Postdiarrheal Hemolytic Uremic Syndrome in United States Children: Clinical Spectrum and Predictors of In-Hospital Death

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Objective To assess the clinical spectrum of postdiarrheal hemolytic uremic syndrome (D+HUS) hospitalizations and sought predictors of in-hospital death to help identify children at risk of poor outcomes.

Study design We assessed clinical variables collected through population-based surveillance of D+HUS in children <18 years old hospitalized in 10 states during 1997-2012 as predictors of in-hospital death by using tree modeling.

Results We identified 770 cases. Of children with information available, 56.5% (430 of 761) required dialysis, 92.6% (698 of 754) required a transfusion, and 2.9% (22 of 770) died; few had a persistent dialysis requirement (52 [7.3%] of 716) at discharge. The tree model partitioned children into 5 groups on the basis of 3 predictors (highest leukocyte count and lowest hematocrit value during the 7 days before to 3 days after the diagnosis of hemolytic uremic syndrome, and presence of respiratory tract infection [RTI] within 3 weeks before diagnosis). Patients with greater leukocyte or hematocrit values or a recent RTI had a greater probability of in-hospital death. The largest group identified (n = 533) had none of these factors and had the lowest odds of death. Many children with RTI had recent antibiotic treatment for nondiarrheal indications.

Conclusion Most children with D+HUS have good hospitalization outcomes. Our findings support previous reports of increased leukocyte count and hematocrit as predictors of death. Recent RTI could be an additional predictor, or a marker of other factors such as antibiotic exposure, that may warrant further study. *(J Pediatr 2015;166:1022-9)*.

The clinical course of children hospitalized for postdiarrheal hemolytic uremic syndrome (D+HUS) varies, ranging from short stays with minimal therapeutic interventions to complex intensive care for multiorgan system failure. Information on the frequency of various complications and outcomes of acute D+HUS hospitalizations may help inform patients and their families and aid in estimating the societal burden of Shiga toxin–producing *Escherichia coli* (STEC) infections.

In addition, the identification of factors present at or near the time of hospital admission that are predictive of in-hospital death could aid in the early triage of children at greatest risk of poor outcomes to tertiary-care hospitals able to provide the highest level of care and monitoring.[1] Previously identified predictors of D+HUS-related in-hospital death include marked leukocytosis[1-3] and greater hematocrit or hemoglobin values.[1-4] Studies that explore how these and other factors interact are lacking and clinical profiles predictive of death have not been well defined.

We analyzed data collected during 15 years of active, population-based surveillance of pediatric D+HUS in selected states to describe the clinical spectrum of hospitalizations, identify predictors of in-hospital death, and, through the use of recursive partitioning, explore how these factors interact.

Methods

A confirmed case of D+HUS was defined as illness in a child (<18 years old) with: (1) a diagnosis of hemolytic uremic syndrome (HUS) made within 21 days after the onset of self-reported or parent/guardian-reported diarrhea; (2) anemia (hemoglobin or hematocrit below age- and sex-specific thresholds);

D+HUS	Postdiarrheal hemolytic uremic syndrome
FoodNet	Foodborne Diseases Active Surveillance Network
HUS	Hemolytic uremic syndrome
RTI	Respiratory tract infection
STEC	Shiga toxin–producing *Escherichia coli*
WBC	White blood cell

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(3) thrombocytopenia (platelets $<150 \times 10^3/\mu L$ [150×10^9/L]); (4) azotemia (serum creatinine $\geq$1.0 mg/dL [88.4 μmol/L] if <13 years, $\geq$1.5 mg/dL [132.6 μmol/L] if $\geq$13 years); and (5) red cell fragmentation. A probable case met all criteria except documented red cell fragmentation.[5] We analyzed cases reported from January 1, 1997, through December 31, 2012. We excluded D$^+$HUS cases with laboratory evidence of *Streptococcus pneumoniae* infection, a known cause of HUS. Day 1 of illness was defined as the day diarrhea began.

