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A Review on Heamolytic Uremic Syndrome

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Abstract

In summary, patients presented with 2 days diarrhea should be subjected to diagnosis for the presence of *E. coli* O157:H7, for those <5 years of age with >3 days of diarrhea, leukocytes >13,000/µL, and proteinuria should be hospitalized and monitored closely since there is no treatment of proven value, and care during the acute phase of the illness is still merely supportive with no substantial changes as compared with the past. There is no clear consensus on whether antibiotics should be administered to treat Stx-*E. coli* infection.

Keywords: diarrhea, *E. coli*, proteinuria, HUS.

Introduction

Hemolytic uremic syndrome (HUS) is a disease of non-immune hemolytic anemia, low platelet count, and renal impairment. Anemia is severe and microangiopathic in nature, with fragmented red blood cells (schistocytes) in the peripheral smear, high serum lactate dehydrogenase (LDH), circulating free hemoglobin, and reticulocytes (Ruggenent *et al*., 2001).

The hemolytic-uremic syndrome (HUS) has been recognized for more than 45 years, it was first described in 1955 by Gasser *et al.*, and occurs predominantly in children younger than 4 years of age. Hemolytic–uremic syndrome (HUS) is a life-threatening disorder caused by a thrombotic microangiopathy resulting in microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to organs, especially the kidneys. The most common form of the syndrome (D+ HUS) occurs in healthy young children (6 month to 5 yrs of age) and is preceded by watery diarrhea that can evolve to hemorrhagic colitis. The diarrhea precedes the haemolysis and thrombocytopenia by 5 to 7 days, oliguria/anuria follows several days later (James and Frank, 2001).

In children, the disease is commonly triggered by shiga-like toxin (stx)-producing *Escherichia coli* (enterohaemorrhagic *E. coli*). Shiga toxin-producing strain of *E. coli* (STEC) is also called verotoxigenic producing *E. coli* (VTEC). They

are each capable of producing one or two potent toxins called Shiga toxins (st1 and st2) because of their cytotoxic effects on African Green Monkey kidney (Vero) cells in cultures (Konowalchuck *et al.,* 1977). In addition to toxin production, another virulence-associated factor expressed by VTEC is a protein called intimin, which is responsible for intimate attachment of VTEC to the intestinal epithelial cells, causing attaching and effacing (AE) lesions in the intestinal mucosa (Paton and Paton, 1998). Intimin is encoded by the chromosomal gene *eae A,* which is part of a pathogenicity island termed the locus for enterocyte effacement (LEE). A factor that may also affect virulence of VTEC is the enterohemolysin (enterohaemorrhagic *E. coli* haemolysin, EHEC-*HlyA*) (Schmidt *et al.,* 1995). Other organisms have also been implicated to cause HUS they are;

The commonest form, D+HUS (presence of diarrhoea) is caused by infection with Enterotoxigenic *Escherichia coli, Shigella, Salmonella or Campylobacter*. D-HUS (absence of diarrhoea) is caused by *Streptococcus pneumoniae,* (Cabrera et al., 1998; Waters *et al*., 2007; Brandt *et al.,* 2002).

Enterohaemorrhagic *E. coli* 0157: H7 is one of the six groups of *E. coli* recognized as an etiological agent of diarrhea (Aboaba *et al*., 2006). Infection with this *E. coli* serotype is associated with a spectrum of illnesses including watery diarrhea, bloody diarrhea, and the haemolytic uremic syndrome. Cattle are the principal etiological agent of infection; other means of infection include consumption of undercooked hamburger, ground beef, raw milk, meat and dairy products, vegetables, unpasteurized fruit juices and water, and other contaminated food products (Chapman *et al*., 1997).

HUS is classified into three primary types:

- Shiga Toxin–Induced Hemolytic Uremic Syndrome due to infections, often associated with diarrhea (D+HUS), also known as Typical HUS.
- HUS related to complement abnormalities or related to factor- ADAMTS13 deficit, such HUS is also known as “atypical HUS” and is not diarrhea associated (D-HUS).
- HUS of unknown etiology that usually occurs in the course of systemic diseases or physiopathologic conditions such as pregnancy, after transplantation or after drug assumption.

