International Journal of Multidisciplinary Research and Growth Evaluation.

Hemolytic Uremic Syndrome

Dr. Desireddy [1*]. Rama Brahma Reddy [2], Kunchala Malleshwari [3], Vagga Suresh [4], Banavath Upendra Naik [5], Mallavarapu Prem Kumar [6]

[1] Principal and Professor, Department of Phyto Chemistry, Nalanda Institute Of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

[2] Associate Professor Department of Pharmaceutics, Nalanda Institute Of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

[3-6] Students of B. Pharmacy, Nalanda Institute Of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

* Corresponding Author: **Vo Thi Anh Dao**

Article Info

ISSN (online): 2582-7138
Volume: 05
Issue: 05
September-October 2024
Received: 05-07-2024
Accepted: 06-08-2024
Page No: 200-205

Abstract

Hemolytic uremic syndrome (HUS) is a clinical syndrome characterized by the triad of thrombotic microangiopathy, thrombocytopenia, and acute kidney injury. Hemolytic uremic syndrome represents a heterogeneous group of disorders with variable etiologies that result in differences in presentation, management and outcome. In recent years, better understanding of the HUS, especially those due to genetic mutations in the alternative complement pathway have provided an update on the terminology, classification, and treatment of the disease. This review will provide the updated classification of the disease and the current diagnostic and therapeutic approaches on the complement-mediated HUS in addition to STEC-HUS which is the most common cause of the HUS in childhood. Haemolytic uraemic syndrome (HUS) is defined by the simultaneous occurrence of nonimmune haemolytic anaemia, thrombocytopenia and acute renal failure. This leads to the pathological lesion termed thrombotic microangiopathy, which mainly affects the kidney, as well as other organs. HUS is associated with endothelial cell injury and platelet activation, although the underlying cause may differ. Most cases of HUS are associated with gastrointestinal infection with Shiga toxin-producing enterohaemorrhagic *Escherichia coli* (EHEC) strains. Atypical HUS (aHUS) is associated with complement dysregulation due to mutations or autoantibodies. In this review, we will describe the causes of HUS. In addition, we will review the clinical, pathological, haematological and biochemical features, epidemiology and pathogenetic mechanisms as well as the biochemical, microbiological, immunological and genetic investigations leading to diagnosis. Understanding the underlying mechanisms of the different subtypes of HUS enables tailoring of appropriate treatment and management.

Keywords: Acute kidney injury, hemolytic anemia, complement, thrombocytopenia, thrombotic microangiopathy

1. Introduction

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TMA) characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. HUS is most commonly caused by Shiga toxin (typical HUS) or, less commonly, infections or genetic abnormalities activating the alternative complement pathway (atypical HUS). Additional causes can be secondary to malignancy, autoimmune disorders, genetic mutations, and medication use. Extrarenal manifestations are common in HUS, particularly neurological symptoms Prompt recognition of HUS's varied etiologies and manifestations

is essential for timely diagnosis and intervention, optimizing patient outcomes. Thrombotic microangiopathy encompasses various systemic diseases in which endothelial damage causes thrombosis in the microvasculature, including capillaries, arterioles, and venules, resulting in consumptive platelet aggregations. This leads to mechanical shearing of the red blood cells (RBCs), Coombs-negative hemolytic anemia, and end-organ damage. The triad of thrombocytopenia, hemolytic anemia, and ischemic end-organ damage defines thrombotic microangiopathy Some of the more common TMAs from which HUS must be differentiated are thrombotic thrombocytopenic purpura (TTP); syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP); and disseminated intravascular coagulation (DIC). Despite similar pathogeneses, the treatments of these entities differ significantly. Prior classifications of HUS often depended on the presence or absence of bloody diarrhea, with its presence used to diagnose typica lHUS associated with Shiga toxin. However, atypical HUS can also present with bloody diarrhea in up to 30% of cases, so an etiology-based classification system is preferred.[2]

