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From Shiga toxin-producing *Escherichia coli* infection to haemolytic uraemic syndrome – bacterial, host and iatrogenic factors in children

Od zakażenia *Escherichia coli* produkującą toksynę Shiga do zespołu hemolityczno-mocznicowego – czynniki bakteryjne, gospodarza i jatrogenne u dzieci

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Abstract

Background: Shiga toxin-producing *Escherichia coli* infection is the most common cause of haemolytic uraemic syndrome in children – a form of thrombotic microangiopathy characterised by haemolysis, thrombocytopaenia, and acute kidney injury. In most cases, Shiga toxin-producing *Escherichia coli*-induced gastroenteritis is self-limiting; however, approximately 5–15% of patients develop haemolytic uraemic syndrome. **Methods:** Focused narrative review based on PubMed/MEDLINE searches covering the past 20 years, with emphasis on the last 5 years. **Results and conclusions:** The development of Shiga toxin-producing *Escherichia coli* and haemolytic uraemic syndrome in children results from gastrointestinal infection with Shiga toxin-producing bacteria, predominantly *Escherichia coli*, in combination with host susceptibility and modifiable clinical factors. Shiga toxin plays a central role in pathogenesis by binding to the Gb_3 receptor and inducing endothelial cell injury, leading to thrombotic microangiopathy. This process is further amplified by the inflammatory response and complement activation. The strongest determinants of severe disease and haemolytic uraemic syndrome development are strains producing Stx2, particularly specific subtypes, which exhibit increased cytotoxicity toward endothelial cells. Virulence factors that promote intestinal colonisation and attaching/effacing injury likely intensify mucosal damage and systemic toxin exposure. The risk of haemolytic uraemic syndrome is higher in younger children, possibly due to increased Gb_3 expression and immaturity of mechanisms regulating inflammation and complement activation. Available data also suggest a role for host genetic factors, particularly those related to complement regulation and endothelial function. Potentially modifiable clinical factors include delayed or insufficient hydration, as well as the use of antibiotics, antimotility agents, and nephrotoxic drugs, all of which may increase the risk of haemolytic uraemic syndrome.

Keywords: risk factors, haemolytic-uraemic syndrome, Shiga toxins, *Escherichia coli* infections

Streszczenie

Wprowadzenie: Zakażenie *Escherichia coli* produkującą toksynę Shiga jest najczęstszą przyczyną zespołu hemolityczno-mocznicowego u dzieci – postaci mikroangiopatii zakrzepowej z hemolizą, małopłytkowością oraz ostrym uszkodzeniem nerek. W większości przypadków zapalenie żołądkowo-jelitowe wywołane przez bakterie produkujące toksynę Shiga ustępuje samoistnie, u około 5–15% pacjentów dochodzi do rozwoju zespołu hemolityczno-mocznicowego związanego z tym zakażeniem. **Metody:** Przegląd narracyjny oparty na bazach PubMed/MEDLINE, obejmujący prace z ostatnich 20 lat, ze szczególnym uwzględnieniem ostatnich 5 lat. **Wyniki i wnioski:** Rozwój zespołu hemolityczno-mocznicowego u dzieci jest konsekwencją zakażenia przewodu pokarmowego bakteriami produkującymi werotoksynę (toksynę Shiga), głównie *Escherichia coli*, w połączeniu z indywidualną podatnością gospodarza oraz modyfikowalnymi czynnikami klinicznymi. Ważną rolę odgrywa toksyna Shiga, która poprzez wiązanie z receptorem Gb_3 indukuje uszkodzenie komórek śródbłonka, prowadząc do mikroangiopatii zakrzepowej. Proces ten ulega nasileniu w przebiegu odpowiedzi zapalnej oraz aktywacji układu dopełniacza. Najsilniejszym determinantem ciężkiego przebiegu i rozwoju zespołu hemolityczno-mocznicowego są szczepy produkujące toksynę Stx2, zwłaszcza jej określone podtypy (np. Stx2a, Stx2d), wykazujące większą cytotoksyczność wobec komórek śródbłonka. Czynniki zjadliwości związane z obecnością genu *eae* (intimina) oraz białka Tir sprzyjają ścisłej adhezji bakterii do enterocytów, zaburzeniu integralności bariery jelitowej oraz zwiększonej translokacji toksyny do krążenia. Ryzyko rozwoju zespołu hemolityczno-mocznicowego jest większe u młodszych dzieci, co może być związane z wyższą ekspresją Gb_3 oraz niedojrzałością mechanizmów regulujących odpowiedź zapalną i aktywację dopełniacza. Dane sugerują ponadto udział czynników genetycznych gospodarza, szczególnie związanych z regulacją układu dopełniacza i funkcją śródbłonka. Do potencjalnie modyfikowalnych czynników klinicznych należą opóźnione lub niewystarczające nawodnienie oraz stosowanie antybiotyków, leków hamujących perystaltykę jelit i substancji nefrotoksycznych, które mogą zwiększać ryzyko rozwoju zespołu hemolityczno-mocznicowego.

