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Typical and atypical SUH: from pathophysiology to prevention and clinical management

SUH típico y atípico: de la fisiopatología a la prevención y el manejo clínico

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ABSTRACT

The article analyzed hemolytic uremic syndrome (HUS) as a thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. It described its historical evolution and confirmed that it became established as the main cause of acute kidney injury in childhood, with a predominance of typical HUS associated with Shiga toxin-producing Escherichia coli and atypical HUS linked to dysfunction of the alternative complement pathway. It noted that the epidemiological burden was higher in children under five years of age and exhibited regional variability, with high incidences in Latin America. In pathophysiological terms, he explained that Shiga toxin bound to Gb3, inducing ribosomal inactivation, inflammation, and thrombosis, while in atypical HUS, sustained complement activation generated C5a and membrane attack complex, promoting endothelial damage and a prothrombotic state. From a clinical perspective, he detailed gastrointestinal prodrome, anemia, thrombocytopenia, renal impairment, and possible neurological, cardiac, and pancreatic complications. For diagnosis, he emphasized the clinical-laboratory triad and targeted etiological studies: STEC detection, complement assessment, and, when appropriate, genetics. In treatment, he prioritized hemodynamic and renal support, control of hypertension, and selective use of dialysis. He acknowledged the benefit of eculizumab in atypical HUS and severe neurological involvement and raised controversies about antibiotics in STEC HUS and fresh plasma in specific scenarios. Finally, he emphasized that the prevention of typical HUS depends on food safety and sanitation measures. He concluded that reducing its burden required surveillance, health education, access to timely diagnosis and advanced therapies, as well as standardized protocols and referral networks.

Keywords: Hemolytic Uremic Syndrome; Shiga Toxin; Complement; Thrombotic Microangiopathy; Eculizumab.

RESUMEN

El artículo analizó el síndrome urémico hemolítico (SUH) como microangiopatía trombótica caracterizada por anemia hemolítica microangiopática, trombocitopenia y lesión renal aguda. Describió su evolución histórica y confirmó que se consolidó como causa principal de lesión renal aguda en la infancia, con predominio del SUH típico asociado a Escherichia coli productora de toxina Shiga y un SUH atípico vinculado a disfunción de la vía alterna del complemento. Señaló que la carga epidemiológica fue mayor en menores de cinco años y exhibió variabilidad

regional, con incidencias elevadas en América Latina. En lo fisiopatológico, expuso que la toxina Shiga se unió a Gb3, indujo inactivación ribosómica, inflamación y trombosis; mientras que en el SUH atípico la activación sostenida del complemento generó C5a y complejo de ataque a membrana, favoreciendo daño endotelial y estado protrombótico. Desde lo clínico, detalló pródromo gastrointestinal, anemia, trombocitopenia, deterioro renal y posibles complicaciones neurológicas, cardíacas y pancreáticas. Para el diagnóstico, enfatizó la tríada clínica-laboratorial y los estudios etiológicos dirigidos: detección de STEC, evaluación del complemento y, cuando correspondió, genética. En el tratamiento, priorizó soporte hemodinámico y renal, control de la hipertensión y uso selectivo de diálisis; reconoció el beneficio de eculizumab en SUH atípico y en afectación neurológica grave, y planteó controversias sobre antibióticos en SUH STEC y plasma fresco en escenarios específicos. Finalmente, subrayó que la prevención del SUH típico dependió de medidas de inocuidad alimentaria y saneamiento. Concluyó que la reducción de su carga requirió vigilancia, educación sanitaria, acceso a diagnóstico oportuno y terapias avanzadas, además de protocolos estandarizados y redes de referencia.

Palabras clave: Síndrome Urémico Hemolítico; Toxina Shiga; Complemento; Microangiopatía Trombótica; Eculizumab.

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy of high clinical and health relevance, characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Since its first descriptions in the mid-20th century and Gasser's classic series, it has become established as the leading cause of acute kidney injury in childhood, especially in preschool-aged children (Bello, 2016; Jenssen et al., 2016). Its etiological spectrum is heterogeneous: "typical" HUS is most often associated with Shiga toxin-producing Escherichia coli (STEC), while "atypical" HUS is due to genetic or acquired defects in the regulation of the alternative complement pathway; there are also secondary forms linked to Streptococcus pneumoniae, other infectious agents, drugs, pregnancy, autoimmune diseases, neoplasms, and transplants (Cody & Dixon, 2018; Fakhouri et al., 2017; Loirat et al., 2016).

