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ARTICLE

Predictors of Fatality in Postdiarrheal Hemolytic Uremic Syndrome

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ABSTRACT

OBJECTIVES. Describe the cause of deaths among patients with postdiarrheal hemolytic uremic syndrome (HUS) and identify predictors of death at the time of hospital admission.

METHODS. Case-control study of 17 deaths among patients with HUS identified from the Intermountain HUS Patient Registry (1970–2003) compared against all nonfatal cases.

RESULTS. Of the 17 total deaths, 15 died during the acute phase of disease. Two died because treatment was withdrawn based on their preexisting conditions, and 1 died because of iatrogenic cardiac tamponade; they were excluded from analysis. Brain involvement was the most common cause of death (8 of 12); congestive heart failure, pulmonary hemorrhage, and hyperkalemia were infrequent causes. Presence of prodromal lethargy, oligoanuria, or seizures and white blood cell count (WBC) $>20 \times 10^9$/L or hematocrit >23% on admission were predictive of death. In multivariate analysis, elevated WBC and elevated hematocrit were independent predictors. The combination of prodromal dehydration, oliguria, and lethargy and admission WBC values $>20 \times 10^9$/L and hematocrit >23% appeared in 7 of the 12 acute-phase deaths.

CONCLUSIONS. Diarrheal HUS patients presenting with oligoanuria, dehydration, WBC $>20 \times 10^9$/L, and hematocrit >23% are at substantial risk for fatal hemolytic uremic syndrome. Such individuals should be referred to pediatric tertiary care centers.

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Key Words
hemolytic uremic syndrome, prognosis, hemolytic uremic syndrome/mortality, death sudden/etiology, CNS diseases/mortality, cause of death

Abbreviations
HUS— hemolytic uremic syndrome
WBC—white blood cell count
CNS— central nervous system
TMA—thrombotic microangiopathy

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ALTHOUGH THE ETIOLOGY of the hemolytic uremic syndrome (HUS) is multifactorial, ~90% of childhood cases occur after diarrhea that is usually bloody.[1–3] Infection with shigatoxin-producing *Escherichia coli*, particularly *E coli* 0157:H7, has been clearly established as the predominant cause of postdiarrheal HUS.[4–7] HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy. Multiorgan involvement can occur resulting in life-threatening illness, long-term sequelae, and even death.[8]

Dialysis has dramatically reduced the mortality from ~21% before 1974[9] to ~4% during the mid-1980s.[10–12] Favorable outcome has been attributed to early diagnosis of the diarrheal form of the disease[13] and early supportive intervention, including careful fluid and metabolic management. Even so, there is still a paucity of information on predictors of death at the time of hospital admission that would identify those in need of early transfer and intensive support. This study was undertaken to describe the clinical characteristics, epidemiology, treatment, and course of fatal cases of HUS in the intermountain West, including cases in Utah and those referred from surrounding states (Nevada, Idaho, Montana, and Wyoming), using a large HUS registry and to identify predictors of fatal outcome at time of hospital admission.

METHODS

The Lois Joy Galler HUS Patient Registry contains data on patients with HUS cared for at the University of Utah-affiliated hospitals since 1970 and includes all of the patients from Utah and those referred from surrounding states (Idaho, Montana, and Nevada, Wyoming, Oregon, and Colorado). The registry contains information regarding epidemiology, prodrome, course of treatment, and features during hospital stay, as well information regarding long-term follow-up. This study was reviewed and approved by the University of Utah Institutional Review Board.

Variables collected at admission include serum urea nitrogen, complete blood cell count, blood smear results, symptoms, vital signs, and demographic and exposure data. The registry was queried for all of the patients <18 years old who were hospitalized with postdiarrheal HUS in Salt Lake City, UT, from 1970 to 2002. We defined HUS as the triad of thrombocytopenia (platelet count $<150 \times 10^9$/L), microangiopathic hemolytic anemia (with microscopic evidence of acute microangiopathic erythrocyte damage), and renal dysfunction, defined as a 50% serum increase in serum creatinine concentration.[12,14,15] Postdiarrheal HUS was defined as the triad after a diarrheal prodrome.[16] From the database query, 358 patients were identified who had presented with postdiarrheal HUS from 1970 to 2002.

There were a total of 17 deaths attributable to HUS from 1970 through 2003. Fifteen died during the acute phase of the disease, whereas 2 experienced delayed deaths as a result of HUS induced organ damage.

