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Shiga Toxin-Producing *E. coli* and Hemolytic Uremic Syndrome: A Study of the 2022 Outbreak in Turkey

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Background: Shiga toxin-producing *Escherichia coli* (STEC) causes serious bacterial illnesses from consuming undercooked meat and foods contaminated with feces. This study aimed to describe the characteristics of an STEC outbreak associated with hemolytic uremic syndrome (HUS) that emerged in Turkey and affected 21 adults.

Material/Methods: The medical records of 21 adult patients who were admitted to Ankara Bilkent City Hospital Internal Medicine Intensive Care Department with the diagnosis of HUS between July and September 2022 were retrospectively evaluated through the system.

Results: While a positive correlation was detected between the length of hospital stay and N-terminus pro-B-type natriuretic peptide (NT-proBNP), lactate dehydrogenase (LDH), and troponin during hospitalization, a negative correlation was detected with glomerular filtration rate (GFR). Patients requiring plasmapheresis had higher creatinine, amylase, and LDH values at the time of admission. In patients given eculizumab, high NT-proBNP and creatinine levels and low GFR levels at the time of admission were found to be statistically significant. The use of antibiotics before admission did not change the length of hospital stay.

Conclusions: A statistically significant difference was detected between LDH, GFR, troponin, NT-proBNP parameters, and length of hospital stay. Creatine and LDH values of patients requiring eculizumab and plasmapheresis at the time of admission were found to be statistically high. It should be kept in mind that eculizumab and plasmapheresis treatment can be required for patients with elevated creatine and LDH at the time of admission.

Keywords: *Escherichia coli* • Plasma Exchange • Renal Dialysis • Hemolytic-Uremic Syndrome

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Introduction

Etiology

In diseases that cause thrombotic microangiopathy, endothelial damage occurs at the microvascular level, increasing the tendency to thrombosis. When diagnosing hemolytic uremic syndrome (HUS), it is important to evaluate other diseases that can cause microangiopathy [1]. HUS is made up of non-immune hemolytic anemia, fragmented red blood cells, low platelets, and acute kidney injury. Shiga toxin-associated HUS is the most common cause of acute kidney injury, accounting for approximately 90% of all HUS cases [2].

Escherichia coli 0157: H7 occurs after consuming undercooked meat or inadequately pasteurized dairy products or after contact with contaminated fomites loaded with Shiga toxin-producing enterohemorrhagic *E. coli* [3]. Shiga toxin-producing strains of *E. coli* (STEC) produce virulent-type toxins, such as Stx-1 and Stx-2. Stx-2 is more toxic, and both toxins are associated with complicated STEC infections; however, the incidence of HUS is higher in the Stx-2 strain [4,5]. In most countries, STEC serotype O157: H7 infection is the most common cause of HUS [6]. Other serotypes, however, have been identified in the disease's etiology [7].

Epidemiology

Each year, STEC causes 43 acute diseases and 3890 HUS cases per 100 000 people [8]. Studies in the literature on STEC-HUS primarily focus on pediatric cases, with an estimated incidence of 0.57 cases per 100 000 children. The incidence of HUS among adults increases as a result of environmental exposure in practices such as cattle breeding and agriculture. Atypical HUS (aHUS), in contrast to HUS, occurs significantly less frequently. However, aHUS exhibits significantly higher morbidity and mortality rates [9].

Pathophysiology

When STEC is taken into the digestive system from an external source, it penetrates the mucosal layer of the intestine and secretes Shiga toxin, which binds to the Gb3 receptor. Shiga toxin/Gb3 complex binds to cell ribosomes, inhibits protein synthesis, and causes inflammatory cytokine release and apoptosis. In addition to cytotoxic effects, Shiga toxin can activate the complement system by inhibiting complement factor H. Once in the bloodstream, Shiga toxin continues to bind to cells via the Gb3 receptor, which is most abundant in the glomerular vascular space. Shiga toxin causes endothelial damage through (1) direct cytotoxicity, (2) disruption of the hemostatic pathway, (3) increased cytokine release, and (4) activation of the alternative pathway. This endothelial damage causes thrombotic microangiopathy [9]. aHUS are usually associated with a genetic abnormality that affects regulation of the alternative complement system in conjunction with a provocative stress, such as infection.

