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ORIGINAL ARTICLE

Hyponatremia: a new predictor of mortality in patients with Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome

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Abstract

Objectives: (1) Evaluate mortality rate in patients with Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome, (2) determine the leading causes of death, and (3) identify predictors of mortality at hospital admission.

Methods We conducted a multicentric, observational, retrospective, cross-sectional study. It included patients under 18 years old with Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome hospitalized between January 2005 and June 2016. Clinical and laboratory data were obtained from the Argentine National Epidemiological Surveillance System of Hemolytic Uremic Syndrome. Clinical and laboratory variables were compared between deceased and non-deceased patients. Univariate and multivariate analyses were performed. ROC curves and area under the curve were obtained.

Results Seventeen (3.65%) out of the 466 patients died, being central nervous system involvement the main cause of death. Predictors of death were central nervous system involvement, the number of days since the beginning of diarrhea to hospitalization, hyponatremia, high hemoglobin, high leukocyte counts, and low bicarbonate concentration on admission. In the multivariate analysis, central nervous system involvement, sodium concentration, and hemoglobin were independent predictors. The best cut off for sodium was ≤ 128 meq/l and for hemoglobin ≥ 10.8 g/dl.

Conclusions Mortality was low in children with Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome, being central nervous system involvement the main cause of death. The best mortality predictors found were central nervous system involvement, hemoglobin, and sodium concentration. Hyponatremia may be a new Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome mortality predictor.

Keywords Thrombotic microangiopathy · Acute kidney injury · Typical hemolytic uremic syndrome · Outcome in typical uremic syndrome

Abbreviations

HUS	Hemolytic uremic syndrome
STEC	Shiga toxin-producing *Escherichia coli*
STEC-HUS	Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome
CNS	Central nervous system
S	Sensitivity
s	Specificity
PPV	Positive predictive values
NPV	Negative predictive values
AUC	Area under the curve
PCR	Polymerase chain reaction
anti-LPS	anti-lipopolysaccharide antibodies

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Introduction

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and variable degrees of renal compromise, ranging from minor urine abnormalities to severe renal disease. Most of the cases are associated with diarrheal prodrome induced by a

Shiga toxin-producing *Escherichia coli* (STEC) infection. It is an endemic disease in Argentina, constituting the leading cause of acute renal failure, responsible for 9% renal transplants in children and adolescents' [1]. Reporting of clinical HUS cases to the National Health Surveillance System, which has been mandatory since 2000, must be immediate and individualized. The incidence reported in the period 2011–2015 was 8.5/100,000 children under 5 years old (http://www.msal.gob.ar/images/stories/boletines/Boletin-Integrado-De-Vigilancia-N327- SE37.pdf). In 1964, Gianantonio et al. described the clinical manifestations of this disease in a group of 64 patients and introduced peritoneal dialysis for the treatment of the acute renal failure [2].

Dialysis reduced the mortality from 15% in 1964 to 2–5.6%, without any significant change in the last decades [2]. Identification of high mortality risk patients at hospital admission may be useful to provide a quick referral to pediatric renal care centers. Previously reported predictors of mortality included leukocytosis, greater hematocrit, and hemoglobin values at hospital admission and respiratory tract infection within 3 weeks before the diagnosis, probably related to antibiotic exposure [3, 4].

The aims of this study were the following: (1) evaluate mortality rate, (2) determine the causes of death, and (3) identify predictors of death at hospital admission in Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome (STEC-HUS) patients.

Methods

Since 2000, all new cases of typical HUS must be uploaded to the National Health Surveillance System. The registry contains information about epidemiology, prodromal, clinical, and laboratory data at admission, treatment, and outcome. Data used in this study were obtained from the registry. This was a multicentric, observational, retrospective, and cross-sectional study.

