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Hemolytic Uremic Syndrome Caused by Shiga Toxin-Producing Escherichia coli Infections: An Overview

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Abstract

The purpose of this manuscript is to provide a current overview on the Shiga Toxin / verotoxin-producing *Escherichia coli* (STEC) hemolytic uremic syndrome (HUS) with emphasis on the epidemiology, clinical and laboratory manifestations, pathogenesis, recommended assessment, treatment strategies and prognosis. Hemolytic uremic syndrome (HUS) is a cause of the community-acquired acute renal insufficiency in young children. The outbreak in Germany illustrated both the emerging importance of non-O157 serotypes as agents of human disease and the potential for large-scale methods of food production and distribution to result in widespread disease. Children with STEC-induced HUS typically have a prodromal illness that can rapidly develop severe and multi-system life-threatening complications. STEC infection is acquired through contaminated food or water. Thrombotic microangiopathy is the mechanism of the development of the characteristic pathologic lesion of HUS. Any patient with a recent history of diarrhea and signs of a multi-organ disorder requires a proper assessment for the possible development of HUS. Appropriate laboratory testing for both O157 and non-O157 serotypes, as well as prompt initiation of infection control procedures for confirmed or suspected cases, will facilitate follow-up investigation to identify the source of disease and will help to prevent secondary transmission. Currently, diagnostic test to predict which patients will develop HUS is not available. Supportive care and intravenous fluid replacement are the cornerstones of treatment because of the current lack of safe and specific therapeutic intervention. Culizumab and/or plasma treatment may be considered in patients with severe CNS involvement who have a poor prognosis. None of the multiple therapeutic agents including antithrombotic agents, plasma exchange and/or plasma infusion, tissue-type plasminogen activator, and oral Shiga toxin-binding agent that have been used is recommended. For most patients with uncomplicated STEC-associated gastroenteritis who are treated with supportive care, the prognosis was excellent. Public health interventions are the key to prevent STEC-associated diarrhea and HUS. Researches will improve the care of patients with different HUS types in the years to come. The identification of genetic factors associated with HUS will contribute to a better insight of the pathogenesis of HUS and will have potential therapeutic and preventive implications.

Introduction

Hemolytic uremic syndrome (HUS) is one of the most common causes of community-acquired acute renal insufficiency in young children. It is divided into diarrhea-positive and diarrhea-negative HUS. Diarrhea-positive HUS (also referred to as diarrhea-associated HUS or typical HUS) is mainly caused by Shiga toxin-producing *Escherichia coli* (STEC) and less frequently by *Shigella dysentery* type 1 infections. Atypical HUS (aHUS) includes all the other causes of HUS. HUS is defined as a triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and injury of organs (especially the kidney and the brain) [1,2].

Epidemiology

Worldwide, STEC O157:H7 accounts for 90 percent of HUS cases in Europe and America, while, in Asia and Southern Africa, Shiga toxin of *Shigella dysentery* type 1 is the main causative agent. It primarily affects children under the age of five years. In the United States and Western Europe, the reported annual incidence of STEC-induced HUS is about two to three per 100,000 children of less than five years of age [**3**]. The remaining childhood HUS is either primary HUS caused by complement dysregulation, with an estimated prevalence of seven per one million children in Europe, or secondary HUS [4]. In adults, STEC infections may cause HUS, although it is more commonly associated with thrombotic thrombocytopenic purpura (TTP) [5]. The reservoir of the STEC is the intestinal tract of the domestic animals usually cows. The disease is transmitted by undercooked meat or unpasteurized milk or applecart. Epidemics have followed ingestion of undercooked, contaminated hamburger at fast food restaurants. HUS outbreaks occur in association with swimming in contaminated ponds, lakes or pools, municipal water supply, petting farms, consumption of cheese or raw spinach contaminated with a toxin. However, spread by person to person within families or child care center may less frequently occur. At 2011 and during the outbreak of Diarrhea-associated HUS in Germany, 3842 people were affected after consuming contaminated fenugreek sprouts which necessitated the hospitalization of many of these individuals. The serotype responsible, E. coli O104:H4, was previously considered of limited

pathogenic potential in humans. However, the outbreak strain was subsequently found to have acquired new virulence factors. The outbreak in Germany illustrated both the emerging importance of non-O157 serotypes as agents of human disease and the potential for large-scale methods of food production and distribution to result in widespread disease [3].