Evaluation

Symptoms, travel status, laboratory data, and dietary history all contribute to the diagnosis of HUS. First, a comprehensive biochemistry panel and complete blood count tests should be performed. The appearance of schistocytes in the peripheral smear accompanied by high lactate dehydrogenase (LDH), indirect bilirubin, and hemoglobin, as well as low haptoglobin levels, is valuable in the diagnosis of hemolytic anemia [10].

Elevated amylase and lipase can be observed in approximately 20% of patients, due to pancreatic damage. In cases in which diarrhea is present, rapid stool sampling should be performed. A negative result for Shiga toxin does not rule out the disease. Although a low complement level is not specific, it is more suggestive of aHUS. Electrolyte disturbances and signs of acute kidney injury can be observed in patients. ADAMTS13 level should be studied to rule out thrombotic thrombocytopenic purpura. Prolonged prothrombin time, activated partial thromboplastin time, and elevated D-dimer levels are suggestive of disseminated intravascular coagulation [11].

Tests for the diagnosis of HUS are very valuable; however, in cases in which clinical suspicion is high, treatment should begin immediately.

Treatment

In the treatment of typical HUS caused by STEC, supportive treatments, such as electrolyte replacement and fluid resuscitation, are performed. The risk of thrombosis should be kept in mind when using blood products. Patients with typical HUS caused by STEC should refrain from using antibiotics. In the treatment of atypical HUS, treatment should be started early, and eculizumab, which forms the basis of treatment, should be given early in patients with an indication [11].

In this study, we examined a large HUS outbreak caused by *E. coli* with serotype O104: H4 that occurred in the Western Black Sea Region of Turkey in July 2022. This major outbreak was primarily caused by a rare strain resembling enteroaggregative *E. Coli* with serotype O104: H4. An important difference of this strain was its ability to secrete Shiga toxin, which is characteristic for enterohemorrhagic *E. coli* (EHEC) strains.

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Material and Methods

All procedures in this study were approved by the Ankara City Hospital Ethics Committee and were performed in accordance with the ethical standards specified in the Declaration of Helsinki and its later amendments (date: 15/02/2023, number: E2-23-3384).

In this study, the medical records of 21 patients who were admitted to Ankara Bilkent City Hospital Internal Medicine Intensive Care Department with the diagnosis of HUS between July and September 2022 were retrospectively evaluated through the system. All patients had a history of living or traveling in the Western Black Sea Region.

The diagnosis of HUS was based on the presence of diarrhea or abdominal pain, hemolysis (anemia, increased serum LDH levels, decreased haptoglobin, and schistocytes on a peripheral blood smear), thrombocytopenia ($<150\times10^3/mm^3$ or a 25% reduction from baseline), and increased serum creatinine and/or proteinuria/hematuria [12]. A microbiological investigation of stool for STEC (culture and/or polymerase chain reaction of Stx) was performed in 21 adults. None of the patients had <10% von Willebrand factor-cleaving protease (ADAMTS-13) activity, abnormalities in coagulation parameters, or a positive direct Coombs test.

The following parameters were evaluated: age, length of hospital stay, relationship between antibiotic use at admission and laboratory parameters, extrarenal complications, and laboratory values at admission: hemoglobin, platelet count, white blood cell count, hematocrit, creatinine, glomerular filtration rate (GFR), LDH, total bilirubin, indirect bilirubin, amylase, lipase, C-reactive protein, and the highest troponin I, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level.

The diagnosis of STEC infection was made by polymerase chain reaction. Stool culture tests were also performed for other *E. coli* pathogens. Slide agglutination and O antiserum tests were also performed for diagnosis. Serum samples were analyzed to detect the presence of antibodies against lipopolysaccharides of serogroups. Serum samples were examined in the laboratories of the Turkish Public Health Institution of the Ministry of Health.

Statistical Analysis

Statistical analysis was made by the Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp, Armonk, NY, USA). Normality of variables was analyzed by the Kolmogorov-Smirnov test. Continuous variables are expressed either as mean±standard deviation or as median and minimum-maximum values, according to normality. The relationship between length of hospital stay and laboratory parameters was examined with the Spearman correlation test. In addition, the relationship between laboratory parameters at the time of admission and patients requiring eculizumab and plasmapheresis was examined with the Mann-Whitney U test. *P* values <0.05 were considered statistically significant.

