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Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome

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SUMMARY
The hemolytic–uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI). The major cause of HUS in childhood (>90%) is infection with verocytotoxin (Shiga-like toxin – "Stx")-producing bacteria, usually enterohemorrhagic *Escherichia coli* (VTEC/STEC). The infection may be transmitted by the consumption of undercooked meat, pasteurized dairy products, contaminated vegetables, fruits and water, or by contact with STEC diarrhea. After an incubation period of three to eight days, patients commonly develop bloody diarrhea followed in 5–22% by HUS that may be complicated by central nervous system, pancreatic, skeletal, and myocardial involvement. HUS is one of the main causes of AKI in children in Europe. The management of HUS includes the usual treatment of children with AKI. Transfusion with packed red blood cells is needed in case of a severe anemia, while platelet transfusions are limited to the need for a surgical procedure or in active bleeding. Currently, there is no consensus on the use of antibiotic therapy. Treatment with plasma and/or plasma exchange has not been proven beneficial in STEC-HUS. Eculizumab has been used for the treatment of STEC-HUS, but the value of this treatment remains to be determined. The mortality of HUS is reported to be 3–5%. About 12% of patients will progress to end-stage renal failure within four years and about 25% will have long-term complications, including hypertension, proteinuria, renal insufficiency, and insulin-dependent diabetes mellitus. Transplantation can be performed without increased risk for the recurrence of the disease.
Keywords: acute kidney injury; children; D-HUS

INTRODUCTION

The leading clinical features of hemolytic uremic syndrome (HUS) are non-immune microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI) [1]. HUS is one of the main causes of AKI in children in Europe [2]. Histopathology of HUS is characterized by thrombotic microangiopathy consisting of endothelial cell injury, activation of coagulation with consequent microvascular thromboembolic occlusion, and organ failure, which is transient in the majority of cases [3, 4, 5]. HUS includes diseases that have similar histopathologic and clinical features, but different pathogenesis. The initial, historical classification of HUS distinguished two of its types: typical or post-diarrheal (D+) HUS due to Shiga toxin (Stx)-producing *Escherichia coli* (STEC) and atypical HUS (aHUS) or diarrheal negative (D-) HUS that included any HUS not due to STEC [6]. This classification of HUS based on pre-diarrheal syndrome proved to be misleading as post-diarrheal onset does not eliminate the diagnosis of aHUS. With increasing the knowledge of HUS, especially with better understanding of its molecular basis, the European Pediatric Research Group for HUS proposed a new classification of HUS and related diseases into two sections. The first section includes diseases with known etiology, and the second one covers diseases with unclear causes (Table 1) [7]. According to this HUS classification, the previous name – diarrhea-positive (D+HUS) or typical HUS – has been replaced by the more accurate term STEC-HUS to underline the essential role of Stx in the pathogenesis of the disorder.

This paper addresses current knowledge about HUS caused by STEC. It reviews the historical features, etiopathogenesis, clinical aspects, and treatment of STEC-associated HUS.

HISTORY

The term HUS was first reported by Gasser et al. [1] who described five fatal patients with hemolytic anemia, renal failure, and thrombocytopenia. After about 30 years, Karmali et al. [8] discovered the cause of this disease and very soon Riley et al [9] described epidemics with painful bloody diarrhea linked by the consumption of undercooked hamburgers contaminated by *E. coli* O157:H7 [9]. O'Brien et al. [10] pointed to the link between the toxic properties of *E. coli* O157:H7 and that of *Shigella dysenteriae* serotype 1.

ETIOLOGY

The major cause of STEC-HUS in childhood is infection with enterohemorrhagic *E. coli* and in some tropical regions *Shigella dysenteriae* type 1 [8, 11]. Verocytotoxin–producing *Citrobacter*

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Table 1. Classification of HUS and related disorders proposed by the European Pediatric Research Group for HUS [7]

Part 1: Etiology advanced
Infection induced (a) Shiga and verocytotoxin (Shiga-like toxin)-producing bacteria (enterohemorrhagic *Escherichia coli*, *Shigella dysenteriae* type 1, *Citrobacter*) (b) *Streptococcus pneumoniae*, neuraminidase, and T-antigen exposure
Disorders of complement regulation (a) Genetic disorders of complement regulation (b) Acquired disorders of complement regulation, for example anti-FH antibody
von Willebrand proteinase, ADAMTS13 deficiency (a) Genetic disorders of ADAMTS13 (b) Acquired von Willebrand proteinase deficiency; autoimmune, drug induced
Defective cobalamin metabolism
Quinine induced
Part 2: Clinical associations or etiology unknown
HIV
Malignancy, cancer chemotherapy, and ionizing radiation
Calcineurin inhibitors and transplantation
Pregnancy, HELLP syndrome, and oral contraceptive pill
Systemic lupus erythematosus and antiphospholipid antibody syndrome
Glomerulopathy
Familial, not included in Part 1
Unclassified