Słowa kluczowe: czynniki ryzyka, zespół hemolityczno-mocznicowy, toksyny Shiga, zakażenia *Escherichia coli*

INTRODUCTION

Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy (TMA) defined by the triad of microangiopathic haemolytic anaemia, thrombocytopaenia, and acute kidney injury (AKI). Detailed diagnostic definitions, relevant cut-off, and additional symptoms are summarised in Tab. 1[1,2].

HUS is typically classified into two categories. Typical HUS, which follows a gastrointestinal infection caused by Shiga toxin-producing *Escherichia coli* (STEC) or less frequently from *Shigella dysenteriae* type 1 infection. All other causes of HUS were referred to as atypical HUS, which is generally attributed to uncontrolled complement activation associated with mutations or autoantibodies that result in dysregulated complement activation[2,11].

STEC infection most often results from ingesting contaminated food or water, and, because the infectious dose is very low, also frequently spreads person-to-person, especially among children. The main reservoir is cattle and other ruminants; human infection is linked to undercooked beef, unpasteurised milk, and secondarily contaminated products such as fresh juices/cider, fermented dairy, and raw vegetables (e.g. lettuce, sprouts, tomatoes). Cases show clear seasonality (peaking in summer–autumn) and mainly affect young children, with increased risk also in older adults[12].

The clinical features of STEC infection typically include painful non-bloody diarrhoea that progresses to bloody diarrhoea within one to three days. Additionally, abdominal pain, vomiting, and fever may occur prior to the onset of diarrhoea. Diarrhoea associated with STEC typically resolves within approximately seven days, regardless of the development of HUS. In cases where the patient develops HUS, symptoms typically manifest around the median of day 7 of the illness, with a variability spanning from 5 to 13 days[13].

Numerous surveillance reports and evaluations reveal that a mere fraction of paediatric STEC infections advance to HUS. The Colorado state health agency indicates that 5–15% of children with STEC infection develop HUS[14].

An examination of US Centers for Disease Control and Prevention (CDC) FoodNet data revealed that 19% of children with confirmed STEC O157:H7 infection in 2012 developed HUS (27 out of 144 cases)[15].

European surveillance data indicated 522 instances of HUS among a total of 10,901 STEC cases, representing around 4.8%[16]. The World Health Organization estimates that "up to 10%" of all STEC infections, regardless of age, result in HUS[17].

In HUS due to STEC infection, no specific treatment with conclusively proven efficacy exists; thus, the primary approach is supportive care. This includes the early correction of dehydration and volume expansion, particularly during the diarrhoea phase and at the onset of the disease[18]. Close monitoring of diuresis, fluid balance, and electrolyte and acid-base disturbances is essential[19]. Management of hypertension which can occur in the course of the disease, along with renal replacement therapy (dialysis) and transfusion of red blood cells in cases of significant anaemia is highly important. Platelet transfusion is typically reserved for instances of impending bleeding or urgent surgical needs[19]. Complement blockade, such as eculizumab, is not a standard treatment for STEC-associated HUS (STEC-HUS) due to equivocal evidence. It is typically considered only in specific, selected situations, such as when atypical haemolytic uraemic syndrome (aHUS) or overlapping mechanisms are suspected[18].

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Component	Diagnostic definition	Practical cut-offs	Common accompanying findings
The HUS triad			
MAHA	Non-immune haemolysis due to mechanical RBC fragmentation[3]	Anaemia (age-adjusted ↓Hb) plus evidence of haemolysis: ↑LDH, ↓haptoglobin, ↑reticulocytes; DAT/Coombs typically negative[3]	Peripheral smear with RBC fragments (schistocytes); may be absent early; repeat smear if evolving TMA suspected. Indirect hyperbilirubinemia may occur[3,4]
Thrombocytopaenia	Platelet consumption within TMA[3,5]	Commonly PLT <150 × 10^9/L (or a clear fall from baseline)[5]	Platelet transfusion is generally avoided unless significant bleeding/procedure need[6]
AKI	Any of: ↑SCr ≥0.3 mg/dL within 48 h OR ↑SCr to ≥1.5 × baseline within prior 7 days OR UO <0.5 mL/kg/h for ≥6 h[1]	KDIGO staging (SCr/UO): Stage 1: 1.5–1.9 × baseline or +0.3 mg/dL; UO <0.5 mL/kg/h for 6–12 h. Stage 2: 2.0–2.9×; UO <0.5 for ≥12 h. Stage 3: 3× or SCr ≥4.0 mg/dL or RRT; UO <0.3 for ≥24 h or anuria ≥12 h[1]	Haemoglobinuria/proteinuria on urinalysis; oliguria/anuria; fluid overload; electrolyte/acid–base disorders[6,7]
Additional symptoms			
Hypertension/volume overload	Frequent clinical consequence of renal involvement in HUS[8]	BP ≥95th percentile for age/sex/height[8]	Oedema, pulmonary congestion; association with cardiac complications reported[6]
Neurologic involvement	CNS complications due to systemic TMA/toxin-mediated injury[9]	No single cut-off; based on clinical exam and neuroimaging as indicated	Seizures, encephalopathy, irritability, coma; occurs in a subset of paediatric STEC-HUS[9]
Multi-organ manifestations		No single cut-off; based on clinical exam and additional tests characteristic for the symptoms	Pancreatitis, hepatic involvement/cholestasis, cardiac microvascular injury, stroke, ischaemia, arrhythmias, cardiomyopathy, bowel necrosis, perforation, ARDS, pulmonary haemorrhage[6,10]

