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Clinical Characteristics of Children With Complicated Pneumonia Caused by *Streptococcus pneumoniae*

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ABSTRACT. *Objective.* The frequency of children who are hospitalized with pneumococcal pneumonia complicated by necrosis, empyema/complicated parapneumonic effusion, and lung abscess seems to be increasing. The factors that contribute to this increase are unclear; therefore, the objective of this study was to describe and compare the relative frequency, clinical characteristics, and outcome of hospitalized children with complicated pneumonia with those of children with uncomplicated pneumonia caused by *Streptococcus pneumoniae* in the era of antibiotic resistance.

Methods. A multicenter, retrospective study of 8 children's hospitals in the United States was undertaken. A total of 368 children who were hospitalized with pneumococcal pneumonia identified from patients enrolled in the US Pediatric Multicenter Pneumococcal Surveillance Study over the period from September 1, 1993, to January 31, 2000 were studied. Demographic and clinical variables, antibiotic susceptibility, pneumococcal serotypes, antimicrobial therapy, and clinical outcome in hospitalized children with complicated versus uncomplicated pneumococcal pneumonia were measured.

Results. A total of 368 patients with pneumococcal pneumonia were identified. Of the 368 isolates, 47 (12.8%) were intermediate and 37 (10.1%) were resistant to penicillin; 18 (5%) were intermediate to ceftriaxone, and 9 (2.5%) were resistant to ceftriaxone. A total of 133 patients met the criteria for complicated pneumonia and had a chest tube placed; 56 of these patients subsequently underwent decortication. The proportion of hospitalized patients with complicated pneumococcal pneumonia increased progressively over the study period from 22.6% in 1994 to 53% in 1999. Patients with complicated disease were older (median age: 45 vs 27 months) and significantly more likely to be of white race and have chest pain on presentation compared with patients with uncomplicated disease. Patients who had complicated disease and underwent decortication were more likely to have pleural fluid lactate dehydrogenase levels of >7500 IU/L compared with those patients who had chest tube placement alone. Fifty-three percent of children who were ≥61 months of age and were hospitalized had complicated pneumonia. This group of children accounted overall for 42% of the patients with complicated pneumonia, 48.2% of the patients who subsequently underwent decortication, and 44% of the patients who had received a course of antibiotics before diagnosis. Pneumococcal serotypes 1, 6, 14, and 19 were the most prevalent serotypes causing disease, with serotype 1 causing 24.4% of the complicated cases versus 3.6% of the uncomplicated cases. Ninety-eight percent of the patients in both groups recovered from their pneumonia. Antibiotic resistance was not found to be more prevalent in those patients with complicated disease.

Conclusions. The relative frequency of complicated disease in hospitalized children with pneumococcal pneumonia is increasing. Patients with complicated pneumococcal disease were older and significantly more likely to be of white race compared with those patients with uncomplicated disease. Pneumococcal serotype 1 caused significantly more disease in patients with complicated versus uncomplicated pneumonia. Patients with complicated disease were not more likely to be infected with an antibiotic-resistant isolate. *Pediatrics* 2002;110: 1–6; *pneumococcal pneumonia, complicated pneumonia, pediatrics.*

ABBREVIATIONS. CXR, chest radiograph; PF, pleural fluid; WBC, white blood cell; CT, chest tube; TD, thoracotomy/decortication; MIC, minimal inhibitory concentration.

Streptococcus pneumoniae is the most common bacterial pathogen that causes community-acquired pneumonia in both adults and children, accounting for an estimated 550 000 cases of pneumonia each year.[1–3] During the last several decades, isolates of *S pneumoniae* that are resistant to penicillin and other antibiotics have become much more prevalent, and the impact that this has had on the treatment and outcome of pneumococcal pneumonia remains unknown.[4,5] Complications associated with pneumococcal pneumonia include the development of necrotizing pneumonia, pleural effusion, pleural empyema, and lung abscess.[6–8] During the past several years, these complications have been noted to be occurring with increased frequency without an apparent explanation.[9,10]

The clinical characteristics and outcome of pneumococcal pneumonia in children in the era of antibiotic resistance were described recently[11]; however, there are few published data regarding the relative frequency, clinical characteristics, and outcome of children with complicated pneumonia attributable to *S pneumoniae*.[9,10] Hardie et al[10] examined 50 cases of pleural empyema that occurred from 1988 to 1994 at a pediatric hospital in Cincinnati; 17 (34%) of the cases occurred within the last 12 months of the study. Forty percent of the cases were caused by *S pneumoniae*. They interpreted this as an increase in the incidence of pleural empyemas in children in their geographical area; however, the reason for the increase was not addressed.

The purpose of our study was to 1) compare the clinical characteristics and outcome of children hospitalized with complicated pneumococcal pneumonia with that of children with uncomplicated pneumonia; 2) determine whether an increasing frequency of complicated pneumonias is occurring in the pediatric population; and 3) determine whether antibiotic resistance plays a role in the occurrence of complicated pneumonias.