Clinical manifestations

HUS complicates 6 to 9 percent of STEC infections and occurs most commonly in preschool and school aged children but can occur in adolescents [1]. Children with STEC-induced HUS typically have a prodromal illness with abdominal pain, fever, vomiting, and Diarrhea that precedes the development of HUS by few days. Diarrhea and gastrointestinal complaints mimic those of other enteric infections, and appendicitis. HUS can be severe and requires hospitalization and can be mild and considered trivial [6-9]. The diarrhea is often bloody but not necessarily so, especially early in the disease. After the prodromal illness, sudden onset of pallor, irritability, weakness and lethargy herald the onset of HUS. Oliguria presents in early stage but may be masked by ongoing Diarrhea because the prodromal diarrhea often overlaps the onset of HUS. Patients with pneumococcus-associated HUS are ill with pneumonia and empyema when they develop HUS. The onset can be insidious in patients with the genetic form of HUS. Some patients who appear mildly affected at presentation can rapidly develop severe and multi-system life-threatening complications. Leukocytosis and severe prodromal enteritis predict a severe course. Organ involvement includes [10,11]:

Central Nervous System (CNS): The majority of patients with HUS have some CNS involvement. Most have mild manifestations with significant irritability, lethargy and non-specific encephalopathic features. CNS involvement includes seizures, coma, stroke, and cortical blindness due to focal ischemia secondary to microvascular CNS thrombosis and small infarction in the basal ganglion and cerebral cortex [12]. In patients with severe neurologic findings, brain magnetic resonance imaging reveals bilateral hypersignal on T2-weighted and hyposignal on T1-weighted images in the basal ganglia, thalami, and brainstem [13]. Severe CNS involvement is associated with increased mortality. Severe hypertension results in CNS symptoms and requires emergent therapy to reduce the blood pressure.

Severe inflammatory colitis: Any area of the gastrointestinal tract can be affected. Severe manifestations are hemorrhagic colitis, bowel necrosis, perforation, rectal prolapse, peritonitis, and intussusception [14,15].

Cardiac dysfunction: Direct cardiac involvement is rare, but dysfunction and/or arrhythmia can occur (without predisposing factor) secondary to fluid overload, severe anaemia, or hypertension that lead to heart failure.

Pancreas: Up to 10 percent of patients develop glucose intolerance during the acute phase and transient diabetes mellitus may occur. Rarely permanent diabetes mellitus will develop years later [14].

Liver: Hepatomegaly and/or increased serum transaminases may occur.

Hematology: Anaemia and thrombocytopenia without purpura or bleeding may develop. The degree of thrombocytopenia is not related to the severity of renal dysfunction. Leucocytosis is common and associated with poor prognosis [16].

Pathogenesis

STEC infection is acquired through contaminated food or water. The STEC harbours bacteriophages that encode the virulence factors 1 and 2. Bacteriophage-encoded Shiga toxins and a chromosomally located pathogenicity island (the locus of enterocyte effacement [LEE]) are characteristic of STEC. The LEE encodes proteins necessary to produce an "attaching effect" as the bacteria attach to intestinal epithelial cells and induce loss of the microvilli on the apical surface [17]. These proteins include intimin, which brings the bacteria into close contact with the epithelial cell, and a type III secretion system, by which bacterial proteins can be injected through the intestinal epithelial cell membrane. STEC survives exposure to gastric acid which in turn induces the expression of intimin and T3SS and facilitates the adhesion to epithelial cells resulting in diarrhea on reaching the lower gastrointestinal tract [18,19]. The E. coli O104:H4 has a bacteriophage-encoded Shiga toxins and its promoter region and also has a CTX-M-15 class extended-spectrum beta-lactamase, as well as a unique combination of enzymes known as Serine Protease Auto transporters of Enterobacteriaceae that contributes to higher intestinal adherence and colonization [20,21]. Once adhered to intestinal epithelial cells, STEC produces and releases Shiga toxin 1 and/or Shiga toxin 2. The latter is most commonly associated with HUS in humans. The released Shiga toxin passes across the intestinal epithelium and delivers to its receptor, globotriaosylceramide (Gb3), by circulating neutrophils [22]. Density of the Gb3 receptor is particularly high in the kidneys, as well as the colon and brain, thus, facilitates the action of the Shiga toxin in these organs [23,24]. Shiga toxin–induced injury to the colonic microvasculature is the cause of bloody diarrhea in STEC infections, whereas the toxin-induced injury to renal endothelial cells leads to the acute kidney injury. The high intracellular concentrations of Shiga toxin induce cell death by modifying the ribosome and inhibiting elongation of the peptide chain, whereas lower intracellular concentrations of Shiga toxin alter gene expression and endothelial cell phenotype [25]. These two mechanisms of damage contribute towards the development of the characteristic pathologic lesion of HUS, Thrombotic Microangiopathy (TMA). Thrombotic Microangiopathy is a term for a histologic lesion of the microvasculature characterized by swelling, detachment of the endothelium, sub-endothelial accumulation of protein or cellular debris and vascular obstruction by fibrin and platelet-rich thrombi (Figure 1) [26]. Shiga toxin up regulates the expression of adhesion molecules on the endothelial cell surface and facilitates the adherence and degranulation of neutrophils [27]. Neutrophil degranulation releases elastase, which result in endothelial cell detachment. Shiga toxins also increase cell surface expression of P-selectin, and both stimulate the release and inhibit the cleavage of ultra large von Willebrand factor leading to platelets adhesion to the endothelial cell surface and thrombosis [2,28,29]. So, bloody diarrhea in HUS occurs due to the actions of the Shiga toxin on the endothelial cells of the gastrointestinal tract.