AKI – acute kidney injury; **ARDS** – acute respiratory distress syndrome; **BP** – blood pressure; **CNS** – central nervous system; **DAT** – direct antiglobulin test; **Hb** – haemoglobin; **HUS** – haemolytic uraemic syndrome; **KDIGO** – Kidney Disease: Improving Global Outcomes; **LDH** – lactate dehydrogenase; **MAHA** – microangiopathic haemolytic anaemia; **PLT** – platelets; **RBC** – red blood cells; **RRT** – renal replacement therapy; **SCr** – serum creatinine; **TMA** – thrombotic microangiopathy; **UO** – urine output.
Arrows: ↑ – increased/elevated; ↓ – decreased/reduced.

Tab. 1. HUS triad and accompanying manifestations: definitions, practical cut-offs, and common clinical/laboratory findings

METHODS

This paper was prepared as a focused review on paediatric STEC infection and risk factors of progression to STEC-HUS. Literature was identified primarily through PubMed/MEDLINE searches using combinations of terms such as: STEC/EHEC, Shiga toxin (Stx1/Stx2), haemolytic uraemic syndrome, thrombotic microangiopathy, children/paediatric, risk factors, dehydration/haemoconcentration, leucocytosis, antibiotics, antimotility agents (loperamide), complement activation, and supportive care/renal replacement therapy. In addition, citation snowballing was applied: reference lists of key reviews, landmark cohort studies, and guideline-style papers were screened to identify further relevant primary studies, and forward citation tracking was used when applicable to capture newer work building on foundational publications. Evidence was synthesised thematically into bacterial, host, and iatrogenic domains and interpreted within a mechanistic framework linking intestinal injury and toxin translocation with complement–inflammation–thrombosis-driven microangiopathy.

ETIOLOGY

Shiga toxins are AB_5 protein toxins composed of one enzymatically active A subunit and a pentameric B subunits. The B-pentamer interacts with host cell glycosphingolipid receptors, predominantly globotriaosylceramide (Gb_3), on target cells[20]. After binding, the toxin is endocytosed and transported retrogradely to the endoplasmic reticulum, where the A subunit is processed and released into the cytosol[21]. The A subunit irreversibly cleaves a specific adenine base from 28S ribosomal RNA, thereby inhibiting protein synthesis. The "ribotoxic" effect induces stress signals and apoptosis in susceptible cells[20].

There are two primary Stx types: Stx1 and Stx2. Stx2 exhibits differences in receptor binding and potency. Stx2 is associated with more severe disease and exhibits a lethality that is 100–400 times greater than that of Stx1 in animal models[22]. Most STEC responsible for HUS typically possess Stx2 (commonly subtype 2a or 2c) in addition to Stx1 or exclusively; strains containing Stx2 have a higher likelihood of inducing HUS[23–25].

Beyond Shiga toxin, STEC can express multiple virulence determinants that promote intestinal colonisation and enhance pathogenicity as their genome is fluid[26]. They can present the intimin-encoding gene *eae* (*E. coli* attaching and effacing), which lies within a pathogenicity island known as the locus of enterocyte effacement (LEE). The suite of proteins encoded by LEE coordinates bacterial adhesion to the intestinal epithelium and drives microvillus damage (effacement). This loss of absorptive surface compromises

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mucosal fluid reuptake, contributing to abdominal pain and prolonged diarrhoea[21,26].

The translocated intimin receptor (Tir) is a key STEC virulence factor, enabling the bacteria to adhere tightly to intestinal epithelial cells. Tir is an effector protein delivered to the host cell and then incorporated into the cell membrane, creating a "target" receptor for bacterial intimin on the enterocyte surface. Binding of intimin to Tir stabilises the bacterium–cell contact and initiates processes leading to characteristic attaching/effacing (A/E) changes, i.e. damage/loss of microvilli and remodelling of the cytoskeletal structure at the site of adhesion. Therefore, Tir, alongside Shiga toxins and intimin, is considered a more reliable marker of STEC infection, as it directly reflects the mechanism of adhesion and colonisation of the intestinal epithelium[27].

Through coordinated delivery of these effectors, STEC induces A/E lesions that disrupt epithelial barrier function and trigger mucosal inflammation, contributing to diarrhoea[21]. Additional accessory virulence factors include plasmid-encoded enterohaemolysin (EhxA) and diverse autotransporters[26,28]. The serine protease EspP, a member of the serine protease autotransporters of *Enterobacteriaceae* (SPATE) family, can cleave complement components C3 and C5, potentially facilitating immune evasion[21,29].

Following the colonisation of the colon by STEC, Stx are picked up by polarised gastrointestinal cells via transcellular pathways and translocate into the circulation[30]. The inflamed colonic mucosa frequently exhibits increased permeability due to the effects of Shiga toxin and lipopolysaccharides (LPS), thereby promoting toxin translocation[31,32].

Co-existing LPS from STEC synergistically enhances the effects of Stx, leading to an amplification of the toxin's impact and an upregulation of Gb_3 on target cells[33,34].