METHODS

The United States Pediatric Multicenter Pneumococcal Surveillance Study Group is composed of investigators at 8 children's hospitals in the following cities: Houston, Texas; Pittsburgh, Pennsylvania; Chicago, Illinois; Columbus, Ohio; Los Angeles, California; Little Rock, Arkansas; San Diego, California; and Winston-Salem, North Carolina. Hospitalized children with pneumonia attributable to *S pneumoniae* were identified retrospectively from patients with systemic pneumococcal infections enrolled in the US Pediatric Multicenter Pneumococcal Surveillance Group study between September 1, 1993, and January 31, 2000. The diagnosis of pneumococcal pneumonia was based on the combination of chest radiograph (CXR) findings and a positive blood and/or pleural fluid culture.

Complicated pneumococcal pneumonia was defined by the presence of 1 or more of the following features: loculated pleural fluid (PF) on CXR, chest ultrasound, or computed tomography; any PF parameters consistent with empyema (cloudy, bloody, or purulent appearance; white blood cell [WBC] count ≥50 000 × 10⁹/L; pH ≤7.1; lactic dehydrogenase level ≥1000 IU/L; glucose level ≤40 mg/dL; positive Gram stain or culture)[9,12]; chest tube (CT) placement; and/or thoracotomy/decortication (TD).

A standardized data form was completed retrospectively for each patient with pneumococcal pneumonia. Information collected included date of birth; gender; race; date of infection; underlying disease; presenting signs, symptoms, and findings on physical examination; peripheral WBC count and differential; CXR findings; duration of hospitalization; duration of fever and oxygen requirement; CT placement and duration; performance of other invasive procedures; antimicrobial therapy; follow-up CXR results; and clinical response. A febrile day was defined as any 24-hour period during which the patient had a temperature ≥100.5°F or 38.1°C. Hypoxia was defined as an oxygen saturation of ≤95% by pulse oximetry (while breathing room air). Clinical response was defined as good if the patient had improvement or resolution of his or her signs and symptoms during therapy.

Determination of the serotype and minimal inhibitory concentration (MIC) for penicillin and ceftriaxone of each isolate was performed in a central laboratory to which all isolates were sent. Serotyping/serogrouping was performed by quellung reaction, using specific capsular antisera (Statens Seruminstitut, Copenhagen, Denmark; Dako, Inc, Carpinteria, CA). Determination of MIC was done by standard broth microdilution. National Committee for Clinical Laboratory Standards guidelines were used for interpretation of MICs.[13] Susceptibility to penicillin was defined as an MIC ≤0.06 µg/mL, intermediate susceptibility was defined as an MIC of 0.1 to 1.0 µg/mL, and resistance was defined as an MIC ≥2.0 µg/mL. Susceptibility to ceftriaxone was defined as an MIC ≤0.5 µg/mL, intermediate was defined as an MIC of 1.0 µg/mL, and resistance was defined as an MIC ≥2.0 µg/mL. Isolates that were intermediate or resistant were considered nonsusceptible to penicillin or ceftriaxone.

Outcome variables were analyzed using χ^2, χ^2 test for trend, Fisher exact test, and Wilcoxon ranked sum test for nonparametric data. Epi Info 6 (Centers for Diseases Control and Prevention, Atlanta, GA) was the statistical program used.

RESULTS

Clinical Characteristics of the Patients

A total of 368 children who were hospitalized with pneumococcal pneumonia were identified during the study period from September 1, 1993, to January 31, 2000. Fifty-eight percent of the patients were boys; 44% were white, 39% were black, 12% were Hispanic, and 5% were other races. A total of 133 of the patients met 1 or more of the criteria for having complicated pneumonia as shown in Table 1. As illustrated in Fig 1, the proportion of children hospitalized with pneumonia that was complicated increased steadily during the study period. Analysis of data from 7 centers with complete case reporting during the study period revealed that the proportion of hospitalized patients with complicated infections increased from 22.6% in 1994 to 53% in 1999 ($P <$ .001). This trend was seen among all of the centers. Although among patients with complicated pneumonia the percentage of isolates that were resistant to penicillin (MIC ≥2.0 µg/mL) increased during the last 4 years of the study, this increase did not differ from that seen with the uncomplicated cases (data not shown).

TABLE 1. Criteria for Definition of Complicated Pneumonia Fulfilled by 133 Hospitalized Children Who Were Infected With *S pneumoniae*

Criteria	Number of Patients
Loculated PF by CXR	114 (85.7%)
Loculated PF by chest ultrasound	35 (26.3%)
Loculated PF by chest computed tomography	65 (49%)
PF parameters consistent with empyema	60 (45%)
CT placement	133 (100%)
TD	56 (42%)