Inclusion criteria were patients under 18 years old with STEC-HUS, hospitalized from January 2005 to June 2016. We defined HUS as the triad: thrombocytopenia (< 150,000/mm^3), microangiopathic hemolytic anemia (esquistocytes in blood smear), and renal dysfunction (increase of serum creatinine concentration and/or proteinuria and/or hematuria). STEC infection was identify by at least one of these three laboratory criteria: screening by polymerase chain reaction (PCR)/isolation of STEC, detection of free Shiga toxin (Stx) in stool and in the last years, by the detection of anti-lipopolysaccharide antibodies O157, O145, O121 (anti-LPS).

We evaluated two groups of variables:

1. Clinical: gender, age (in months), days since the beginning of diarrhea to hospitalization, use of antibiotics and/or anticholinergic drugs before admission, anuria (< 1 ml/kg/day), hemorrhagic colitis, hydration state (dehydration, proper hydration, over hydration), central nervous system (CNS) involvement (normal, irritability, somnolence, seizures, and coma). The state of hydration and CNS involvement were assessed by the admitting pediatrician at hospital admission. In patients with more than one CNS symptoms, only the worst was considered for the analysis.
2. Laboratory: leukocytes (cell count per mm^3), neutrophils (%), hematocrit (%), hemoglobin (g/dl), platelets (count per mm^3), sodium and potassium concentration (mEq/l), pH, bicarbonate (mEq/l), creatinine (mg/dl), and urea values (mg/dl).

To determine death predictors, we compared deceased and non-deceased patients.

The information analyzed was the data at hospital admission.

This study was approved by the Review Boards and Ethics Committees of the hospitals. The requirement to obtain informed consent was waived by the institutional review boards.

Statistical methods

Sample size estimated to know the STEC-HUS prevalence in Argentinean children under 18 years old was 412 patients.

Statistical analysis Quantitative variables between deceased and non-deceased patients were compared with ANOVA. Homogeneity of variances was validated with the Levene test.

Association between categorical variables and the patient mortality (i.e., presence-absence) was analyzed by Chi-square test. To identify predictors of mortality, simple logistic regression models were conducted. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. ROC curves and area under the curve (AUC) determined the predictive capacity (PC) of the models.

A multivariate logistic regression analysis was performed with those variables that were significant in the simple regression models. ROC and AUC were also obtained. Sensitivity (S), specificity (s), and positive and negative predictive values (PPV and NPV, respectively) were obtained for each predictor factor.

Sodium concentration and hemoglobin level at patient admission were correlated with Pearson's correlation analysis (R). Sodium concentration was also compared to the hydration status of the patient (proper hydration/over hydration/dehydration). In this case, ANOVA test was used.

Software Epidat-4.2 software was used for statistical analysis. Significance level considered was $P < 0.05$.

Results

We analyzed the data of 952 children with HUS from the National Health Surveillance System. Four hundred eighty-six were excluded because they were STEC negative. Four hundred sixty-six children with STEC-HUS (49%) were included. STEC was identified by isolation or PCR in 328 patients (70.3%), detection of free Stx in stool in 114 patients (24.5%), and detection of anti-LPS in 24 children (5.2%).

Clinical variables are shown in Table 1. During hospitalization, 17 of the 466 (3.65%) patients died; 15 of the 17 had a cause of death related to severe CNS involvement and 2 had pulmonary hemorrhage. Four of them also had hemorrhagic colitis and 2 myocardial infarction. Two hundred two patients (43%) required dialysis. Peritoneal dialysis was performed in 197 children and hemodialysis in 5.

Table 2 compares all the variables between deceased and non-deceased patients. CNS involvement was present in 88% of the patients who died vs 37% of those who did not ($P = 0.00003$). The number of days since the beginning of diarrhea to hospitalization was significantly shorter in patients who died ($P = 0.03$). Other clinical variables did not show statistically significant association with mortality (Table 2).