The Foodborne Diseases Active Surveillance Network (FoodNet) sites (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York) conduct active population-based surveillance for pediatric D$^+$HUS. Sites began surveillance between 1997 and 2004 by establishing a network of pediatric nephrologists and hospital infection control practitioners. FoodNet personnel routinely contacted network members to identify cases. To augment case finding, all FoodNet sites except New Mexico reviewed hospital discharge databases annually for hospitalizations assigned *International Classification of Disease, Clinical Modification* codes suggestive of D$^+$HUS.[5]

FoodNet personnel completed a report form for each case by interviewing treating physicians, abstracting medical records, or both. Data collected included: (1) selected comorbidities present during the 3 weeks before the diagnosis of D$^+$HUS was made (eg, pre-existing kidney disease, acute illnesses); (2) microbiologic findings; (3) selected laboratory measures; and (4) selected information on in-hospital treatment and complications. Data used in this analysis were collected as part of routine public health surveillance. The Centers for Disease Control and Prevention Institutional Review Board approved the secondary analysis of this surveillance data. The requirement to obtain informed consent was waived by the institutional review board.

The primary outcome evaluated was all-cause in-hospital death. For each death, we queried state and local vital records departments for all reported causes of death reported on death certificates. We then excluded reported causes of death that were a component of the D$^+$HUS case definition. To further describe the spectrum of hospitalizations, we assessed the frequency of in-hospital transfusions and dialysis and the frequency of continued dialysis requirement at time of hospital discharge.

Seventeen variables were selected as candidate predictors of in-hospital death on the basis of existing literature, biologic plausibility, and to assess for geographical variation. Five candidate laboratory predictors included the greatest (serum creatinine, blood urea nitrogen, peripheral white blood cell [WBC] count) or lowest (platelet count, hematocrit) value observed during the 7 days before to 3 days after the date of HUS diagnosis. These 5 laboratory measurements, along with patient age and duration from diarrhea onset to hospitalization, were treated as continuous variables. The remaining candidate predictors were treated as categorical variables and included sex, type O blood, bloody stools, illness during June through September, treatment of the prodromal diarrheal illness with antibiotics, respiratory tract infection (RTI) during the 3 weeks before HUS diagnosis, urinary tract infection during the 3 weeks before HUS diagnosis, the type of STEC infection identified (STEC O157 vs non-O157), seizure occurring on or before day 7 of illness, and state of residence. Information on recent RTI was collected by interviewing the attending physician or through abstracting medical records; the specific symptoms comprising an RTI were not strictly defined.

Information on several candidate predictors was missing for <10% of children. More than 10% of children did not have information on hematocrit (11.4%) or blood type (17.4%). The 88 patients with no reported hematocrit all had hemoglobin values reported; for these patients, we estimated the missing hematocrit value through a linear regression model calibrated based on 578 patients with data reported for both hematocrit (dependent variable) and hemoglobin (independent variable): hematocrit = 4.22 + 2.26*(hemoglobin in g/dL); *P* value for hemoglobin measurement <.0001, $R^2 = 0.62$ (eg, this equation would convert a hemoglobin concentration of 8 g/dL to a hematocrit of 22). Laboratory findings that we could not include as candidate predictors because of large amounts of missing data were serum amylase, proteinuria, and hematuria.

We performed univariable analyses to assess for differences between groups with different outcomes by using the Wilcoxon rank-sum test for continuous variables and the Fisher exact test for categorical variables. To quantify effect size of univariable associations, exact ORs were calculated for all variables; for this calculation, continuous variables were categorized by their median or quartile values.

A conditional inference tree, a type of recursive partitioning model,[6] was used to identify clinical profiles of the risk of death. It classified patients into groups, or nodes, with differing probabilities of in-hospital death. Profiles were developed by selecting the best candidate predictors to split the parent node into 2 daughter nodes with maximal discrepancy in class frequency based on a permutation statistical test found within the party package in R.[6,7] The candidate predictor variable selected to split a given group was the candidate predictor with the smallest *P* value for the association with death among patients within that group.[6] The process stopped when no significant association was found between death and any candidate predictor based on a Bonferroni-adjusted level of significance of .05 or the prespecified minimum group size (set to 25 cases) was reached. The recursive process could select the same variable or different values of the same variable to partition different groups. When the cases had missing information for the splitting variable, up to 3 surrogate variables were used for splitting, which generated a similar partition as the missing splitting predictor did.[6] For tree-building, only predictors with a two-tailed significance level of less than 0.2 by univariable analyses were included.