Overlapping HUSs occur when two or more of the above-mentioned conditions coexist in the same patient (Maurizio and Elisabetta , 2013).

Pathogenesis of typical HUS

Cattle and Sheep are the main sources for EHEC. Infection in humans generally occurs as a result of consumption of food contaminated with animal stool. The most common causes include undercooked meat, unpasteurized milk and dairy products, fruit juices, water, fruits and vegetables. Transmission by contact with animals, direct transmission from human to human and transmission from mother to baby is possible (Vaillant *et al*.,2009). It is most commonly observed in summar and autums months (Tarr *et al*., 2005).

E.coli O157:H7 is considered an emerging disease pathogen (Nataro and Kaper, 1998), which has eluded the skillful eyes of microbiologists because of its peculiar biochemical characteristics, its inability to ferment Sorbitol - a nutrient not incorporated in the growth medium routinely used for the isolation of *E. coli* from stool specimens. Infection with this organism causes hemorrhagic gastrointestinal disease and Hemolytic Uremic Syndrome (HUS), a renal complication mostly affecting children. This pathogen has become more significant than other well-recognized food-borne pathogens for reasons including the severe consequences of infection that affect all age groups, their low infectious dose, their unusual acid tolerance, and their apparent special but inexplicable association with ruminants that are used for food (Buchanan and Doyle, 1997).

Pathogenicity of typical HUS

Following intake of contaminated food, the bacteria enters the intestines. In the intestines, Stx (STx1 and Stx 2) is secreted by *E. coli*. These exotoxins are absorbed in the epithelium of the gastrointestinal system and reach the target organ. They are bound to globotriaosylceramide (Gb3) which a glycopeptides surface receptor in the epithelium of the target organ, inhibits protein synthesis and leads to endothelial damage, cell death, increase in inflammatory response and thrombocyte activation, (Trachtman *et al*., 2012) thought that the toxin also triggers action on P-selectin which is an adhesion molecule and complement regulating molecules .

Pathogenesis and pathogenicity of Atypical HUS (aHUS)

The pathogenesis of aHUS remained obscure for decades. Altered serum complement levels (that is reduced C3 and normal C4) in some patients led to the hypothesis that complement activation through the alternative pathway might be involved in the pathogenesis of aHUS. Subsequent investigations demonstrated that approximately half of patients with aHUS have hereditary defects involving soluble or membrane-bound proteins that regulate complement activity. In addition, emerging evidence suggests that endothelial cell dysfunction may contribute to the development of aHUS.

The activity of complements is kept in check by several soluble and membrane-bound regulators. Soluble complement regulatory proteins include factor I (FI), factor H (FH), and C4-binding protein (C4BP). Synthesized mainly in the liver, FI is a serine protease that suppresses complement activity by breaking down fluid-phase and cell-bound C3b and C4b. A 155-kDa glycoprotein synthesized mainly in the liver, FH serves as a cofactor for FI and facilitates FI-mediated C3b degradation. By removing Bb from C3bBb, FH also accelerates decay of the alternative pathway C3 convertase. C4BP has similar effects on the classical and lectin pathway C3 convertase. Complement regulatory proteins are also found on the surface of most human cells. Membrane cofactor protein (MCP; CD46) is a membrane protein expressed by all cells except erythrocytes. Genetic mutations involving complement regulatory proteins and complement components are found in 40%–60% of patients with aHUS (Noris *et al*., 2010).

Loss-of function and inactivating autoantibodies directed against FH have also been associated with aHUS. In addition, some patients with aHUS demonstrate gain-of-function mutations involving factor B and C3. A recent study demonstrated that single and combined genetic mutations were present in 41% and 3% of patients with aHUS, respectively. Although combined mutations occurred in only 8%–10% of patients with FH, C3, or FB mutations, 25% of patients with MCP or FI mutations had a combination of mutations. Approximately 50% of patients with combined MCP mutations developed end-stage renal disease within 3 years. It is conceivable that there are additional complement abnormalities associated with aHUS.