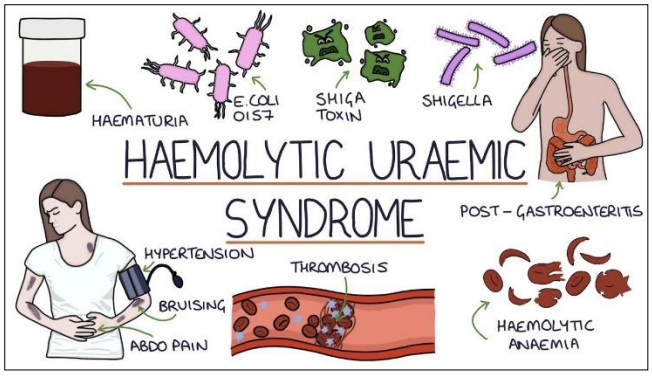

Fig 1: Haemolytic uraemic syndrome

Ethilogy

Shiga toxin causing typical HUS can be divided into 2 main subtypes—*Stx1* and *Stx2*. *Stx2* is associated with more severe disease and a greater need for renal replacement therapy. Traditionally, *Escherichia coli 0157:H7 (E coli 0157:H7)* has been linked to typical HUS; however, in recent years, non-0157 serotypes have become dominant. The most common cause of typical HUS in North America and Europe is *E coli 026:H11*. Shiga toxin from *Shigella dysenteriae* produces a similar disease pattern to STEC, except symptoms are much more severe, and the fatality of HUS with *Shigella dysenteriae* is estimated at 36%. Rarely, *Salmonella spp* are also associated with HUS caused. The cause of aHUS is the abnormal activation of the alternative complement pathway. The complement system is part of the innate immune system and is composed of 3 pathways of activation: classical, alternative, and lectin-binding. The initial steps of each separate pathway converge at the step of forming C3 convertase, leading to the formation of the membrane-attack complex (MAC), which then lyses target cells. [2]

Epidemology

EHEC-associated HUS occurs primarily in children younger than 5 years of age and in the elderly. After an incubation period of 4–7 days, EHEC-infected patients develop diarrhoea and approximately 15% of cases develop HUS within an additional 2–10 days. Patients may be infected by intake of contaminated food including raw, processed or undercooked meat, vegetables, unpasteurized juice or milk products, cross-contamination of food products and utensils, intake of contaminated water, even from swimming pools, person-to-person transmission or contact with animals bearing the strain Transmission occurs more often in summer requires a very low number of bacterial organisms and occurs in outbreaks or sporadically. Very large outbreaks have occurred in Japan and in Germany, but smaller outbreaks have been reported in numerous countries. In countries in which intake of raw meat is higher, EHEC infection is endemic and HUS rates are thus higher, such as in Argentina. The incidence in Argentina has been reported to be as high as 12.2 cases per 100 000 children younger than 5 years of age It is difficult to assess the annual incidence of EHEC-associated HUS, but overall rates corresponding to two per 100 000 for all age groups have been reported and up to six per 100 000 in children younger than 5 years of age. [1]

Types of HUS

Hemolytic uremic syndrome has different etiological classifications in the literature Some of these classifications overlap with TMA classifications in terms of underlying diseases. In clinical practice, the commonly used classification is typical and atypical HUS classification. Typical HUS is used for STEC-HUS. On the other hand, some controversies related with the definition of atypical HUS (aHUS) exist in the literature. Until recently, the definition of aHUS has been used for all HUS cases other than STEC-HUS. In recent years, it has started to be used only for complement-related HUS by some authors. In the review which was published at the time of writing of this article and which had the characteristics of being an international consensus report for treatment of aHUS, the classification of HUS was updated and it was stated that limitation of the definition of aHUS only to complement-related HUS was still controversial In this report, it was recommended that the definition of aHUS should be limited to the cases of HUS excluding HUS “secondary” to malign diseases, autoimmune diseases, drugs, organ transplantation and HIV infection “HUS with coexisting diseases. [1]