Once in the bloodstream, free Stx is infrequently detected in plasma; rather, Stx associates with circulating cells. Erythrocytes, platelets, and monocytes can transport Stx through surface Gb_3[35–37].

Human neutrophils, which do not express Gb_3, interact with Stx through Toll-like receptor 4 (TLR4). Blood-cell carriers release microvesicles that contain Stx, and occasionally complement factors, facilitating the delivery of Stx to renal cells[21,38,39]. Stx utilises blood and microvesicles to transport itself to the kidney and other target organs[39].

Glomerular endothelial cells exhibit elevated expression of the Gb_3 receptor, rendering them the principal target of Stx in the renal system[40,41].

Upon Stx interaction: the transcription factor NF-κB is increased, leading to enhanced production of adhesion molecules and proinflammatory cytokines. Elevated concentrations of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), along with the chemokines monocyte chemoattractant protein 1 (MCP-1) and fractalkine (CX3CL1), have been noted, promoting leukocyte adherence to the endothelium[21,42–45].

Concurrently, Stx diminishes the anticoagulant characteristics of endothelial cells by promoting the release of thrombomodulin and enhancing the expression of P-selectin on their surface. This facilitates platelet adhesion to the endothelium, frequently in conjunction with multidomain variants of von Willebrand factor, and the development of platelet-fibrin clots within the glomerular capillaries[45–47]. Consequently, TMA ensues, characterised by capillary obstruction and erythrocyte fragmentation[6,21,48].

Podocytes express Gb_3 and respond to Stx, leading to the secretion of inflammatory cytokines such as interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF-α), which further enhance Gb_3 receptor expression. Stx promotes the p38 and p42/44 mitogen-activated protein kinase (MAPK) signalling pathways in podocytes, as well as the transcription factors NF-κB and activator protein 1 (AP-1)[42]. This results in heightened synthesis of endothelin-1 (ET-1), a vasoconstrictive peptide produced by podocytes. ET-1 functions in an autocrine manner via endothelin A receptors (ET_A), inducing cytoskeletal rearrangement and contraction of podocyte extensions. *In vitro* studies demonstrate that the inhibition of ET_A receptors prevents Stx-2, induced alterations in podocyte cytoskeletal structure. Consequently, the podocyte extensions become distended (effacement), detach, and the filtration barrier is compromised[42]. Comparable alterations have been noted *in vivo* – podocytes exhibit swelling due to Stx, whereas the basement membrane of the glomerular capillaries is characterised by constriction and fusion of the podocyte slits. These changes contribute to podocyte dysfunction, detachment, and ultimately disruption of the glomerular filtration barrier[49–51].

The complement system amplifies vascular injury in STEC-HUS. Clinical studies show that during acute STEC-HUS, markers of alternative pathway activation are elevated: plasma C3 levels are often low while split products (C3b, C3a, C3d) and Bb are increased[52–55]. Renal biopsies from HUS patients reveal glomerular deposits of C3 and membrane attack complex (C5b-9) along with fibrin[56–58]. Experimentally, Shiga toxin itself can directly activate complement: Stx2 binds to factor H (FH) and FH-related proteins, hindering FH regulation of C3b[59,60]. Stx2 also downregulates endothelial CD59 (a membrane inhibitor of C5b-9). Thus, complement converts into a destructive force: generation of C3a/C5a (pro-inflammatory anaphylatoxins) and C5b-9 (which damages cells and releases tissue factor)[61–63]. Activated complement contributes to microvascular thrombosis. For example, platelet and red-cell derived microparticles bearing C3 fragments and C5b-9 are found in HUS, linking complement to haemolysis and coagulopathy[11,64].

Innate immune responses also amplify injury. Endothelial release of cytokines and chemokines recruits neutrophils and monocytes[43,65].

In HUS, neutrophils become primed: they adhere more avidly to Stx-activated endothelium and can damage it.

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Neutrophils bind Stx via TLR4; genetic variations in TLR4 can affect HUS susceptibility[66,67].

Shiga toxin and co-delivered LPS induces a cytokine storm including TNF-α, interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and others, which further activate endothelium and leukocytes[68,69]. Together, complement and cytokines create a feedback loop: endothelial injury leads to inflammation and complement activation, which in turn worsens microvascular thrombosis.

EPIDEMIOLOGY

From January 2012 to June 2023, the Polish Registry of Paediatric Haemolytic Uraemic Syndrome recorded a total of 301 cases, yielding a mean incidence of 3.9 cases per million in the age-related population[70]. In England, an analysis of national surveillance data indicates an incidence rate of 0.07 per 100,000 per year (0.07–0.08) for STEC-HUS, with a total of 601 cases reported between 2009 and 2023[71]. Between 1997 and 2021, the incidence rate in the USA was 0.6 cases per 100,000 children[72]. Ten-year observation period of Northern Italy population brought a similar result with 5.6 cases per million of the age-related population (MARP) aged <18 years[73]. The incidence of HUS is minimal in Australia.