Dialysis treatment was withheld from 2 patients because of preexisting severe developmental delay and multiple neurologic deficits. One patient died as a result of hemodialyis catheter-related cardiac tamponade. These 3 patients were not included in statistical analysis.

Two patients with long-term complications of HUS died after discharge. One child never recovered renal function and had end-stage renal disease at hospital discharge; he later died of complications of chronic renal failure. The other child died 4 years after HUS, which had left him with chronic hypertension, mild (1+) proteinuria, and borderline atzotemia because of an anaphylactic reaction to a bee sting. These children were not included in the statistical analysis of predictors (Fig 1).

To determine predictors of death, we compared the 12 acute-phase deaths to all of the other cases. Prodromal, demographic, and laboratory (values on admission) variables noted previously as indicative of poor outcome[17] were analyzed. Values for acute-phase death variables were verified by chart audit. Categorical variables were analyzed by Fisher's exact tests. Because of small sample size, Mann-Whitney nonparametric tests were used to evaluate continuous data. Significance was defined as a $P < .05$. For catatgorical analysis of white blood cell count (WBC), we analyzed WBC as both above and below the median value and using 20 000 as a cutoff. Results were similar. To make the data consistent with past published data and more clinically useful, we present data using a cutoff of 20 000. All of the statistical analyses were performed using the SPSS Statistical Package (SPSS Inc, Chicago, IL) and Microsoft Excel (Microsoft, Redmond, WA).

Conditional logistic regression was used to develop a multivariate model. Variables for inclusion in the multivariate models were restricted to those with univariate $P < 0.1$.

RESULTS

Causes of Death

The 12 acute-phase fatalities ranged in age from 1.15 years to 8.6 years. The median age was 2.1 years (mean:

TABLE 1 **Cause of Death by Systemic Involvement**

Primary Causes of Death During the Acute Phase of HUS				
Brain Damage	Congestive Heart Failure	Pulmonary Hemorrhage	Hyperkalemia	Withdrawal of Support
8/14 (57%)	1/14 (7.1%)	1/14 (7.1%)	1/14 (7.1%)	2/14 (21%)

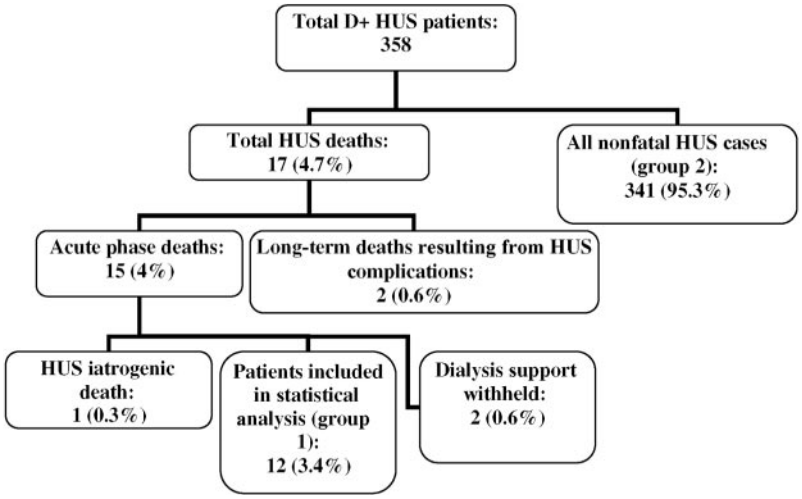

FIGURE 1
Outcome of patients with postdiarrheal HUS 1970–2003.

3.2 years). Eight (67%) of the 12 children who died were female. Figure 2 shows the total death rate analyzed by decade; patients dying from long-term complications have also been shown to calculate total death rates. The median time from admittance until death was 3 days (range: 0–12 days). Six of the 12 patients required dialysis (4 received peritoneal dialysis and 2 hemodialysis). One patient had a complicated course lasting 165 days before expiration, although this value has been removed from this description as an extreme outlier.

Autopsies were performed on 7 of the 12 acute-phase deaths. Autopsy reports were reviewed for the individuals for whom they were available; hospital and clinical charts were reviewed for patients for whom autopsy reports were unavailable. Table 1 summarizes acute causes of death by organ system.