The patterns of renal involvement include [27,28]:

Glomerular TMA: It is characterized by a thickening of the capillary walls, with widening of the subendothelial space. Endothelial cells are swollen and may obstruct the capillary lumen. The lesions affect the preglomerular arterioles and the glomerular capillaries, but, glomerular lesions may extend to the afferent arterioles. The mesangial matrix has a fibrillar appearance. The glomeruli are enlarged and the capillaries contain red cells and platelets.

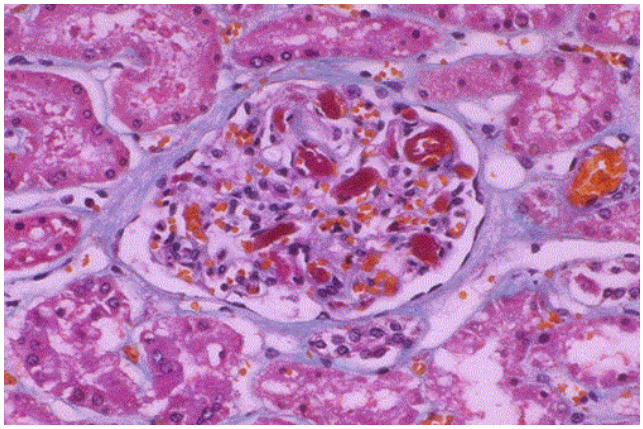

Figure 1: Characteristic fibrin thrombi in glomerular capillaries typical of thrombotic microangiopathy in HUS (From PathologyOutlines.com)

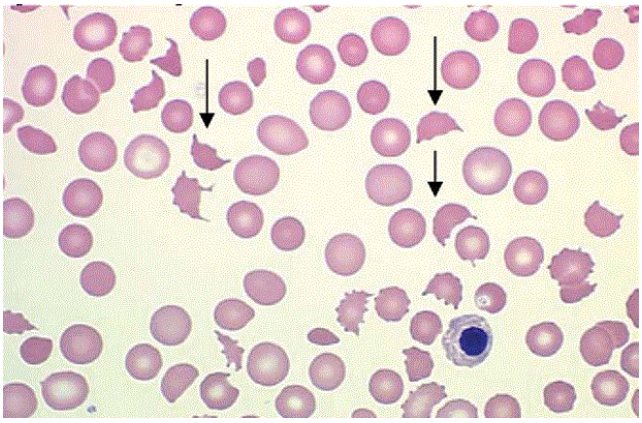

Figure 2: Peripheral blood smear of a patient with microangiopathic haemolytic anemia with schistocytes in HUS (arrows) (from http://www.clevelandclinicmeded.com)

Patchy or diffuse cortical necrosis: It occurs in the most severe disease with prolonged anuria and affects the entire cortex. It carries a high risk of chronic renal failure development.

Arterial TMA: The arterioles and interlobular arteries are severely affected with intimal edema, necrosis of the arteriolar wall, luminal narrowing, and thrombosis. The glomeruli are ischemic and shrunken, with splitting of the capillary wall and wrinkling of the glomerular basement membrane. This lesion is responsible for severe hypertension in STEC-induced HUS [29].