A clear correlation is observed between urbanisation levels in a region and the prevalence of diseases, linked to insufficient sanitation conditions. The likelihood of STEC infections is reduced in urban regions[74]. Interaction with farm animals significantly influences outcomes. Epidemiological studies indicate that children residing in rural areas or in proximity to farms with elevated densities of cattle, sheep, and goats exhibit a higher likelihood of contracting STEC. In the Netherlands, a greater prevalence of STEC O157 infections was observed in rural regions compared to urban regions, indicating a correlation between infection rates and cattle density[75]. A recent study conducted in Minnesota established that the presence of each additional animal reservoir in a specific area correlates with an elevated risk of disease in children. Specifically, an increase in the number of cattle or sheep on 10 acres was linked to an approximate 30–135% rise in the risk of STEC O157 infection. This effect was observed irrespective of the child's direct interaction with animals, indicating pervasive environmental contamination[76].

Nevertheless, the risk of progression from STEC infection to HUS does not seem to be significantly affected by these factors. A prospective English study identified no significant correlation between socioeconomic status or rural residence and the risk of developing HUS in children infected with STEC. This suggests that while environmental and socioeconomic factors affect the incidence of the infection, the progression to HUS in individuals' post-infection is mainly influenced by other variables, such as the child's age, the specific STEC strain, or the treatment administered[77].

RISK FACTORS

Bacterial factors

Infection with various STEC strains presents differing risks for HUS. The primary bacterial determinants are the strain type and the type of Shiga toxin. The serotype O157:H7 has been previously recognised as the predominant cause of HUS worldwide[78]. Additional serogroups, including O26, O55, O80, O103, O104, O111, and O145, have been also identified as causative agents. Nevertheless, serogroup O157 is slightly more likely to cause HUS[79].

The type of Shiga toxin also influences the likelihood of HUS occurrence. Experimental studies demonstrate the heightened nephrotoxicity of Stx2 class toxins, hence strains possessing the *stx2* gene, particularly the *stx2a* subtype, demonstrated a markedly elevated risk of HUS[79,80]. Experimental studies have shown a distinct dose-dependent variation in the nephrotoxicity associated with Shiga toxins. A single administration of Stx2 at a dose of 50 ng/kg in a primate model resulted in a severe clinical presentation consistent with HUS and nearly 100% mortality within 5 days. In contrast, Stx1 showed lethal effects only at a significantly higher dose of 100 ng/kg[81]. In a mouse model, consistent results indicated that oral administration of Stx-II (functionally analogous to Stx2) led to acute renal cortical necrosis and mortality, while Stx-I did not exhibit a lethal effect[80]. The data indicate that infections caused by STEC strains that produce solely Stx2 are typically more virulent than those caused by strains that produce only Stx1. In clinical practice, the identification of the *stx2* gene in an *E. coli* isolate serves as a critical indicator of heightened risk for developing HUS, independent of other strain characteristics[82–84].

The authors of the Finnish study performed an analysis comparing the genes of different STEC strains associated and not associated with HUS. Numerous genes were identified, including cytolethal distending toxins-encoding genes; the autotransporter serine protease gene *espP*; and type III secretion system effector-encoding genes; however, none were associated with the severity of the disease[85]. As previously noted, the genomic fluidity of STEC allows for the expression of additional pathogenic components, which can influence whether an infected patient will develop HUS.

In practice, this means that clinical severity reflects not only the presence of Shiga toxin, particularly Stx2 (often subtypes 2a/2c), which is most consistently linked with HUS risk and greater lethality[22–25] but also the co-occurrence of colonisation and mucosal-damage modules such as the LEE-encoded A/E machinery (*eae*/intimin and its effector Tir), which strengthens epithelial adherence, disrupts the brush border, prolongs diarrhoea, and promotes inflammatory barrier dysfunction[21,26,27]. Accessory factors, including plasmid-encoded EhxA, diverse autotransporters, and the SPATE protease EspP, which is capable of cleaving complement components C3/C5, potentially aiding immune

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evasion and can further amplify mucosal inflammation and facilitate systemic toxin access[21,26,28,29]. Collectively, strains with a "high-risk" virulence constellation are more likely to generate a permissive intestinal environment for Stx translocation (aided by inflammation and LPS synergy) and efficient delivery to renal targets, thereby increasing the probability of the endothelial injury; thromboinflammatory cascade that culminates in thrombotic microangiopathy and HUS[21].

Host genetics

Research shows that certain children infected with STEC develop HUS not solely due to the strain's virulence but also due to their genetic predisposition to TMA. A population-based CDC FoodNet study involving 641 individuals with diarrhoea due to STEC O157:H7, analysed 200 genetic *loci*. The findings indicated that polymorphisms in various genes, may influence the risk of developing HUS. Notable associations were identified in genes influencing various critical pathogenic mechanisms: platelet function and haemostasis (e.g. GP1BA), endothelial activation and integrity along with vascular tone regulation (EDN1), innate immunity and pathogen recognition (e.g. TLR4), inflammatory/cytokine signalling (e.g. IL6R, IL1RN), and iron transport alongside mechanisms of nutritional immunity (TFRC, B2M). This indicates that individuals with particular genetic variants may experience a heightened dysregulated inflammatory response, increased platelet activation, endothelial damage, and microthrombi formation upon exposure to Shiga toxin, potentially resulting in the development of HUS. The authors highlight that these observations are exploratory and necessitate validation in independent cohorts[66].