Typical HUS

Shiga toxin–producing *Escherichia coli* (STEC), called typical HUS, is the most common cause of HUS. Typical HUS comprises 90% to 95% of HUS cases and commonly arises from consuming contaminated food or drink and through person-to-person contact. The incidence of HUS among individuals infected with STEC ranges from 5% to 15%, predominantly affecting children younger than 5. Typically, a presentation of bloody diarrhea occurs around day 2 or 3 following exposure, with HUS onset developing 3 to 10 days after the start of diarrhea. Other common symptoms are vomiting (67%), fever (37%), and abdominal pain (29%). [2]

Atypical HUS

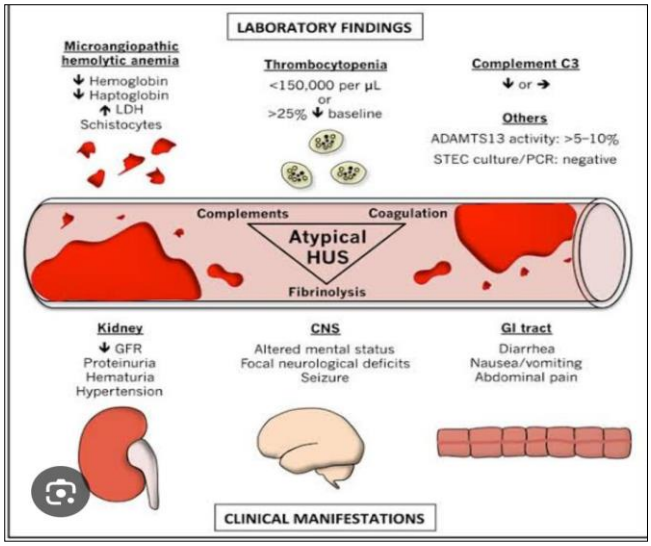

Fig 2: Atypical HUS

Atypical HUS (aHUS) constitutes 5% to 10% of HUS cases and is linked to genetic mutations affecting the alternative complement pathway. Under physiological conditions, the alternative complement system is continuously active at low levels. However, inflammatory conditions such as infections can induce endothelial damage, triggering the activation of the coagulation cascade and causing a TMA presentation. The initial clinical manifestation of aHUS typically involves nonspecific symptoms like fatigue, pallor, or somnolence. These symptoms can progress to signs of acute kidney injury (AKI), including oliguria, uremia, and fluid overload. The risk of progression to stage 3 or 4 chronic kidney disease (CKD) and end-stage renal disease (ESRD) in aHUS is high. In contrast to typical HUS, patients with aHUS often fail to regain kidney function without treatment. Untreated, approximately 50% of aHUS cases progress to dialysis dependency, with a mortality rate of 25%. Similar to typical HUS, aHUS may exhibit extrarenal manifestations, notably cardiac and neurological, including heart failure, pulmonary hypertension, seizures, coma, and blindness. These manifestations significantly contribute to the morbidity and mortality associated with aHUS. In contrast to typical HUS, patients with aHUS commonly relapse; patients must be monitored closely for relapse after treatment is discontinued.[2]

Secondary HUS

The last category of HUS involves patients with HUS secondary to underlying conditions or infections, commonly presenting as aHUS with abnormal complement system activation. The most significant component of this category is HUS caused by S*treptococcus pneumoniae*, accounting for 5% to 15% of all cases of HUS in children. *S pneumoniae* releases neuraminidase, exposing cellular antigens and activating the alternative complement system. This is the only cause of Coombs-positive HUS, and early antibiotic administration is indicated.

