

ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease and Hypertension

Non-Enteropathic Hemolytic Uremic Syndrome: Causes and Short-Term Course

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● **Background:** Nondiarrheal or *Streptococcus pneumoniae*-related hemolytic uremic syndrome (HUS) represents a heterogeneous group of disorders. This study was performed to: (1) describe the current incidence, causes, demographic features, hospital courses, and short-term outcomes of non-enteropathic HUS; (2) compare findings in patients with non-enteropathic HUS with those obtained from a contemporaneous cohort of children with enteropathic or diarrhea-associated HUS (D⁺ HUS) diagnosed and treated at the same clinical sites; and (3) identify clinical or laboratory features that differentiate these 2 groups and predict disease severity and the short-term outcome in patients with non-enteropathic HUS. **Methods:** Data were collected from patients screened between 1997 and 2001 for enrollment in a multicenter trial of SYNSORB Pk (SYNSORB Biotech Inc, Calgary, Alberta, Canada) in D⁺ HUS, but who were ineligible because of lack of a diarrhea prodrome. The following features were recorded: age; sex; ethnicity; prodromal symptoms; cause; nadir values for hemoglobin, hematocrit, and platelet count; use of dialysis; and length of hospitalization. **Results:** Twenty-seven of 247 children with HUS had non-enteropathic HUS (11%). Twenty-four patients (15 boys, 9 girls), whose medical records were complete and available for review, comprise the study cohort. Mean age at onset was 4.2 ± 0.9 (SE) years. Infection caused by *S pneumoniae* was diagnosed in 9 patients (38%). Dialysis was performed in 17 patients (71%) for 40 ± 27 days. Median length of hospitalization was 22 days (range, 2 to 71 days). Children with *S pneumoniae*-related HUS had a longer hospital stay than those with other causes of non-enteropathic HUS, but all patients with *S pneumoniae*-related HUS recovered kidney function. Dialysis therapy was required more often (17 of 24 versus 59 of 145 children; *P* = 0.025) and hospital stays were longer (median, 22 versus 9 days; *P* = 0.002) in children with non-enteropathic HUS compared with patients with D⁺ HUS who were enrolled in the SYNSORB Pk clinical trial. **Conclusion:** (1) The incidence of non-enteropathic HUS is approximately one tenth that of D⁺ HUS; (2) patients with non-enteropathic HUS require dialysis therapy more often and are hospitalized more than twice as long during the acute episode compared with those with D⁺ HUS; (3) infection caused by *S pneumoniae* accounts for nearly 40% of cases of non-enteropathic HUS; and (4) although *S pneumoniae*-related HUS is associated with a less favorable short-term course than other types of non-enteropathic HUS or D⁺ HUS, the long-term prognosis for recovery of renal function appears to be good in these patients. *Am J Kidney Dis* 43:976-982.

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HEMOLYTIC uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Most cases are caused by an antecedent infection with Shiga toxin-producing strains of *Escherichia coli* (STEC), predominantly *E coli* serotype O157:H7. Although the term STEC-related HUS is probably most appropriate in the majority of these episodes, it often is difficult in clinical practice to confirm STEC enteritis at the onset of HUS. This unfortunate circumstance has hindered widespread adoption of the label STEC-HUS. Instead, these cases currently are still classified as enteropathic or diarrhea-related HUS (D⁺ HUS).¹ Forty percent to 50% of children with D⁺ HUS require temporary dialysis support. D⁺ HUS is a multisystem

disease with substantial morbidity and extrarenal complications, especially involving the neurological and cardiovascular systems. The mortality rate during the acute phase is 3% to 5%, and an undetermined number of patients develop long-term sequelae.¹⁻³

HUS can be caused by infectious agents other than STEC and may be associated with malignancies, medications, and autoimmune disorders, and it can occur sporadically or in families.⁴ Atypical nondiarrheal HUS is less common than D⁺ HUS.^{5,6} We propose the term non-enteropathic HUS to categorize these heterogeneous forms of HUS. The incidence, optimal treatment, and prognosis of these rare conditions are unknown.