Table 1 Clinical variables at hospital admission

Clinical variables	
Female *n* (%)	269 (57.7)
Age (months) media (± SD)	30 (± 23.6)
Days since the beginning of diarrhea to hospitalization mean (interval)	5 (0–24)
Antibiotics treatments before admission *n* (%)	77 (16.5)
Anticholinergic treatments before admission *n* (%)	7 (1.5)
Anuria at admission *n* (%)	152 (32.6)
Hemorrhagic colitis *n* (%)	55 (11.8)
Hydration status *n* (%)	273 (58.6)
Proper hydration	117 (25.1)
Dehydration	75 (16.1)
Over hydration	1 (0.2)
w/d	
CNS involvement *n* (%)	183 (39.3)
Seizures	67 (14.4)
Somnolence	63 (13.5)
Irritability	44 (9.4)
Coma	6 (1.3)
w/d	3 (0.6)

The percentages were calculated based on 466 children. *CNS* central nervous system, *n* number of patients, *SD* standard deviation, *w/d* without data

In univariate analysis, sodium concentration, hemoglobin, leukocytes, hematocrit, and bicarbonate were significantly different between deceased and non-deceased patients (Table 3). In multivariate analysis, only CNS involvement, sodium concentration, and hemoglobin remained significant (Table 3).

Severe CNS involvement had $S = 88.24\%$, $s = 62.58\%$, with PPV = 8.2% and NPV = 99.3%. AUC was 0.75 (95% CI = 0.619–0.89) (Table 4).

Sixteen out of the 17 deceased patients had sodium concentration < 135 mEq/l. The best cut off for sodium concentration was ≤ 128 mEq/l ($S = 70.59\%$, $s = 79.03\%$, PPV = 11.7%, NPV = 98.6%). ROC curve showed an AUC of 0.77 (95% CI = 0.64–0.90).

The best cut off for hemoglobin was ≥ 10.8 g/dl ($S = 68.75\%$, $s = 79.56\%$, PPV = 11.6%, NPV = 98.5%), with an AUC of 0.77 (95% CI = 0.63–0.90). Sodium concentration and hemoglobin levels presented an inverse statistically significant correlation ($R = -0.18$; $P = 0.0002$). Mean sodium concentration did not differ among the hydration status of the patient (proper hydration/over hydration/dehydration) ($F = 2.31$; $P = 0.10$). In our study, the presence of SNC involvement, high hemoglobin level, and low sodium concentration all predicted death (AUC: 0.888, CI 95% 0.781–0.994).

Discussion

In this retrospective multicenter study, we describe the causes of deaths among patients with STEC–HUS and identify predictors of death at hospital admission. Patients with CNS involvement, hyponatremia (sodium ≤ 128 mEq/L), and hemoglobin ≥ 10.8 g/dl had a higher probability of in-hospital death.

Previous observational studies identified leukocytosis, greater hematocrit or hemoglobin, CNS complications, hemorrhagic colitis, and recent respiratory tract infection as death predictors or poor outcome in children with post diarrhea HUS [3–6].

CNS involvement occurs in 17–50% of children with STEC-HUS [6, 7] and is the most threatening complication associated with increased morbidity and mortality [4–8]. The mechanisms of damage in the CNS are frequently considered to be due to multiple factors, including local microangiopathy, hypertension, and hyponatremia. In this study, mortality was specially associated with coma and seizures.

Hyponatremia in typical HUS has been associated with brain damage and renal impairment [7–9], but it has not been previously established as a death predictor at hospital admission.

Milford et al. reported a significant association between hyponatremia and seizures in HUS patients. Eighty-four percent of patients with seizures had hyponatremia vs 50% of those children without seizures [9]. Like them, we did not find correlation between the state of hydration, as assessed by the

Table 2 Clinical and laboratory variables compared between deceased and non-deceased patients