The dataset was unbalanced, with fatal cases accounting for <3% of all cases. Therefore, to increase utility of the model as a tool for identifying predictors related to increased

probability of death, differential weights were applied so that fatal cases weighed 5 times as much as nonfatal cases during the tree-building process.

To quantify differences in the risk of death among patients with different clinical profiles, we calculated ORs for children in each terminal node (ie, a group that was not further partitioned). We defined the referent profile as the terminal node with the lowest proportion of fatal cases. We did not calculate CIs because available methods do not account for the uncertainty introduced by the conditional nature of the model partitions.

To further explore the association between recent RTI and in-hospital death, we assessed the frequency of death and recent RTI among the patients excluded because of evidence of *S pneumoniae* infection. In addition, we assessed the association between recent RTI and laboratory evidence of infection with STEC and, for cases occurring during 2004-2012, the association between recent RTI and antibiotic treatment for indications other than diarrhea during the 3 weeks before HUS diagnosis (this information was not collected before 2004).

Results

We identified 783 cases of D^+HUS; 13 (1.6%) had laboratory evidence of *S pneumoniae* infection, but no evidence of STEC infection, and were excluded. Of the remaining 770 cases (641 confirmed, 129 probable), the median age of children was 3.7 years (range 2.3 months to 17.8 years), and 56% were female. The median time to hospitalization was day 5 of illness (IQR 3-7) and the median time to diagnosis of HUS was day 7 of illness (IQR 5-8).

During hospitalization, 430 (56.5%) of 761 children required dialysis, 698 (92.6%) of 754 required a transfusion (685 [91.0%] of 753 received red blood cells, 296 [40.0%] of 740 received platelets, 61 [8.4%] of 723 received fresh frozen plasma), and 22 (2.9%) children died. The median time of in-hospital death was day 10 of illness (IQR 8-14 days). Death certificate records were obtained for 17 of 22 in-hospital deaths; of these, 13 contained contributing factors other than criteria used to define D^+HUS. More than one-half of these patients had a cause of death related to the central nervous system (Table I). At time of discharge 52 (7.3%) of 716 required ongoing dialysis. These clinical characteristics did not differ significantly between children with confirmed and probable D^+HUS: in-hospital dialysis (57.7% of confirmed cases vs 50.4% of probable cases, $P = .14$), red cell transfusions (91.2% vs 89.6%, $P = .61$), or persistent dialysis requirement (7.6% vs 5.7%, $P = .57$). Similarly, in-hospital death did not differ significantly (3.1% of confirmed cases vs 1.6% of probable cases, $P = .56$). The median duration of hospitalization was significantly shorter for children who did not require dialysis (9 days) than for children who did (17 days, $P < .0001$).

In univariable analyses, the following factors were associated with increased risk of death at a significance level <0.2: younger age, bloody stools, recent RTI, greater WBC count, greater hematocrit value, shorter duration from diarrhea onset to initial medical presentation, and seizures occurring on or before day 7 of illness (Table II). Of these factors, recent RTI and shorter duration to presentation had the smallest effect sizes; greater WBC count and seizures had the largest (Table II). These 7 factors were used as candidate predictors for conditional inference tree-building.

The unweighted tree model contained 2 partitions, both by WBC count (Figure 1), resulting in 3 groups of children. The probability of in-hospital death increased with increasing maximum WBC count as follows: WBC ≤25 400/μL (25.4×10^9/L) (0.7% probability of death, OR = 1), WBC >25 400/μL and ≤41 900/μL (41.9×10^9/L) (n = 571, 5.8% probability, OR 8.7), WBC >41 900/μL (n = 155, 20.5% probability, OR 37).