Diagnosis

Any patient with a recent history of diarrhea (possibly bloody) who presents with symptoms and signs of a multi-organ disorder requires a proper assessment for the possible development of HUS. The laboratory manifestations of HUS include [9]:

Anaemia: It is mild at presentation, progress and of microangiopathic haemolytic anemia (MAHA) type. MAHA is caused by non-immune red blood cells destruction due to shearing of the RBCs as they pass through platelet micro thrombi in the microcirculation. The hemoglobin levels decrease to less than 8 g/dL with negative Coombs' tests (except in pneumococcal-induced HUS where Coombs' tests is usually positive), and the hemolysis causes life-threatening hyperkalemia. Peripheral blood smear shows the large number of schistocytes (caused by the red cell fragmentation), burr cells and helmet cells (Figure 2). The hemolysis is associated with increased serum indirect bilirubin concentration, decreased serum haptoglobin concentration and very high serum lactate dehydrogenase (LDH) level. There is no correlation between the severity of anemia and the extent of renal injury [3].Leucocytosis is present in most cases.

Thrombocytopenia: It is an invariable finding in the acute phase with platelet count levels between 20 and 100 $X10^9$/L. However, if the platelet count obtained within seven days of the onset of acute illness is higher than 150 $X10^9$/L, other diagnosis should be considered. However, there is usually no purpura or active bleeding and the degree of thrombocytopenia is unrelated to the severity of renal dysfunction. Prothrombin and partial thromboplastin times are within normal limit.

Renal injury: The severity of renal insufficiency varies from acute renal failure (occurs in one-half of cases) to mild elevation of BUN and creatinine (≥ 1.0 mg/dL in children less than 3 years-old or ≥ 1.5 mg/dL in children older than 3 years-old), microscopic haematuria (found in most patients) and low-grade proteinuria. Dehydration at presentation is associated with dialysis and fifty percent of HUS requires dialysis during the acute phase [10]. The renal function is generally recovered, even when dialysis was performed.

Testing for Shiga toxins: ELISA, stool culture, and serologic testing for IgM and anti-lipopolysaccharide antibodies against the most frequent STEC serotypes are required. IgM antibodies have a 95 and 99 percent sensitivity and specificity respectively [30,31]. However, the accuracy of these findings in patients with similar clinical symptoms, but without positive cultures for E. coli 0157:H7 is unclear. Further studies are needed to clarify their clinical role. Stool culture screening for E. coli O157:H7 is performed with sorbitol MacConkey agar as the organism ferments sorbitol slowly. Results from stool cultures are unreliable because the bacteria are only present in the stools for a few days and, even if present, may not be detected by culture from stool samples. However, culture of stool specimens is the current gold-standard method for diagnosis of EHEC infections. Current guidelines from the Centres for Disease Control and Prevention (CDC) in the United States recommend that all stool samples submitted with a diagnosis of acute, community-acquired diarrhoea be tested for Shiga toxin–producing E. coli in Sorbitol MacConkey [SMAC] agar [2,32]. E. coli O157:H7, unlike most of the E. coli, cannot ferment sorbitol, and therefore appear as colourless colonies on SMAC. Normal gastrointestinal tract flora–associated E. coli typically ferment both sorbitol and lactose and therefore appear as pink colonies on the same media. Latex agglutination is a confirmative test for O157 serotype of

any colourless colonies. Agglutination with O-specific antisera for the most common serotypes may also be performed. Due to the increasing clinical importance of non-O157 Shiga toxin–producing serotypes, the CDC recommends that all samples submitted for acute diarrhoea be tested for non-O157 serotypes including the E. coli O104:H4 outbreak strain (can be cultured on either MacConkey agar or SMAC and can be confirmed as Shiga toxin producers by enzyme immunoassay for the Shiga toxin, or by polymerase chain reaction for the Shiga toxin genes stx1 and stx2). Blood cultures are rarely useful in diagnosing STEC as the patients usually have no bacteraemia even during HUS and the Shiga toxin is detected in the blood only transiently; thus, blood culture is not the proper diagnostic tool [31-34].

The detection of Shiga toxin depends on the finding of positive stool culture, detection of Shiga toxin genes in stools by polymerase chain reaction, or the presence of serum IgM antibodies against lipopolysaccharides of major enterohaemorrhagic E. coli [35-37].

Currently, diagnostic test to predict which patients will develop HUS is not available. However, high-risk children to develop HUS have higher levels of prothrombotic factors and endothelial-active cytokines than those with uncomplicated STEC disease [33,34]. Serum angiopoietin-1 (a mediator of endothelial cell quiescence) declines with progressive stages of complicated E. coli O157:H7 infection and can partially discriminate between those children who will have an uncomplicated course of STEC infection and those who will develop HUS [31]. Although none of these markers is sufficiently specific, the combinations of markers may aid in predicting the course of the HUS disease [1]. The need for renal biopsy is rare, however; it is indicated to exclude other causes of MAHA and thrombocytopenia (as in malignant hypertension and bilateral renal vein thrombosis).