Most reports on non-enteropathic HUS emanate from a single center or a relatively small number of clinical sites.^{7,8} Many multicenter reports have been from registries or have focused on a single genetic cause of the disease.^{9,10} This may limit the general applicability of the findings. For the present report, all patients with newly diagnosed HUS were screened as part of a multicenter trial of SYNSORB Pk (SYNSORB Biotech Inc, Calgary, Alberta, Canada) in the treatment of D⁺ HUS.¹¹ The cohort of children with non-enteropathic HUS identified during the course of this clinical trial constitutes the subject of this report. Although many previous publications have described groups of patients with non-enteropathic HUS, this report is unique because it describes all children with non-enteropathic HUS who were diagnosed at the same time because all cases of D⁺ HUS were being documented by a geographically large network of clinical sites.

In view of this, the aims of this study are to describe the incidence, causes, demographic features, clinical courses, and short-term outcomes of patients with non-enteropathic HUS and compare this group with a well-defined contemporaneous cohort of children with prototypical D⁺ HUS who were enrolled in the SYNSORB Pk trial.¹¹ Attempts were made to identify clinical or laboratory features that could distinguish between the 2 groups and predict disease severity and short-term outcomes of patients with non-enteropathic HUS.

METHODS

Patients

All children with HUS, defined as anemia with fragmented erythrocytes, platelet count less than $140,000 \times 10^9/L$, and evidence of renal injury (azotemia, hematuria, and proteinuria) who were screened between 1997 and 2001 for participation in The National Institutes of Health-sponsored multicenter trial of SYNSORB Pk and who were excluded because they did not have diarrhea within 7 days of the onset of HUS were eligible for inclusion in this study. Two hundred forty-seven cases of HUS were identified during the 4-year study period. There were 220 children with D⁺HUS. Of these patients, 37 eligible subjects declined, 7 others were not offered the opportunity to participate, 26 patients did not satisfy the specific entry criteria for the SYNSORB Pk clinical trial, and 5 patients withdrew after being administered 1 or fewer dose of study medication, leaving 145 patients in a modified intent-to-treat group. Twenty-seven children had non-enteropathic HUS; the 24 patients with complete medical records available for review are the subject of this report.

Clinical Survey

A questionnaire was sent to the investigators at the participating centers who identified children with non-enteropathic HUS during pre-enrollment screening. Patients included in this series were evaluated at the following participating centers: Schneider Children's Hospital of Long Island Jewish Medical Center (New Hyde Park, NY), Duke University (Durham, NC), North Shore University Hospital (Manhasset, NY), Wake Forest University Medical Center (Winston-Salem, NC), Columbus Children's Hospital (Columbus, OH), University of Alberta, (Calgary, Alberta), Medical College of Virginia (Richmond, VA), Westchester Medical Center (Valhalla, NY), University of Virginia Medical Center (Charlottesville, VA), Robert Wood Johnson Medical School (New Brunswick, NJ), The Children's Hospital of Philadelphia (Philadelphia, PA), Children's Hospital of Denver (Denver, CO), and A.I. DuPont Children's Hospital (Wilmington, DE). Demographic data were tabulated, including age, sex, ethnicity, previous episodes of HUS, and a family history of HUS. Signs and symptoms that occurred before the diagnosis of HUS, duration of symptoms before hospitalization, any site of infection, and microbial organisms identified were recorded. Data on the course of non-enteropathic HUS, specifically, nadir values for hemoglobin, hematocrit, and platelet count; number of transfusions (erythrocyte and/or platelet); and renal replacement therapy (type and duration of dialytic therapy) were tabulated. Information about urine output and duration of oligo-anuria in individual patients was unavailable for review. Finally, the occurrence of other extrarenal complications, such as pancreatitis, diabetes mellitus, liver dysfunction, neurological symptoms, hypertension, cardiac involvement, and duration of hospitalization, was recorded.

Statistical Methods

Incidence, sex, time of year, need for dialysis therapy, need for transfusion, and presence of serious extrarenal

complications are summarized by frequencies and compared across groups by means of Fisher's exact test. Age, duration of hospitalization, and platelet count nadir are summarized by median and range and compared by using Wilcoxon's rank-sum test because they are skewed. Nadir hematocrit value is summarized by mean \pm SEM and compared by means of a *t*-test. *P* of 0.05 is considered significant. Because the aim of this study is descriptive and hypothesis generating, no correction for multiple comparisons was applied.