The weighted tree model, with fatal cases weighted 5 times greater than nonfatal cases, contained 4 partitions: the same 2 partitions by WBC as in the unweighted tree in addition to 1 by hematocrit value, and 1 by recent RTI, resulting in 5 groups of children (Figure 2). Each of the 5 groups represented a distinct clinical profile with varying likelihood of in-hospital death. The largest group identified (Group 4) had the lowest odds of death

Table I. Causes of death for 13* patients with specific contributors to death recorded on death certificates other than those included in our D^+HUS case definition

Causes	No. of patients	Specific contributions to death (not included in D^+HUS case definition)†,‡
Central nervous system	7	Cerebral edema (2 patients), brain death (2 patients), cerebral herniation, cerebral infarct with diffuse edema, intracranial hypertension, unspecified encephalopathy, cerebral vasculitis, neurodevelopmental delay
Gastrointestinal	4	Acute vascular disorders of intestine, vascular insufficiency of intestine, noninfective gastroenteritis and colitis unspecified, bacterial intestinal infection, *E. coli* enterotoxin
Infectious	3	Sepsis (2 patients), septic shock, bacterial infection of unspecified site
Renal	2	Hyperkalemia (2 patients)
Hematologic	2	Hereditary hemolytic anemia, unspecified, coagulopathy
Cardiovascular and respiratory	2	Arrhythmia, pulmonary hemorrhage caused by intrathoracic hemorrhage

*Death certificates were obtained for 17 of the 22 children who died in the hospital; for 4, only causes included in our D^+HUS cases definition were listed: acquired hemolytic anemia (3 patients), and thrombotic thrombocytopenic purpura in a patient with bloody diarrhea reported.
†In 12 of 13 children, more than 1 cause (range, 2-5) was reported.
‡The following diagnoses included in our D^+HUS case definition that were reported as additional contributors to these 13 deaths were: HUS (9 patients), acquired hemolytic anemia, nonautoimmune hemolytic anemia, thrombotic angiography, thrombocytopenia, acute kidney failure, and unspecified kidney failure.

Table II. Associations between candidate predictors and in-hospital death in pediatric D$^+$HUS

Candidate predictors	Frequency of death, %	OR	*P* value*
All patients (n = 770)	2.9		-
Diarrhea onset during June-September			.51
No (n = 306)	2.3	Reference	
Yes (n = 464)	3.2	1.4 (0.54-4.2)	
Sex			.99
Male (n = 339)	3.0	1.1 (0.41-2.7)	
Female (n = 431)	2.8	Reference	
Age, y			.10†
0 to <2 (n = 168)	5.4	4.2 (0.85-41)	
2 to <4 (n = 251)	2.8	2.1 (0.40-21)	
4 to <7 (n = 151)	1.3	Reference	
7 to <18 (n = 200)	2.0	1.5 (0.21-17)	
Bloody stool			.03
No (n = 130)	0	Reference	
Yes (n = 623)	3.5	6.7 (1.5-∞)‡	
Treatment of prodromal diarrhea with antibiotics§			.99
No (n = 516)	3.1	Reference	
Yes (n = 188)	2.7	0.85 (0.24-2.5)	
RTI§			.19
No (n = 690)	2.5	Reference	
Yes (n = 57)	5.3	2.2 (0.40-7.9)	
Urinary tract infection§			.51
No (n = 730)	2.7	Reference	
Yes (n = 25)	4.0	1.5 (0.03-10)	
Blood type O			.99
No (n = 330)	3.0	Reference	
Yes (n = 306)	3.3	1.1 (0.40-2.9)	
Highest serum creatinine, mg/dL¶,**			.60†
<3.3 (n = 381)	2.1	Reference	
≥3.3 (n = 389)	3.6	1.7 (0.67-4.8)	
Highest blood urea nitrogen, mg/dL¶,††			.56†
<76 (n = 372)	3.2	Reference	
≥76 (n = 392)	2.6	0.79 (0.30-2.0)	
Lowest hematocrit, %¶,‡‡			.006†
<20% (n = 402)	1.2	Reference	
≥20% (n = 368)	4.6	3.8 (1.3-13)	
Lowest platelet count, $\times 10^3/\mu$L¶,§§			.23†
<32 (n = 375)	2.1	Reference	
≥33 (n = 395)	3.5	1.7 (0.65-4.7)	
Highest leukocyte count, /μL¶,¶¶			<.0001†
<13 300 (n = 187)	0	Reference	
13 300-17 700 (n = 184)	0.5	1.0 (0.05-∞)‡	
17 800-24 200 (n = 192)	1.0	2.4 (0.28-∞)‡	
≥24 300 (n = 188)	9.6	28 (6.0-∞)‡	
Time from diarrhea onset to hospitalization, d			.03†
<4 (n = 310)	4.2	2.2 (0.85-5.9)	
≥4 (n = 459)	2.0	Reference	
Seizure occurring on day 7 of illness or earlier			.002
No (n = 735)	2.2	Reference	
Yes (n = 23)	17	9.4 (2.1-33)	
Type of STEC detected			.74
STEC 0157 (n = 512)	3.3	1.6 (0.56-5.5)	
Non-0157 STEC (n = 23)	0	1.5 (0.0-8.6)‡	
No STEC detected (n = 235)***	2.1	Reference	
State			.46
California	0		
Colorado	1.9		
Connecticut	1.7		
Georgia	2.8		
Maryland	0		
Minnesota	1.9		
New Mexico	0		
New York	6.9		
Oregon	3.6		
Tennessee	5.2		