Clinical and laboratory variables	Non deceased patients	Deceased	*P* value
Number of patients	449	17	–
Age (months) media (S.D)	29.9 (± 23.9)	32.3 (± 14.6)	0.679
Female *n* (%)	259/449 (57.7)	10/17 (58.8)	0.567
Male *n* (%)	190 (42.3)	7/17 (41.2)	
CNS involvement *n* (%)	168/449 (37.4)	15/17 (88.2)	*0.00003**
Coma *n* (%)	4/449 (0.9)	2/17 (11.8)	*0.005**
Seizures *n* (%)	57/449 (12.7)	10/17 (58.8)	*0.0000008**
Somnolence *n* (%)	60/449 (13.4)	3/17 (17.6)	0.893
Irritability *n* (%)	44/449 (9.8)	0/17 (0)	0.347
Dehydration	112/449 (24.9)	5/17 (29.4)	0.899
Over hydration	74/449 (16.5)	1/17 (5.9)	0.406
Proper hydration	262/449 (58.4)	11/17 (64.7)	0.609
Anuria *n* (%)	144/449 (32.1)	8/17 (47.1)	0.196
Hemorrhagic colitis *n* (%)	54/449 (12)	4/17 (23.5)	0.253
Antibiotics treatment *n* (%)	73/449 (16.3)	4/17 (23.5)	0.304
Anticholinergic treatment *n* (%)	7/449 (1.56)	0/17 (0)	0.770
Sodium (mEq/l) mean (SD)	133 (±6.16)	126.5 (±6.4)	*< 0.00001**
Hemoglobin (g/dl) mean (SD)	8. 7 (±2.2)	10.9 (±2.1)	*0.0001**
Leukocytes ($\times 10^3/mm^3$) mean (SD)	18,960.2 (±8.510)	26,023 (±12,576)	*0.001**
Hematocrit (%) mean (SD)	25.9 (±6.5)	30.5(± 9.8)	*0.005**
Days since the beginning of diarrhea to hospitalization mean (SD)	5 (±3.3)	3.2 (±2.7)	*0.030**
Bicarbonate (mEq/l) mean (SD)	17.2 (±5.0)	14.6 (±4.6)	*0.033**
pH mean (SD)	7. 34 (±0.08)	7.31 (±0.07)	0.06
Neutrophils (%) mean (SD)	57.5 (±14.7)	63.5(±15.3)	0.103
Potassium (mEq/l) mean (SD)	4.2 (±0.8)	4 (±0.8)	0.248
Urea (mg/dl) mean (SD)	135.4 (±93.4)	110.7 (±60.6)	0.281
Platelets (per mm^3) mean (SD)	97,716.9 (±91,452)	120,570.6 (±103,158)	0.315
Creatinine (mg/dl) mean (SD)	2.4 (±1.8)	2.2 (±1.3)	0.645

The percentages were calculated about 466 children. *CNS* central nervous system, *n* number of patients, *SD* standard deviation. Quantitative variables were compared with ANOVA. Qualitative variables were analyzed by Chi-square test. **P* values showed statistically significant differences ($P < 0.05$)

admitting pediatrician, and hyponatremia. No differences in the sodium plasma concentration were found between the three groups of children: over loaded proper hydration or dehydrated.

Hyponatremia was a significant finding in deceased patients in our study. This fact might well reflect hyponatremic hypovolemia with extracellular fluid volume contraction, due to both fluid losses (diarrhea) and decreased fluid intake and subsequent water retention as a direct result of the release of antidiuretic hormone. Intake of electrolyte-free water in amounts that exceed the losses composite of electrolyte-free water would result in a positive electrolyte-free water balance [10]. On the other hand, hyponatremia might also result from hemodilution caused by hypotonic fluid retention (administered intravenously or orally), associated with oliguria.

Acute hyponatremia results in brain swelling and intracranial hypertension and can progress to life-threatening neurologic complications, which can lead to permanent brain damage or death [10]. Such progression can occur suddenly and might explain why it was identified as a death predictor at hospital admission in this study.

The majority of studies, including our own, conclude that greater hemoglobin or hematocrit upon admission are major death predictors [3, 4].