Results

Demographic Results

In this study, we presented the follow-up data of 21 adult patients who were admitted to our İntensive Care Unit (ICU) with HUS diagnosis in July 2022. The outbreak lasted for 2.5 months. Adult patients with HUS requiring treatment in the İntensive Care Unit were followed up in a single center. The average length of stay was 17 (2-56) days. The ages of the patients ranged between 22 and 81 years, and 4 were men and 17 were women. All patients lived in the Western Black Sea Region, where the outbreak occurred. All patients had a history of eating fruits and vegetables exposed to contaminated water. Eight patients (38.10%) had a history of antibacterial use (ciprofloxacin and meropenem) before admission to the ICU. Hemorrhagic diarrhea was present in 10 patients (47.6%). Oliguria was present in 16 patients (76.1%) at the time of admission.

Clinical Results

Cardiogenic involvement was seen in 1 patient (4.76%), neurogenic involvement in 5 patients (23.81%), pulmonary involvement in 19 patients (90.48%), and abdominal involvement in 21 patients (100%). Hemodialysis was performed in 10 patients (47.62%), and plasmapheresis was performed in 7 patients (33.33%). Acute kidney injury was present in 19 patients (90.4%) at the time of admission. Acute kidney injury developed in 20 patients (95.2%) during follow-up. Four patients (19.05%) received eculizumab treatment. All patients were defined as confirmed HUS cases.

Cardiac involvement developed in 1 patient, and the patient's ejection fraction level decreased from 60% to 20% within 1 week, and pericardial effusion was detected. The patient's cardiac magnetic resonance imaging revealed right atrial and right ventricular myocardial dysfunction. In the echocardiography performed before discharge, it was observed that the ejection fraction level of the patient increased up to 55%, and the pericardial effusion decreased, but the global mild hypokinetic state continued. After 3 months of follow-up, the patient's ejection fraction level returned to normal. Pulmonary edema was detected in 19 patients. Non-massive hemoptysis developed in 2 of these patients. Five patients showed signs

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Table 1. Evaluation of demographic characteristics, treatments, and extrarenal findings at admission.

Age	**Median (min-max):** 55 (22-81)
Male	4 (19.05%)
Female	17 (80.95%)
Oliguria	16 (76.1%)
Hemorrhagic diarrhea	10 (47.6%)
Total length of hospital stay	**Mean±SD:** 20.71±11.49 **Median (min-max):** 17 (2-56)
Eculizumab	4 (19.05%)
Plasmapheresis	7 (33.33%)
Hemodialysis	10 (47.67%)
Antibiotic	8 (38.10%)
Cardiogenic involvement	1 (4.76%)
Neurogenic involvement	5 (23.81%)
Abdominal involvement	21 (100.00%)
Pulmonary involvement	19 (90.48%)

Table 2. Evaluation of laboratory parameters on admission.

Laboratory test result On admission	Mean±SD	Median (min-max)
Hemoglobin (g/dL)	11.31±1.61	11.2 (8.7-16)
Platelet (10^9/L)	103.285±113.889	77 (23-473)
White blood count (10^9/L)	16.303±6.341	15.63 (7.39-30.34)
Hematocrit (%)	34.63±4.85	34.2 (25.3-48.3)
Creatinine, (mg/dL)	2.34±1.47	1.99 (0.73-5.25)
Glomerular filtration rate (mL/min/1.73 m^2)	38.37±24.81	32.68 (9.24-90.97)
Lactate dehydrogenase (U/L)	1045.76±658.28	904 (221-2614)
Total bilirubin (mg/dL)	1.56±1.03	1.2 (0.27-3.27)
Indirect bilirubin (mg/dL)	0.97±.63	0.8 (0.2-2.24)
Amylase (U/L)	62.67±56.60	42 (19-272)
Lipase (U/L)	41.88±26.16	33 (18-128.7)
Complement-c3 convertase (g/L)	1.01±.24	0.95 (0.56-1.52)
Complement-4 (g/L)	0.2±.07	0.2 (0.1-0.35)
Troponin I (ng/L)	382.09±1538.23	12 (3-7086)
NT-proBNP (ng/L)	6541.14±10257.68	2150 (275-35000)

NT-proBNP – N-terminus pro-B-type natriuretic peptide.