Eight children died of disease involving the central nervous system (CNS). Brain involvement was confirmed by autopsy in 4 patients; by clinical criteria and brain computed tomography in 1; by clinical criteria, brain computed tomography, and intracranial pressure monitoring in 1; and by clinical criteria in 2. At autopsy, cerebral edema without infarction was found in 1, infarction without cerebral edema in 1, and infarction plus cerebral edema in 2, 1 of whom experienced herniation syndrome. Bowel and renal cortical necrosis were also noted in all 4 at autopsy. The child who died of congestive heart failure was found at autopsy to have thrombotic microangiopathy (TMA) of the heart muscle. Acute hemorrhagic lung involvement characterized by intraalveolar hemorrhage and fibrinopurulent exudate was found at autopsy in 1 patient. Glomerular TMA and acute tubular necrosis was also observed. The death because of hyperkalemia was associated with extensive renal cortical necrosis, hemorrhagic pneumonia, and

FIGURE 2
HUS death rates and type of fatalities by decade. Cases, death, and mortality rate in postdiarrheal HUS by decade.

TABLE 2 **Contributing Factors to Death by Organ System**

Organ System	Number of Patients	Specific Contributions to Death[a]
CNS	8	Hemorrhagic stroke (2); neuronal necrosis (2); edema (1); increased intracranial pressure (4)
Gastrointestinal	5	Colonic necrosis (3); dehydration because of gastroenteritis (2)
Cardiovascular	1	Congestive heart failure (secondary acute myocardial infarction caused by thrombotic microangiopathy)
Respiratory	5	Pulmonary arrest secondary to neurological damage (5)
Liver	2	Liver necrosis (2)
Renal	1	Renal cortical necrosis with severe hemorrhage

[a] In many cases, multiple systemic involvement was common.

widespread necrosis of the pancreas. Factors contributing to death are shown in Table 2.

Predictors of Death on Admission

Patients who died did not differ significantly in age or gender distribution from those who survived. Univariate analysis of the clinical characteristics on admission to the hospital is shown in Table 3. Compared with survivors, children who died during the acute phase were substantially more likely to have oliguria (66.7% vs 43.7%; $P = .012$), anuria (41.7% vs 20.1%; $P = .026$), edema (33.3% vs 22.8%; $P = .035$), dehydration (58.3% vs 31.3%; $P = .043$), and lethargy (91.7% vs 49.1%; $P = .016$).

Comparison of laboratory variables on admission revealed that acute-phase fatal cases had significantly higher WBCs at the time of admission to the hospital (median: 28.8×10^9/L [range = 14.2×10^9/L to 58.1×10^9/L] vs 17.9×10^9/L [range = trace to 98×10^9/L]; $P = .004$). Patients who died also had a higher mean hematocrit (median: 24.1%; range: 17–35.4%) than those who survived the acute phase of the disease (median: 18.2%; range: 6.7–43%; $P < .001$). To be sure that this unexpected finding was not because of blood transfusions before transfer to our tertiary centers (Primary Children's Medical Center, University of Utah Hospital), charts were carefully reviewed, and no evidence of blood transfusions before transport was found. There were no other statistically significant differences between laboratory data and demographic variables between the 2 groups. In multivariate analysis, only WBC $>20 \times 10^9$/L and hematocrit >23% remained in the model as independently associated with death.

DISCUSSION

Causes of Death

This study represents one of the largest clinical analyses of causes of death after postdiarrheal HUS. Other studies involving the research groups of Robson et al[18] and Dolezel et al[13] report on 4 and 9 acute-phase deaths, respectively; a larger study of 22 acute-phase deaths was performed by Sieniawska et al[19] of University Hospital (Marszalkowska, Poland), although no analysis of prognostic factors on admission was reported. A renal histopathology investigation of 18 deaths was reported recently by Inward et al[20] at Children's Hospital (Birmingham, AL), although this study did not consider possible clinical predictors. A larger study also considering pathologic markers was reported as part of the Southwestern Study Group for HUS, which considered 24 cases.[21]

Because the only tertiary renal care facilities in the intermountain west (Utah, Nevada, Idaho, Montana,

TABLE 3 **Clinical Characteristics on Admission to Hospital; Acute-Phase Fatalities Compared With Survivors**

Clinical Illness at Time of Admission	Fatal Cases ($n = 12$)	Nonfatal Cases ($n = 340$)	Relative Risk	*P*
Bloody diarrhea	10/12 (83.3)	242/340 (71.2)	1.14	0.38
Oliguria	8/12 (66.7)	148/339 (43.7)	1.79	0.012
Anuria	5/12 (41.7)	68/339 (20.1)	2.58	0.026
Fever	6/12 (50)	190/340 (55.9)	0.93	0.51
Seizures	2/5 (40.0)	4/85 (4.7)	8.5	0.034
Coma	1/12 (8.3)	3/334 (0.9)	9.36	0.13
Edema	4/12 (33.3)	77/337 (22.8)	1.35	0.35
Vomiting	10/12 (83.3)	275/340 (80.9)	1.09	0.43
Dehydration	7/12 (58.3)	106/339 (31.3)	1.91	0.043
Lethargy	11/12 (91.7)	225/340 (66.1)	1.39	0.3
WBC $>20 \times 10^9$/L	10/12 (83.3)	110/340 (32.4)	2.58	0.025
Hematocrit >23%	7/12 (58.3)	26/338 (7)	7.58	0.00045

n report/*N* with data (%).

