Streptococcus pneumoniae-associated Hemolytic Uremic Syndrome Among Children in North America

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Background: To better characterize *Streptococcus pneumoniae*-associated hemolytic-uremic syndrome (SP-HUS), we report the largest series of SP-HUS among children in North America.

Methods: We surveyed pediatric members of the Emerging Infections Network to identify SP-HUS cases. Respondents contributed clinical and laboratory features of these pediatric cases.

Results: A total of 37 cases occurring between 1997 and 2009 were submitted. Of them, 33 cases (89%) were culture-confirmed and 4 (11%) were diagnosed clinically. The median patient age was 2 years, and 28 (76%) patients had completed their heptavalent pneumococcal conjugate vaccination (PCV7) series. Most patients presented with pneumonia (84%) and bacteremia (78%), whereas other clinical manifestations such as pericardial effusion (14%) and meningitis (11%) were less common. Of 29 patients, with bacteremia 6 (21%) had *S. pneumoniae* concurrently isolated from cerebrospinal fluid or pleural fluid. Severe illness was common with 35 (95%) patients requiring admission to the intensive care unit, over half requiring mechanical ventilation and chest tube placement or video-assisted thoracoscopic surgery, and 27 (73%) requiring dialysis during hospitalization. Among 30 patients with follow-up of 6 months, 7 (23%) remained dialysis dependent, 3 (10%) had undergone renal transplantation, 4 (13%) had neurologic sequelae, and 1 (3%) died. Among 24 serotyped isolates, 96% were non-PCV7 serotypes, most commonly 19A (50%), 92% are included in PCV13, and 10% were penicillin nonsusceptible (minimal inhibitory concentration >2 μg/mL).

Conclusions: North American children with SP-HUS had severe clinical manifestations and significant morbidity. In this series, nearly all cases were caused by serotypes that are not in PCV7 but are included in PCV13.

Key Words: hemolytic uremic syndrome, *Streptococcus pneumoniae,* pneumococcus, pneumococcal serotypes

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Nondiarrheal hemolytic uremic syndrome (HUS) is defined as microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in the absence of diarrheal illness or infection with Shiga-toxin expressing *Escherichia coli* (STEC). Nondiarrheal HUS occurs following infection with a variety of pathogens[1] or exposure to certain medications, and in individuals with complement dysregulation.[2]

Streptococcus pneumoniae (SP) is the most common infectious cause of nondiarrheal HUS.[3–7] *S. pneumoniae*-associated HUS is a severe disease, usually associated with complicated pneumonia and empyema.[4,8] Patients with SP-HUS have more morbidity and mortality than other forms of invasive pneumococcal disease or diarrhea-associated HUS,[6,9–11] although most studies describing SP-HUS are single center case series with limited clinical and microbiologic data.

Few studies have examined the clinical and molecular epidemiology of SP-HUS following licensure of the heptavalent pneumococcal conjugate vaccine (PCV7).[7,12,13] The overall decline in invasive pneumococcal disease rates in the post-PCV7 era was accompanied by an increase in invasive disease due to non-vaccine *S. pneumoni*ae serotypes, most commonly 19A.[14–16] Furthermore, while the hospitalization rates for childhood pneumonia have decreased following widespread vaccination, the incidence of hospitalizations for pneumonia complicated by empyema has increased,[17] most dramatically in children younger than 4 years.[18,19]

The incidence of SP-HUS is likely underestimated due to the lack of awareness of this disease among physicians, and to the overlap in symptoms between SP-HUS and disseminated intravascular coagulopathy from *S. pneumoniae* sepsis. To further increase awareness and understanding of this rare and severe disease, the objective of this study was to report the clinical and laboratory features for the largest series, to date, of culture-confirmed SP-HUS among children in North America.

METHODS

We queried the pediatric members of the Emerging Infections Network (EIN) during fall in 2009 to identify members who had cared for pediatric patients with SP-HUS between 1997 and 2009. The EIN consists of 259 pediatric infectious disease physicians throughout North America. Membership is drawn from the Infectious Diseases Society of America and The Pediatric Infectious Diseases Society. The pediatric members practice in 44 states and 3 Canadian Provinces. Members who indicated that they had seen SP-HUS cases were then asked to complete an electronic case history form detailing demographic, clinical, and laboratory features for each patient. No patient identifiers were collected, and all data were analyzed in aggregate, making this study exempt from Institutional Review Board approval, in accordance with the Code of Federal Regulations (45 CFR 46). In this series, 12 cases were included in earlier publications.[7,12]

Patients were included if they met the Center for Disease Control's definition of HUS: evidence of microangiopathic hemo-

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lytic anemia, renal injury, and thrombocytopenia (<150,000/mL) at presentation, or within 7 days of onset.[20] Confirmed cases had *S. pneumoniae* isolated from a sterile body site. Probable cases had evidence of Gram-positive diplococci on Gram stain of a normally sterile body fluid, but did not have positive cultures.