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Table 3. The relationship between the history of antibiotic use and laboratory parameters before admission.

On admission	Antibiotic		*P*
	No	Yes	
	Mean±SD	Mean±SD	
Hemoglobin (g/dL)	11.49±1.91	11.03±1.01	0.664
Platelet (10^9/L)	103.846±113.539	102.3±122.3	0.447
White blood count (10^9/L)	15.477±4.988	17.646±8.301	0.515
Hematocrit (%)	35.07±5.6	33.91±3.52	0.744
Creatinine, (mg/dL)	2.21±1.32	2.56±1.76	0.913
Glomerular filtration rate (m/min/1.73 m^2)	38.13±24.79	38.76±26.55	0.885
Lactate dehydrogenase (U/L)	925.23±532.96	1241.63±824.82	0.515
Total bilirubin (mg/dL)	1.67±1.03	1.37±1.07	0.405
Indirect bilirubin (mg/dL)	1±0.63	0.92±0.68	0.800
Amylase (U/L)	52.54±27.5	79.13±85.77	0.744
Lipase (U/L)	47.88±29.93	32.13±15.59	0.088
Troponin-I (ng/L)	27.23±43.91	958.73±2478.56	0.119
NT-ProBNP (ng/L)	2545.92±3103.58	13033.38±14363.23	**0.020**

Analysis conducted with the Mann-Whitney U test. NT-proBNP – N-terminus pro-B-type natriuretic peptide.

of neurological involvement. All of these patients had visual impairment, 3 had seizures, and 2 had impaired consciousness and extremity paresis. In patients with visual impairment, there were symptoms of decreased visual field and blurred vision. One patient developed transient blindness. In addition, visual impairment was the first observed neurological symptom. Before discharge, patients' visual impairments improved.

Abdominal involvement (abdominal pain, vomiting, bleeding) was observed in all patients hospitalized in the ICU. Lower gastrointestinal system bleeding occurred in 2 patients and required erythrocyte suspension replacement. Evaluation of laboratory parameters, demographic characteristics, treatments, and extrarenal findings at the time of admission are shown in **Tables 1 and 2**.

Twenty-one patients, followed up for 3 months after ICU discharge, did not experience any permanent sequelae. Eight patients (38.10%) had a history of antibiotic use (ciprofloxacin and meropenem) before admission to the ICU. There was no significant difference in laboratory values performed during hospitalization between the patients who received and did not receive antibiotics prior to ICU admission. However, the highest NT-proBNP value was found to be significantly higher in those receiving antibiotics (P=0.02).The relationship between antibiotic use and laboratory parameters in patients with a history of antibiotic usage is shown in **Table 3**.

An inverse correlation was found between the total length of stay in the hospital and the GFR value at admission. A positive correlation was found between the length of hospital stay and LDH at admission, highest troponin I, and highest NT-proBNP values during follow-up. The relationship between total length of hospital stay and laboratory parameters is shown in **Table 4**.

Four patients who developed serious neurological complications received eculizumab treatment. Two of the patients received eculizumab treatment as a double dose, and 2 patients as a single dose. Two patients received eculizumab treatment on the second day of their ICU hospitalization, while the other 2 patients received it on the sixth day. It was observed that the creatinine, LDH, and NT-pro BNP values at the time of admission were significantly higher in patients receiving eculizumab. The relationship between laboratory test results of the patients during hospitalization and the patients who required eculizumab is shown in **Table 5**.

In patients treated with 2 doses of eculizumab (patient 7 and patient 14), there were 72 h between doses. Although low hemoglobin and thrombocyte levels persisted in the first 24 h of treatment in those receiving eculizumab, the patients' neurological findings improved. Patients whose neurological symptoms improved did not receive the second dose of eculizumab after the first dose. We administered a second dose of eculizumab to 2 patients (patients 7 and 14) whose neurological

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Table 4. The relationship between total hospital stay and laboratory parameters.