HUS – hemolytic uremic syndrome; FH – factor H; HELLP – hemolytic anemia, elevated liver enzymes, and low platelets; HIV – human immunodeficiency virus; ADAMTS – a disintegrin-like and metalloprotease with thrombospondin type I repeats

Table 2. Annual incidence of hemolytic uremic syndrome (HUS) in children

Region	Study time period	Cases of HUS/100,000 children (age, years)	STEC-HUS (%)	Reference
British Isles	1985–88	0.65–0.91 (<16)	95	21
Argentina	2002	12.2 (<5)	>90	22
France	1998	0.7 (<15)	83	23
Germany	1997–2000	0.7 (<15)	83	24
Norway	1999–2008	0.5 (<16)	81	25
USA	2000–2007	0.78 (<18)	90	26
Australia	1994–1998	0.64 (<15)	84	27
Austria	1997–2000	0.37 (<15)	83	24
Italy	1988–2000	0.28 (≤15)	73	28
Serbia	2011–2014 (all) 1985–2014 (D ± PE)	0.28 (≤15) 0.11	70	/

D – dialysis; PE – plasma exchange; STEC-HUS – Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome

freundii has also been reported [12]. Synonymous for enterohemorrhagic *E. coli* (EHEC) are verotoxigenic, verocytoxin-producing, or verocytotoxigenic *E. coli* (VTEC/STEC). STEC expressing somatic (O) antigen 157 and flagellar (H) antigen 7 are the serotype most frequently associated with HUS, but at least during certain periods, non-O157:H7 STEC appears to be more common [13–17].

E. coli produces Shiga toxins 1 (Stx1) and 2 (Stx2). These toxins consist of two A and five B subunits. B subunits have affinity to globotriaosylceramide (Gb3Cer) receptors located in the membranes of glomerular, colonic, and cerebral epithelial or microvascular endothelial cells, as well as in renal mesangial and tubular cells, monocytes, and platelets. The A subunit causes cell death by its N-glycosidase activity, which inhibits protein synthesis at the level of 28S ribosomal RNA [18].

EPIDEMIOLOGY

Most STEC infections are asymptomatic, or manifested by non-bloody diarrhea, while minority have bloody diarrhea and HUS. The majority of STEC-HUS cases are sporadic, although large outbreaks have been reported [19]. Cattle are a major reservoir of STEC infection, which does not cause disease in them because their vascular endothelial cells have no Gb3Cer receptors. The infection may be transmitted by the consumption of undercooked meat, pasteurized dairy products, contaminated vegetables, fruits, and water, or by contact with STEC diarrhea. The risk of HUS development is higher in patients infected with EHEC O157:H-, in children younger than five years of age, those who use antimotility agents while use of antibiotics remains controversial [20]. Bloody diarrhea, fever, vomiting, leukocytosis, and not receiving intravenous hydration and volume expansion were also recognized as risk factors for HUS development [21].

An average annual incidence for HUS in children under 15 years of age is about 0.7 per 100,000 [21–28]. The highest HUS incidence worldwide occurs in Argentina (12.2 cases/100,000 children aged < 5 years) [22], and the lowest incidence was reported in Italy (0.28 cases/100,000 children ≤15 years old [28]. The incidence rate in Serbia is also low (Table 2). The reasons for variable incidence in different regions are unclear, but it may be related to exposure to STEC, and potential genetic susceptibilities of specific populations.

STEC-HUS is a dominant form of HUS in children with the participation of 72–95% of all cases of HUS. It is more common in younger children, with most cases occurring in summer's months. At the beginning of May 2011, a large outbreak of STEC infections started in northern Germany [19]. More than 3,800 cases of *E. coli*-positive infections were reported, including 845 patients with HUS. Majority (88%) of the patients with HUS were adults, with an overrepresentation of women. This may be explained by ingestion of infected sprouts, which are rarely consumed by young children.

