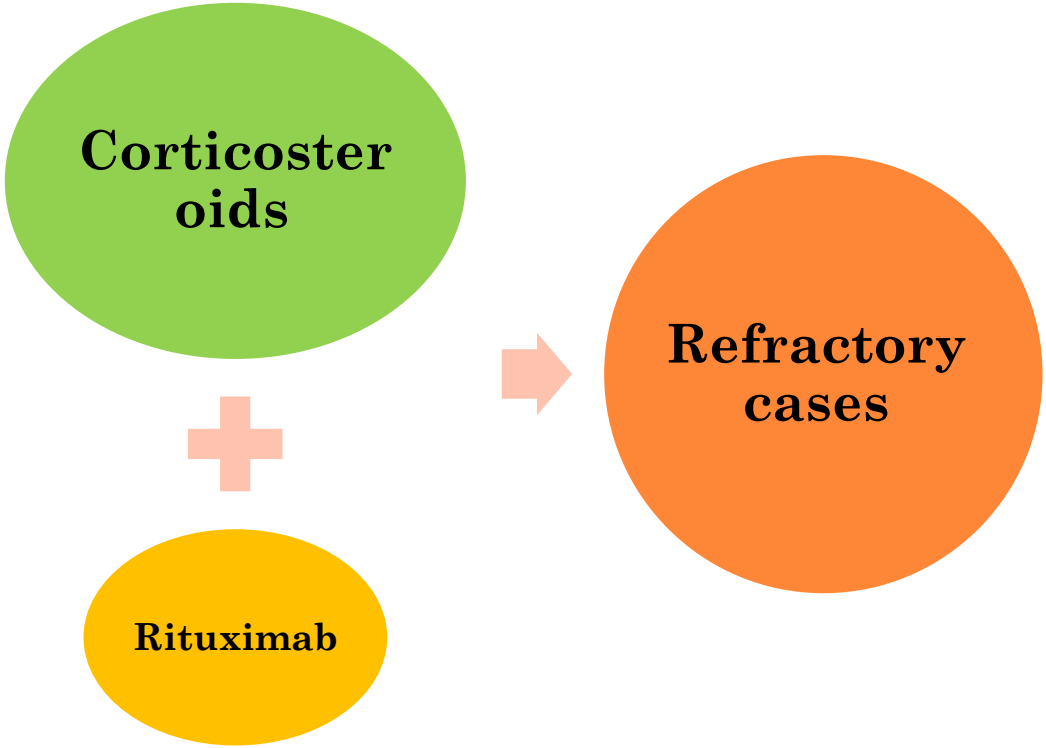
- In patients who respond to plasma exchange, the mean time to resolution of neurologic changes is approximately 3 days
- to a normal LDH is 5 days
- to a normal platelet count is 10 days
- to normal renal function is 15 days.

PLASMA INFUSION

- **In those patients refractory to plasma exchange, using cryopoor plasma (or cryosupernatant) has sometimes led to a response.**

- **This is fresh frozen plasma that has had the cryoprecipitate removed and is thus depleted of high-molecular-weight von Willebrand multimers, which have a pathogenic role in TTP.**

TREATMENT OF TTP



- **Untreated, TTP** has a **mortality rate** of as high as **90%**.

- **With plasma exchange, the mortality rate is reduced to 10-20%.**

COMPILICATION OF TTP

- **Acute morbidities include ischemic events:**

- **Stroke**
- **Transient ischemic attacks**
- **Myocardial infarction and arrhythmia**
- **Bleeding**
- **Azotemia.**

- **TTP during pregnancy may precipitate fetal loss.**

CASE PRESENTATION

- A 29-year-old woman was admitted to the hospital with abdominal pain and bloody diarrhea.
- She was previously healthy and had no specific past medical history.
- Stool culture was performed and she received intravenous hydration.
- On hospital day 2, her urine volume decreased, and generalized edema developed.
- She was transferred to Chonnam National University Hospital (CNUH).
- Upon admission her blood pressure was 120/70 mmHg, pulse rate was 72/min, respiration rate was 32/min, and body temperature was 36.6℃.
- The abdomen was slightly tender but not distended.
- Laboratory tests showed a serum creatinine of 4.2 mg/dL, blood urea nitrogen of 35.4 mg/dL, hemoglobin 9.2 g/dL, platelet count 19,000/mm3, corrected reticulocyte count 5.4%, lactate dehydrogenase 3150 IU/L, haptoglobin 7.69 mg/dL, total bilirubin 1.31 mg/dL, and direct bilirubin 0.19 mg/dL.
- Peripheral blood smear showed microangiopathic hemolytic anemia