The sample size for the clinical trial with D⁺ HUS was based on the ability to detect differences between 2 treatment groups. The sample size for this study was based solely on the number of cases identified with non-enteropathic HUS while the clinical trial was ongoing. The obtained sample size of 24 is large enough to detect 60% differences in proportions within subgroups with non-enteropathic HUS and large enough to detect 30% differences between the non-enteropathic HUS and D⁺ HUS groups at the level of *P* less than 0.05. However, comparisons between patients with D⁺ HUS and those with nonenteropathic HUS were corrected for multiple outcomes by using a Bonferroni correction, and *P* less than 0.004 is considered statistically significant.

RESULTS

Demographic Data and Epidemiological Findings

During the 4-year study period (1997 to 2001), non-enteropathic HUS was diagnosed in 27 children. Of 24 patients with complete documentation, 17 were white, 2 were black, 2 were Asian-Pacific Islander, 1 was Native American, and 2 were other, an ethnic distribution similar to that observed for children in the general population. There were 15 boys and 9 girls (boy-girl ratio, 1.7:1). Age at onset ranged from 4 months to 15 years, with a median of 2 years. One patient had experienced a previous episode of non-enteropathic HUS, and another patient had a family history of non-enteropathic HUS. One child had received a haploidentical bone marrow transplant and developed non-enteropathic HUS 3 months after tacrolimus was added to the therapeutic regimen. Ten cases of non-enteropathic HUS occurred in the winter months; 3 cases, in the summer; 6 cases, in the fall; and 5 cases, in the spring.

Presenting Illness

A prodromal febrile illness occurred in 16 patients (67%) and lasted for an average of 5 ± 1 days. Symptoms of upper respiratory tract infection were present at the time of diagnosis of

non-enteropathic HUS in 16 children (67%). Infectious conditions (≥ 1) identified at the time of diagnosis of non-enteropathic HUS were pneumonia in 9 patients, urinary tract infection in 2 patients, meningitis in 2 patients, and bacteremia in 5 patients. *Streptococcus pneumoniae* was isolated from the blood, cerebrospinal fluid, or pleural fluid of 9 patients (38%).

Hospital Course

Thrombocytopenia, hemolytic anemia, and renal failure were identified within 48 hours of hospitalization in 22 of 24 patients (92%). Dialysis therapy was initiated in 17 patients (71%). Three children (12.5%) remained on long-term dialysis therapy at the last follow-up visit. In the remaining 14 patients, mean duration of dialysis support was 40 ± 27 days. All patients with *S pneumoniae*-related disease recovered renal function. A single patient with non-enteropathic HUS, who had presented with an upper respiratory tract infection prodrome, was treated with plasmapheresis. Transfusions of packed red blood cells were administered to 20 patients (83%) for a nadir hematocrit of 16.9 ± 4.6 vol%. Fourteen patients (61%) were administered platelet transfusions for a nadir platelet count of $25 \times 10^9/L$ (range, 3 to $100 \times 10^9/L$). The requirement for red blood cell transfusion was independent of the need for dialysis therapy; 15 of 17 dialyzed versus 5 of 7 nondialyzed children (*P* = 0.55).

A wide spectrum of extrarenal complications occurred in these children. Hypertension, the most common complication, developed in 17 patients (71%), whereas cardiomyopathy with congestive heart failure was seen in 3 patients. Three patients had seizures, and 2 of these patients had focal deficits. There were elevated transaminase concentrations (alanine aminotransferase and/or aspartate aminotransferase) in 11 patients (46%). Increased serum amylase and lipase activities were documented in 5 patients. One patient developed insulin-dependent diabetes mellitus. Median duration of hospitalization was 22 days (range, 2 to 71 days) in the cohort of children with non-enteropathic HUS.