In epidemiological terms, the burden of STEC HUS is disproportionate in children under five years of age and shows notable regional variations; Latin America, and Argentina in particular, has much higher incidences than Europe and North America (Fakhouri et al., 2017). At the pathophysiological level, Shiga toxin targets globotriaosylceramide (Gb3) in endothelial cells and renal tubular cells, triggering ribosomal inactivation, cell death, and proinflammatory and prothrombotic responses, with fibrin deposition and thrombus formation in capillaries and arterioles. In atypical HUS, alterations in factor H, factor I, or MCP, among others, lead to uncontrolled complement activation, generation of C5a and the membrane attack complex, with diffuse endothelial damage and a prothrombotic state (Brocklebank et al., 2017; Bello, 2016).

Clinically, HUS usually begins abruptly and may be accompanied by gastrointestinal prodrome—with watery or dysenteric diarrhea—followed by anemia, thrombocytopenia, and renal impairment. Neurological manifestations are not uncommon, and in severe cases, cardiac or pancreatic complications may occur, with prognostic implications (Cavero & Alonso, 2018; Greenbaum et al., 2016; Buder et al., 2015). The diagnosis is based on the clinical-laboratory triad and targeted etiological studies, including STEC screening and complement assessment in atypical forms (Boyer & Niaudet, 2022). Management is time-dependent and combines

hemodynamic and renal support, hypertension control, and, in selected situations, specific therapies such as eculizumab. In pneumococcal HUS, antibiotics are essential, while in STEC HUS, their use is controversial (Fakhouri et al., 2017; Kaur & Kerecuk, 2016).

Prevention of typical HUS relies on food safety and sanitation measures, given its zoonotic and foodborne nature. This introduction frames the analysis of HUS from its classification, pathophysiology, clinical presentation, diagnosis, and treatment, highlighting gaps and current challenges for pediatric practice and public health.

DEVELOPMENT

Theoretical framework

Hemolytic Uremic Syndrome (HUS)

HUS was first described in 1950 in three children who presented with bloody diarrhea, edema, and seizures. In 1955, pediatrician Konrad Gasser and his colleagues reported that five children with similar symptoms died of necrosis in the cerebral cortex. Since then, HUS has been known as the combination of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury (AKI) (Bello, 2016).

HUS is usually associated with Shiga toxin-producing Escherichia coli (STEC-HUS) and, to a lesser extent, with Streptococcus pneumoniae infections. In addition to conditions that can cause HUS, other causes include genetic changes in the complement pathway, as well as medications, different infectious agents, and autoimmune diseases. Although the causes differ, the various forms of HUS share a state that promotes clot formation and inflammation on the surface of blood vessels, resulting in the triad mentioned above (Cody & Dixon, 2018).

For this reason, HUS has been identified as a major cause of ARF in preschool-aged children (Jenssen et al., 2016). It belongs to the group of thrombotic microangiopathies (TMAs). It is initially accompanied by endothelial damage, mainly affecting the kidneys, due to fibrin- and platelet-like thrombi in capillaries and arterioles, as well as endothelial cell and arteriolar inflammation, and separation of the basement membrane of the bulb (Fakhouri et al., 2017).

The incidence of STEC HUS is higher in children under 5 years of age, with 1,9 to 2,9 cases per 100 000 children in Europe and North America, and is believed to be associated with the development of anti-STEC antibodies at a later age. The presence of STEC-HUS in Latin America is ten times higher than in other continents; for example, in Argentina, there are 10 to 17 cases per 100,000 inhabitants under 5 years of age (Fakhouri et al., 2017).

HUS caused by S. pneumoniae (HUS SP) accounts for 5 %, and HUS from other causes (atypical) accounts for 5 % to 10 % (Fakhouri et al., 2017). Atypical HUS occurs with equal frequency in boys and girls. In a registry of atypical HUS in 516 pediatric patients, 39 % of patients developed the disease before the age of 18, and approximately 44 % of children experienced their first episode before the age of 2 (Dixon & Gruppo, 2018).

