Volume Resuscitation and Progression to Organ Failure in Shiga Toxin-Producing<br>Escherichia coli Infection in Adults

OBJECTIVES: Shiga toxin-producing Escherichia coli infection is associated with dysentery and the hemolytic uremic syndrome, marked by the triad of microangiopathic hemolytic anemia, acute kidney failure, and thrombocytopenia. Descriptions of Shiga toxin-producing Escherichia coli outbreaks causing hemolytic uremic syndrome in adults are sparse, and management strategies are largely adapted from pediatric literature where aggressive fluid administration is recommended. However, these may not be ideal for adults.

DESIGN: We present a case series of an Shiga toxin-producing Escherichia coli outbreak in U.S. Marine Corps recruits.

SETTING: We review the clinical course, laboratory data, and fluid resuscitation used in hospitalized patients during the 2017 Shiga toxin-producing Escherichia coli outbreak at Marine Corps Recruit Depot, San Diego.

PATIENTS: Patients admitted to the hospital for complications from Shiga toxin-producing Escherichia coli infection. All were previously healthy men between the ages of 17 and 20 years.

INTERVENTIONS: Isotonic crystalloid fluid resuscitation during the first 72 hours.

MEASUREMENTS AND MAIN RESULTS: Of 244 identified cases of Shiga toxin-producing Escherichia coli infection, 30 required hospitalization, 15 progressed to hemolytic uremic syndrome, and five required hemodialysis. Patients were admitted and given aggressive IV fluid hydration. Those who progressed to hemolytic uremic syndrome received on average 8.4 L of isotonic crystalloid over the initial 72 hours, with up to 18% of body weight delivered. The six critically ill patients received a mean 12.2 L in the first 72 hours. Those who did not progress to hemolytic uremic syndrome received a mean 3.0 L of crystalloid. If oligoanuria developed, a net-even fluid balance was maintained. The amount of volume infused was not associated with improved outcomes. The patients with the highest fluid balance totals more often required dialysis than those who received less fluid. One hemolytic uremic syndrome patient developed flash pulmonary edema.

CONCLUSIONS: The aggressive IV hydration protocols (as a percentage of body weight) in the pediatric literature may not be applicable to adults diagnosed with hemolytic uremic syndrome. A more conservative fluid strategy in adults with hemolytic uremic syndrome merits further investigation.

KEY WORDS: acute renal failure; Escherichia coli O157:H7; hemolytic uremic syndrome; Shiga toxin-producing Escherichia coli; Shiga toxin-producing Escherichia coli–associated hemolytic uremic syndrome; volume resuscitation

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Shiga toxin-producing *Escherichia coli* (STEC) is a foodborne infection associated with dysentery and, in more severe cases, the hemolytic uremic syndrome (HUS), a syndrome marked by the triad of microangiopathic hemolytic anemia, acute kidney injury (AKI), and thrombocytopenia. STEC infections frequently occur in large outbreaks and are most often the result of the consumption of contaminated foods. Notable recent outbreaks have been attributed to contaminated spinach, flour (1), and fenugreek seeds (2) in a well described outbreak in Germany in 2011. The most common culprit is *E. coli* O157:H7 in the United States, whereas *Shigella dysenteriae* and other *E. coli* serotypes are more often associated with the development of HUS in other countries (3). Outbreaks of STEC are associated with considerable rates of morbidity and mortality, particularly in children. Indeed, the majority of the treatment data comes from the pediatric population as STEC-associated HUS (STEC-HUS) traditionally affects children, with a typical age of occurrence of 3–5 years (3).

Data are limited regarding HUS management in adults, and exact management strategies are often adapted from pediatric literature and experience. The pediatric literature suggests that aggressive fluid resuscitation is the best available management to avoid renal failure and the subsequent need for dialysis, particularly in those patients with have suspected *E. coli* O157:H7 who have not yet developed HUS or have nonoligoanuric HUS (4). Published experience in children often recommends 12–14% of body weight given in isotonic crystalloid with variable administration speeds (5, 6).

We present an STEC outbreak in 2017 occurring among U.S. Marine Corps recruits in southern California. All hospitalized patients were young men 17–20 years old who were living together in a military barracks environment prior to presentation. All patients were previously healthy without significant comorbidities. They all contracted STEC at the same approximate time and presented with dysentery with days of one another. The hospitalized patients were treated similarly and predominantly at the same facility. Based on aforementioned data published on pediatric cases of HUS, we pursued aggressive fluid resuscitation in our adult HUS patients in order to avoid kidney injury with close monitoring of urine output. Once oligoanuria developed, a net even resuscitation strategy was employed followed by deresuscitation as tolerated.