Hemolytic-Uremic Syndrome

- **A diagnosis of HUS was made based on the occurrence of acute renal failure, hemolytic anemia, and thrombocytopenia.**
- **Escherichia coli O104:H4 was identified in the stool culture performed at the hospital where she was first admitted by using polymerase chain reaction for virulence-associated genes of EHEC. but other EHEC related serogroups including Escherichia coli O157:H7 were not found at Chonnam Institute of Health and Environment.**
- **She received hemodialysis for four days, and plasma exchange and fresh frozen plasma for two weeks.**

- **On hospital day 14, tonic seizure occurred suddenly but was not presented until the following day.**
- **The brain computed tomography (CT) and electroencephalogram (EEG) did not show any abnormalities.**
- **On hospital day 20, her platelet count rose to 299,000/mm3, hemoglobin rose to 10.6 g/dL, reticulocyte count dropped to 1.5%, lactate dehydrogenase dropped to 507 IU/L, and blood urea nitrogen and serum creatinine fell to 17.5 mg/dL and 1.0 mg/ dL, respectively.**
- **Peripheral blood smear did not show evidence of hemolytic anemia.**
- **After hospital day 21, two successive stool specimens yielded negative results for Escherichia coli O104:H4.**
- **On hospital day 27, she was discharged and received follow-up care as an outpatient.**

- **Although the role of plasma exchange in HUS secondary to EHEC infection remains controversial.**

- **They suggest that plasma exchange may improve the outcome in adult bloody diarrhea-associated HUS.**

- A Case of Hemolytic Uremic Syndrome Caused by Escherichia coli O104:H4, Yonsei Med J. 2006 Jun 30; 47(3): 437–439.
- Published online 2006 Jun 30. doi: [10.3349/ymj.2006.47.3.437]

HEMOLYTIC-UREMIC SYNDROME (HUS)

- **Hemolytic-uremic syndrome (HUS) is a clinical syndrome characterized by**

Progressive renal failure
Microangiopathic hemolytic anemia
Thrombocytopenia.

- **HUS is the most common cause of acute kidney injury in children.**

PATHOPHYSIOLOGY

- HUS

- Shiga Toxin
- E coli O157:H7
- Enterohemorrhagic E. coli (EHEC)

- Acute diarrheal illness

- Endothelial damage

- Platelet activation & aggregation

- Microthrombi

- **Shiga-like toxin (verocytotxin) that may cause direct renal and endothelial cell damage and may adhere to intestinal epithelium resulting in bloody diarrhea.**

- **Thrombocytopenia occurs as a consequence of platelet consumption, and hemolytic anemia results from intravascular fibrin deposition, increased red blood cell fragility, and fragmentation.**

- HUS is classified into two main categories, depending on whether it is associated with **Shiga-like toxin (Stx) or not.**

- **Shiga-like toxin** caused by
- **Shigella dysenteriae**
- **Escherichia coli**.

} **Contaminated food & water**

TYPICAL (STX–ASSOCIATED) HUS

- **Typical HUS (Shiga-like toxin)**
- **is the classic, primary or epidemic form of HUS.**
- **Occur in children younger than 2-3 years.**
- **Acute diarrheal illness (abdominal pain + bloody diarrhea + no fever**
- **Acute kidney injury occurs in 55-70% of patients.**
- **70% of Stx-associated HUS cases are secondary to E coli serotype O157:H7.**

ATYPICAL (NON–STX-ASSOCIATED) HUS

- **Atypical HUS, is less common than Stx-HUS and accounts for 5-10% of all cases.**
- **It is more frequent in adults and occurs without prodromal diarrhea.**
- **The familial form is associated with genetic abnormalities of the complement regulatory proteins.**
- **It has a poor outcome**
- **50% may progress to end-stage renal disease (ESRD) or irreversible brain damage.**
- **Up to 25% of patients die during the acute phase.**