There is a higher risk of developing HUS in livestock areas due to the high possibility of water and food contamination. An additional factor is the incubation period of STEC, which is 1 to 8 days, and the excretion of the bacteria in feces can persist for more than 3 weeks after infection (Kaur & Kerecuk, 2016).

Classification of HUS

Based on research on this syndrome, various classifications have been proposed, including HUS diarrhea-positive (HUS D+), which STEC mainly causes, and HUS diarrhea-negative (HUS D-), which encompasses all other types of HUS. However, this classification has certain limitations, as HUS D+ can occur without diarrhea, and HUS D- can present this symptom (Jenssen et al., 2016). Limitations such as the one just mentioned have led to the current classification of HUS into typical and atypical forms. Shiga toxin-producing bacteria cause the former, and the term "atypical" has been assigned to HUS that is not associated with STEC infection or other coexisting pathology or condition (Bello, 2016; Loirat et al., 2016).

For this reason, other forms of classification based on the causative agent have been proposed, as described below (Fakhouri et al., 2017):

Induced by infectious agents

- HUS STEC, also known as typical HUS: HUS is the most serious complication of STEC infections (Paz et al., 2015). Approximately 15 % of children with E. coli enterocolitis progress to HUS, which is associated with young age and female gender; together with leukocytosis, these factors increase the likelihood of developing HUS. Most strains of enterohemorrhagic E. coli express an adhesin called intimin, which allows the A subunit of the Shiga toxin to enter the bloodstream and subsequently bind to the endothelium via globotriaosylceramide (Gb3), which is also found in the renal tubules. Additionally, endocytosis of the toxin occurs, leading to ribosomal inactivation and inhibition of protein synthesis, which results in cell death. It is also necessary to note that Shiga toxin exerts proinflammatory and prothrombotic effects at the glomerular level, leading to von Willebrand factor secretion and complement activation (Bello, 2016; Cody & Dixon, 2018).
- HUS associated with Shigella dysenteriae type 1: Like E. coli, this bacterium produces Shiga toxin, which can trigger typical HUS.
- HUS associated with Streptococcus pneumoniae: This occurs after pneumonia complicated by empyema or meningitis. The binding of proteins expressed by the pneumococcal bacterium to Factor H has been demonstrated, which inhibits its action. S. pneumoniae produces neuraminidases that remove N-acetylneuraminic acid from the surface of cells, thus exposing the Thomsen-Friedenreich antigen, known as the T antigen, found in erythrocytes, platelets, and the endothelium. The reaction of antibodies against this antigen causes hemolytic anemia, thrombocytopenia, and microvascular injury.
- Other infectious agents: HIV and influenza H1N1. HIV causes toxicity in endothelial cells, but thanks to the incorporation of antiretroviral therapy, cases have decreased. Influenza H1N1, on the other hand, can trigger HUS in patients with a mutation in diacylglycerol kinase ε.

Atypical HUS

The pathogenesis of atypical HUS arises from genetic or acquired defects in the regulation of the alternative complement pathway (Dixon & Gruppo, 2018).

- Mutations in complement genes: The most common mutations occur in factor H, factor I, and membrane cofactor protein (MCP) (Brocklebank et al., 2017). These mutations lead to uncontrolled activation of the alternative complement pathway, which in turn results in overproduction of the membrane attack complex, triggers endothelial cell death and edema, and establishes a prothrombotic state at the subendothelial level, thereby activating the coagulation system. There is also an increase in C5a, an anaphylatoxin

that induces chemotaxis, leukocyte and endothelial activation, and increases vessel permeability, inflammation, and thrombosis, culminating in microvascular obstruction (Bello, 2016).