On admission	Total length of hospital stay	
	r	*P*
Hemoglobin (g/dL)	-0.262	0.251
Platelet (10^9/L)	-0.347	0.123
White blood count (10^9/L)	0.018	0.937
Hematocrit (%)	-0.288	0.205
Creatinine (mg/dL)	0.424	0.055
Glomerular filtration rate (mL/min/1.73 m^2)	-0.433	**0.050**
Lactate dehydrogenase (U/L)	0.454	**0.039**
Total bilirubin (mg/dL)	0.187	0.417
Indirect bilirubin (mg/dL)	0.192	0.406
Amylase (U/L)	0.100	0.665
Lipase (U/L)	-0.066	0.777
Troponin-I (ng/L)	0.640	**0.002**
NT-ProBNP (ng/L)	0.634	**0.002**

Analysis conducted with the Spearman correlation test. NT-proBNP – N-terminus pro-B-type natriuretic peptide; r – correlation coefficient; *P* – statistical significance.

Table 5. The comparison of laboratory test results during hospitalization and follow-up of patients, according to eculizumab treatment.

On admission	Eculizumab treatment		*P*
	No	Yes	
	Mean±SD	Mean±SD	
Hemoglobin (g/dL)	11.38±1.72	11.03±1.15	0.788
Platelet (10^9/L)	114.823±123.98	54.25±22.881	0.127
White blood count (10^9/L)	15.117±5.389	21.347±8.44	0.179
Hematocrit (%)	34.89±5.04	33.5±4.37	0.754
Creatinine (mg/dL)	1.95±1.25	4.01±1.23	**0.018**
Glomerular filtration rate (mL/min/1.73 m^2)	43.73±24.57	15.58±5.25	**0.020**
Lactate dehydrogenase (U/L)	838.06±497.52	1928.5±534.18	**0.007**
Total bilirubin (mg/dL)	1.61±1.06	1.36±1.01	0.654
Indirect bilirubin (mg/dL)	0.98±.66	0.94±.58	0.858
Amylase (U/L)	48.82±25.61	121.5±110.26	0.282
Lipase (U/L)	43.77±27.46	33.85±20.79	0.193
Troponin-I (ng/L)	439.18±1713.28	139.46±149.20	0.073
NT-ProBNP (ng/L)	2714.47±2897.9	22804.5±14867.29	**0.005**

Analysis conducted with the Mann-Whitney U test. NT-proBNP – N-terminus pro-B-type natriuretic peptide.

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Table 6. Hemoglobin, platelet, creatinine, and lactate dehydrogenase (LDH) values before and after treatment with eculizumab.

Eculizumab treatment	Hemoglobin (g/dL)		Platelet (10^9/L)		Creatinine (mg/dL)		LDH (U/L)	
	B.E.	E.1	B.E.	E.1	B.E.	E.1	B.E.	E.1
Patient 7 *2 doses*	8.2	8.7	66	41	5.4	5.06	2033	2008
Patient 14 *2 doses*	5.7	8.8	58	75	4.5	4.3	1354	1422
Patient 8 *1 doses*	6.7	7.4	18	24	4	3.65	1560	1416
Patient 10 *1 dose*	7.3	6.3	57	81	5.3	4.58	976	448

Patient 14: Patient with no improvement in neurological findings. B.E. – before eculizumab treatment; E.1 – after first dose of eculizumab treatment.

Table 7. Comparison of laboratory test results at the time of hospitalization, according to plasmapheresis treatment.

On admission	Plasmapheresis treatment		*P*
	No	Yes	
	Mean±SD	Mean±SD	
Hemoglobin (g/dL)	11.76±1.58	10.41±1.35	0.073
Platelet (10^9/L)	126.285±134.446	57.285±19.189	0.067
White blood count (10^9/L)	15.451±5.494	18.008±7.971	0.654
Hematocrit (%)	36.16±4.32	31.57±4.63	0.062
Creatinine (mg/dL)	1.84±1.17	3.35±1.56	**0.040**
Glomerular filtration rate (mL/min/1.73 m^2)	43.61±21.69	27.89±28.98	0.052
Lactate dehydrogenase (U/L)	796.57±444.51	1544.14±762.67	**0.025**
Total bilirubin (mg/dL)	1.52±1.03	1.64±1.11	0.765
Indirect bilirubin (mg/dL)	0.88±.58	1.14±.73	0.296
Amylase (U/L)	40.79±12.34	106.43±83.65	**0.025**
Lipase (U/L)	35.67±11.92	54.3±41.26	0.970
Troponin-I (ng/L)	517.14±1890.67	111.98±120.33	0.062
NT-ProBNP (ng/L)	2444±2070.92	14735.43±14964.46	0.117

Analysis conducted with the Mann-Whitney U test. NT-proBNP – N-terminus pro-B-type natriuretic peptide.

symptoms did not improve. In 1 patient (patient 14), neurologic symptoms did not improve despite eculizumab treatment. Hemoglobin, platelet, creatinine, and LDH values before and after eculizumab treatment are shown in **Table 6**.