Subgroup Analysis

Patients with non-enteropathic HUS were analyzed according to the requirement for renal replacement therapy. Children with non-entero-

Table 1. D⁺ HUS and Non-Enteropathic HUS: Clinical Characteristics and Outcomes

	Non-Enteropathic HUS (n = 24)	D ⁺ HUS (n = 145)	P
Sex (M:F)	15:9	62:83	0.081
Age (y)	2 (0.33-15.1)	4.2 (0.68-16.6)	0.015
Hematocrit nadir (vol%)	16.9 ± 4.6	18.7 ± 3.9	0.045
Platelet count nadir (n/L)	25 (3-100)	30 (4-140)	0.34
Fatalities	0	4	>0.99
Neurological complications	2	5	0.26
Pancreatitis/diabetes	6	11	0.019
Cardiac complications	2	5	0.26
Other complications	11	8	<0.0001
Median length of hospital stay (d)	22 (2-71)	9 (2-53)	<0.0002
Total serious extrarenal complications	21 (91)	27 (18)	<0.0001
Dialysis	17 (71)	59 (42)	0.025

NOTE. Data are reported as median (range), mean ± SEM, or number (percent). *P* based on Fisher's exact test for dichotomous variables and Wilcoxon's rank-sum test for continuous variables, except hematocrit, for which a 2-sample *t*-test was performed.

pathic HUS who needed temporary dialysis therapy were significantly younger than those who did not require renal replacement therapy (median, 16 months versus 11 years; *P* = 0.01). Mean nadir hematocrit (16.3 versus 17.0 vol%; *P* = 0.76) and median nadir platelet count (27 versus 11 × 10⁹/L; *P* = 0.17) were similar in children with and without dialysis treatment. As expected, hospitalization duration was prolonged in children who required dialysis compared with those who did not (median, 25 versus 7 days; *P* = 0.003). Finally, residual hypertension occurred more often in patients requiring dialysis therapy; 15 of 17 compared with 2 of 7 children who recovered without requiring temporary renal replacement therapy (*P* = 0.01).

When patients with infection caused by *S pneumoniae* versus other forms of non-enteropathic HUS were compared, the following differences were noted: age (17 ± 10 versus 58 ± 54 months; *P* = 0.007), length of prodromal illness before diagnosis (9.9 ± 5.4 versus 4.6 ± 4.3 days; *P* = 0.03), nadir platelet count (21 ± 11 versus 43 ± 36 × 10⁹/L; *P* = 0.046), duration of thrombocytopenia with platelet count less than 100 × 10⁹/L (7.0 ± 2.1 versus 3.9 ± 2.3 days; *P* = 0.006), and duration of hospitalization (33 ± 18 versus 17 ± 15 days; *P* = 0.043). Male-female ratio was 2:1 in patients with *S pneumoniae*-related illness compared with 1.5:1 in those without infection caused by *S pneumoniae* (*P* = 0.32). The number of cases of non-

enteropathic HUS attributed to causes other than *S pneumoniae* was too small for subgroup analysis.

Comparison between patients with non-enteropathic HUS and those with D⁺ HUS showed some interesting differences, listed in Table 1. Patients with non-enteropathic HUS tended to be younger (median, 2 years versus 4 years 2 months; *P* = 0.015). Moreover, the D⁺ HUS season was in the summer (May to October), and non-enteropathic HUS did not occur primarily in these months (*P* < 0.0001). Duration of hospital stay was significantly longer for patients with non-enteropathic HUS (*P* < 0.002). In addition, the total number of serious extrarenal complications was greater in patients with non-enteropathic HUS (*P* < 0.001), and the spectrum of these events was not the same in the 2 groups. Finally, there was a clear clinical trend with a greater percentage of patients requiring dialysis therapy in the non-enteropathic HUS group (17 of 24 versus 59 of 145 patients; *P* = 0.025). There was no difference observed in platelet count nadir and a borderline difference, in the hematocrit nadir.

DISCUSSION

The screening procedure for the SYNSORB Pk clinical trial enabled us to identify all cases of HUS seen at the participating centers during the study period.¹¹ This provided a unique opportunity to analyze a heterogeneous unselected group of patients with non-enteropathic HUS and esti-

mate the relative incidence and clinical features of non-enteropathic HUS in comparison to a contemporaneous cohort of patients with D⁺ HUS at the same locales.