This association between high hematocrit and the severity of STEC-HUS likely reflects dehydration and hemoconcentration [7, 8, 12]. Patients who are clinically dehydrated at admission are more likely to have reduced tissue perfusion and ischemia [7]. These patients have a higher risk of developing neurological involvement and

Table 3 Simple and multivariate logistic regression models

Variables	OR	95% CI		*P* value
Univariate analysis				
CNS involvement	12.55	2.83	55.54	*0.001**
Coma	14.73	2.50	86.82	*< 0.003**
Seizures	9.75	3.57	26.64	*< 0.0001**
Somnolence	1.38	0.39	4.94	0.622
Irritabilility	0.00	0.00	–	0.9999
Hemoglobin	1.51	1.22	1.86	*< 0.0001**
Hematocrit	1.10	1.03	1.18	*0.006**
Leukocytes	1.002	1.001	1.003	*0.002**
Sodium	0.85	0.79	0.92	*< 0.0001**
Days since the beginning of diarrhea to hospitalization	0.76	0.60	0.97	*0.025**
Bicarbonate	0.89	0.80	0.99	*0.033**
pH	0.00	0.00	1.25	0.059
Neutrophilus	1.03	0.99	1.07	0.107
Hemorrhagic colitis	2.40	0.75	7.64	0.138
Anuria	1.88	0.71	4.98	0.202
Potassium	68	0.36	1.30	0.244
Urea	1.00	0.99	1.00	0.278
Dehydration	1.06	0.36	3.13	0.911
Over hydration	0.32	0.04	2.53	0.282
Platelets	1.00	1.00	1.00	0.319
Antibiotic treatment	1.59	0.50	5.00	0.432
Creatinine	0.93	0.69	1.26	0.645
Age	1.00	0.99	1.02	0.678
Gender	1.05	0.39	2.80	0.926
Anticholinergic treatment	0.00	0.00	–	0.9999
Multivariate logistic regression analysis				
CNS involvement	8.66	1.85	40.60	*0.006**
Hemoglobin	1.53	1.19	1.98	*0.001**
Sodium	0.89	0.82	0.98	*0.012**

CNS central nervous system, *OR*: Odds ratio, 95% confidence intervals (95%CI). **P* values showed statistically significant differences ($P < 0.05$)

anuria, requiring dialysis for longer periods than non-dehydrated patients do. The possible effect of hemoconcentration on the severity of STEC-HUS has been recently evaluated in a meta-analysis by Grisaru et al. [12], who identified two predictors of poor outcomes among STEC-infected children who progressed to HUS. These included both the lack of intravenous fluid administration prior to the establishment of HUS and a higher hematocrit value at admission. These findings point to an association between dehydration and adverse outcomes among children with HUS. However, from our data, deceased patients were not more dehydrated than non-deceased patients. As deceased patients had a shorter time to hospital admission, perhaps the duration of hemolysis was shorter and had not yet led to low hemoglobin levels. Mortality in our patients could be due to a more severe cerebral microangiopathy leading to hyponatremia via early onset syndrome of inappropriate antidiuretic hormone secretion, irrespective of the hydration status.

More importantly, an increase leukocyte count on peripheral blood at diagnosis is one of the most consistent parameters associated with poor prognosis and death [3, 4]. Polymorphonuclear neutrophils directly contribute to renal inflammation and endothelial injury during HUS, based on its great cytotoxic and oxidative potential [13].

We found that leukocyte counts were higher in patients who died, but the multivariate analysis did not identify this factor as being related to death. However, this unexpected finding can be explained because in our study, we only analyzed laboratory variables at hospital admission; other studies registered the highest value observed during a defined period of time before and after HUS diagnosis [4].