Many patients with complement abnormalities remain asymptomatic for decades before developing aHUS. Similarly, STEC-HUS develops only in a subset of patients infected with Shiga toxin-producing E. coli. Therefore, elusive factors other than known triggers (infection, trauma, surgery, pregnancy, etc.) may predispose individuals to the development of HUS.

Endothelial cell injury and dysfunction, probably because of the effects of complement activation, represent an intermediate stage in the pathophysiologic cascade culminating in aHUS. Vascular endothelial growth factor (VEGF) plays a pivotal role in vasculogenesis and angiogenesis. Reduced VEGF expression in podocytes is linked to the development of a thrombotic microangiopathy (Eremina *et al*.,2008).

Table 2.1. Complement abnormality in atypical HUS

	Nonfamilial, %	Familial, %
FH	15–20	40–50
Anti-FH antibodies	6–10	N/A
MCP	6–10	7–15
C3	4–6	8–10
FI	3–6	5–10
TM	2	9
FB	Rare	1–2

FB - factor B; FH -factor H; FI -factor I; N/A, not applicable; TM – Thrombomodulin (Source: Noris *et al*., 2010).

Epidemiology of HUS

Infections caused by Shiga toxin-producing *E. coli* serotype O157:H7 are the most common cause of HUS in North America, west Europe, Japan, South America, Africa and Australia (Peacock *et al.,* 2001). HUS D+ (HUS with diarrhea) is more often sporadic, but large outbreaks have been reported. Cattle and sheep are the main reservoirs, and the major transmission route is believed to be food contaminated with animal feces (CDC, 2008; Guh, 2008). Contaminated water has also been recognized as a Source (Walkerton, 2000), and direct human-to-human and animal-to-human transmission have been reported (Mead and Griffin, 1998). *E. coli* O104:H4 recently caused a large outbreak in 4000 HUS D+ patients, with 50 deaths in Germany and 15 other countries (Blaser ,2011).

The incidence rate of HUS D+ differs according to countries and climate and is higher in colder countries. For example, the incidence rate in Scotland (3.4×10^5 children under age 5) is higher than the overall incidence rate in Great Britain (1.54×10^5 children under age5) (Lynn *et al.*, 2005).

England and France have similar incidence rates, both of which are higher than that in Italy. The HUS D+ incidence rate is highest in children aged one-to-five years in Europe and North America, while, the incidence rate in Argentina is higher in younger children (6 month to 4 years). In some tropical regions, Shigella dysenteriae type 1 is the most common cause of Stx-induced HUS (Mark ,2008). Table3.1

Examples of South American Epidemiologic Studies of Stx-induced HUS

Country	Age group	N studied	Presentation/ parameter studied	Significant findings
Argentina	Children, 6 mo–15 y	2,435	Diarrhea	Patients with bloody diarrhea show more often EHEC infections, 8 of 93 EHEC children (8.6%) developed HUS.
Argentina	Students (preadolescent children)	883	Hygiene	95% consumed precooked hamburgers, 30.2% washed hands after toilet use, only 43.5% hand-washing before eating.
Argentina	Children <5 y	n/a	Hygiene	Food prepared outside home and vegetables independent risk factors associated with STEC infection.
Argentina	Children <5 y	437	Acute diarrhea	STEC in 10%, STEC more prevalent in warm months; 8% progressed to HUS.
Brazil	Children 8 mo–6.25 y	13	Postdiarrheal HUS cases in ICUs	*E. coli* serotypes O26:H11, O157:H7 and O165: H- in 3 cases, high levels of IgM against LPS O111 ($n = 2$) and O157 ($n = 7$) detected.
Peru	Children <3 y	2,212	Diarrhea in the community setting	EHEC in only 0.4%, most common serotype O26:H11 (14%), benign course, none developed HUS or other complications.
Chile	Children 2–8 y	587	Characteristics of patients with the diagnosis of HUS	92% had diarrhea, most frequent agent was *E. coli*., mortality 2.9% in acute phase, 12% evolved to CKD.