Demographics, clinical and laboratory characteristics of patients infected with *S. pneumoniae* serogroup 19 (predominantly comprised of serotype 19A) were compared with those infected with other serogroups using the Wilcoxon rank sum test for continuous variables and Fisher exact test for binary variables. A 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

Epidemiology

Fifteen respondents from 11 centers in North America submitted 37 cases hospitalized between January 1997 and February 2010. Of 37 cases, 34 (92%) were culture-confirmed, whereas 3 (8%) were probable cases diagnosed clinically by the presence of pneumonia, microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia. Two of the 3 probable cases had Gram-positive cocci in pairs detected in pleural fluid and had received antibiotics before pleural fluid drainage. In all, 33 (89%) cases occurred between 2003 and 2010, with most cases during 2008. Of total, 28 cases occurred during winter (November through March) most commonly in the month of March (12 cases), whereas 9 cases occurred during summer. Patients resided in 10 different locales in the South, Northeast, Western United States, and 1 province in Canada.

Clinical Presentation

Clinical features of SP-HUS patients are shown in Table 1. The median patient age at presentation was 2 years. Most patients were previously healthy and had completed the PCV7 vaccination series. No patients had asplenia or human immunodeficiency virus infection. Four patients had confirmed concurrent viral infections with adenovirus (1), human metapneumovirus (1), and respiratory syncytial virus (2 patients). Three patients had sick contacts among family members at presentation. Nearly all patients had fever at presentation for a median duration of 5 days (range, 3–7 days). Chest radiograph abnormalities, including moderate or large effusions, cavitary lesions, and pericardial effusions were commonly identified (Table 1). Twelve (32%) patients had an abnormal neurologic examination on presentation. Nine patients underwent lumbar puncture for suspected meningitis and 4 of these had laboratory confirmed meningitis, with growth of *S. pneumoniae* from cerebrospinal fluid (CSF) cultures. Two patients had both meningitis and pneumonia.

Laboratory Results

S. pneumoniae was cultured in 34 patients (92%). Twenty-two (65%) patients had isolates from a single sterile site including blood (22), pleural fluid (3), CSF (1), and bronchoalveolar lavage (1). Seven patients had *S. pneumoniae* isolated from multiple sterile sites including blood and CSF (3), blood and pleural fluid (3), or blood and urine (1) (Table 1).

Additional laboratory data were available for 35 (95%) patients and are shown in Table 1. Among 17 patients with peripheral smear results reported, 15 (88%) had evidence of hemolysis. Of 5 patients tested for Thomsen-Friedenreich antigen activation, 4 had a positive result. Of 14 patients, 8 had a positive Coombs test result.

Bacteriology

Serotyping was performed on 24 of 34 isolates (71%) (Table 2). Serogroup 19 was most common and identified in 12 patients (with serotype 19A identified in 11 patients, and 19-non F in 1 patient). Serogroup 19 was not identified in patients seen prior to 2001, but caused 63% of cases reported in 2003 and later years. Only one patient was infected with a *S. pneumoniae* serotype included in PCV7 (serotype 14). In contrast, 22 patients (92%) were infected with serotypes included in PCV13. The penicillin

TABLE 1. Clinical Characteristics and Laboratory Values at Hospital Admission for Patients With SP-HUS

Clinical Characteristics	N (%)
Median age (yr)	2
PCV7 up to date	28 (76)
Comorbidities*	5 (13)
Fever on admission	33 (89)
Pneumonia	34 (92)
Moderate-large pleural effusion	23 (68)
Cavitary PNA	10 (29)
Pericardial effusion	5 (15)
Meningitis	4 (11)
Streptococcus pneumoniae culture	34 (92)
Blood	22 (65)
Blood + pleural fluid	3 (9)
Blood + CSF	3 (9)
Pleural fluid	3 (9)
Blood + urine	1 (3)
CSF	1 (3)
BAL	1 (3)
Laboratory Values	**Median (Range)**
Hemoglobin (g/dL)	10.2 (2.2–12.6)
WBC ($\times 10^9$/L)	6.7 (0.5–34.2)
Platelets ($\times 10^9$/L)	84 (8–630)
AST (U/mL)	287 (26–1092)
Creatinine (mg/dL)	0.9 (0.2–4.6)
Total bilirubin (mg/dL)	2.1 (0.2–52)
Fibrinogen (mg/dL)	651 (326–1902)
PT (s)	15.7 (10.6–22.9)
INR	1.2 (1–3.9)

*Includes sickle cell trait, history of stem cell transplantation, prematurity, and mannose-binding lectin deficiency.