Terms currently used to describe cases of HUS are a subject of considerable debate. The understanding of the pathophysiological characteristics of diarrhea-associated disease has improved dramatically in the last decade. Thus, it is increasingly clear that most patients with a diarrhea prodrome and even some patients without an obvious antecedent gastrointestinal illness have disease caused by previous STEC infection. It is worth noting in this context that the 2 patients with non-enteropathic HUS preceded by a urinary tract infection may represent an unusual manifestation of STEC-mediated disease.^{12,13} Ideally, the term STEC-related HUS should be adopted to describe these cases. However, rapid diagnostic tests for the O157 antigen or free Shiga toxin (Stx) in stool are still not widely available for use in clinical microbiology laboratories.¹⁴ Therefore, the term D⁺ HUS continues to be used in clinical practice. This is reflected in the SYNSORB Pk study design, in which the operational term "diarrhea-associated HUS" was used to determine eligibility, rather than confirmation of STEC infection.¹¹ Because cases described in this report were identified during the course of the SYNSORB Pk clinical trial, by necessity, they represent the non-D⁺ cases of HUS encountered during the study period.

The smaller group of non-STE C-related HUS continues to represent a heterogeneous assortment of seemingly unrelated disorders that are linked only by the shared phenotype of thrombotic microangiopathy.⁶ The classification scheme for nondiarrheal-HUS is likely to change as more information emerges about the regulation of endothelial cell function and underlying genetic causes. In the interim, we have introduced the nomenclature non-enteropathic HUS to highlight that the gastrointestinal tract is not the primary site of disease or that diarrhea is not the precipitating event, in the hope that this term will not add to the confusion for investigators working in this area.

The incidence of D⁺ HUS in pediatric patients is approximately 1 to 3 cases/100,000 total population per year.¹⁵ No figure is available for non-enteropathic HUS. This study is unique because all cases of non-enteropathic HUS were identi-

fied concurrently with and at the same institutions as the cases of D⁺ HUS that were evaluated for the SYNSORB Pk clinical trial.¹¹ Thus, during 1997 to 2001, non-enteropathic HUS cases represented 11% of all HUS cases (27 of 247 cases) treated at the participating sites. Thirty-eight percent of non-enteropathic HUS, or 4.7% of all cases of HUS, were caused by infection by *S pneumoniae*. This suggests an annual incidence of all forms of non-enteropathic HUS of approximately 2 cases/1,000,000 total population and an incidence of *S pneumoniae*-related HUS of, at most, 1 case/1,000,000 total population. The true incidence of disease may be greater because not all patients with HUS in a geographic region presented to a participating center during the SYNSORB Pk trial. In addition, it is important to recognize that the frequency of isolation of the responsible pathogen in patients with pneumococcal infection is only approximately 40%.¹⁶ In the absence of readily available and reliable alternative diagnostic tests, it remains possible that the incidence of *S pneumoniae*-induced HUS also has been underestimated in the present study. However, there is no a priori reason to assume that either of these factors would have altered the distribution of cases between D⁺ HUS and non-enteropathic HUS.

The preponderance of non-enteropathic HUS during the winter and spring (63%) contrasts sharply with the peak occurrence of D⁺ HUS during the summer months.^{11,17-19} Incomplete clinical information about antibiotic use during the prodromal illness precludes us from commenting on the potential impact of antibiotic therapy on the development of non-enteropathic HUS compared with D⁺ HUS.^{15,20} Our data are consistent with previous reports showing that the incidence of *S pneumoniae*-related HUS is greatest in children younger than 2 years. D⁺ HUS is more prevalent in slightly older children (Table 1).^{11,17} Four of 24 children with non-enteropathic HUS identified themselves as black or African American, approximately corresponding to the general census data for the US population. This contrasts with the significantly lower representation of black patients with D⁺ HUS in the SYNSORB Pk trial; namely, 3%.¹¹ The reason for this discrepancy is enigmatic.