Age and demographics

The greatest risk of HUS is identified in the youngest paediatric population. Recent data suggest that approximately two-thirds of HUS cases are observed in children under the age of five[86,87]. An underdeveloped immune system among the youngest population is characterised by a diminished response to pathogens and reduced immune memory, hence younger children exhibiting greater susceptibility to STEC infections and a diminished capacity to neutralise Shiga toxin. Epidemiological studies indicate that children's heightened vulnerability to STEC is attributed to an immature immune system and insufficient hygiene practices. This encompasses an absence of previous exposure to toxin-producing *E. coli* and a deficiency of neutralising antibodies, both of which exacerbate the severity of infection and facilitate the onset of HUS[88,89].

The Shiga toxin receptor, Gb_3, located on renal and intestinal endothelial cells, serves as the binding site for the toxin. Research indicates that, contrary to earlier assumptions, the quantity of Gb_3 in the kidneys does not significantly differ between children and adults. During the initial phase of infection, variations in receptor expression on intestinal cells or changes in bacterial adhesion factors may affect colonisation and tissue damage in children[90].

The physiology and microbiome maturate for the first 3 to 5 years of children's life. Their digestive system is characterised by lower stomach acidity and a less stable intestinal microflora, which promote bacterial survival and proliferation[89,91,92]. Studies demonstrate that the intestinal microbiome of children experiencing diarrhoea exhibits distinct differences compared to that of healthy children, notably marked by reduced diversity and an increased prevalence of *Enterobacteriaceae* family bacteria. The disruption of the microbiome diminishes the colonisation resistance of the intestine, resulting in prolonged persistence of pathogenic *E. coli* in the digestive tract[92,93].

In vitro studies indicate that STEC strains are eliminated at a slower rate in the simulated intestinal environment of young children compared to adults, leading to extended toxin release. The intestinal barrier in infants and young children exhibits greater permeability, potentially allowing toxins to enter the bloodstream more easily[89].

Females have been reported in some paediatric datasets to develop HUS more often than males, but the evidence is inconsistent across studies. In the outbreak cohort by Bell et al., demographic characteristics, including sex, were not associated with HUS risk[94]. In contrast, in a multicentre emergency-department cohort, girls were slightly overrepresented among children who subsequently developed HUS (55.6% vs. 45.9%), although this difference was only borderline significant[95]. Other observational paediatric studies have also noted a higher proportion of females among HUS cases, suggesting a possible association[96].

Severity of prodromal symptoms

Severe acute diarrhoea symptoms increase the risk of developing HUS. Research demonstrates that severe bloody diarrhoea, persistent vomiting, leucocytosis and high fever are enriched among children who subsequently develop HUS[77,97–99]. In a US study, patients with HUS were found to be approximately three times more likely to exhibit fever compared to those without HUS[100]. It is important to note that when controlling for multiple factors in multivariate statistics, the influence of fever, vomiting, or bloody stools on the risk of HUS was diminished. This may be attributed, in part, to the composition of the control group in many studies, which often included hospitalised patients experiencing severe diarrhoea, indicating that prodromal symptoms were prevalent[98].

In paediatric populations, the most consistently validated laboratory predictor of progression from STEC infection to HUS is early leucocytosis during the diarrhoeal phase[94]. In a classic cohort of 278 children with confirmed *E. coli* O157:H7 infection, a white blood cell count ≥13,000/μL within the first three days of illness was associated with

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an approximately seven-fold higher risk of HUS (38% vs. 5%)[94], and other paediatric analyses similarly confirmed an independent association between leucocytosis and subsequent HUS in multivariable models[99,101]. Likewise, in a large multicentre cohort of children evaluated in the emergency department, an elevated leukocyte count (with an optimal cut-point of $13.0 \times 10^3/\mu L$) was among the few baseline parameters that predicted later HUS[95].

By contrast, thrombocytopaenia is primarily a feature of established HUS and typically emerges with evolving microangiopathy[6]; importantly, in the emergency-department cohort, the median platelet count at first presentation was similar in children who later developed HUS and in those who did not, although a platelet count $<250 \times 10^3/\mu L$ was used as a risk marker in multivariable prediction[95].

Concomitant diseases

The existing literature lacks definitive analyses regarding the influence of chronic childhood illnesses on the risk of HUS. Sporadic case reports suggest that compromised immune system may increase the severity of STEC infection. A case of STEC-HUS in 12-year-old male with ataxia-telangiectasia (A-T) which is a genetic immunodeficiency, was reported, highlighting his significant susceptibility to infections[102].

Severe STEC-HUS has been documented in adult organ transplant recipients. A retrospective analysis of 35 adult kidney transplant recipients revealed that STEC-HUS, was associated with high mortality rates, with 38% of patients requiring dialysis and 26% experiencing graft loss[103]. Prior reports on transplant cases highlight the infrequency of typical STEC-HUS within this population, as well as the propensity for delayed diagnosis and unfavourable outcomes[104].