PATHOGENESIS

A major event in the pathogenesis of HUS is the EHEC colonization of the colon. EHEC strains express adhesins by which they adhere to the intestinal epithelial cells. [18]. They may cause colitis with bloody diarrhea due to intestinal cell death and vascular damage. Infected intestinal cells secrete cytokines in the intestine and into the circulation. It is proposed that Stx is transported in circulation by

leukocytes and platelets, which also transport Stx to the microvasculature of the target organs that possess Gb3Cer receptors [18]. After B subunit of Stx binds to the Gb3Cer receptor, A subunit is transported to the Golgi apparatus and releases a protease which inhibits ribosomal function, leading to cell death. This process can also activate signaling pathways which induce an inflammatory response in affected cells. In fact, binding of Stx to its receptors has at least dual effect – the first one stimulating the release of cytokines including TNF-a, IL-1, and IL-6, and the second effect being cytotoxic, directly killing the cells. [18]. The released cytokines induce an inflammatory reaction, which amplifies further secretion of cytokines, and in association with Stx, lipopolysacharide, and other virulence factors increase the cytotoxic damage. Thus, Stx is capable of stimulating cells to release cytokines as well as inducing cell death by inhibition of protein synthesis or by apoptosis. In contrast to the brain, kidneys and other Gb3Cer-endowed organs prone to inflammatory and cytotoxic EHEC effects, monocytes, polymorphonuclear cells, and platelets are resistant to the Stx cytotoxic effects [18]. Stx provokes direct endothelial damage by a ribotoxic stress response and by increasing inflammation stimulating expression of cytokines and chemokines. These lead to the formation of microthrombi, followed by injury of the target organs, especially the kidney and the brain. In addition, damaged endothelium causes fragmentation of erythrocytes with consequent hemolytic anemia while platelet consumption results in thrombocytopenia. Glomerular thrombi and damage to tubular epithelial cells decrease glomerular filtration and cause AKI.

The role of complement activation in STEC-HUS is still a subject of debates. *In vitro* studies of endothelial cells have demonstrated that exposure to Stx increases expression of P-selectin, which binds and activates C3 via the complement alternative pathway [29]. The C3a that is produced following the cleavage of C3 potentates the activation of the alternative pathway of complement, reduces the expression of thrombomodulin, and promotes thrombus formation [29]. Reports of low serum levels of C3 in children with STEC-HUS date back to the early 1970s [30]. More recent studies have confirmed C3 reductions in severe cases of STEC-HUS [31].

CLINICAL ASPECTS

The interval between ingestion of *E. coli* and the onset of diarrhoea is usually three days. About 50% of these patients develop nausea and vomiting. Only 30% have fever. Bloody diarrhea occurs in about 90% of cases. The colon can be quite severely affected. Severe colitis can result in transmural necrosis with perforation and/or later development of colonic stricture. HUS is typically attained about a week after the onset of diarrhoea in 5–15% of cases, but during outbreaks it may increase up to 30%. Thrombocytopenia is the first abnormality in most patients. Patients suffer from hemolytic anemia, thrombocytopenia, and renal failure [6]. Elevation of pancreatic enzymes is common, and edema of the pancreas, indicative of pancreatitis, can be detected by ultrasound or computed tomography scan. Hematological manifestations include the following: acute decay of hemoglobin, fragmented erythrocytes, low or undetectable levels of haptoglobin, thrombocytopenia, and massive increase of lactate dehydrogenase (LDH). By definition, all patients with STEC-HUS manifest some degree of renal insufficiency. Approximately 30–40% of the patients will require dialysis therapy for an average duration of 10 days.

The majority of patients show a complete restitution. Poor prognostic factors for chronic renal disease include neutrophilia >20,000/ml, shock during the acute phase, anuria for more than two weeks, central nervous system involvement, severe colitis and/or rectal prolapse, renal cortical necrosis, extensive renal thrombo-microangiopathic lesions (50% glomeruli), and proteinuria at one year [20, 32–35]. The multivariate model which included all markers for severe acute disease showed that the association with poor long-term outcome was stronger for the use of plasma treatment than for other markers of severe acute disease such as neurological symptoms, hypertension, use of dialysis, and longer duration of dialysis [34]. Neurological complication occurs in 20–25% of patients with STEC-HUS [34]. They represent a combined effect of Stx-induced vascular injury, endothelial dysfunction, hypertension, and electrolyte disorders. Their manifestations may be seizures, loss of consciousness, thrombotic strokes, and cortical blindness, but also sudden death [34]. Skeletal muscle involvement and myocardial lesions are rare clinical manifestations.

Mortality rates in pediatric STEC-HUS range from 1–5% in sporadic cases, but in some outbreaks may be even up to 11%. Acute mortality rate declined dramatically with the introduction of early dialysis for severely affected oligo-anuric patients. Brain involvement is the most common cause of death, and less frequent causes are congestive heart failure, pulmonary hemorrhage, hyperkalemia/arrhythmia, and bowel perforation/hemorrhagic colitis. Having in mind long term complications, it is important to follow up patients who had HUS for at least five years, and over longer periods if indicated. Strict blood pressure regulation and normalization of proteinuria is very important for control of chronic kidney disease progression [36].