Plasmapheresis was performed on 7 patients (33.33%) who exhibited clinical deterioration and a change in consciousness. Since there was no clinical improvement in 4 of 7 patients, eculizumab was subsequently added to the treatment.

It was observed that the creatinine, LDH, and amylase values were significantly higher in patients receiving plasmapheresis at the time of admission. The relationship between laboratory tests during hospitalization for patients receiving plasmapheresis is shown in **Table 7**.

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Discussion

In this study, we presented the data of 21 adult patients who were admitted to the ICU with the diagnosis of HUS in July 2022 and were followed in a single center for approximately 3 months.

Cardiogenic involvement was observed in 1 patient (4.76%), neurogenic involvement was observed in 5 patients (23.81%), pulmonary involvement was observed in 19 patients (90.48%), and abdominal involvement was observed in 21 patients (100%). At the time of admission, 19 patients (90.4%) had acute kidney injury. During follow-up, acute kidney injury developed in 20 patients (95.2%). All patients were identified as confirmed cases of HUS.

A total of 7 patients (33.33%) underwent plasmapheresis. It was observed that creatinine, LDH, and amylase values were significantly higher in the group receiving plasmapheresis at the time of admission. A total of 4 patients received eculizumab. It was observed that the creatinine, LDH, and NT-proBNP values were significantly higher in the group receiving eculizumab at the time of admission.

We detected a positive correlation between the length of hospital stay and NT-proBNP, LDH, and troponin levels during hospitalization, but a negative correlation with GFR. In the literature, the median white blood cell count value in patients who developed STEC-HUS was reported as 10.8. However, in our study, it was higher, at 15.63. We thought that the reason for this difference was that all the patients in our study required intensive care follow-up [13]. STEC-HUS outbreaks are important from a public health perspective because they cause an increased burden on the health system and can cause serious renal and extrarenal sequelae or death in adults. A detailed epidemiological assessment of any outbreak is important to identify the source and prevent the spread of infection.

A rare serotype, O104: H4, was detected in patients. Only a limited number of STEC-HUS cases were detected in the literature related to this serotype: in Germany in 2011 (2 cases) and Korea in 2006 (1 case) [14,15]. It was shown that 63% to 97% of the STEC-HUS cases in these outbreaks were caused by the O157 strain.

In our study, the rates of neurological complications such as seizures, visual impairment, and drowsiness in patients with HUS were similar to those of other studies in the literature (5 patients, 23.81%) [16]. We observed that neurological complications have a negative impact on the severity of the disease. In the study of Spinale et al, especially central nervous system symptoms were strongly associated with a worse prognosis [17].

It has been stated that using antibiotics to treat *E. coli* infections can increase the risk of developing HUS [18]. Since all patients included in our study were confirmed STEC-HUS cases, the risk of HUS development was not evaluated. Unlike the literature, we found that antibiotic use after the development of HUS had no relationship with laboratory results and hospitalization time.

It is recommended not to use antibiotics because bactericidal antibiotics increase the release of toxins and therefore the risk of developing HUS [19,20]. In the literature, unlike the O157: H7 serotype, the O104: H4 strain did not produce Stx toxin after incubation with therapeutic concentrations of ciprofloxacin, meropenem, fosfomycin, or chloramphenicol [21].

In our study, 1 patient who developed pericardial effusion had an ejection fraction decrease from 60% to 20% within a week. Echocardiography performed before discharge after treatment showed that the patient's ejection fraction increased by up to 55%, and pericardial effusion decreased. The literature on cardiac involvement in patients with HUS is sparse and is mainly in the form of isolated case reports. The clinical manifestations of myocardial involvement in HUS are diverse and include myocardial dysfunction, myocarditis, cardiac tamponade, dilated cardiomyopathy, and even myocardial infarction [22,23]. Cardiological evaluation in patients with HUS is essential due to these possible complications, and healthcare professionals should be careful.