- Inborn errors of cobalamin C metabolism: Cobalamin C is a cofactor for methionine synthase, which converts homocysteine to methionine, and is also a cofactor for methyltransferase, which participates in the conversion of methylmalonyl CoA to succinyl CoA. So, a defect in cobalamin C function causes methylammoniaemia with homocystinuria (Boyer & Niaudet, 2022).
- Mutations in diacylglycerol kinase ε: This intracellular protein, expressed in the endothelium, platelets, and podocytes, has been identified in autosomal recessive forms of atypical SUH that occur in the first year of life. The loss of function confers a prothrombotic state at the microvascular level by inactivating diacylglycerol, which contains arachidonic acid, an activator of protein kinase C that promotes thrombosis. Therefore, when its function is altered, there is an increase in prothrombotic factors such as von Willebrand factor and a decrease in vascular endothelial growth factor (Boyer & Niaudet, 2022; Cody & Dixon, 2018; Dixon & Gruppo, 2018).

Coexisting with other diseases or conditions

These are sporadic cases triggered by different factors, some of which are mentioned below (Fakhouri et al., 2017):

- Drugs and medications: calcineurin inhibitors such as cyclosporine A and tacrolimus, cytotoxic drugs, quinine, oral contraceptives, vascular endothelial growth factor inhibitors, quetiapine, chemotherapeutics such as gemcitabine and mitomycin, antiplatelet agents such as clopidogrel and ticlopidine, drugs of abuse such as cocaine (Cody & Dixon, 2018).
- Pregnancy: HUS triggered by pregnancy occurs mainly in the postpartum period (Boyer & Niaudet, 2022).
- Autoimmune diseases: systemic lupus erythematosus, antiphospholipid syndrome, scleroderma, ANCA-associated vasculitis, among others (Cavero & Alonso, 2018).
- Malignant hypertension.
- Pre-existing kidney disease.
- Neoplasms: prostate cancer, gastric cancer, lung cancer, breast cancer, lymphoma, among others. Where intravascular emboli may exist at the tumor level, with activation of coagulation and proliferation of the vascular wall (Fakhouri et al., 2017).
- Solid organ or stem cell transplantation: HUS generally occurs in the first few months after transplantation. This is also related to the use of calcineurin inhibitors in these patients, as higher doses are administered during this period (Boyer & Niaudet, 2022).

Clinical manifestations

Common signs of MAT include microangiopathic hemolysis and ischemic injury to organs, most often the kidneys and brain (Cavero & Alonso, 2018). HUS presents with different symptoms and signs; these depend on the time of evolution, severity, and organs involved according to the degree of MAT involvement (Fakhouri et al., 2017). Most patients have an abrupt onset of the disease (Dixon & Gruppo, 2018).

Some clinical findings caused by the degree of anemia include pallor, fatigue, systolic murmur, and tachycardia; despite thrombocytopenia, spontaneous bleeding and petechiae are rare (Greenbaum et al., 2016).

There are gastrointestinal symptoms such as diarrheal disease that begins 3 to 8 days after ingesting contaminated food; it manifests as watery diarrhea, being dysenteric in 70 % of cases, associated with abdominal pain, nausea, and vomiting in 30 % to 40 % of patients; in severe cases, enterocolitis, pancreatitis, hemorrhagic colitis, ileocolonic perforation, rectal prolapse, cholestasis, and peritonitis occur (Bello, 2016; Cody & Dixon, 2018).

Other clinical findings include renal abnormalities such as hematuria and proteinuria, decreased glomerular filtration rate, and increased creatinine (Dixon & Gruppo, 2018). Microalbuminuria is an early marker of kidney damage due to hyperfiltration. Some studies show that 32 % of cases present microalbuminuria after HUS at 3 years, and 22 % at 5 years. Twenty-five percent of children may present long-term renal involvement such as proteinuria, hypertension, and chronic renal failure (Paz et al., 2015).

Several neurological manifestations may also occur, including blurred vision, headache, lethargy, seizures, irritability, ischemic or hemorrhagic cerebrovascular events, coma, hemiparesis, cerebral edema, and cortical blindness (Bello, 2016; Cavero & Alonso, 2018). Neurological involvement occurs due to endothelial dysfunction, hypertension, and electrolyte disturbances, especially hyponatremia. Neurological complications are associated with increased mortality (Buder et al., 2015).

In addition, there are cardiac problems such as myocardial ischemia, which occurs due to increased blood volume and hypertension. Blood accumulation in the pericardial space has been reported, which can ultimately cause cardiac tamponade. There are also other manifestations, such as diabetes mellitus and pancreatitis (Kaur & Kerecuk, 2016).