Other causes of secondary aHUS are as follows:

- inherited vitamin B12 (cobalamin) metabolism disorders;
- diacydiacylglycerol kinase ε (DGKE) mutations;
- HIV;
- influenza virus;
- autoimmune disease, eg, systemic lupus erythematosus, antiphospholipid antibody syndrome;
- drugs, eg, quinine, calcineurin inhibitors, chemotherapeutic agents; and
- malignant hypertension. [2]

Patho physiology

HUS is typically associated with bacterial infection resulting from the consumption of undercooked beef, unpasteurized milk, or other food or drink contaminated by cattle manure; cattle are asymptomatic carriers of STEC. Once ingested, STEC penetrates the mucous layer of the intestine and secretes Shiga toxin, which binds to the receptor Gb3. The Shiga toxin/Gb3 complex binds to cell ribosomes, inhibiting protein synthesis and causing apoptosis; inflammatory cytokines are also produced. In addition to cytotoxic effects, Shiga toxin is capable of activating the complement system by inhibiting complement factor H. Upon entering the bloodstream, Shiga toxin persists in binding to cells via the Gb3 receptor, with the highest prevalence found in the glomerular microvasculature. Endothelial damage is caused by 1) direct cytotoxicity of Shiga toxin, 2) disturbance of the hemostatic pathway, 3) increased cytokine release, and 4) alternative pathway activation This endothelial damage then initiates the pathology associated with TMA. In aHUS, the alternative complement pathway is activated as described above, with particular emphasis on regulatory Factor H that stabilizes C3 and inactivates C3b. aHUS is usually associated with a genetic abnormality affecting the regulation in the alternative complement system coupled with an inciting stress such as infection. Secondary HUS generally follows the same pathophysiology pattern as Ahus. [1]

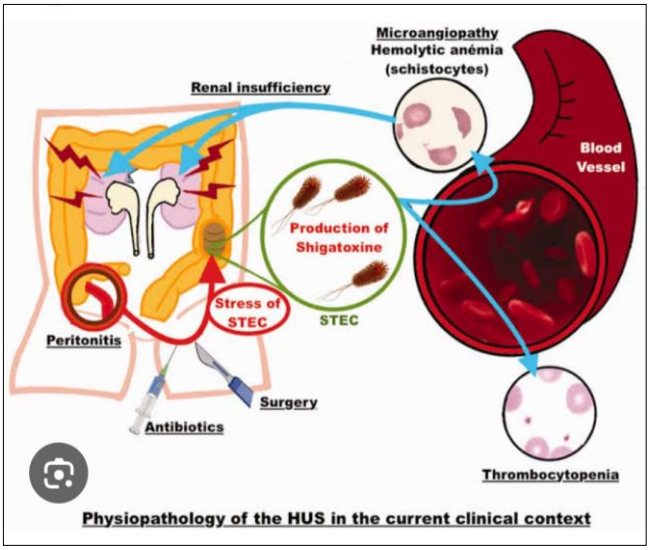

Fig 3: Physiopathology of the HUS in the current clinical context

Symptoms

- The symptoms of hemolytic uremic syndrome vary, depending on the cause. The first symptoms of hemolytic uremic syndrome caused by E. coli bacteria might include:
- Diarrhea, which is often bloody.
- Pain, cramping or bloating in the stomach area.
- Fever.

- Vomiting.
- All forms of hemolytic uremic syndrome damage blood vessels. This damage causes red blood cells to break down, called anemia. The condition also causes blood clots to form in the blood vessels and, in turn, damage the kidneys.
- Symptoms of these changes include:
- Loss of color the skin.
- Extreme tiredness.
- Easy bruising.
- Unusual bleeding, such as bleeding from the nose and mouth.
- Decreased urinating or blood in the urine.
- Swelling, called edema, of the legs, feet or ankles. Swelling occurs less often in the face, hands, feet or entire body.
- Confusion, seizures or stroke,
- High blood pressure.[9]