Abbreviations: CKD, chronic kidney disease; EHEC, enterohemorrhagic *Escherichia coli*; HUS, hemolytic uremic syndrome; ICU, intensive care uni month; N, number; n/a, not available; Ref., reference; STEC, Shiga toxin producing *Escherichia coli*; Stx, Shiga toxin; y, years.

(Source: Hofer *et al*., 2014)

Table 3.2 Examples of Asian Epidemiologic studies of Stx-induced HUS

Country	Age group	*N* studied	Presentation/ parameter studied	Significant findings
India	Children <5 y	73	Causes of AKI, HUS patients characteristics	HUS cause of AKI in 34%, Shigella in 7 cases, *E. coli* in 11 cases but not further characterized.
India	Children <12 y	52	Causes of AKI	HUS most common cause of AKI (31%).
India	Children <12 y	230	Causes of AKI	ATN secondary to septicemia common cause of AKI, HUS cause of AKI in only 12% of cases.
India	Children <13 y	215	Causes of AKI	HUS accounted for only 4% of AKI cases.
India	Children, mean 5.9 y	305	Causes of CKD	HUS accounted for 0.6% of CKD cases.
Pakistan	Children <18 y	n/a	Renal biopsy findings	Lupus nephritis most common, followed by amyloidosis and HUS.
Pakistan	Infants and children <12 y	46	Causes of AKI	HUS most common cause (54%) in younger patients.
China	All age groups (only 2 less than 20 y)	195	O157:H7 outbreak	HUS caused 177 deaths, majority > 50 years.
Kuwait	Children <18 y	25	HUS patients characteristics	56% D+ HUS, no pathogens isolated. Mortality significantly higher in the D- patients.
Saudi Arabia	Children, mean 3.9 y	100	Causes of AKI	HUS second most common cause, 14% of cases of AKI.
Saudi Arabia	Children, median 2.2 y	28	HUS patients characteristics	All had prodromal diarrhea, one died, mortality rate 3%.
Saudi Arabia	Children, mean 4.5 y	42	Epidemiologic findings in *S. dysenteriae* outbreak	24% progressed to HUS, all received antibiotics.
Saudi Arabia	Children, mean 7 mo–11 y	24	Epidemiology of typical post diarrhea HUS	Clustering of cases during spring and autumn, *S. dysenteriae* most common microorganism.
Jordan	Children, mean 7.5 y	202	Causes of CKD	HUS accounted for 4.5% of CKD cases.

Abbreviations: AKI--acute kidney injury; ATN-- acute tubular necrosis; CKD-- chronic kidney disease; D+--diarrhea positive; HUS--hemolytic uremic syndrome; mo--month; N-- number; n/a--not available; Stx--Shiga toxin, Y-- years.

(Source: Hofer *et al*., 2014)

Table 3.3 Examples of African Epidemiologic studies of Stx-induced HUS

Country	Age group	*N* studied	Presentation/ parameter studied	Significant findings
Nigeria	Children, mean 6 y	123	Causes of AKI	HUS accounted for 5.5% of AKI cases.
Egypt	Children < 12 y	82	Causes of AKI	HUS most common cause, accounted for 28% of AKI cases.
Ethiopia	Children, median 2.2 y	30	Causes of AKI	HUS most common cause (77%), 60% death rate from HUS, Shigella most common isolate.
Kenya	Children, median 19 mo	31	HUS patients characteristics	68% diarrhea-associated, mortality rate 55%, Shigella most common isolated organism in the stools.
Zimbabwe	Children (age not specified)	91	Dysentery outbreak	14 cases (15%) developed HUS, most stool cultures negative, high mortality.
Central African Republic	All age groups	n/a	Acute bloody diarrhea	*E. coli* O157:H7 isolated from two fatal adult cases, smoked meat implicated.
South Africa	Children 1–121 mo	81	HUS patients characteristics	Stools positive for *Shigella dysenteriae* type I in 7 (9%) patients, Stx assays were not performed.