CAUSES OF NON–STX-ASSOCIATED HUS

- Drugs (cyclosporine, tacrolimus)
- Malignancies
- Transplantation
- Pregnancy
- In rare case (eg, antiphospholipid syndrome, systemic lupus erythematosus)

Clinical Presentation

- **Prodromal gastroenteritis (83%) - Fever (56%), bloody diarrhea (50%) for 2-7 days before the onset of renal failure**
- **Irritability, lethargy**
- **Seizures (20%)**
- **Acute renal failure (97%)**
- **Anuria (55%)**

Physical Examination

- Hypertension
- Edema, fluid overload
- Pallor & jaundice
- Echymatic & purpura rash

Laboratory Studies

- **Urinalysis:**
- **Benign mild proteinuria**
- **Red blood cells (RBCs) and RBC casts**

- **Blood urea nitrogen (BUN), serum creatinine, and serum electrolyte levels**

- **Hematologic determination:**
- **Severe anemia may be present.**
- **peripheral blood smear for schistocytes**
- **Thrombocytopenia**

- **Hemolytic workup:**
- **Bilirubin levels may be elevated.**
- **Lactate dehydrogenase (LDH) levels may be elevated.**
- **Haptoglobin levels may be decreased.**

- **Stool culture:**
- **Evaluate especially for E coli 0157:H7 and Shigella bacteria.**

TREATMENT

- **Supportive therapy**
- **Maintain fluid and electrolyte balance**
- **Adequate blood-pressure control and adequate renin-angiotensin blockade is helpful for patients who have chronic kidney disease after an episode of Stx-HUS**
- **For seizure control, consider prophylactic phenytoin in patients with neurologic symptoms (20-40% of patients have seizures)**
- **Control azotemia by dialysis**
- **Optimize nutrition**

- **Avoid of antibiotics unless patient is septic.**

- **Antibiotics increase toxin production due to location of stx genes within antibiotic.**

- **Renal transplantation is safe and effective for children who progress to end-stage renal disease (ESRD).**
- **The recurrence rate in patients who undergo renal transplantation for HUS is 0-10%.**
- **Eculizumab used for the treatmant of atypical hemolytic uremic syndrome.**
- **This monoclonal antibody inhibits complement-mediated thrombotic microangiopathy.**

Plasma exchange is not recommended as initial therapy in typical HUS.

NON–STYX-ASSOCIATED HUS

- **Plasma exchange is the initial treatment of choice in all adult patients with:**

- **Non-Stx-HUS (atypical HUS)**
- **Thrombotic thrombocytopenic purpura (TTP)**

- **Plasma treatment should be started within 24 hours of the patient's presentation, to decrease treatment failures.**

- **It should be continued once or twice a day for at least 2 days after complete remission.**

ROLE OF PLASMA INFYSION ON LONG TERM

- **high-dose plasma infusion (30 mL/kg) at weekly intervals over 30 months, but the long-term effects are still unknown.**

- **Renal transplantation is not an option for non–Stx-HUS because of the 50% recurrence rate and >90% rate of graft failure in patients with recurrence.**

CONCLUSION

Clinical differentiation of hemolytic-uremic syndrome (HUS) and TTP can be problematic.

- **Differentiation is often based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.**

- **Role of bacterial Shiga toxin in HUS and of a deficiency in a protease ADAMTS13 in TTP.**

Interventions for hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: a systematic review of randomized controlled trials.

Review article

Michael M, et al. Am J Kidney Dis. 2009.

Show full citation

Abstract

BACKGROUND: Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are related conditions with similar clinical features of variable severity. The objective of this systematic review is to evaluate the benefits and harms of available

CONCLUSIONS: No additional therapy has been shown to increase efficacy over plasma exchange for TTP. No intervention has been shown to be superior to supportive therapy in patients with postdiarrheal HUS.

PMID: 18950913 [Indexed for MEDLINE]

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Fever	+/-	-/+	-	+/-
Liver impairment	+/-	+/-	+++	+/-
Hypertension	-/+	+/-	+/-	-
Hemolysis	+++	++	++	+
Thrombocytopenia	+++	++	++	+++
Coagulopathy	-	-	+/-	+++


THANK YOU!