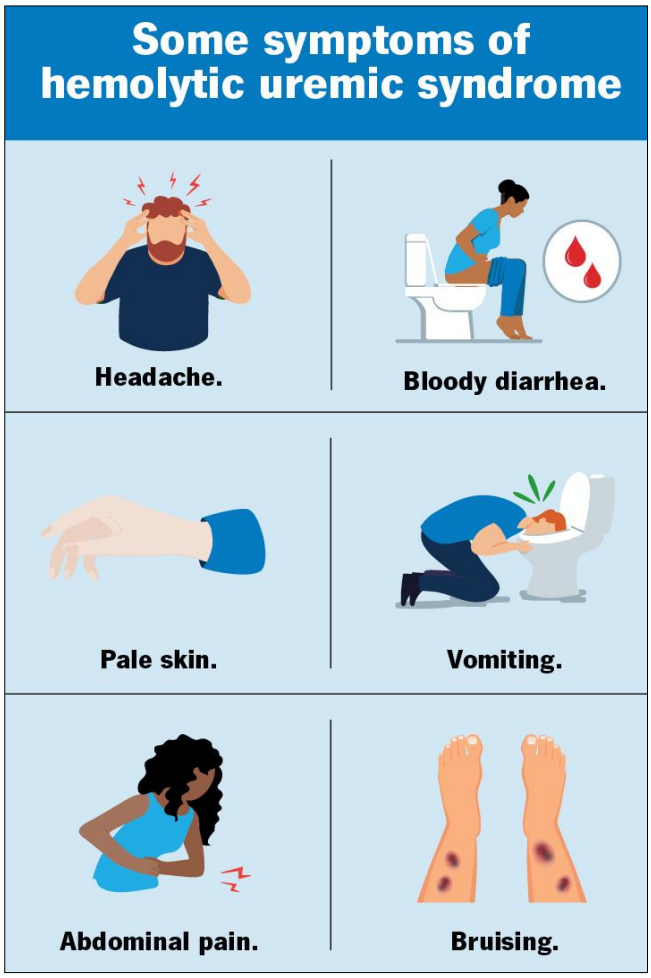

Fig 4

Diagnosis

The diagnosis is made by clinical and laboratory findings of microangiopathic hemolytic anemia, thrombocytopenia and acute renal damage and demonstration of the disruption in regulation of the complement system. Decreases serum C3 level is a warning finding. C4 is normal in all patients. The definite diagnosis is made by serological and genetic tests related with the complement system. Serum CFH, CFI and CFB levels, anti-factor H antibody measurement and genetic mutations of the complement proteins are the tests performed for this objective. However, these tests are not widely used and easily applicable.The disease which cause to complement-related HUS show differences in terms of age of onset, laboratory findings and prognosis. These differences give an idea both in terms of the diagnosis and prognosis, but the definite diagnosis is made by demonstration of the genetic mutations.[8]

Complications

Hemolytic uremic syndrome can cause life-threatening complications, including:

- Kidney failure, which can be sudden, called acute, or happen over time, called chronic.
- High blood pressure.
- Stroke or seizures.
- Coma.
- Clotting problems, which can lead to bleeding.
- Heart problems.[7]

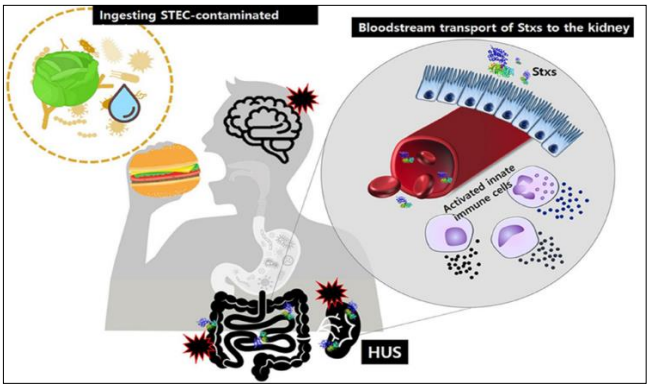

Fig 5

Treatment

There is no specific therapy. Priority should be given to supportive treatment.