The first studies describing outcomes in patients with Shiga toxin-associated HUS treated with plasmapheresis date back to the 1980s, and reports indicate the potential effectiveness of this treatment [24,25].

There are not enough randomized controlled studies in the literature evaluating plasmapheresis treatment in STEC-HUS, and plasmapheresis treatment still remains controversial [26,27].

Shiga toxins have been shown to be present in plasma within the first 24 to 48 h of enterohemorrhagic *E. coli* infection, and their concentrations decrease rapidly thereafter. This suggests that plasmapheresis treatment will be less effective or not effective at all if started late in the course of the disease [28,29].

In our study, a total of 7 patients (33.33%) underwent plasmapheresis. It was observed that the creatinine, LDH, and amylase values were significantly higher in patients receiving plasmapheresis at the time of admission. Five of the 7 patients who received plasmapheresis had neurological involvement. Although there was not an exact indication for patients undergoing plasmapheresis, we wanted to emphasize that close follow-up should be done in patients with elevated creatine, LDH, and amylase values [30].

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There is limited data on the use of eculizumab in patients with typical HUS. The first report on the use of eculizumab for STEC-HUS was published in 2011 [31]. In some clinical studies, eculizumab treatment has been effective in the recovery and prevention of complement-mediated thrombotic microangiopathy, renal function, and hematological recovery in patients with aHUS [32-34]. Garcia et al found that eculizumab treatment provided clinical improvement in STEC HUS infection. In our study, eculizumab treatment led to a similar clinical improvement in 3 out of 4 patients [35]. Eculizumab is an anti-C5 monoclonal antibody that inhibits complement activation and prevents the formation of the membrane attack complex [36-39]. Pape et al found that eculizumab treatment can be beneficial in patients with neurological involvement who had complement activation with Shiga toxin [40]. In our study, the use of eculizumab in 3 patients with neurological involvement resulted in improvement in neurological symptoms within 48 h. Despite 2 doses of eculizumab treatment in 1 patient, the clinical signs did not improve, and the patient was intubated. Most case series in the literature report immediate improvement in neurological complications of typical HUS after the first dose of eculizumab [41]. In the study of Rasa et al, early use of eculizumab was found to be beneficial for typical HUS and neurological involvement; however, it was found to be less beneficial in severe HUS patients with late and rapidly progressive multiple organ involvement [42]. We gave eculizumab treatment to 4 patients who developed rapid and serious neurological complications. Benjamin et al found that eculizumab treatment provided clinical improvement. In addition to this study, we thought that it would be important to use LDH levels in treatment follow-up in patients who would be treated with eculizumab [43].

In the patient whose neurological symptoms did not improve after eculizumab treatment, an increase in LDH level was detected after the first dose. Controlled studies should be performed to monitor the continuation of treatment with LDH levels in patients without neurological improvement. Since studies are generally conducted in the pediatric age group, a limited number of cases have been reported in the literature in the evaluation of eculizumab treatment in typical adult HUS. Additionally, there is no study in the literature examining the length of stay and laboratory data of patients requiring intensive care follow-up. In this respect, we thought that our study would contribute to the literature.

Study limitations

The limitations of our study are that the number of participants is relatively limited and does not represent a large population. In addition, stool culture could not be performed in all patients before admission to the ICU. Detailed microbiological characterization of the strains was therefore missing in some patients. One of our limitations was a lack of a specific indication for eculizumab treatment. The simultaneous application of plasmapheresis and eculizumab in some patients made it difficult to make a clear comparison in terms of prognosis. For future studies, we recommend conducting prospective studies with a larger population.

Conclusions

We want to point out that *E, coli* infections in adults are more likely to progress to HUS in epidemics, and that these infections are an important public health problem. We want to emphasize the importance of starting the treatment at an early stage and managing it at a single center, with a multidisciplinary approach. However, more comprehensive studies are needed. STEC is a significant health problem that causes serious illnesses. In this study, a statistically significant difference was detected between LDH, GFR, troponin, NT-proBNP parameters, and the length of hospital stay. Creatine and LDH values of patients requiring eculizumab and plasmapheresis at the time of admission were found to be statistically high. It should be kept in mind that eculizumab and plasmapheresis treatment can be required for patients with elevated creatine and LDH levels at the time of admission. Additionally, directing patients to centers where these treatments can be given can be important for early treatment.

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