Abbreviations: AKI—acute kidney injury; HUS—hemolytic uremic syndrome; mo—month; N—number; stx—shiga toxin
(Source: Hofer *et al*., 2014)

The study carried out by Reuben and Gyar (2015), on the prevalence of *E. coli* O157:H7 from diarrhoeic HIV/AIDS patients in Lafia, Central Nigeria, showed a low prevalence (1.9%) of *E.coli* 0157: H7 infection thus confirming the presence of this emerging pathogen in this locality as the first report of a systematic surveillance study on the prevalence of *E. coli* 0157: H7 isolated from diarrhea patients in the study area.

In another study, the prevalence of infection with *E. coli* O157:H7 among subjects studied within three senatorial districts of Edo State showed, Out of the 1000 persons screened, 19 (5.3%) were infected of which 12 (4.2%) were within 0-9 years(Isibor, *et al.*, 2013)

Atypical Hemolytic Uremic Syndrome (aHUS)

Atypical Hemolytic Uremic Syndrome (aHUS) is more properly linked to complement abnormalities, although several authors discuss it alongside thrombotic thrombocytopenic purpura (TTP). Atypical Hemolytic Uremic Syndrome and TTP share a common pathologic lesion (thrombotic microangiopathy) but have different clinical manifestations. Atypical Hemolytic Uremic Syndrome is less common than typical HUS and is characterized by a worse outcome. The disease may have a familial or a sporadic pattern and, may arise due to genetic abnormalities or be acquired. The incidence of aHUS in The United States of America is approximately two per million. In Europe, five national and continental registries report more than 1000 patients with complement abnormalities with an incidence of approximately 1.5 - 1.8 per million inhabitants. Overall, aHUS accounts for 5% of all HUS cases. Atypical HUS may develop in patients of any age, though 70% of pediatric diseases have an onset before two years and 25% have an onset before the age of 6 month. HUS occurring before 6 months of age is suggestive of aHUS because less than 5% of D+HUS cases occur before the age of 6 month.

Because of the difficulties associated with the accurate diagnosis of atypical HUS (aHUS), only a few detailed reports from developing countries on this type of HUS exist(Hamed , 2002).

The major limitation of those reports is that the classification was solely based on the occurrence of diarrhea. Leban *et al* from Tunisia retrospectively studied four adult cases of "atypical HUS," three of whom had normal C3, C4, complement factor H (CFH), and complement factor B (CFB) levels. A decrease in C3, C4, and CFH levels was found in one patient. In all patients, CFH antibodies (CFH-Ab) were absent (Leban *et al.*, 2011) .

Laboratory diagnosis and treatment

The disease is characterized by prodromal diarrhea followed by acute renal failure. The average interval between *E. coli* exposure and illness is 3 days (range, 1 to 8). Illness typically begins with abdominal cramps and non-bloody diarrhea; diarrhea may become hemorrhagic in 70% of cases usually within 1 or 2 days (Chandler et al., 2002). Vomiting occurs in 30 to 60% of cases, and fever occurs in 30%. Leukocyte count is usually elevated, and a barium enema may demonstrate "thumb-printing," suggestive of edema and sub-mucosal hemorrhage, especially in the region of the ascending and transverse colon. HUS is usually diagnosed 6 days after the onset of diarrhea. After infection, Stx-*E. coli* may be shed in the stools for several weeks after the symptoms are resolved, particularly in children 5 years of age.

Diagnosis rests on detection of Stx-*E. coli* in stool cultures. Serologic tests for antibodies to Stx and O157 LPS can be done in research laboratories, and tests are being developed for rapid detection of *E. coli* O157:H7 and Stx in stools.