Differential Diagnosis

Other enteric infections (infection with Salmonella, Campylobacter, Yersinia, amebiasis, and Clostridium difficult). The absence of thrombocytopenia and haemolytic anemia distinguish these enteric infections from HUS. Bloody diarrhoea, severe abdominal pain, and absent fever is more consistent with STEC infection than other enteric infections [1].

Henoch-Schönlein purpura (IgA vasculitis): The patterns of skin rash and presence of arthralgia differentiate it from HUS. Patients typically have other systemic symptoms (such as arthralgia and skin rash), do not have a prodromal diarrhoea and the neurologic involvement is characteristically peripheral rather than central.

Disseminated intravascular coagulation (DIC): It is distinguished from HUS by the presence of abnormal coagulation studies (pathologically prolonged prothrombin time and activated partial thromboplastin time, increased fibrin degradation products and D-dimer, low fibrinogen concentration and decreased platelet count). In general, DIC occurs in the seriously ill paediatric patients and those with septic shock or who have undergone massive tissue injury which is not the case of patients with HUS [38].

Thrombotic thrombocytopenic purpura (TTP): Von Willebrand factor cleaving protease deficiency caused by mutations of the ADAMTS13 gene is the cause of the familial TTP and its diagnosis is confirmed by the finding of abnormally low ADAMTS13 activity. Paediatric TTP is rare, and the affected children usually present at birth with hemolytic anaemia and thrombocytopenia. Renal involvement occurs later in life and has a progressive course. HUS has clinical features in common with TTP. However, the aetiology and pathophysiology of the more common forms of HUS clearly delineate childhood HUS as a separate entity from TTP.

Non-Shiga toxin-producing Escherichia coli (STEC) HUS: Patients do not usually present with the diarrheal prodrome. The two most common causes of non-STEC HUS are:

Pneumococcal-associated HUS: Affected patients have severe pneumococcal infection (e.g., pneumonia or meningitis).

Complement-mediated HUS: Patients have severe clinical course, recurrent disease, and a positive family history. Genetic testing or identifying antibodies to complement components confirms its diagnosis.

Management

Supportive care and intravenous fluid replacement are the cornerstones of treatment because of the current lack of safe and specific therapeutic intervention. But, eculizumab and/or plasma treatment may be considered in patients with severe CNS involvement who have a poor prognosis. Renal hypoperfusion during the STEC disease increases the risk of oliguria or anuria and early parenteral volume expansion with isotonic intravenous solutions prevents its occurrence. Antibiotics and antimotility drugs increase the toxin release, do not decrease the duration of gastrointestinal symptoms, exacerbate the disease and thus, should not be given to patients with confirmed or suspected STEC diarrhoea. A strong association between antibiotics use and the eventual development of HUS was reported in many studies, whereas other meta-analysis studies found no such association [39-42]. Antimicrobial treatment does not increase the risk of *Shigella dysentery* type 1-associated HUS (In contrast to STEC infections). Currently, the prognosis of HUS has improved because of the early institution of supportive treatment and improvements in intensive care and renal replacement therapy. The supportive treatment is aimed to treat the following:

Anemia

Patients with HUS can rapidly develop severe anaemia. About 80 percent of children with STEC HUS need the red blood cell concentrate transfusion. Red blood cells concentrate transfusion threshold is haemoglobin (Hb) level less than 6 g/dL or haematocrit less than 0.18 l/l to avoid cardiovascular and pulmonary compromise [43]. The aim of the blood cell concentrate transfusion is not to restore the Hb level to the normal level because the increased intravascular volume may cause heart failure, pulmonary oedema, and hypertension [9]. A post-transfusion Hb. level between 8 and 9 g/dL is recommended to prevent cardiac and pulmonary complications resulting from high output cardiac failure. In pneumococcus-associated HUS, washed red blood cells use for transfusion is recommended to remove the residual plasma because the endogenously immunoglobulin-M directed against the revealed T-antigen can play a pathogenic role. The red blood cell concentrate should be slowly and cautiously infused with frequent monitoring of the patient's vital signs [10]. Blood transfusions termination is recommended if the vital signs suggest cardiopulmonary overload (e.g., hypertension, tachycardia, and/or tachypnea). The red blood cell concentrate is preferably depleted of leukocytes to avoid alloimmunization (to lower the risk of graft rejection in patients who may require renal transplantation). If the patient is undergoing hemodialysis, transfusions should be given during dialysis to minimize the risks of hypervolemia and hyperkalaemia. Most patients do not

need iron treatment, as iron from haemolysed blood is available for erythropoiesis. Furthermore, there is no indication for the routine use of erythropoietin.