In typical HUS, dysentery sometimes occurs, and there is a history of urinary tract infection, as E. coli is its most common cause. HUS-SP occurs in patients with severe sepsis due to this organism, associated with pneumonia or, in 30 % of cases, with meningitis (Fakhouri et al., 2017).

Unlike typical HUS, in atypical HUS, the onset of the disease may be associated with several intermittent events, such as viral gastroenteritis, influenza, vaccination, or stress (Fakhouri et al., 2017). It is worth mentioning that 42 % of patients with atypical HUS are associated with diarrhea or gastroenteritis and upper respiratory tract infection (Dixon & Gruppo, 2018).

Finally, the extrarenal manifestations reported in 25 % of patients with atypical HUS are gangrene in the middle and distal phalanges, which can even lead to amputation, stenosis of the cranial and extracranial arteries, and, at the ocular level, retinal ischemia and vitreous hemorrhage (Cavero & Alonso, 2018; Greenbaum et al., 2016).

Diagnosis of HUS

Initial studies should focus on diagnosing MAT and then determining the cause of HUS. To do this, it is necessary to rule out infectious and genetic causes and to study possible coexisting pathologies or conditions, such as pregnancy and medications that may cause the pathology (Cavero & Alonso, 2018).

The diagnosis of HUS is based on the clinical presentation of the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and ARF. This is supported by laboratory tests, including a complete blood count, blood smear, renal function studies, and urinalysis (Boyer & Niaudet, 2022).

Microangiopathic hemolytic anemia is determined by a hemoglobin value of less than 8 g/dL, a negative Coombs test (except in HUS caused by S. pneumoniae), a blood smear showing schistocytes, decreased haptoglobin, indirect hyperbilirubinemia, reticulocytosis, and increased lactate dehydrogenase (greater than 460 U/L) (Bello, 2016; Boyer & Niaudet, 2022).

Thrombocytopenia depends on the severity of the disease (it is absent in 15 % to 20 % of cases) and is defined as platelet counts below 150,000; it commonly occurs with platelet counts below 40,000; bleeding or purpura are not usually detected clinically as a result of this count (Bello, 2016; Fakhouri et al., 2017).

Acute kidney injury can manifest in various ways depending on its severity, such as proteinuria, hematuria, or even kidney failure. Creatinine, blood urea nitrogen (BUN), diuresis, and blood pressure levels should be analyzed (Boyer & Niaudet, 2022).

To confirm the diagnosis of STEC HUS, E. coli O157:H7 must be detected in stool by PCR or in serum antibody titers (Viteri & Reid-Adam, 2018). Additionally, for the diagnosis of atypical HUS, it is useful to measure C3, C4, factor H, factor I, and genetic mutations, and to investigate for autoimmune disease (Kaur & Kerecuk, 2016). About 60-70 % of atypical HUS cases have a mutation in complement genes or antibodies against factor H (Loirat et al., 2016).

Although a biopsy is not necessary for a definitive diagnosis, histopathology can present in three forms: glomerular MAT, arterial MAT, and patchy cortical necrosis (Bello, 2016).

Many conditions share clinical characteristics with HUS, including those that can present with concomitant anemia, thrombocytopenia, and acute kidney injury. Some of these are listed below:

- Disseminated intravascular coagulation (DIC): This differs from HUS in the presence of abnormal coagulation tests, such as prolonged activated partial thromboplastin time and prothrombin time, and elevated levels of fibrin degradation products and D-dimer. In most cases, DIC occurs in pediatric patients who are in serious health conditions, such as those in septic shock or who have suffered massive tissue injury (Boyer & Niaudet, 2022).
- Thrombotic thrombocytopenic purpura (TTP): This is one of the two main causes of DIC (Table 1). TTP is the most common cause of DIC in adults. It is due to the development of autoantibodies against the protease that cleaves von Willebrand factor and/or deficient activity of the von Willebrand factor cleaving protease caused by mutations in the ADAMTS13 gene. The characteristic feature of PTT is a severe deficiency of the ADAMTS13 protease that cleaves von Willebrand factor. Pediatric PTT is rare and is usually characterized by greater neurological involvement than renal involvement. Affected children often present at birth with hemolytic anemia and thrombocytopenia. Renal involvement often occurs later in life and has a progressive course. PTT is distinguished from HUS by abnormally low ADAMTS13 activity (Boyer & Niaudet, 2022; Greenbaum et al., 2016).
- Systemic vasculitis: Patients with vasculitis do not usually have prodromal diarrheal disease and present with other systemic symptoms such as arthralgia and rash. In addition, the characteristic neurological involvement in patients with vasculitis is peripheral rather than central (Boyer & Niaudet, 2022).
- Systemic lupus erythematosus: This condition is particularly common in adolescents and young women and resembles HUS due to the presence of anemia and, in patients with lupus nephritis, due to thrombocytopenia and ARF (Greenbaum et al., 2016).