No studies were found indicating that children with chronic diseases, such as diabetes, chronic kidney disease, metabolic disorders, or cancer, possess an inherently elevated risk of HUS. In an analysis of adult European patients with the STEC O104:H4 strain, approximately 37% had chronic diseases, including hypothyroidism, hypertension, or chronic kidney disease. However, these factors did not serve as independent predictors of HUS in a multivariate model[105].

One report details a case of HUS in an infant that was caused by vertical transmission of a low-pathogenic STEC strain (O146:H28), suggesting that even minimally pathogenic bacteria can induce HUS in newborns[106].

Iatrogenic factors

Fluid therapy

The extent of dehydration during diarrhoea significantly influences the disease progression and the potential for kidney damage. Clinical dehydration, characterised by weight loss exceeding 5% correlates with diminished renal function recovery and an increased incidence of chronic renal sequelae in paediatric patients with HUS[107]. Insufficient hydration results in haemoconcentration, and negatively impacts renal microcirculation, potentially aggravating vascular damage induced by Shiga toxin. Early and aggressive fluid therapy, initiated during the prodromal phase of diarrhoea, has demonstrated benefits. Observational studies indicate that intensive isotonic fluid administration decreases the incidence of anuria/oliguria and reduces hospital stay duration[108].

One meta-analysis established that elevated haematocrit upon admission, indicative of dehydration, and the absence of early intravenous infusions were independent predictors of a poorer outcome in HUS[108]. In practice, preventing excessive dehydration during the initial stage of diarrhoea, through careful oral or intravenous rehydration, is a crucial intervention that mitigates the risk of severe kidney damage in children with STEC infection[109].

Antibiotics

Numerous studies demonstrate that extensive antibiotic use in cases of STEC diarrhoea elevates the risk of HUS[77,99]. A classic cohort study conducted by Wong et al. demonstrated that antibiotic treatment in children with *E. coli* O157:H7 infection was linked to a markedly increased risk of developing HUS (relative risk ≈ 17)[110]. Many other clinical and observational studies provide evidence that the use of antibiotics, especially β-lactams, increases the risk of developing HUS[96,111]. Nevertheless, the data are inconclusive across all drug classes. In Japan, early administration of fosfomycin, which show bacteriostatic properties, was implemented, resulting in a significant reduction in the risk of HUS[112].

Other observational study indicates that antibiotic use, specifically fosfomycin, may lower the risk of HUS in children[98]. Although Freedman et al. conducted a meta-analysis encompassing 17 studies with nearly 1,900 patients, revealing no significant increase in risk associated with antibiotics. However, after the exclusion of low-quality studies, a significant association was found[113]. The authors determined that, although complete clarity is lacking, prophylactic antibiotics for STEC are not advised. The CDC advises against the routine administration of antibiotics for STEC, as they may elevate the risk of HUS[114].

Antimotility drugs

Medications that slow gut motility, such as loperamide and diphenoxylate, are typically contraindicated in cases of haemorrhagic diarrhoea linked to STEC. This mechanism results from the retention of bacteria and toxins, which is thought to promote the spread of infection[115]. Research indicates a detrimental effect: a significant study conducted in Japan demonstrated that the administration of antimotility medications roughly doubled the risk of subsequent HUS[98]. Previous studies, such as those by Nelson et al., indicated a higher prevalence of antidiarrhoeal medications among patients diagnosed with HUS[116].

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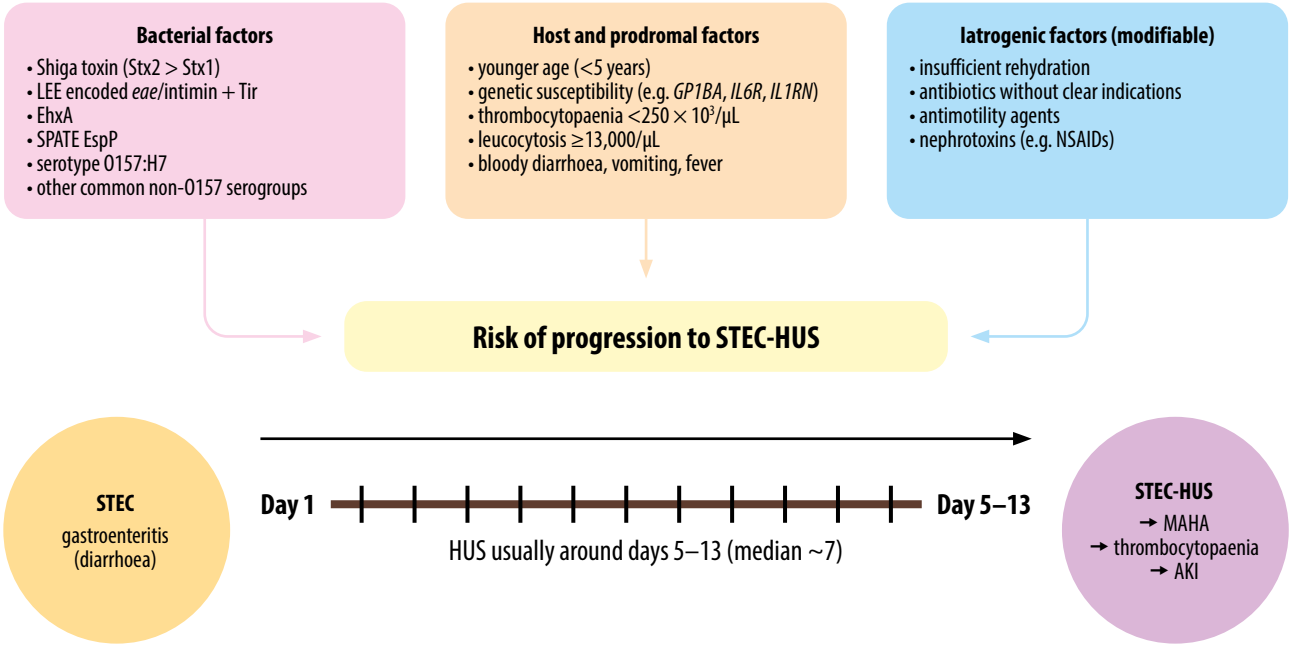