Thrombocytopenia

Platelet transfusions are indicated for patients with active bleeding, prior to a required invasive procedure (ie, peritoneal dialysis catheter or central venous catheter placement), and in patients with platelet counts less than $10X10^9$/L [44,45]. The transfused platelets consumption by the active coagulation can theoretically worsen the clinical course. However, despite low platelet count, severe bleeding is very rare in patients with HUS.

Fluid management

It is based on the intravascular fluid status and renal function assessment results which guide the fluid management. Decreased volume results from vomiting, decreased oral intake, or diarrhoea, while increased intravascular volume arises from oliguria or anuria. In some cases, fluid expansion may be indicated to counteract renal hypo-perfusion in volume-depleted patients. However, fluid restriction is needed in patients with increased intravascular volume due to oliguria/anuria. Initial weight gain is not an accurate marker for intravascular volume because hypo-albuminuria and capillary leakage cause an oedematous state, resulting in increased total body water volume, but a decreased intravascular volume. Patients with increased intravascular volume need dialysis treatment to remove fluid, especially if there is cardiac and pulmonary compromise. Once the patient has anuria or oliguria, frequent monitoring of fluid balance until renal function returns to normal with monitoring of weight, and vital signs are imperative. If circulatory overload is suspected, fluids should be restricted, and a trial of furosemide (2 to 5 mg/kg per dose) to induce diuresis, particularly in patients with cardiopulmonary overload may be attempted. Dialysis treatment is recommended when fluid restriction and/or diuretic treatment fail to improve the circulatory overload of the patient. Electrolytes' disturbance occurs secondary to acute renal insufficiency or failure including hyperkalaemia, hypophosphatemia, and metabolic acidosis [44].

Acute kidney injury and dialysis

For patients with HUS, who develops renal insufficiency, the dosing of drugs that are excreted by the kidney must be readjusted, and nephrotoxic medications should be stopped. The indications for dialysis include:

Azotaemia with BUN ≥ 80 to 100 mg/dL (29 to 36 mmol/L).

Severe fluid overloads refractory to medical treatment.

Severe electrolyte abnormalities (such as, hyperkalaemia and acidosis) that is refractory to medical treatment.

Earlier research suggested that the peritoneal dialysis is effective to remove the pro-coagulant plasminogen-activator inhibitor type 1 which may have a role in the pathogenesis of HUS [46]. However, there is no evidence of more benefit of peritoneal dialysis compared with haemodialysis. Moreover, peritoneal dialysis is contraindicated if there is abdominal complication requiring surgical intervention.

Hypertension

It is caused by intravascular volume expansion and/or ischemia-induced activation of the renin-angiotensin system [47]. Management is directed toward correcting the fluid status and the use of antihypertensive agents including calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors may exacerbate renal injury by diminishing renal perfusion in children with HUS [10]. However, ACE inhibitors have the reno-protective effect in children with long-term sequelae of HUS (e.g., proteinuria, renal insufficiency, and hypertension) [48,49].

Neurological dysfunction

Serious complications of the CNS, such as seizures and strokes, are predictors of poor outcome and radiological imaging should be performed to assess the CNS. Severe CNS manifestations may be due to severe hypertension, and its control leads to resolution of some of the CNS manifestations. However, seizures secondary to severe hypertension is refractory to blood pressure control. Seizures are treated with parenteral antiepileptic agents including diazepam, phenytoin or fosphenytoin. Plasma exchange is indicated in patients with severe CNS involvement (e.g., seizure or stroke), and it is often useful in patients with complement-mediated HUS.

Other organs involvement: It is less common than renal and neurologic complications. This includes gastrointestinal complications, cardiac dysfunction, pancreatitis [16,43] and respiratory complications. The latter is secondary to increased intravascular volume. Management of these complications includes:

Gastrointestinal complications

Severe colitis may progress to necrosis and intestinal perforation. Parenteral nutrition and surgical intervention (if required) are the management.

Cardiac dysfunction: occurs due to cardiac ischemia and fluid overload. Pericarditis may be associated with uraemia. Treatment includes the use of inotropic agents, fluid restriction, and/or dialysis [3].