SP-HUS indicates *Streptococcus pneumoniae*-associated hemolytic-uremic syndrome; CSF, cerebrospinal fluid; BAL, bronchoalveolar lavage; PNA, pneumonia; AST, aspartate aminotransferase; PT, prothrombin time; PCV7, heptavalent pneumococcal conjugate vaccinate; WBC, white blood cells; INR, international normalized ratio.

TABLE 2. Microbiologic Characteristics of SP-HUS Patients

Serogroup	Number (%) N = 24
19*	12 (50)
7†	4 (17)
3	3 (13)
1	2 (8)
22‡	2 (8)
14	1 (4)
PCN MIC (mcg/mL)	**Number (%) N = 32**
S (<0.06)	19 (59)
I, (0.12–2)	10 (31)
R (>2)	3 (10)

*Includes 11 serotype 19A and 1 serotype 19 non F.

†Includes 3 serotype 7F.

‡Includes 1 serotype 22F.

SP-HUS indicates *Streptococcus pneumoniae*-associated hemolytic-uremic syndrome; PCN, penicillin; MIC, minimum inhibitory concentration for treatment of meningitis; S, susceptible; I, intermediate; R, resistant.

and ceftriaxone-resistant isolates were serogroups 19 and 14 and occurred in patients from diverse geographic areas.

Of 32 isolates, 19 (59%) had penicillin minimal inhibitory concentrations (MIC's) in the susceptible range (≤0.06 μg/mL), 10 isolates (31%) had intermediate susceptibility to penicillin (MIC, 0.06–2 μg/mL), and 3 isolates (10%) were resistant to penicillin (MIC >2 μg/mL). All isolates were considered penicillin-susceptible using revised breakpoints for intravenous therapy for nonmeningitis infections.[21,22] Four isolates (12%) were resistant to ceftriaxone with MICs >1 μg/mL.

Outcomes

Outcomes are shown in Table 3. Patients with SP-HUS required high acuity care. In all, 35 (95%) patients required admission to the intensive care unit with median intensive care unit length of stay of 11 days (range, 1–23 days). Twenty-seven patients (73%) required dialysis during hospitalization and median duration of dialysis was 15 days (range, 2–130 days). In all, 22 (59%) patients required mechanical ventilation for a median duration of 6.5 days (range, 1–15 days). In all, 25 (68%) patients required invasive procedures such as chest tube placement (13), video-assisted thorascopic surgery (9), lobectomy/pneumonectomy (2), or pericardiocentesis (1). Median length of hospitalization was 22 days (range, 3–103 days). Nine (24%) patients developed extrarenal complications or sequelae including pancreatitis (2), purpura fulminans and amputation of 1 hand and both legs below the knee (1), cholecystitis (1), *Pseudomonas* bacteremia (1), inferior vena cava thrombus (1), hearing loss (2), and ventriculoperitoneal shunt placement (1).

One (3%) patient with meningitis died during hospitalization. Among 30 patients with a median follow-up time of 6 months (range, 0.25–69 months), 12 (40%) had no renal or neurologic sequelae, while the remainder had elevated serum creatinine concentrations (37%), proteinuria (20%), hypertension (30%), or neurologic deficits (13%). Three patients (10%) had undergone renal transplantation.

Comparison of Serotype 19A With Other Serotypes

Demographics, laboratory values, and outcomes were compared between 12 patients infected with serogroup 19 (primarily serotype 19A) and 12 patients infected with other serotypes. Patients with serogroup 19 infections were older (median age, 2.1 vs. 1.0 years; $P = 0.029$), had lower admission hemoglobin concentration (median 8.5 vs. 11.2 g/dL; $P = 0.002$), and higher total serum bilirubin concentration (2.4 vs. 0.6 mg/dL; $P = 0.015$) than patients infected with other serotypes. Serotype 19A isolates were more frequently penicillin-nonsusceptible (MIC >0.06 μg/mL) compared with other serotypes (n = 55% vs. 18%; $P = 0.183$), although this was not statistically significant. There were no differences in clinical characteristics or outcomes between these patient groups.