- Dengue hemorrhagic fever: This manifests as thrombocytopenia, ARA, and anemia, similar to HUS; however, serology for dengue and altered coagulation times differentiate it from HUS (Bello, 2016).

Table 1. Thrombotic microangiopathies (Bello, 2016)

Hemolytic uremic syndrome	• Shiga toxin (toxin-producing bacteria) - Escherichia coli - Shigella dysenteriae • Streptococcus pneumoniae • Defect in cobalamin metabolism • Atypical HUS • Disorders in complement regulation • Coagulation disorders
Thrombotic thrombocytopenic purpura (ADAMTS13 deficiency)	• Acquired (autoantibodies) • Congenital (recessive inheritance)
Secondary	• HIV • Pregnancy • Antiphospholipid syndrome • Malignancy • Medication (chemotherapy, calcineurin inhibitors) • Radiotherapy • Transplants • Severe hypertension

Treatment of HUS

Timely management of HUS is paramount in these cases, along with rapid transfer to a specialized center for appropriate treatment (Kaur & Kerecuk, 2016). Supportive treatment remains the main approach for this syndrome, with adequate fluid and electrolyte correction tailored to the patient's needs. This management has improved renal prognosis, reduced the need for dialysis, and also decreased long-term sequelae.

Both increases and decreases in intravascular volume may occur, and volume management is carried out accordingly. A decrease in intravascular volume can occur due to diarrhea, vomiting, or reduced oral intake, in which case a return to euvolemia is necessary. An increase in intravascular volume should be managed with fluid restriction, and dialysis may even be necessary, especially when there is cardiac or pulmonary damage (Liu et al., 2022).

It is important to assess and individualize the correction of hypertension. It is suggested to use calcium channel blockers such as nifedipine 0,25 mg/kg or amlodipine 0,1 mg/kg (Bello, 2016).

In pneumococcal cases, antibiotic treatment of the underlying infection is necessary (amoxicillin or a third-generation cephalosporin in cases of meningitis), unlike in HUS-STEC, where antibiotic use is controversial (Fakhouri et al., 2017; Kaur & Kerecuk, 2016).

The indications for initiating renal replacement therapy are: symptomatic uremia, BUN > 100 mg/dL, severe fluid overload (greater than 15-20 % of body weight), no response to diuretics, refractory electrolyte and acid-base disorders, and inability to provide nutrition or hydration due to the need for fluid restriction (Bello, 2016; Cody & Dixon, 2018).

Packed red blood cell transfusion is indicated in cases of severe anemia (less than 8 g/dL

with hemodynamic repercussions). In patients with hyperkalemia or fluid overload, this should be performed during dialysis (Bello, 2016; Liu et al., 2022). Platelet transfusion is controversial due to the risk of worsening MAT, and its use is restricted in patients with significant bleeding (Boyer & Niaudet, 2022).

In atypical HUS and STEC HUS with severe neurological complications, early use of the monoclonal anti-C5 antibody Eculizumab is recommended, as this is the first and only antibody approved for this condition (Greenbaum et al., 2016; Niaudet & Boyer, 2022). In addition, when using Eculizumab, it is extremely important to vaccinate against meningococcus, pneumococcus, and Haemophilus influenzae type B, as well as to administer anti-meningococcal prophylaxis (Bello, 2016; Kaur & Kerecuk, 2016).