**METHODS**

Hospitalized patients with STEC infection, defined as the presence of dysentery and either a positive culture for *E. coli* O157:H7, positive polymerase chain reaction, and/or positive stool antigen test for Shiga toxin 1 or Shiga toxin 2, were included in this study. Patients who progressed to HUS were defined as defined by the presence of AKI (using the standard Kidney Disease: Improving Global Outcomes criteria [7]), thrombocytopenia less than 100,000 per mL, and anemia with a hemoglobin value < 10). Dates of admission ranged from October 26, to November 9, 2017. Criteria for admission during this outbreak were not prespecified; rather, hospital admission decisions were based upon the clinical judgment of the emergency, internal, or critical care medicine physicians at time of presentation. Patients were admitted to the medical-surgical floor or the ICU based on clinical status and presence or absence of HUS. The patients’ charts were retrospectively reviewed for fluid administration within the first 72 hours as well as their initial and subsequent hemoglobin, WBC counts, creatinine, and platelet counts. Note was taken of whether hemodialysis was required as a treatment for those patients who either presented with or developed significant AKI during their admissions.

In order to delineate patient disease severity, Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated for all patients in the study; scores were obtained at the time of initial hospitalization for those patients who did not require admission to the ICU during their stay and at time of ICU admission or transfer for those who did require an escalation of care. The APACHE II scores were then compared for all patients (excepting those without full data available due to treatment at an outside military medical facility) in relation to the volume status at 72 hours, expressed as a percentage (%) of admission body weight in kilograms (kg). Clinical indicators of hypervolemia (radiographic evidence of pulmonary edema or pleural effusions or bedside physical examination assessment of hypervolemia) were also recorded. This study was reviewed by the Uniformed Services University of the Health Sciences institutional review board (IDCRP-83-9704 [IDCRP-118]) and was approved (reference number 911664).
RESULTS

Two-hundred forty-four cases of STEC were identified in total. Thirty patients required hospitalization, and 15 of these patients progressed to HUS (Table 1). Of those with HUS, six patients were transferred to the ICU (predominantly due to worsening encephalopathy, seizures, respiratory failure, and/or hemodynamic instability). Of the 15 patients with HUS, five patients required hemodialysis despite aggressive fluid administration. Three patients required mechanical ventilation: two for encephalopathy and one for acute hypoxic respiratory failure due to flash pulmonary edema.

Laboratory data in patients with HUS were noted to have higher initial mean total leukocyte counts (average $26.6 \times 10^3$ vs $15.4 \times 10^3$ cells/mL), with initial counts greater than $32 \times 10^3$ cells/mL only seen in the HUS cases (Table 1). Initial platelet counts were variable in HUS patients depending on when their initial assays were drawn in their HUS course. However, all were in the normal range for patients without HUS.

Patients were admitted and given aggressive IV fluid hydration with isotonic crystalloid, either lactated Ringer (LR)’s solution or 0.9% normal saline (NS), depending on physician preference. Data on NS versus LR were incomplete and are not included in this analysis. Those who progressed to HUS had a mean positive fluid balance of 8.4 L of isotonic crystalloid over the initial 72 hours, with up to 24% of body weight delivered (Fig. 1). Those who did not progress to HUS had a mean positive 3.0 L of crystalloid in the initial 72 hours (Table 2).

However, the higher fluid administration did not decrease the incidence of renal replacement therapy, and one patient developed flash pulmonary edema requiring emergent intubation and mechanical ventilation. In total, five patients required renal replacement therapy (administered exclusive by means of hemodialysis), six required ICU admission, and three required mechanical ventilation (Fig. 2). All patients eventually had return of baseline kidney function.

Patients who developed pleural effusions, pulmonary edema, and clinically assessed hypervolemia received an average of 13, 20, and 8 L of volume within the first 72 hours of hospitalization (Fig. 3). The APACHE II scores and volume administered in the first 72 hours, expressed as percentage of admission body weight (kg), for the individual patients with HUS requiring hemodialysis, with HUS but not requiring hemodialysis, and with STEC infection without development of HUS are graphically presented (Fig. 4). The mean APACHE II scores in each of these three patient categories were then compared with mean volume status at 72 hours, again as a % of admission body weight (Fig. 5). Hospitalized patients who did not develop HUS had a mean APACHE II score of 3 at admission and received an average of 3 L of volume within the first 72 hours. Patients who developed HUS, but did not require dialysis, had a mean APACHE II score of 8 and received an average of 11 L of volume in the first 72 hours. Those patients with HUS who required renal replacement therapy had a mean APACHE II score of 14 and received an average of 15 L in the first 72 hours.