and Wyoming) are in Salt Lake City, our study probably captured almost all of the HUS deaths from 1970 to 2003. Some children from surrounding states are referred to Seattle or Denver, so this analysis is not of a population-based cohort. It also provides the most in-depth analysis as to potential clinical predictors of death at the time of hospital admission.

In recent decades, the overall death rate in Utah has remained fairly constant at ~4%. The death rate in regions where dialysis and critical care supportive therapy is not available can approach 70%.[18] This improvement can largely be attributed to the advent and increase in availability of dialysis for infants at the beginning of the 1970s. Further declines in HUS fatality may also be attributed to early diagnosis and referral to tertiary care centers capable of treating children with complex multisystem involvement.[13,18]

Children presenting with postdiarrheal HUS often have complex multisystem disease, including large bowel, brain, cardiovascular, lung, and pancreatic involvement.[22] We found, however, that CNS involvement was the primary cause of death HUS, as has been noted by other investigators.[13,17,18,23]

It is interesting to note that at time of admission not all of the children who died had clear signs of severe CNS involvement (stroke or coma). Indeed, it was much more common for these neurologic conditions to develop later during the course of hospitalization. However, nearly all of the children who died presented with lethargy (11 of 12 [91.7%]) and later developed more severe degrees of CNS involvement (eg, severe increase in intracranial pressure, seizures, stroke, or coma). This is consistent with observations reported by Sieniawska et al.[19] In that study, however, insufficient information was available to determine the precise onset of neurologic involvement. Eriksson et al[24] of Malmo General Hospital in Sweden found electroencephalogram to be of limited prognostic usefulness, with abnormalities of the occipital and temporal regions being the most predictive of poor outcome.

Onset of CNS disturbances (particularly increased intracranial pressure and stroke) are often rapid and unexpected. In the case of an 8-year-old male, onset of increased intracranial pressure occurred at the time of discharge, and the patient expired 6 hours after transfer to the pediatric intensive care unit. In a second patient, sudden seizure-like onset of stroke also rapidly deteriorated to death. Reports of unexpected deterioration can be found in the literature; most notable is an article by Manton et al,[8] which described a similar unexpected onset of fatal increased intracranial pressure in a 4-year-old female. Exact incidence and cause of such rapid, unexpected CNS deterioration are unknown and require further study.

Cardiovascular involvement has been shown to be a substantial contributor to acute-phase mortality in other studies,[23,25–28] although it was not a significant cause of death in this study (1 of 14 [7.1%]). Other reports have described higher incidence of cardiovascular involvement, with Sieniaswska et al[19] reporting that cardiovascular disturbances (defined as a pulse rate of 140–180, the presence of arrhythmia and/or other electrocardiogram disturbances, and cardiac enlargement, which persisted after resolution of fluid overload by dialysis) were the single most important predictors of fatal outcome. These conditions (particularly irregular heart beat and electrocardiogram abnormalities) were also present in many of the acute-phase deaths included in our study (8 of 12 [66.67%]). However, they were often not seen until just prior (3 hours ± 1 hour SD)* to cardiopulmonary arrest and, thus, do not seem to represent helpful early predictors of death.

Predictors of Death

The literature provides limited information that identifies specific predictors of death, particularly at the time of hospital admission. Previous studies focused primarily on poor outcome (commonly defined as end-stage renal failure and death) and are limited primarily to an analysis of prodromal and nonlaboratory features.[13,17,22,23,26,27,29,30] The study of Havens et al[29] identifies some laboratory predictors, although these are not specific to death, but rather to all outcomes.

Because of the unpredictable nature of the disease, specific predictors of death at time of admission may help primary care providers rapidly transfer patients to tertiary care centers. It may also provide guidance for emergency department physicians to accurately triage patients to intensive care units.

The predictors of death that we identified are generally similar to predictors of poor outcome, which we have identified previously.[17] Duration of oliguria and anuria has been a predictor of other types of long-term outcome in most studies.[17,26] However, because many patients in this study died relatively early, duration of oliguria/anura did not prove to be a helpful predictor of death.