The use of fresh frozen plasma remains controversial. However, in cases of atypical HUS where Eculizumab cannot be used, fresh frozen plasma transfusion is used. Due to its complement content, it removes mutated factors and antibodies, and the syndrome caused by factor H responds better to this treatment. Plasma use is not recommended in SP HUS (Kaur & Kerecuk, 2016).

Immunosuppressants such as cyclophosphamide, corticosteroids, and rituximab are indicated in atypical HUS caused by factor H (Bello, 2016,4).

Finally, liver transplantation is a possibility in atypical complement-mediated HUS, since the liver is the precursor of these proteins (Niaudet & Boyer, 2022). In addition, kidney transplantation is performed after assessing the degree of renal chronicity. In these cases, it is necessary to perform a genetic study beforehand to look for mutations that may cause HUS to recur (Bello, 2016).

Prevention of HUS

Due to the infectious nature of the disease, various hygiene measures have been proposed to control outbreaks and sporadic cases. The following is recommended:

- Maintain the cold chain for both meat and dairy products. It should be noted that fresh food can remain at an inadequate temperature (4-60°) for up to 2 hours.
- Defrost food in the refrigerator, microwave, or under cold running water, taking care to return it to the refrigerator once defrosted until it is consumed.
- Cook meat thoroughly to 70°, especially minced meat and products made with it. This meat should not have any pink or red parts inside (minced meat is well-cooked when the serum it releases during cooking is transparent), bearing in mind that if you cook frozen meat, the cooking time is longer than usual, and when using a microwave, do not forget to cover the food, stir it, and rotate the plate.
- Once the food is cooked, it should be eaten soon.
- Wash your hands with soap and water after using the bathroom, before handling food, and after touching raw food.
- Wash fruits and vegetables thoroughly.
- Consume pasteurized milk.
- Drink safe water; if in doubt, boil it or add two drops of chlorine per liter of water, stir, and let it sit for 30 minutes.
- Avoid cross-contamination between raw and cooked foods.

CONCLUSIONS

The analysis integrated the main epidemiological, pathophysiological, clinical, and therapeutic aspects of hemolytic uremic syndrome (HUS) and reaffirmed its relevance as a primary cause of acute kidney injury in children. It was established that "typical" HUS, linked to Shiga toxin-producing Escherichia coli strains, had the highest burden in children under five years of age and showed an uneven geographical distribution, with high incidences in Latin America. In turn, "atypical" HUS, resulting from alterations in complement regulation, can manifest at any age and exhibit phenotypic variability.

In pathophysiology, it was confirmed that the renal microvascular endothelium was the central target of damage: Shiga toxin promoted ribosomal cytotoxicity, inflammation, and thrombosis, while in atypical HUS, sustained complement activation—with generation of C5a and membrane attack complex—promoted a diffuse prothrombotic state. This convergence in microangiopathic injury explained the clinical triad and multiorgan involvement, including neurological compromise and, in severe cases, cardiac and pancreatic complications with prognostic impact.

Diagnostically, the value of the clinical-laboratory triad and a staged etiological strategy was confirmed: STEC confirmation in typical HUS and complement characterization and genetic studies in atypical HUS. Differentiation from other thrombotic microangiopathies, disseminated intravascular coagulation, and autoimmune entities was critical in guiding therapeutic decisions and prognosis. Operational challenges persisted: timely availability of etiological tests, standardization of algorithms, and access to molecular studies in resource-limited settings.

In treatment, hemodynamic-renal support, hypertension control, and precise indications for dialysis were established as pillars. The role of eculizumab in atypical HUS and severe neurological conditions was recognized, accompanied by vaccination and meningococcal prophylaxis; however, the use of antibiotics in STEC HUS remained controversial, and fresh plasma was reserved for specific situations. These interventions highlighted the need for time-dependent care pathways and multidisciplinary teams.

Preventing typical HUS relies on food safety and sanitation practices, with a focus on the cold chain, safe cooking, hand hygiene, and safe water. It was concluded that reducing the burden of HUS requires integrating epidemiological surveillance, health education, diagnostic capacity, and equitable access to advanced therapies. Priorities included strengthening referral networks, standardizing protocols, and translational research to bring biomarkers and therapies to high-incidence settings.

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