*Except where indicated, *P* values are based on the 2-tailed Fisher exact test.
†*P* value based on the 2-tailed Wilcoxon rank-sum test.
‡Median unbiased estimate.
§During the 3 weeks before diagnosis of HUS.
¶During the 7 days before to 3 days after diagnosis of HUS.
**To convert to μmol/L, multiply by 88.4.
††To convert to mmol/L, multiply by 0.357.
‡‡To convert to proportion of 1.0, multiply by 0.01.
§§To convert to $\times 10^9$/L, multiply by 1.
¶¶To convert to $\times 10^9$/L, multiply by 0.001.
****Shigella dysenteriae* type 1 was isolated from 1 child.

(n = 533 patients, 3 deaths, 0.6% probability of death, OR 1). The tree identified 3 greater risk clinical profiles in which the odds of death were at least 4-fold greater than that observed in Group 4. These were: (1) WBC count >41 900/μL (Group 1, n = 44, 9 deaths, 20.5% probability of death, OR 45); (2) WBC count 25 400-41 900/μL and hematocrit >19.6% (0.196) (Group 2, n = 86, 8 deaths, 9.3% probability of death, OR 18); and (3) WBC ≤25 400/μL and recent RTI (Group 5, n = 37, 1 death, 2.7% probability of death, OR 4.9).

Although no children with nonbloody stools died, the presence or absence of bloody stools was not identified by the model as a predictor of death. Children with nonbloody stools had significantly lower WBC counts (median 14 900/μL [14.9 × 10^9/L]) than children with bloody stools (median, 19 100/μL [19.1 × 10^9/L]; $P < .0001$). Furthermore, children with nonbloody stools had significantly lower hematocrit values (median, 18.7 [0.187]) than children with bloody stools (median, 20 [0.2]; $P = .002$).

Although the presence of seizure on or before the seventh day of illness was associated with death in univariable analysis, the model did not identify it as a predictor of death. Compared with children without early seizure, children with early seizure tended to have greater WBC counts (median 20 100/μL vs 18 000/μL; $P = .08$) and greater hematocrit values (median 21.7 vs 19.7; $P = .11$).

The 13 children excluded because of *S pneumoniae* infection were more likely to die during hospitalization than were the 770 children included in the analysis (15.4% vs 2.9%, $P = .009$). Children with *S pneumoniae* infection also were more likely to have had a recent RTI than were children included in our analyses (75% [9 of 12] vs 7.6% [57 of 747]). Six of the 13 children with *S. pneumoniae* infection had bloody diarrhea in the 3 weeks before HUS diagnosis, 5 had nonbloody diarrhea, and data were missing for 2 patients.