Pancreatitis

Results in insulin deficiency that requires insulin therapy for hyperglycaemia

Pulmonary complications

Management of pulmonary oedema and effusions due to intravascular fluid overload include fluid restriction, diuretics, dialysis, and/or ventilator support.

Specific treatment

None of the multiple therapeutic agents including antithrombotic agents, plasma exchange and/or plasma infusion, tissue-type plasminogen activator, and oral Shiga toxin-binding agent that have been used is recommended. However, there may be a role for plasma exchange / plasmapheresis, and eculizumab in patients with central nervous system (CNS) involvement. Non-steroidal anti-inflammatory drugs should also be avoided because of the theoretical risk of worsening the gastrointestinal bleeding and/or acute kidney injury.

Plasma infusion and plasma exchange: Their use has not been proved effective in any randomized controlled trial [50]. The role for plasma exchange in EHEC-associated HUS is lacking because Shiga toxin is detectable in the circulation only very early in the disease. Furthermore, Shiga toxin–induced endothelial and vascular dysfunction precedes the development of HUS. Plasma infusion to supply a deficient anticoagulant factor or plasma exchange to supply a deficient anticoagulant and/or remove pro-coagulant factors is successful in patients with complement-mediated HUS. There are no randomized controlled studies that evaluated the plasma exchange efficiency in children with STEC-induced HUS. Report described that plasma exchange shortened the duration of acute kidney injury leading to better long-term renal function [51]. Plasma exchange is used in children with severe CNS involvement based upon reported benefits of plasma exchange in adults with TTP and severe neurologic dysfunction; although there is no evidence that it is useful in the treatment of STEC-induced HUS. The volume of exchange is 40 to 60 mL/kg and fresh frozen plasma are used as a replacement fluid. In a meta-analysis that evaluated plasma exchange from four observational studies, there was no clinical benefit found with plasma exchange in patients with STEC-induced HUS [52].

Eculizumab

A humanized monoclonal antibody against C5 of the complement system and blocks the formation of membrane attack complex (MAC) is an effective life and kidney-sparing treatment for patients with complement-mediated HUS. Its use is useful in patients with STEC-induced HUS and CNS involvement. It was an established treatment for atypical HUS and was also used during the E. coli O104:H4 outbreaks in Germany. The rationale for its use is based on the evidence of complement activation in typical STEC-induced HUS. A successful use of eculizumab in three young children with severe STEC-induced HUS was reported [53-55]. During the E. coli O104:H4 outbreaks, administration of eculizumab did not affect the need for dialysis or mechanical ventilation nor the occurrence of seizures and death [54]. Eculizumab effectiveness in STEC-induced HUS is unproven yet. However, the finding of microparticles with surface-bound C3 and C9 derived from platelets and monocytes in plasma samples from 13 patients with STEC-induced HUS during the acute phase of their illness provides support for the use of eculizumab [56]. Levels of microparticles and C3/C9 binding decreased during the recovery period and approached the levels detected in samples from control patients. However, this medication is costly, and it may not be available on a wide base. The dose of eculizumab for patients with complement-mediated HUS depends on patient's body weight (5 to <10 kg – 300 mg, 10 to <40 kg – 600 mg, and ≥40 kg – 900 mg). If plasmapheresis treatment is also performed, repeat dose is given after each plasmapheresis session.

Antithrombotic agents

Their use was based on the histologic evidence of thrombus formation. However, this disorder is primarily characterized by platelet rather than fibrin consumption. The use of anticoagulant, antiplatelet and fibrinolytic therapy is specifically contraindicated because they increase the risk of severe bleeding. Two reported trials have compared combinations of antithrombotic agents (such as, either urokinase and heparin or dipyridamole and heparin) with supportive care or supportive care alone. The duration of renal failure, haemolysis, and thrombocytopenia, and the long-term outcome were all similar in both control and treated groups. Furthermore, haemorrhagic complications were more common in these trials [57-59]. Accordingly, antithrombotic agents are not recommended in patients with STEC-induced HUS because there is no evidence of clinical benefit, and there is an increased risk of haemorrhagic complications. In one report, normalization of plasma plasminogen activator inhibitor-1 levels correlated with improvement in renal function [16].

Oral Shiga toxin-binding agent: Synsorb-Pk, an oral specific Shiga-toxin binder, did not improve clinical outcome as reported in a randomized study of 145 children with HUS. Death or severe extra-renal events were found in 18 and 20 percent of the treated and control groups respectively [60].