DISCUSSION

Despite the well documented E. coli 0104:H4 outbreak in Germany in 2011 (2), there remains a dearth of published literature regarding adults with STEC-HUS beyond several small case series and case reports. There are generally more data about the prevalence, epidemiology, etiology, diagnosis, and management of STEC-HUS in the pediatric population. We tried to explore the applicability of these practices to adults with infectious HUS by retrospectively reviewing a case series of Marine Corps recruits admitted with foodborne bacterial gastroenteritis.

The literature on fluid balance and preservation of renal function in the adult HUS patient is extremely sparse. In our case series, we based our clinical judgment of fluid balance on the best available literature from pediatrics and on personal consultations with pediatric HUS researchers during the acute phase of the patients’ illness. Indeed, no literature to date has shown an intervention that can completely prevent the development of STEC-HUS or to mitigate the severity of renal dysfunction once HUS has occurred (8). However, the existing pediatric literature has demonstrated some improvements in clinical outcomes when greater quantities of IV fluid are administered within the first few days of STEC infection, prior to HUS development (8). The theoretical advantage here is optimization of renal perfusion in the pre-HUS period, where the Shiga toxin is causing direct renal injury with subsequent microthrombus formation and further renal injury (8).
### TABLE 1.
Clinical and Laboratory Characteristics of Hospitalized Patients With Shiga Toxin-Producing *Escherichia coli* Infection

| Admission WBC (1,000/µL) | Admission Creatinine (mg/dL) | Peak Creatinine (mg/dL) | Nadir Platelet Count (1,000/µL) | 72-hr Fluid Balance | Overall Fluid Balance (L) | Hemolytic Uremic Syndrome | Dialysis |
|--------------------------|-----------------------------|------------------------|---------------------------------|---------------------|--------------------------|---------------------------|----------|
| 10.6                     | 1.0                         | 4.3                    | 35                              | 10.0                | 10.0                     | Yes           | Yes      |
| 23.5                     | 0.9                         | 10.1                   | 18                              | 13.0                | 16.0                     | Yes           | Yes      |
| 13.6                     | 1.2                         | 9.8                    | 35                              | 13.0                | 13.5                     | Yes           | Yes      |
| 12.0                     | 1.0                         | 9.6                    | 32                              | 13.0                | 12.5                     | Yes           | Yes      |
| 18.4                     | 2.9                         | 3.6                    | 32                              | 13.0                | 8.3                      | Yes           | No       |
| 20.9                     | 1.0                         | 1.0                    | 155                             | –1.0                | –1.4                     | No            | No       |
| 19.6                     | 1.0                         | 1.0                    | 206                             | 11.0                | 11.1                     | No            | No       |
| 23.8                     | 1.1                         | 1.1                    | 249                             | 7.3                 | 7.3                      | No            | No       |
| 12.7                     | 1.0                         | 1.0                    | 257                             | –5.0                | –5.0                     | No            | No       |
| 20.3                     | 0.9                         | 0.9                    | 285                             | 3.2                 | 3.2                      | No            | No       |
| 13.9                     | 1.1                         | 1.1                    | 196                             | 7.6                 | 7.6                      | No            | No       |
| 16.6                     | 0.7                         | –                      | –                               | –                   | –                        | No            | No       |
| 13.6                     | 0.9                         | 0.9                    | 228                             | –3.9                | –3.9                     | No            | No       |
| 9.9                      | 0.8                         | –                      | –                               | –                   | –                        | No            | No       |
| 9.0                      | 1.2                         | 1.2                    | 185                             | –0.6                | –0.6                     | No            | No       |
| 15.6                     | 0.9                         | 0.9                    | 186                             | 0.8                 | 0.8                      | No            | No       |
| 6.8                      | 0.9                         | 1.0                    | 297                             | 2.8                 | 2.8                      | No            | No       |
| 18.0                     | 0.8                         | –                      | –                               | 8.3                 | –                        | No            | No       |
| 31.7                     | 1.0                         | 1.0                    | 22                              | 9.5                 | 9.5                      | Yes           | No       |
| 31.3                     | 1.2                         | 2.9                    | 24                              | 8.4                 | 16.2                     | Yes           | No       |
| 15.3                     | 1.2                         | 1.4                    | 62                              | 6.9                 | 6.9                      | Yes           | No       |
| 7.2                      | 1.0                         | 1.0                    | 113                             | –0.5                | –0.5                     | No            | No       |
| 10.4                     | 1.5                         | 1.5                    | 101                             | 4.8                 | 4.8                      | No            | No       |
| 36.8                     | 2.2                         | 8.0                    | 28                              | 5.8                 | 4.6                      | Yes           | Yes      |
| 12.8                     | 1.4                         | 1.0                    | 19                              | 2.5                 | –1.6                     | Yes           | No       |
| 8.8                      | 1.8                         | 1.8                    | 58                              | 7.8                 | 5.2                      | Yes           | No       |
| 8.0                      | 2.4                         | 2.4                    | 10                              | 5.8                 | 11.4                     | Yes           | No       |
| 17.1                     | 1.5                         | 1.7                    | 52                              | 4.4                 | 5.0                      | Yes           | No       |
| 39.4                     | 2.1                         | –                      | –                               | 4.5                 |–                        | Yes           | No       |
| 8.9                      | 2.1                         | 2.1                    | 22                              | 6.1                 | 8.7                      | Yes           | No       |