DIAGNOSIS

The tests required for a diagnosis of STEC-HUS are presented in Table 3. Main clinical diagnostic criteria include combination of microangiopathic anemia, thrombocytopenia and AKI. The criterion for anemia is age-dependent and sex-dependent and the confirmation of the microangiopathic character is based on microscopic review of the peripheral smear and detection of schistocytes. In addition to monitoring the hemoglobin, hemolytic parameters (LDH, haptoglobin), hematocrit, and platelet count, parameters of level of renal function, amylase, lipase, glucose, and liver function studies should be performed during the

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Table 3. Tests for diagnosing hemolytic uremic syndrome

General investigations:
Chemistry including renal and liver function, LDH, glucose, urate, lipase, amylase
Full blood count, microscopic review of the peripheral smear and detection of schistocytes
Clotting screen
Urine examination, proteinuria, albuminuria
Stool microscopy and culture
VTEC serology (ELISA and western blot)
Molecular diagnosis of STEC in stool directly with ELISA or indirectly by VT PCR
Selective investigations:
Direct Coombs test
Thorax and abdominal X-ray
Renal and abdominal ultrasound
Abdominal CT
ECG
EEG
MRI (or CT) of the brain
Renal biopsy if required

LDH – lactate dehydrogenase; VTEC – verocytotoxigenic *Escherichia coli*; ELISA – enzyme-linked immunosorbent assay; STEC – Shiga toxin-producing *Escherichia coli*; VT PCR – verotoxin polymerase chain reaction; ECG – electrocardiogram; EEG – electroencephalogram; MRI – magnetic resonance image; CT – computed tomography

acute phase of the disease. Screening for and isolation of EHEC from stool specimens has the highest likelihood of positive culture on the third day. Molecular diagnosis of STEC can be done in stool directly with the detection of Stx with enzyme-linked immunosorbent assay (ELISA) or indirectly (Stx genes) with polymerase chain reaction (PCR). Specific serogroup identification can be achieved using ELISA and western blot with specific antibodies detection, both in the acute and convalescent periods. *E. coli* O157: H7 can best be detected by plating of fresh feces on sorbitol-MacConkey agar. This agar has sorbitol, not lactose, as a carbon source. Unlike most human fecal *E. coli*, O157:H7 strains cannot ferment sorbitol after overnight incubation on sorbitol-MacConkey agar, and they therefore appear as colorless colonies.

Selective investigations include Coombs test, which is negative in HUS, thorax and abdominal X-ray, renal and abdominal ultrasound. In case of pancreatitis or suspect collection, it is necessary to perform abdominal computed tomography. Electrocardiogram should be done in case of presented cardiac failure and/or severe electrolyte disturbance. Neurological examination screens for central nervous system involvement, electroencephalogram and magnetic resonance imaging / radiographic imaging is needed in symptomatic patients. Renal biopsy is very rarely required. In the renal histology, the arteriolar afferentes – and more rarely the arteriolar efferentes – show swelling of the endothelial cell, subendothelial deposits of fibrinoid substances, and thrombosis of the arterioles. In the glomerulus, swelling of capillary endothelial cells and capillary dilatation are found. The deposits of fibrin in the capillaries, including thrombosis and hyalinosis, are also described. Tubular damage, focal or segmental, with necrosis and atrophy is of significance for long-term outcome.

THERAPY

There is no specific therapy for STEC-HUS. The management of HUS includes the usual treatment of children with AKI [37]. Early diagnosis and supportive care are of major importance. Maintaining an appropriate renal perfusion is very important in preventing HUS. Studies show that adequate pre-HUS volume expansion is associated with lesser AKI in HUS [35]. Packed red cell transfusion is indicated for Hb <6 g/dl, or in case of Hb <7 g/dl, but symptomatic. It may worsen hyperkalemia and cause volume overload. Platelet transfusion is rarely indicated unless invasive surgery is planned or there is intracranial hemorrhage. Preferred treatment for hypertension is with vasodilators [38]. Renal replacement therapy should be implemented according to the usual indications in AKI [39]. Medication that could elevate the risk or worsen AKI (diuretics, NSAIDs, ACE inhibitors, and nephrotoxic agents) should be avoided. Currently, much controversy revolves around antibiotic treatment of EHEC. They are not a part of routine management. However, recent data suggest that fluoroquinolones and azithromycin might actually be beneficial in preventing HUS or decreasing the severity of symptoms in STEC-HUS patients [40, 41]. Well-designed studies are needed to establish the role of antibiotics in this setting.