Selective plating and identification of *E. COLI* O157:H7 colonies

A loop full of each stool specimen is cultured for *E. coli* on Eosin Methylene Blue Agar (Oxoid CM 0069) and incubated at 44°C for 24 h as described by Okeke *et al*. (2001) and screened for E. coli O157:H7 on Sorbitol MacConkey Agar (Oxoid, CM813) enriched with Cefixime-Tellurite supplement (Oxoid SR 172). *E. coli* colonies have green metallic sheen appearance on EMB while typical *E. coli* O157:H7 appeared as non-sorbitol fermenter colonies (NSFC) which are characterized as having a slightly transparent, almost colourless with a weak pale brownish appearance on CT-SMAC. Discrete colonies were randomly selected and then examined for the presence of gram-negative rods using Gram staining technique .

Biochemical test

The strains were characterized biochemically using Microbact 12E (MB1130A+, Oxoid) according to the manufacturer's instruction. Identification of *E. coli* strains was done following a series of 12 biochemical tests.

Serological test

Presumptive *E. coli* O157:H7 colonies were serologically confirmed by using *E. coli* O157:H7 latex agglutinations assay (R30959601, Oxoid), containing latex particles coated with antibodies specific for *E. coli* O157 and *E. coli* H7 antigen. Isolates were tested separately with anti- O157, and H7 antisera. Identification of *E. coli* O157:H7 was carried out following the manufacturer's instruction, hence colonies that agglutinated to the separate antisera were considered to be *E. coli* O157:H7.

Bloody diarrhea, fever, vomiting, elevated leukocyte count, extremes of age, and female gender as well as the use of antimotility agents (Beatty *et al*., 2004) have been associated with an increased risk of HUS after *E. coli* infection. Stx-HUS is not a benign disease. Seventy-percent of patients who develop HUS required red blood cell transfusions, 50% needed dialysis, and 25% had neurologic involvement, including stroke, seizure, and coma. Although mortality for infants and young children in industrialized countries decreased when dialysis became available, as well as after the introduction of intensive care facilities, still 3 to 5% of patients die during the acute phase of Stx-HUS. A recent meta-analysis of 49 published studies (patients, mean follow-up of 4.4 yr) describing long-term prognosis of patients who survived an episode of Stx-HUS reported death or permanent ESRD in 12% of patients and GFR 80 ml/min per 1.73 m2 in 25% (Garg *et al*., 2003). The severity of acute illness, particularly central nervous system symptoms, and the need for initial dialysis were strongly associated with a worse long-term prognosis. Stx-HUS that is precipitated by *S. dysenteriae* infection is almost invariably complicated by bacteremia and septic shock, systemic intravascular coagulation, and acute cortical necrosis and renal death and has a high mortality rate (approximately 30%) (Date *et al*., 1982).

Treatment and prevention

There is no treatment of proven value, and care during the acute phase of the illness is still merely supportive with no substantial changes as compared with the past. There is no clear consensus on whether antibiotics should be administered to treat Stx-*E. coli* infection. Wong *et al*. (2000) showed that antibiotic therapy at the stage of gastrointestinal infection with Stx-*E. coli* increases—by approximately 17-fold—the risk for full-blown HUS. It was postulated that antibiotic-induced in- jury to the bacterial membrane might favor the acute release of large amounts of toxins. However, a recent meta-analysis on 26 reports failed to show a higher risk for HUS associated with antibiotic administration (Safdar *et al*., 2002). Of note, in the study by Wong *et al*., (2000) none of the patients had bacteremia. Although bacteremia is very common in Stx-HUS precipitated by *S. dysenteriae* type 1 and these patients eventually progress to death unless antibiotics are started early enough (Oneko *et al.,* 2001). Such complication is only exceptionally found in Stx-HUS sustained by *E. coli* O157:H7 infection. However, a recent report of an adult patient with *E. coli* O157:H7–induced HUS with bacteremia and urinary tract infection showed that early antibiotic therapy rapidly resolved hematologic and renal abnormalities (Chiurchiu *et al*., 2003). On the basis of available data, we suggest that in patients with Stx-*E. coli* gastrointestinal infection, antibiotics should be avoided unless in cases with sepsis. A study with an Stx-binding agent, SYNSORB Pk, composed of particles of silicon linked to the globotriaosylceramide, given orally (Trachtman *et al*., 2003), failed to find any effect of SYNSORB over placebo. Most treatments, including plasma therapy, intravenous IgG, fibrinolytic agents, antiplatelet drugs, corticosteroids, and antioxidants , have been shown to be ineffective in controlled clinical trials in the acute phase of the disease (Garg *et al*., 2003). Careful BP control and rennin-angiotensin system blockade may be particularly beneficial on the long term for patients who experience chronic renal disease after an episode of Stx-HUS. A recent study in 45 children who had renal sequelae of HUS and were followed for 9 to 11 years documented that early restriction of proteins and use of angiotensin-converting enzyme inhibitors may have a beneficial effect on long-term renal outcome, as documented by a positive slope of 1/Cr values over time in treated patients (Caletti *et al*., 2004).