Dashes indicate data unable to recovered from review of patients’ electronic medical record.
Ardissino et al (6) showed that a mean increase in body weight of 12.5% due to isotonic IV fluid repletion improved CNS involvement, less need for renal replacement therapy, less intensive care support, and needed fewer days of hospitalization. Without any specific guidance in adult patients, we started patients on an aggressive fluid repletion strategy, using predominantly LR solution while in the ICU. The choice of isotonic fluid was at the discretion of the treating physicians, but most patients ended up with a mix of LR and normal saline, precluding a specific analysis of the benefits of one fluid versus another. It was evident that the patients who received more volume in the first 72 hours of admission were those with the highest mean illness severity scores and that patients with less severe disease received lesser volume within the first 72 hours of admission—with those patients with dysentery alone (i.e., those without evidence of renal or hematologic abnormalities) receiving the least volume (Fig. 5).

Aside from being a case series of adult patients with HUS, our patient population afflicted with STEC-HUS is likely somewhat unique for several reasons. The initial fluid balance of patients with STEC-HUS is an important clinical variable, and the outlying military medical clinics that initially triaged and managed these patients primarily followed an aggressive oral hydration strategy. Although the precise fluid balance of these patients at admission is not known, our patients were relatively euvoletic compared with a younger pediatric population of patients in the same clinical scenario. This was likely a consequence of the point-of-care Marine recruit training environment that was extremely supportive of hydration. Most recruits in the military are required to carry a canteen of water with them at all times to ensure adequate hydration, and Marine Corps Recruit Depot - San Diego is no exception, with the staff repeatedly reminding recruits to drink liberally.

**Figure 1.** Fluid balance (L) in the first 72 hr for patients diagnosed with Shiga toxin-producing *Escherichia coli*, stratified by those who did not develop hemolytic uremic syndrome (HUS), all hospitalized patients with HUS, and those with HUS who were critically ill (admitted or transferred to the ICU during hospital admission).

**Figure 2.** Number of Shiga toxin-producing *Escherichia coli*–associated hemolytic uremic syndrome (HUS) patients that suffered adverse hospital outcomes (i.e., need for hemodialysis, ICU admission, and mechanical ventilation).
The administration of more aggressive volume replacement was both discretionary, based on the available pediatric literature, and also representative of individual patient illness severity. Clinically relevant outcomes that were studied in this cohort of patients were the progression to HUS and the subsequent requirement of renal replacement therapy. Thereafter, the clinical courses of all hospitalized patients with STEC infection were believed to be manifestations of their disease progression and subsequent resolution with either conservative therapy or renal replacement therapy, with the aggressiveness of volume resuscitation deescalated eventually in all patients based on overall improvement.

By the end of the initial 72 hour window, the urine outputs of the sickest patients (i.e., lowest platelet counts, lowest hemoglobin levels, and highest peak creatinine values) were decreasing significantly despite achieving (or surpassing) our target of the 12–13% body weight increase with IV fluid administration. Perhaps even more importantly, nine patients exhibited evidence of hypervolemia, as manifested by radiographic evidence of pulmonary edema or pleural effusions, or clinical assessment of hypervolemia. Interestingly, the average fluid administered, as a percentage of admission body weight (kg), for patients who developed pleural effusions was 12.5%, the quantity associated with improved clinical outcomes by Ardissino et al (6). As a result, we began to reconsider our primarily aggressive fluid administration strategy. We then transitioned to a net even fluid balance strategy in these most critically ill patients and allowed the more stable patients to self-manage their fluid status through normal oral means.