Among the 770 children, a smaller percentage of patients with recent RTI (59.6%) had laboratory evidence of STEC infection compared with patients without recent RTI (71.3%) ($P = .07$). Among the 502 children with HUS during 2004-2012, those with recent RTI were more likely than those

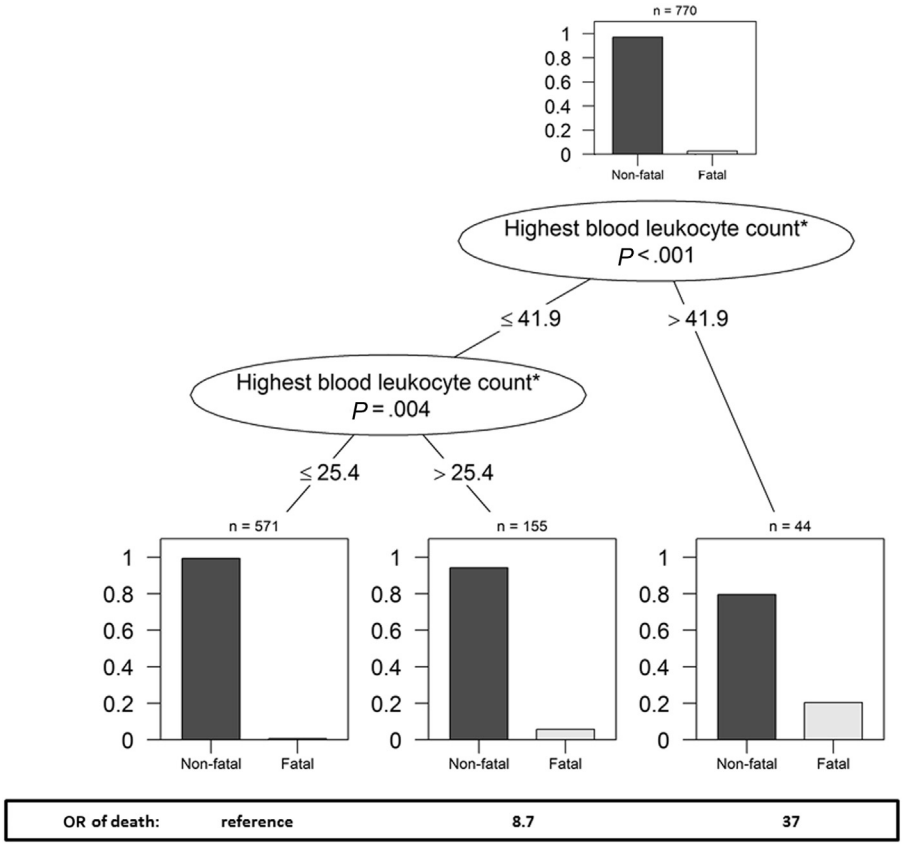

Figure 1. Unweighted classification of in-hospital death among 770 children with D+HUS. The Y-axis of the bar plots above the root node and in the 3 terminal nodes is the outcome probability; *black bars* indicate nonfatal outcome and *light gray bars* indicate death. *During the 7 days before to 3 days after diagnosis of HUS; blood leukocyte counts shown in units of $\times 1000/\mu L$.

without recent RTI to have been treated with antibiotics for indications other than diarrhea during the 3 weeks before HUS diagnosis (32.3% [10 of 30] vs 10.5% [43 of 408], $P = .001$). The one child who died in Group 5 (**Figure 2**) had STEC infection but was treated with an antibiotic for an indication other than diarrhea during the 3 weeks before HUS diagnosis.

Discussion

Through the analysis of surveillance data, we described a population-based spectrum of pediatric D+HUS hospitalization severity. Our tree-based model identified several clinical profiles associated with a greater probability of in-hospital death. The model substantiates leukocytosis and greater hematocrit as predictors of poor outcome in children with D+HUS. In addition, we identified a possible association between recent RTI and death during hospitalization for D+HUS. Like others, we identified central nervous system complications as the most common contributing factors to in-hospital death.[1]

Past observational studies have identified leukocytosis[1-3,8-13] and greater hematocrit or hemoglobin,[1,2,4,8,12,14] as predictors of death and other poor outcomes in children with D+HUS. Our analyses of a large dataset using tree models confirm these findings. Because observational studies are prone to finding false associations,[15] the reproducibility of findings in different observational studies improves scientific evidence.[16] Similar to others who have found a dose-response relationship between degree of leukocytosis in children with STEC O157 infections and the likelihood of developing D+HUS,[17] we found an association of increasing WBC count with increased probability of death.