Supportive treatment: Adjustment of fluid and electrolyte balance, control of blood pressure and regulation of dialysis and hematological variables constitute the essentials of supportive treatment. Fluid and electrolyte treatment: This is evaluated according to the fluid status and renal function of the patient. In the begining of the disease, vomiting, diarrhea and decreased oral intake may lead to dehydratation. In this case, fluid support with appropriate electrolyte content is given. In presence of hypertension and edema, fluid restriction is applied. In patients with oliguria, edema and hypertension, the daily fluid which should be given is calculated as follows=insensible losses (400 cc/m^2/day+urinary output (mL/h) + additional losses. In patients with severe fluid loading, furosemid may be tried (2 mg/kg/dose); treatment is not continued in cases where no treatment response is obtained. Fluid loading unresponsive to diuretic treatment and electrolyte disorders unresponsive to drug treatment require dialysis treatment. Hypertension: Primarily, increased fluid loading should be corrected. The first-line drugs in antihypertensive treatment in the acute period of the disease are calcium channel blockers; nifedipin at a dose of 0.25 mg/ kg or amlodipin at a dose of 0.1 mg/kg can be intitated. In urgent cases of increased blood pressure including hypertensive encephalopathy, intravenous treatment is preferred. Sodium nitroprusside (0.5–8 µg/kg/min intravenous infusion) and esmolol (50–200

μg/kg/min intravenous infusion) which are available in our country may be used for this objective. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) should be avoided in the acute phase. Dialysis: Symptomatic uremia (uremic encephalopathy, pericarditis, hemorrhage), azotemia (BUN≥80–100 mg/dL), severe fluid loading unresponsive to diuretics (hypertension, heart failure), electrolyte and acid-base disorders unresponsive to drug medical therapy (K^+>6.5 mEq/L, Na<120 mEq/L, pH<7.1) and inability to provide treatment and nutrition because of fluid restriction are the indications of dialysis treatment. Anemia: Erythrocyte transfusion is recommended in patients with a hemoglobin level of <6 g/dL. Erythrocyte transfusion may be needed at higher hemoglobin levels (<7 g/dL) in symptomatic patients. In patients with hyperpotassemia and fluid loading, erythrocyte transfusion should be performed during dialysis. Considering the possibility of future renal transplantation leukocyte filter should be used to decrease the risk of alloimmunization. Thrombocytopenia: Platelet transfusion is recommended only for patients with life threatening bleeding or in the preperation period of surgery Plasma treatment: There is no sufficient evidence indicating that administration of plasma or plasma exchange is beneficial in STEC-HUS Plasma exchange may be useful in patients with neuron detail in the part of "complement-related HUS".[10]

HUS in Pediatrics

Eculizumab: Eculizumab is a monoclonal C5 antibody which inhibits complement activation and used in treatment of complement-related HUS. It can be used in cases of STEC-HUS with neurological involvement The last two therapies will be explained the most common cause of hemolytic uremic syndrome in children is an *Escherichia coli (E. coli)* infection of the digestive system. The digestive system is made up of the gastrointestinal, or GI, tract—a series of hollow organs joined in a long, twisting tube from the mouth to the anus—and other organs that help the body break down and absorb food, harmless strains, or types, of *E. coli* are found in the intestines and are an important part of digestion. However, if a child becomes infected with the *O157:H7* strain of *E. coli*, the bacteria will lodge in the digestive tract and produce toxins that can enter the bloodstream. The toxins travel through the bloodstream and can destroy the red blood cells. *E. coli O157:H7* can be found in

- Undercooked meat, most often ground beef
- Unpasteurized, or raw, milk
- Unwashed, contaminated raw fruits and vegetables
- Contaminated juice
- Contaminated swimming pools or lakes