We observed that patients with non-enteropathic HUS developed hemolytic anemia, thrombocytopenia, and azotemia within 48 hours of

hospitalization. In this series, patients not only rapidly reached nadir values for hemoglobin level and platelet count, they also had a prolonged disease course compared with patients with D⁺ HUS. This result is consistent with previous reports.^{21,22}

There were 2 patients with familial or recurrent non-enteropathic HUS in our case series (8%). Assays of factor H levels or mutational analysis of the factor H or membrane cofactor protein genes, 2 complement regulatory proteins, were not performed as part of this cohort study.²³⁻²⁵

The majority of cases in this series were the result of infectious processes. In 40% of cases, *S pneumoniae* was isolated from cerebrospinal fluid, blood, or pleural fluid. This underscores the importance of *S pneumoniae* as a major microbiological cause of non-enteropathic HUS and mirrors recent reports from Europe and the United States.^{17,26-31} The risk for *S pneumoniae*-related HUS is increased in patients with invasive disease, primarily meningitis; liver involvement; or empyema.^{18,19,32,33} The prognosis of *S pneumoniae*-related HUS is guarded. In 1 report, 9 of 11 children required dialysis therapy, and 4 children died.¹⁶ Five patients developed end-stage renal disease 4 to 11 years later; 1 patient underwent transplantation and is well. In our series, patients with *S pneumoniae*-related disease had a longer prodromal illness and longer hospital stay than those with other causes of non-enteropathic HUS, suggesting that this is a more severe form of non-enteropathic HUS during the acute phase. In contrast to other reports,^{22,27-29} all patients with *S pneumoniae*-related HUS in our series recovered renal function. However, the limited number of patients in this group should engender caution before generalizing these findings.

Treatment of non-enteropathic HUS is supportive medical care, including transfusions of red blood cells or platelets for hemorrhage and renal replacement therapy with either peritoneal dialysis or hemodialysis for anuric patients. Generally, there is no convincing evidence to support the use of "washed" red blood cells or plasmapheresis, although some familial cases seem to benefit from the latter treatment modality. Availability of a national registry for non-enteropathic HUS may facilitate case identification and perfor-

mance of clinical trials to determine the optimal treatment of patients with this group of diseases.

We could not identify specific risk factors for any of the serious extrarenal complications. Hypertension is very common in children with non-enteropathic HUS, especially those who require dialysis therapy. It is critical to diagnose and treat the elevated blood pressure promptly and effectively to avoid its complications. Hypertension has been described as one factor associated with a relapsing course in patients with non-enteropathic HUS.²

Younger children with non-enteropathic HUS needed dialysis therapy more often than older children, in agreement with recent reviews. A subgroup of patients with non-enteropathic HUS also appears to have a tendency to follow a relapsing course. Children requiring dialysis therapy were hospitalized for longer periods than nondialyzed patients and were more likely to have persistent hypertension. The acute phase of the illness was more severe, with an increased frequency of serious extrarenal complications; there was a trend for more patients to require dialysis therapy; and hospital stays were longer in children with non-enteropathic HUS than those with D⁺ HUS. Interestingly, although 3 patients (12.5%) with non-enteropathic HUS who required immediate dialysis therapy had not recovered kidney function at their last evaluation, irreversible renal failure was documented in only 2 children (1.4%) at the final 60-day follow-up visit during the SYNSORB Pk trial.¹¹ Together, findings indicate that children with non-enteropathic HUS constitute a group with more severe underlying disease compared with D⁺ HUS. However, we are unable to comment on the long-term prognosis of patients with non-enteropathic HUS because the study was not designed to collect extended follow-up information about children who were excluded from the SYNSORB Pk therapeutic trial. Clearly, prolonged follow-up of patients with non-enteropathic HUS will provide much-needed data with respect to the long-term prognosis.

In conclusion, (1) non-enteropathic HUS is less common than D⁺ HUS, but affected patients require dialysis therapy more often and are hospitalized more than twice as long during the acute episode; (2) infection caused by *S pneumoniae* accounts for nearly 40% of cases of non-enteropathic HUS; and (3) although *S pneumoni-*

ae-related HUS is associated with a less favorable short-term outcome than other forms of non-enteropathic HUS and D⁺ HUS, it does not have an increased risk for causing chronic renal failure.

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