The association between greater hematocrit and poor D+HUS outcomes likely reflects dehydration. Others have identified dehydration and higher hematocrit values at time of hospital admission as predictive of in-hospital dialysis requirements among children with D+HUS.[18] In another study, the only factor associated with prolonged incomplete recovery of renal functions (median duration of follow-up of >7 years) was dehydration at time of admission.[19] A causative role of early dehydration as a predictor of poor outcomes is further supported by observational studies showing that intravenous volume expansion within 4 days of diarrhea onset is associated with nephroprotection in children who go on to develop D+HUS[20,21]; clinical reviews are available that describe the approach to volume expansion used in these studies.[22,23]

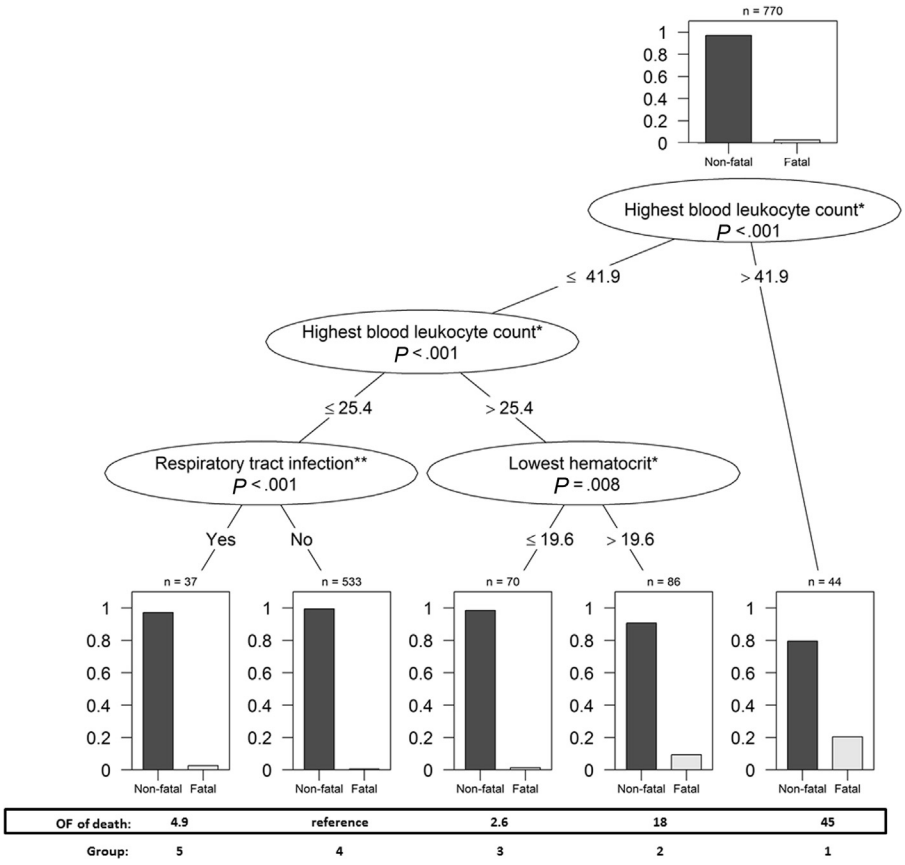

Figure 2. Weighted classification of in-hospital death among 770 children with D+HUS. Fatal cases were weighted 5 times greater than nonfatal cases. The Y-axis of the bar plots above the root node and in the 5 terminal nodes is the outcome probability; *black bars* indicate nonfatal outcome, and *light gray bars* indicate death. *During the 7 days before to 3 days after diagnosis of HUS; blood leukocyte counts shown in units of $\times 1000/\mu$L. **During the 3 weeks before diagnosis of HUS.