AKI – acute kidney injury; ***eae*** – *E. coli* attaching and effacing gene encoding intimin; **EhxA** – enterohaemolysin A; **EspP** – extracellular serine protease, plasmid-encoded; ***GP1BA*** – glycoprotein Ib alpha chain (gene); **HUS** – haemolytic uraemic syndrome; ***IL1RN*** – interleukin-1 receptor antagonist (gene); ***IL6R*** – interleukin-6 receptor (gene); **LEE** – locus of enterocyte effacement; **MAHA** – microangiopathic haemolytic anaemia; **NSAIDs** – nonsteroidal anti-inflammatory drugs; **O157:H7** – *Escherichia coli* O157:H7 serotype; **SPATE** – serine protease autotransporters of *Enterobacteriaceae*; **STEC** – Shiga toxin-producing *Escherichia coli*; **STEC-HUS** – Shiga toxin-associated haemolytic uraemic syndrome; **Stx** – Shiga toxin; **Tir** – translocated intimin receptor.

Fig. 1. From STEC gastroenteritis to STEC-HUS in children: factors associated with progression

Given these risks, public health guidelines unanimously advise against their use, as the CDC explicitly advises against the use of loperamide in cases of STEC infections, and the Food and Drug Administration (FDA) explicitly contraindicates loperamide in invasive bacterial enterocolitis[114,117].

Prebiotics

Interest has grown in manipulating gut microbiota for STEC, but human data are lacking. *In vitro* and animal studies show certain probiotics can antagonise STEC. Notably, the probiotic *E. coli* Nissle 1917 sharply inhibited growth and Shiga-toxin expression of O157:H7 in culture[118]. Other experiments found *Lactobacillus* strains (e.g. *L. plantarum*, *L. fermentum*) reduce STEC adhesion and toxin release[119]. A piglet model even showed that an engineered probiotic expressing a Shiga-toxin receptor mimic bound and cleared toxin from the gut[120]. Nevertheless, the availability of practical clinical data is restricted. A recent cohort study found no significant protective effect of probiotics, as their use did not notably change the risk of HUS (modified odds ratio ≈ 0.86, not significant)[98].

Nonsteroidal anti-inflammatory drugs

Research on nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and aspirin, in relation to STEC-HUS is limited. In a prospective paediatric cohort study examining risk factors for HUS, the exposure to NSAIDs during the illness was evaluated and found no significant association with the development of HUS (odds ratio ≈ 1.0; not significant). The small number of children using NSAIDs resulted in wide confidence intervals[99]. Simultaneously, irrespective of the risk of HUS development during STEC infection, NSAIDs are recognised as a cause of AKI in children, particularly in the context of hypovolemia (diarrhoea/vomiting/dehydration), which is significant in STEC cases[121,122]. A paediatric study involving dehydrated children with acute gastroenteritis found that ibuprofen exposure was linked to a greater than two-fold increase in the risk of developing AKI in approximately 54% of the subjects who received ibuprofen[121].

Consequently, reviews and studies regarding the treatment of STEC/HUS highlight the importance of avoiding nephrotoxins. In practice, paracetamol is the preferred antipyretic/analgesic, while NSAIDs should be avoided, particularly in cases of suspected STEC, severe diarrhoea, vomiting, and dehydration risk, despite the lack of definitive evidence linking NSAIDs to the causation of HUS[123].

All the factors and viabilities are depicted in Fig. 1.

CONCLUSIONS

The transition from paediatric STEC infection to STEC-HUS involves the interaction of high-risk bacterial virulence factors, particularly Stx2 and its subtypes, host susceptibility factors such as young age and potential genetic variations in immune systems, as well as modifiable clinical exposures. Shiga toxin-induced endothelial and podocyte damage, exacerbated by inflammation and complement

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activation, leads to TMA characterised by haemolysis, thrombocytopaenia, and AKI. Early and sufficient rehydration is the primary preventive strategy, although antibiotics (unless explicitly indicated), antimotility agents, and NSAIDs should typically be avoided; management is predominantly supportive.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: JH. Collection, recording and/or compilation of data; analysis and interpretation of data: JH, BW, MJB. Writing of manuscript: JH, BW, MJB, ALO. Critical review of manuscript; final approval of manuscript: ALO.

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