Most interestingly and perhaps counterintuitively, hematocrit >23% proved in our population to be the strongest predictor of fatal outcome (Table 3). Although the precise cause of this finding is unknown, we speculate that in those destined to die, there is widespread TMA that severely occludes microvascular blood flow, thus minimizing red blood cell fragmentation and limiting the severity of anemia. It is also possible that the comparatively higher hematocrits could reflect a more fulminant toxemic insult, with nonthrombotic cellular consequences, and the hematocrit has yet to fall, because the thrombi have yet to completely evolve. It should also be noted that the higher hematocrit may be

* Our patient with congestive heart failure has been removed from this analysis.

a surrogate marker for dehydration. Although careful analysis of dehyradation-related markers (clinical evaluation and serum urea nitrogen/creatinine ratio) appears to indicate that dehydration is not an important contributor to higher hematocrit, small numbers make it difficult to definitely rule out this possibility.

This finding is also consistent with observations made by Havens et al.[29] They found a higher hematocrit (mean: 24%; SD: 0.06%) among those more likely to have poor outcome compared with those with better prognosis (mean: 21%; SD: 6%). Poor outcome in their study was defined as children who were discharged from the hospital with focal or global neurologic defects, children requiring long-term dialysis, or individuals with hypertension requiring drug therapy, as well as fatal cases.[29] Although the higher hematocrit in the study by Havens et al[29] was not found to be statistically significant ($P > .05$), the lack of statistical significance may have been partly because of the inclusion of other outcomes in the data group. Coad et al[30] also reported that elevated hematocrit was associated with poor outcome.

Although multiple multivariate predictive models were explored, the combination of prodromal dehydration, oliguria, and lethargy with admission laboratory WBC values $>20 \times 10^9$/L and hematocrit >23% appeared in 7 of the 12 acute-phase deaths and proved to be the most predictive markers of death. Other combinations, including presence of dehydration, oliguria, and lethargy with high WBC also captured more fatal cases (8 of 12 [67.67%]) but also many more nonfatal cases (ie, more sensitive but less specific).

CONCLUSIONS

Patients with postdiarrheal HUS presenting with oligoanuria, dehydration, WBC $>20 \times 10^9$/L, and hematocrit >23% are at substantial risk for fatal HUS. Given the unpredictable nature of the disease, HUS patients should be transferred to tertiary pediatric renal care centers at the first available opportunity. In addition, even after a patient has stabilized and transferred to a nonintensive care nursing unit, the possibility of neurologic deterioration is real, and patients should still be followed closely.

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STUDY MAY SHOW TRIGGER FOR ASTHMA

"Scientists have identified a new type of immune cell in the lungs of asthma patients, a finding that could change the understanding of what triggers the disease and open new avenues of treatment. A study being published in the New England Journal of Medicine found that asthma patients' lungs had a high level of 'natural killer T' cells – which are part of the body immune system – while healthier people and those suffering from other respiratory ailments had almost none. Although a normal level of such cells is benign, too many can lead to tissue inflammation. It had been thought that a different kind of immune cell was the main culprit in asthma. Those cells, called 'helper T cells,' can cause asthma patients to be sensitive to proteins such as dust mites or pollen. The natural killer cells, on the other hand, are sensitive to a different irritant – lipid, which is essentially fat that is found in the body and in some plants and food. Practically, the findings mean doctors may have found new triggers for asthma. . . . Natural killer T cells are a normal component of the immune system, fighting infections, and in instances, preventing some autoimmune diseases. The problem occurs if a person gets too many or if the cells get activated inappropriately, releasing inflammatory agents that can lead to such things as colitis or heart disease. They aren't usually found in the lungs. . . . The researchers examined the bronchial fluid for natural killer T cells – and discovered 63% of the cells found in asthma patients contained killer T cells. By contrast, only 2% of the cells in the fluid from either controls or patients with sarcoidosis contained the cells. Dr. Dale Umetsu [of Karp Laboratories, Boston, MA] called the findings 'striking' and said they could lead to research for treatments targeting new cells. The study comes several months after another one in the Journal of Immunology found killer T cells in the blood of asthma patients, while the latest one looked at the lungs. An editorial by A. Barry Kay, from the National Heart and Lung Institute in London, in the Journal of Medicine, said . . . more research was needed to determine whether the prominence of natural killer T cells in the airway is the cause of the asthma or the result of it."

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