Table 4 Sensibility, specificity, predictive values, and area under the ROC curve for each variable

Variables	S	s	PPV	NPV	AUC	95% CI	
Univariate analysis							
CNS involvement	88.24	62.58	8.20	99.30	0.754	0.619	0.890
Coma	11.76	99.10	33.30	96.70	0.554	0.411	0.698
Seizures	58.82	87.22	14.90	98.20	0.730	0.592	0.869
Somnolence	17.65	86.55	4.80	96.50	0.521	0.379	0.663
Irritability	0.00	95.97	0.00	90.20	0.549	0.406	0.693
Hemoglobin	68.75	79.56	11.60	98.50	0.766	0.628	0.904
Hematocrit	58.82	78.59	9.60	98.00	0.675	0.532	0.818
Leukocytes	58.82	78.79	9.90	98.00	0.678	0.535	0.821
Sodium	70.59	79.03	11.70	98.60	0.770	0.637	0.904
Days since the beginning of diarrhea to hospitalization	81.25	65.62	7.80	99.00	0.712	0.568	0.857
Bicarbonate	76.47	48.32	5.70	98.00	0.640	0.495	0.785
pH	62.50	63.39	6.30	97.70	0.637	0.488	0.786
Neutrophilus	70.59	57.64	7.10	97.70	0.640	0.495	0.785
Hemorrhagic colitis	23.53	88.64	7.30	96.80	0.561	0.417	0.705
Anuria	47.06	67.93	5.30	97.10	0.575	0.431	0.719
Potassium	52.94	72.16	7.00	97.50	0.601	0.456	0.746
Urea	70.59	47.06	4.90	97.70	0.558	0.414	0.701
Dehydration	29.41	75.00	4.30	96.60	0.522	0.380	0.664
Over hydration	1.33	95.91	5.88	83.52	0.553	0.410	0.697
Platelets	41.18	76.78	6.70	97.00	0.572	0.428	0.716
Antibiotic treatment	23.53	83.74	5.20	96.70	0.536	0.394	0.679
Creatinine	76.47	40.96	4.80	97.80	0.500	0.360	0.640
Age	82.35	41.29	5.10	98.40	0.612	0.467	0.757
Gender	58.82	42.32	3.70	96.40	0.506	0.365	0.646
Anticholinergic treatment	0.00	96.30	0.00	98.44	0.508	0.367	0.648
Multivariate analysis							
CNS involvement + hemoglobin + sodium	100.0	95.9	38.5	100.0	0.888	0.781	0.994

CNS central nervous system, S Sensibility, s specificity, PPV positive predictive value, NPV negative predictive value, AUC area under the ROC curve, 95% CI 95% confidence interval

Recently, a shorter period of time between the onset of diarrhea and a diagnosis of diarrhea-associated HUS was recognized by Ninchoji et al. as a risk factor for more severe clinical course [14]. We also found in our study that the number of days since the beginning of diarrhea to hospitalization was significantly shorter in the group of deceased patients.

Rahman et al. [5] performed a retrospective analysis of patients with diarrhea-associated HUS between 1981 and 2009 and showed that although relatively uncommon, hemorrhagic colitis was a major complication with strong association with severe acute renal failure and longer anuric periods, as well as major neurologic involvement and high mortality rate. We were not able to demonstrate that hemorrhagic colitis was a death predictor at hospital admission. This fact could be explained by a number of factors, including better recognition of this severe condition, improvements in the surgical approach, and an intensive care management in the last decades.

There are two major limitations to our study. First, it is retrospective in nature. Secondly, although the studied patient population was significant, the number of deaths was low.

Despite these limitations, this multicenter retrospective analysis is the first to our knowledge to provide clinical and laboratory predictors of in-hospital death in patients with confirmed STEC-HUS.

Our results are consistent with findings by other researchers since we demonstrated a significant association between high hemoglobin level and CNS involvement at the time of HUS onset and poor outcome, but we also identified hyponatremia as a new predictor of in-hospital death.

Conclusions

We observed that mortality was low in STEC-HUS patients and CNS involvement was the main cause of death. The best

mortality predictors were CNS involvement, hemoglobin, and sodium concentration. Hyponatremia showed a strong association with high mortality rate and may be a new STEC-HUS predictor of poor outcome and death.

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Compliance with ethical standards

This was a multicentric, observational, retrospective and cross-sectional study. This study was approved by the Review Boards and Ethics Committees of the hospitals. The requirement to obtain informed consent was waived by the institutional review boards.

Conflict of interest The authors declare that they have no conflicts of interest.

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