TABLE 3. Outcomes of SP-HUS Patients During Hospitalization and After Median Follow-up of 6 Months

Hospitalization	Number (%) N = 37
Death	1 (3)
Dialysis	27 (73)
ICU admission	35 (95)
Invasive procedures*	25 (68)
Mechanical ventilation	22 (59)
Follow-up	**Number (%) N = 30**
Dialysis	7 (23)
Elevated creatinine	11 (37)
Proteinuria	6 (20)
Hypertension	9 (30)
Neurologic deficits	4 (13)
Renal transplantation	3 (10)

*Includes chest tube, video-assisted thoracoscopic surgery, pneumonectomy, and pericardiocentesis.

SP-HUS indicates *Streptococcus pneumoniae*-associated hemolytic-uremic syndrome; ICU, intensive care unit.

DISCUSSION

We report, to our knowledge, the largest, multicenter series of SP-HUS among North American children, and the largest collection of serotyped isolates associated with SP-HUS. Our findings were similar to those of prior reports, in that most patients with SP-HUS were 2 years of age, had complicated pneumonia and empyema, and required intensive care and prolonged hospitalization.[7,12,13] Nearly all serotypes associated with SP-HUS in this series are included in PCV13.

An important finding from the present series of cases is the continued high morbidity rate associated with SP-HUS. Three patients (10%) in this series underwent renal transplantation, and nearly 25% developed severe complications during hospitalization. In addition, at follow-up, nearly a quarter of patients remained on dialysis, and 40% had evidence of chronic kidney disease. In our series, morbidity is comparable to that in other SP-HUS series[7,11] and greater than that reported for diarrhea-associated HUS, in which 5% of survivors develop end-stage renal disease or permanent neurologic injury.[23] Mortality was lower in this series than in earlier studies.[9,24,25] In this series, 1 death occurred in a patient with meningitis, which has also been observed in prior studies.[7,13] It is surprising that no coinfections with influenza were reported, since the association between influenza and *S. pneumoniae* is well known. Four patients reported to have coinfections with respiratory viruses did not have worse outcomes.

This series, like others,[7,13] highlights the emergence of serotype 19A as the predominant serotype associated with SP-HUS following the introduction of PCV7 in 2001. The predominance of serotype 19A in recent years may be due to serotype replacement following vaccination with PCV7,[14] antibiotic selection,[26] or a combination of clonal expansion, capsular switching, and antibiotic or vaccine selection.[27] Importantly, no cases of 19A occurred among children with SP-HUS in Utah, emphasizing the importance of variability in local epidemiologic patterns.[12] We found that compared with other serotypes, 19A more frequently caused infections in older children, but was not associated with worse outcomes compared with other pneumococcal serotypes.

Better understanding of the mechanism of SP-HUS is needed to develop accurate testing and effective therapies. It is hypothesized that bacterial neuraminidase cleaves sialic acid residues and exposes the Thomsen-Friedenreich antigen (T-antigen) on the surface of red blood cells, platelets, and glomerular endothelial cells. Preformed IgM antibodies then bind to this antigen, leading to thrombotic microangiopathy and HUS.[24,28,29] Intriguingly, pneumococcal neuraminidase expression is higher in lung than in blood in mouse models, and greater in bacteria growing in biofilms than in planktonic forms, perhaps explaining why SP-HUS is strongly associated with empyema and observed infrequently among patients with isolated bacteremia.[30,31]

SP-HUS remains a clinical diagnosis without specific diagnostic tests, or treatment guidelines. Although the Coombs test,[32] Thomsen-Friedenreich antigen activation, or peanut lectin assays have been suggested as specific tests for SP-HUS,[7,8,10,13,24,29] they

have not been validated for clinical use and are not offered in many laboratories.[33] It is also not known whether the patients who develop SP-HUS have mutations in complement regulatory genes, similar to patients with forms of familial or sporadic atypical HUS.[2] Future surveillance for SP-HUS is needed to identify host and pathogen factors associated with this disease.

The design of this study is subject to certain limitations. Because cases were passively reported by respondents from a survey, it is not population-based and therefore cannot yield estimates of epidemiologic trends. It was also retrospective, and not all patients had follow-up. Additionally, there may be a spectrum bias among our cases with physicians disproportionately submitting severe cases as milder cases may not have been recognized or were less likely to be reported.

Using the pediatric membership of the EIN, we were able to obtain clinical and laboratory information from multiple centers about SP-HUS, a relatively rare condition, which illustrates the utility of this network in assembling case series. Clinicians should be aware that SP-HUS is a severe disease, and in this series this was most commonly caused by serotype 19A. Since nearly all serotypes associated with SP-HUS in this series are included in PCV13, vaccination with PCV13 has potential to decrease the incidence of SP-HUS and its associated morbidity. Greater surveillance of SP-HUS is warranted.

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