In another study, 8 to 15 yr of treatment with angiotensin-converting enzyme inhibitors after severe Stx- HUS normalized BP, reduced proteinuria, and improved GFR (Van Dyck and Proesmans, 2004). Finally, kidney transplant should be considered as an effective and safe treatment for children who progress to ESRD. Indeed, the outcome of renal transplantation is good in children with Stx-HUS: Recurrence rates range from 0 to 10% (Loirat and Niaudet, 2003), and graft survival at 10 yr is even better than in control children who had other diseases and received a transplant (Ferraris *et al.,* 2002).

Despite that non–Stx-HUS has a poor prognosis, after plasma manipulation was introduced, the mortality rate has dropped from 50 to 25% (Hollenbeck *et al*., 1998). However, debate still exists on whether plasma is or is not effective in the treatment of acute episodes. Published observations (Lara *et al*., 1999) and our own experience indicate that a consistent number of patients with non–Stx-HUS respond to plasma treatment. It has been proposed that plasma exchange might be relatively more effective than plasma infusion because it might remove potentially toxic substances from the patient's circulation.

However, in situations such as renal insufficiency or heart failure, which limit the amount of plasma that can be provided with infusion alone, plasma exchange should be considered as first-choice therapy. Plasma treatment should be started within 24 h of presentation as delay in treatment initiation may increase treatment failure. Usually one plasma volume (40 ml/kg) is exchanged per session (Allford *et al*., 2003). Treatment can be intensified by increasing the volume of plasma replaced. The twice-daily exchanges of one plasma volume are probably the treatment of choice for refractory patients to minimize the recycling of infused plasma. As for plasma infusion, the recommended dose is 30 to 40 ml/kg on day 1, then 10 to 20 ml/kg per day. Daily plasma therapy should continue for a minimum of 2 day after complete remission is obtained (Allford *et al*., 2003).

Conclusion

Hemolytic uremic syndrome (HUS) is a disease of non-immune hemolytic anemia, low platelet count, and renal impairment. Anemia is severe and microangiopathic in nature, with fragmented red blood cells (schistocytes) in the peripheral smear, high serum lactate dehydrogenase (LDH), circulating free hemoglobin, and reticulocyte. In children, the disease is commonly triggered by shiga-like toxin (stx)-producing *Escherichia coli* (enterohaemorrhagic *E. coli*). Cattle and Sheep are the main sources for EHEC. Infection in humans generally occurs as a result of consumption of food contaminated with animal stool. Following intake of contaminated food, the bacteria enters the intestines. In the intestines, Stx (STx1 and Stx 2) is secreted by *E. coli*. These exotoxins are absorbed in the epithelium of the gastrointestinal system and reach the target organ. They are bound to globotriaosylceramide (Gb3) which a glycopeptides surface receptor in the epithelium of the target organ, inhibits protein synthesis and leads to endothelial damage, cell death, increase in inflammatory response and thrombocyte activation. Plasma exchange has been advocated as a first line f treatment especially in cases of kidney failure.

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