Less common causes, sometimes called atypical hemolytic uremic syndrome, can include

- Taking certain medications, such as chemotherapy
- Having other viral or bacterial infections
- Inheriting a certain type of hemolytic uremic syndrome that runs in families [10]

Medication

Eculizumab is used in adults to treat myasthenia gravis or neuromyelitis optica spectrum disorder. Eculizumab is also used to prevent the breakdown of red blood cells in adults with paroxysmal nocturnal hemoglobinuria. Eculizumab is used in adults and children weighing at least 11 pounds (5 kilograms) to treat a blood disease called atypical hemolytic uremic syndrome. Eculizumab is available only under a special program. You must be registered in the program and understand the risks and benefits of eculizumab. Eculizumab may also be used for purposes not listed in this medication guide.[11]

Fig 6

Side Efeects

Get emergency medical help if you have These symptoms may occur during the injection. signs of an allergic reaction: hives; chest pain, difficult breathing; feeling like you might pass out; swelling of your face, lips, tongue, or throat.

Seek emergency medical attention if you have symptoms of meningitis:

- Fever and a headache or skin rash;
- Headache with nausea and vomiting;
- Body aches, flu symptoms;
- Confusion, increased sensitivity to light; or
- Stiffness in your neck or back.[12]

Conclusion

Given limited diagnostic capabilities and lack of access to eculizumab, international guidelines on aHUS are not likely to be implemented in developing countries in the near future. The present guidelines provide a systematic and algorithmic approach to management of patients with HUS, tailored to the distinct epidemiology and available repertoire of investigations and therapy. The guidelines underscore the importance of appropriate supportive care, and need for regular and prolonged follow-up. Capacity building for diagnosis and therapy of HUS and other complement related disorders is also required.

References

1. Canpolat N. Haemolytic uremic syndrome. Journal of Turk Pediatri Ars. 2015;50(2):73-82.
2. Bhandari J, Rout P, Sedhai Y. Haemolytic uremic syndrome. Journal of National Library of Medicine, National Institute of Health; c2024.
3. Bhandari J, Rout P, Sedhai YR. Haemolytic uremic syndrome. StatPearls; c2024.
4. Karpman D, Loos S, Tati R, Arvidsson I. Haemolytic uraemic syndrome. Journal of Internal Medicine. 2017;281(2):123-148.
5. Canpolat N. Haemolytic uremic syndrome. Journal of Turk Pediatri Ars. 2015;50(2):73-82.

6. Asif A, Vachharajani T, Salman L, Nayer A. A simplified approach to the diagnosis of atypical HUS: Clinical considerations and practical implications. Journal of Crossmark; c2010.
7. Canpolat N. Haemolytic uremic syndrome. Journal of Turk Pediatri Ars. 2015;50(2):73-82.
8. Kim JS, Lee MS, Kim JH. Recent updates on outbreaks of Shiga toxin-producing Escherichia coli and its potential reservoirs. Journal of Frontiers in Cellular and Infection Microbiology. 2020;10(33):273-279.
9. Rodgers GP. Haemolytic uremic syndrome in children. Journal of National Institute of Diabetes and Digestive and Kidney Diseases. 2022;31(4):38-46.
10. Khandelwal P, Thomas CC, Rathi BS, Hari P, Tiwari AN, Sinha A, *et al*. Membrane-filtration based plasma exchanges for atypical hemolytic uremic syndrome: Audit of efficacy and safety. Journal of Clinical Apheresis. 2019;34(55):389-396.
11. Asif A, Vachharajani T, Salman L, Nayer A. A simplified approach to the diagnosis of atypical HUS: Clinical considerations and practical implications. Journal of Crossmark; c2010.
12. Karpman D, Loos S, Tati R, Arvidsson I. Haemolytic uraemic syndrome. Journal of Internal Medicine. 2017;281(2):123-148.