The association we identified between recent RTI and death may be explained by several factors. First, it may be related to a small burden of D+HUS caused not by STEC, but rather by *S pneumoniae* (ie, pneumococcus-associated HUS). Pneumococcus-associated HUS can be preceded by a bloody or nonbloody diarrheal illness, and the HUS typically is more severe than STEC-associated HUS.[5,24] The fact that a smaller percentage of children with recent RTI had laboratory evidence of STEC infection than did children without recent RTI suggests that pneumococcus or another etiology other than STEC infection may have caused some D+HUS. Thus, although not directly supported by our findings, suspicion of and testing for *S pneumoniae* infection among children presenting with D+HUS, especially those with recent RTI (even those with bloody stools) may help identify patients at risk for poor outcomes including death. Second, antibiotics used to treat RTI or other conditions may increase the likelihood of poor outcome of STEC infection acquired during or soon after the treatment. Antibiotics may alter intestinal flora in a way that leads to severe STEC infection[25] or, if present at subtherapeutic levels at the onset of STEC infection, could increase release of Shiga toxin.[26] Others have identified antibiotic use during the 4 weeks before onset of STEC O157 diarrhea as a predictor of D+HUS.[27] The 1 child in group 5 with an RTI who died had evidence of STEC infection, making an unrecognized *S pneumoniae* infection unlikely. However, this child had been treated recently with an antibiotic for an indication other than diarrhea. Finally, RTI may have only been associated incidentally with death, or correlated with other causal factors such as underlying immune function. Even if recent RTI is truly associated with death, the effect size is very small relative to WBC count and hematocrit. The absence of an RTI should not be interpreted as predictive of a benign clinical course.

All patients without bloody stools survived. Although our tree models did not identify bloody stools as a predictor of in-hospital death, likely because of association of bloody stools with both WBC count and hematocrit, the absence of bloody stools could serve as a simple clinical marker of less severe disease. However, children with D+HUS often initially present with nonbloody diarrhea that may quickly turn bloody by day 2 or 3 of illness. Because early volume expansion may reduce the risk of anuria,[20,21] early diagnosis of STEC infections is necessary. Therefore, all stool specimens

submitted for bacterial testing to clinical laboratories from patients with community acquired diarrhea, even if non-bloody, should be promptly cultured for *E coli* O157 and assayed for Shiga toxins.[5,28]

Likewise, although our tree models did not identify early seizures as a predictor of in-hospital death, seizures occurring on or before the seventh day of illness are strongly associated with in-hospital death. Others also have found early seizures to be significantly associated with increased risk of in-hospital death in univariable analyses but not in multivariable models.[1] This finding suggests that early seizures are correlated with other predictors of death, including WBC count and hematocrit.

Our study has several limitations. Identifying predictors of clinical outcomes is not a primary objective of our D^+HUS surveillance,[5] which does not collect detailed clinical information specific to initial medical presentation. For example, because our surveillance does not collect the specific date of certain laboratory values observed during the 7 days before to 3 days after HUS diagnosis, it is not possible to associate the laboratory predictors of in-hospital death that we identified with a specific day of illness. Despite this limitation, our laboratory predictor findings are consistent with findings by other researchers who were able to apply time specification.[1] Therefore, we think that our use of a relatively wide time window for assessment was reasonable. Furthermore, it is possible that other predictors were not assessed; this, coupled with the fact that a very small percentage of patients died, limited our ability to build a model to predict fatal cases in the early stages of D^+HUS. In addition, our inclusion of probable D^+HUS cases may have resulted in misclassifying some illness as D^+HUS. Although we did not observe statistically significant clinical differences between confirmed and probable cases, a smaller percentage of probable cases required dialysis, suggesting the probable cases may have had less severe illness. However, the overall dialysis percentage we observed (57% of all patients) is very similar to the 61% reported by researchers that did not include a probable case definition.[29] Finally, our surveillance form does not specify criteria to define RTI, which introduces uncertainties about the generalizability of the RTI findings.

Our tree-based models provide important information about clinical profiles associated with in-hospital death. Tree-based models are useful for exploring interactions among predictors of a clinical outcome. For example, our data suggest that recent RTI may be an important predictor of death among patients without extreme leukocytosis, which suggests that the mechanism by which recent RTI may influence HUS severity differs from that underlying the well-established association with leukocytosis. Although our findings are inadequate for clinical decision-making, our approach could be applied with more detailed clinical measures to develop a predictive tool for D^+HUS outcomes. ■

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