Prognosis and follow-up

For most patients with uncomplicated STEC-associated gastroenteritis who are treated with supportive care, the prognosis was excellent. However, recent evidences suggest that the long-term sequel is possible in the adult population [1]. The mortality rate is less than 5 percent [61,62], but another 5 percent of patients have significant sequel (e.g., stroke or end-stage renal disease) [17]. A similar result was also observed in children who were affected during the large German HUS outbreak in 2011 [63]. Increased risk of death is associated with CNS involvement, hyperkalemia, heart failure, pulmonary hemorrhage, and in patients with oliguria, anuria, dehydration, elevated total white blood cell count more than 20X 10^9/L and hematocrit < 0.23 l/l. However, 20-30% of patients are left with some degree of renal insufficiency. [63]. The long-term complications are associated with [15,60-67]:

Leukocytosis (more than 20 X10^9/L) at presentation (neutrophil activation lead to tissue damage and resulting from the release of neutrophil chemoattractant from monocytes).

Persistent initial anuria for more than 5 day.

Oliguria for more than 10 days.

Prolonged dialysis.

Glomerular microangiopathy (affects more than 50 percent of glomeruli), arterial microangiopathy, and / or cortical necrosis.

The glomerular filtration rate (GFR) is normalized in most children with STEC-induced HUS. However, renal blood flow may be persistently reduced by 10 to 20 percent, indicating a permanent subclinical nephron loss [38]. Permanent and severe renal sequelae are reported in 5 to 25 percent of children with STEC-induced HUS [68]. Patients with persisting hypertension, residual renal insufficiency or urinary abnormalities require good follow-up. Yearly evaluation of patients with STEC-induced HUS is recommended to monitor for signs of hypertension, proteinuria, and renal insufficiency for at least five years [63]. Each visit should include blood pressure measurement and laboratory evaluation of renal function including urinalysis and serum creatinine concentration. For patients who become pregnant, assessment for elevated blood pressure and proteinuria is recommended. Long-term follow-up revealed an increased incidence of hypertension, mild proteinuria (usually less than 1000 mg per day), subclinical decline in GFR with plasma creatinine concentration remaining in the normal range, chronic kidney disease and end-stage renal disease [69,70]. Rarely, recurrence of HUS occurs after renal transplantation (0 to 10 percent) [71]. In one report of 118 children, there was only one case of recurrence with allograft loss (0.8 percent)

and the allograft survival in patients with STEC-induced HUS is similar to survival in those with other causes of chronic renal diseases [72]. The diagnosis of recurrence of HUS after renal transplantation may be difficult. In addition, it is difficult to distinguish recurrence of HUS from severe acute vascular or chronic rejection on a renal biopsy. However, patients who recovered completely with no residual abnormality are unlikely to manifest long-term sequelae [73].

Prevention

Public health interventions are the key to prevent STEC-associated diarrhoea and HUS. Primary prevention of infections involves avoidance of common sources of bacteria or elimination of the bacteria through cooking or hand washing. Unpasteurized foods and raw foods, particularly leafy greens, should be washed thoroughly before eating even if pre-packaged and prewashed. Ground beef should be cooked to an internal temperature of 71°C. Lake or pool water should not be swallowed while swimming, and strict hand-hygiene protocols should be followed in petting zoos and after contact with animals. Hand's hygiene for both the infected patient and close contacts is also a key element in the prevention of secondary transmission. For hospitalized patients, contact precautions that include the use of gowns, gloves, and a single-bedded room are recommended. Patients with ongoing faecal shedding should be temporarily excluded from settings with a high risk of transmission (commercial food preparation, day care centres) in accordance with local public health guidelines [1]. The uses of antimotility drugs and antibiotics have been largely unsuccessful.

Summary

STEC causes food-borne infectious diarrhoea secondary to a breach of proper food handling, sanitation and water processing, or hand hygiene procedures. Appropriate laboratory testing for both O157 and non-O157 serotypes, as well as prompt initiation of infection control procedures for confirmed or suspected cases, will facilitate follow-up investigation to identify the source of disease and will help to prevent secondary transmission. Supportive care and close monitoring for complications are also crucial. However, there are no proven means to predict which patients will develop HUS and no specific therapies to either prevent progression or treat HUS once it develops. Given that nearly half of patients with aHUS currently have no identifiable complement abnormalities [74], further researches are needed as inherited or acquired complement dysregulation does not seem to be always the mechanism of atypical HUS [75]. Researches will improve the care of patients with different HUS types in the years to come. The identification of genetic factors associated with HUS will contribute to a better insight of the pathogenesis of HUS and will have potential therapeutic and preventive implications [1,4].

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