One of the critically ill patients suffered flash pulmonary edema after about 72 hours of aggressive fluid administration (approximately 13% of his body weight). Although this patient’s intubation was uncomplicated, he remained difficult to oxygenate for several hours afterwards, although improved significantly over the course of the next several days. Indeed, those patients with HUS who required ICU-level care and/or renal replacement therapy, regardless of the aggressiveness of their initial volume resuscitation approach, experienced more protracted hospitalizations before ultimately recovering to discharge.

The main limitation of this study is its retrospective case series design and the above limitation of unknown hydration status prior to hospital admission. Furthermore, some data points were incomplete for the few patients initially treated at outside facilities. Ultimately, the amount of volume infused, particularly within the first 72 hours of hospital admission, was not associated with improved outcomes in our case series of adults diagnosed with STEC-HUS. The patients with the highest fluid balance totals more often required hemodialysis than those who received less fluid, which is likely a manifestation of their disease severity at presentation. However, it also suggests that early aggressive IV fluid repletion in adults with STEC-HUS may not improve clinical outcomes related to renal failure and the subsequent need for renal replacement therapy. Furthermore, the most emergent life-threatening event of the outbreak was the episode of flash pulmonary edema. This underpins the risks of aggressive IV hydration in the adult population, even among those with excellent

![Figure 3. Mean fluid administered within the first 72 hr, expressed as percentage of admission weight (kg) for patients who exhibited signs of hypervolemia—radiographic evidence of pleural effusions or pulmonary edema, or clinical assessment of hypervolemia.](image-url)
Figure 4. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and fluid administered within the first 72 hr, expressed as percentage of admission weight (kg) to patients who developed hemolytic uremic syndrome (HUS) and required hemodialysis (A), patients who developed HUS but did not require dialysis (B), and patients who were admitted with Shiga toxin-producing *Escherichia coli* (STEC) but did not develop HUS (C).
baseline health. Fortunately, there were no deaths, and all patients requiring hemodialysis had recovery of their kidney function, whereas previous studies have indicated that nearly 25% of pediatric patients with STEC-HUS have chronic renal dysfunction after recovery from infection (9).

Based on our experience during this outbreak, the aggressive IV hydration protocols (as a percentage of body weight) in the pediatric literature may not be applicable to adults. There were no signals of improved outcomes in those who received high volumes of fluids, and definite harm was identified in several cases. A more conservative fluid administration strategy in adults with HUS merits further investigation. Although the design limitations and power of this study limit any definitive recommendations regarding the optimal fluid resuscitation of adults with STEC infection at risk for development of HUS, it does offer direction for future studies. Researchers may consider randomizing hospitalized adults with STEC infection to receive fluid resuscitation in accordance with pediatric literature versus a more restrictive (< 10% of admission body weight) approach to determine the impact on such outcomes as progression to HUS and the development of the need for renal replacement therapy. Further, studies could attempt to determine the whether the type of crystalloid, such as normal saline versus LR solution, impacts these outcomes. The overall management of STEC infection, with or without progression to HUS, is centered on supportive care. As such, the optimal approach should be further investigated to supportive care in these patients to potentially reduce the development of renal failure and the requirement for hemodialysis.

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**TABLE 2.**

Seventy-Two-Hour and Overall Fluid Balance for Hospitalized Patients With Shiga Toxin-Producing *Escherichia coli* Infection

| Disease Category | 72-hr Fluid Balance (L) | Overall Fluid Balance (L) |
|------------------|--------------------------|---------------------------|
| Hemolytic uremic syndrome | 8.45 ± 3.89 | 9.02 ± 4.86 |
| Shiga toxin-producing *Escherichia coli* without hemolytic uremic syndrome | 2.68 ± 4.93 | 2.19 ± 4.88 |

Values in the table are mean fluid balance with sd.
It highlights some of the potential differences in the management of adult patients hospitalized with STEC infection compared with that of pediatric patients. Aggressive fluid administration, commonly employed for prevention of the development of hemolytic uremic syndrome in pediatric patients with STEC infection, may not be the ideal management strategy for adult patients. As such, further research is indicated to determine the optimal volume resuscitation strategy for hospitalized adults with STEC infection.

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