Plasma treatment is currently the treatment of choice for atypical HUS patients and is at times used in severe pediatric patients with STEC-HUS without proven beneficial effects [19, 20]. The assumption that plasmapheresis can remove the Stx from the circulation is not based on hard evidence [42]. Unlike the usual practice for the limited application of plasmapheresis in pediatric patients with STEC-HUS, in adult patients plasma therapy has until recently been "the cornerstone of treatment" [43, 44]. Multicenter retrospective case-control study which included 298 adult patients with STEC-HUS, in which plasmapheresis was carried out in 84% of the patients, questioned this traditional therapeutic approach as no benefit or only marginal benefit was found [42]. Neutralizing monoclonal antibody of Stx is promising amongst new therapies in the development of Stx [41]. The Synsorb® Pk (Synsorb Biotech Inc., Calgary, Canada) was not found to be beneficial, but Starfish has been shown to bind to Stx 1,000 times more efficiently than Synsorb® Pk [41]. Eculizumab is a recombinant, humanized, monoclonal immunoglobulin G antibody directed against C5 protein, inhibiting activation of the terminal complement pathway. It is clearly indicated in some children with atypical HUS, but its value in patients with STEC-HUS remains to be determined [19, 45]. Anti-motility agents, anticoagulation, antiaggregation and fibrinolysis are not associated with better outcome. Corticosteroids, plasmapheresis, and plasma infusion are not superior to supportive therapy. Renal transplantation in "classic" HUS is rare and recurrence of STEC-HUS is the absolute exception [21]. Therefore, in patients with Stx-associated HUS, transplantation can be performed without increased risk for transplant failure.

PREVENTION

Preventive measures and effective therapies remain important goals. They can be summarized into three categories: (1) infection prevention (exposure reduction, active immunization against 'protective' bacterial antigens and Stx), (2) primary or causal therapies targeting Stx directly, and (3) secondary therapies, aiming at downstream molecular and pathological events (inhibitors of stress-activated protein kinases, apoptosis, the thrombotic cascade) [41]. More recently, advanced, multibranched Stx receptor analogs and polymers, and peptide-based intracellular toxin inhibitors have been developed with therapeutic potential for oral and intravenous application [41]. However, hygienic measures and education remain the basic management in reducing the incidence of STEC infection and HUS.

CONCLUSION

Most commonly (70–90%), HUS is due to STEC infection. STEC-HUS usually affect children <5 years of age occurring in the summer months. Usually, it is a self-limiting disease with current mortality rates less than 4% during the acute illness. Due to long term renal and non-renal sequelae, it is important to follow up these patients for at least five years, and over longer periods if indicated.

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Хемолитички уремијски синдром изазван ешерихијом коли која продукује токсин шига

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КРАТАК САДРЖАЈ

Хемолитички уремијски синдром (ХУС) карактерише микроангиопатска хемолизна анемија, тромбоцитопенија и акутно оштећење бубрега (АОБ). Главни узрок ХУС (>90%) у детињству је инфекција изазвана бактеријама које продукују вероцитотоксин (сличан токсину шигела – „*stx*"), најчешће ентерохеморагијском ешерихијом коли (*VTEC*/*STEC*). Инфекција се може пренети употребом некуваног меса, пастеризованих млечних производа, контаминираног поврћа, воћа и воде, или контактом са особама које имају дијареју. После инкубационог периода од три до осам дана болесници обично добију хеморагијски колитис, после којег се код 5–22% оболелих развија ХУС који може бити компликован екстрареналним поремећајима укључујући поремећаје централног нервног система, панкреаса, скелетног мишића и срца. *STEC* ХУС је један од главних узрока АОБ код деце у Европи. Лечење ХУС код деце обухвата уобичајени третман АОБ. Трансфузија еритроцита је потребна код тешке анемије, а трансфузија тромбоцита само пре хируршке интервенције или код активног крварења. Употреба антибиотика није јасно дефинисана. Није доказано корисно дејство инфузија плазме или плазмаферезе. Ецулизумаб је примењен код оболелих од *STEC* ХУС-а, али корист овог третмана остаје тек да се тачније сагледа. Стопа морталитета је 3–5%. Код око 12% болесника ХУС проградира у терминалну бубрежну инсуфицијенцију у току четири године, а у 25% ће имати дуготрајне компликације укључујући хипертензију, повећану протеинурију, бубрежну инсуфицијенцију и инсулин-зависни дијабетес мелитус. Трансплантација бубрега се може применити без ризика од повратка болести.

Кључне речи: акутно оштећење бубрега; деца; Д-ХУС

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