Fig 1. Complicated pneumococcal pneumonia cases from 1994 to 1999. The numbers above the bars represent the number of hospitalized children who had complicated cases of pneumococcal pneumonia. The numbers in parentheses represent the percentage of complicated cases that were resistant to penicillin (MIC ≥2.0 μg/mL).
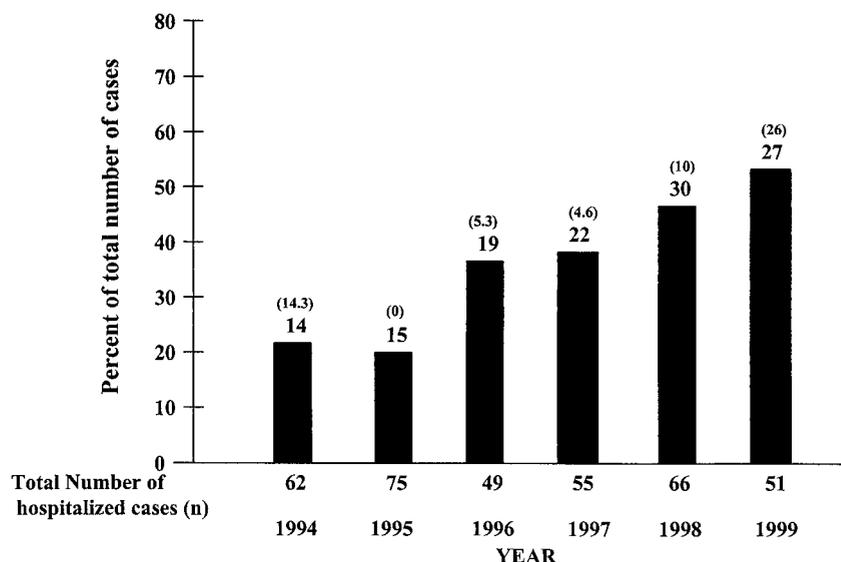
Patients With Complicated Versus Uncomplicated Disease

Selected clinical characteristics of the patients with uncomplicated versus complicated disease are listed in Table 2. Hospitalized patients with complicated pneumonia were older (median age: 45 vs 27 months; $P = .008$) and were significantly more likely to be of white race ($P < .001$) and to have chest pain ($P < .001$) on presentation. The mean duration of fever before diagnosis was 3.1 days (median: 2 days; range: 0.06–20 days) for the uncomplicated versus 5.7 days (median: 5 days; range: 1–28 days) for the complicated patients ($P < .001$). Not surprising, children with complicated infection had more extensive parenchymal disease than children with uncomplicated pneumonia. The mean time to defervescence for patients with uncomplicated disease was 2.5 days (median: 2 days; range: 0.33–18 days) versus 8.3 days (median: 6 days; range: 1–52 days) for patients with complicated disease ($P < .001$). Ninety percent of the patients in the uncomplicated group were afebrile by day 5 of hospitalization versus day 15 of hospitalization in the complicated group. Furthermore, the mean duration of oxygen requirement was 4.4 days (median: 2.5 days; range: 0.33–25 days) versus 10

days (median: 6 days; range: 0.5–59 days) for patients with uncomplicated and complicated disease, respectively ($P < .001$). Underlying illnesses or conditions were present in 48.5% of the uncomplicated versus 22.6% of the complicated disease ($P < .001$). The most common underlying illnesses or conditions in both groups were genetics disorders, hemoglobinopathies, central nervous system disorders, leukemia, human immunodeficiency virus, gastrointestinal disorders, and heart disease. With the exception of leukemia ($P = .006$), gastrointestinal disorders ($P = .026$), and genetic disorders ($P = .04$), which were significantly more prevalent in the uncomplicated group, there was no significant difference between the 2 groups with regard to the proportion of patients with each of the other underlying conditions.

Patients With Complicated Disease

The PF parameters for the patients who had complicated pneumonia and had only CT placement ($n = 77$) versus TD ($n = 56$) were examined. Overall, 69 (61.6%) of 112 specimens had a positive PF Gram stain and 85 (69.7%) of 122 had a positive PF culture. Compared with patients who had CT placement

TABLE 2. Clinical and Radiographic Characteristics of Children Hospitalized With Uncomplicated Versus Complicated Pneumococcal Pneumonia

Characteristic	Uncomplicated ($n = 235$)	Complicated ($n = 133$)	P Value
Age (mo; median, range)	27 (0.067–311)	45 (0.25–215)	.0080
White race	85 (36%)	77 (58%)	<.0001
Underlying disease	114 (48.5%)	30 (22.6%)	<.0001
Antibiotic usage before diagnosis	30 (12.8%)	25 (19%)	.12
Chest pain	18 (7.7%)	39 (29.3%)	<.0001
Fever before diagnosis >3 d	70 (31.4%)	82 (65.1%)	<.0001
Penicillin-resistant isolates	22 (9.4%)	15 (11.3%)	NS
CXR findings			
≥2 lobes	87 (37%)	86 (65%)	<.0001
Consolidation	97 (41.3%)	120 (90.2%)	<.0001
Hospital duration (d; mean [median, range])	6.45 (4, 1–45)	17.70 (13, 1–176)	<.0001
Defervescence >2 d	53 (26.4%)	111 (86.1%)	<.0001
Oxygen requirement >2 d	46 (52.3%)	100 (88%)	<.0001

NS indicates not significant.

alone, patients who underwent a decortication drainage procedure were significantly more likely to have PF with lactate dehydrogenase levels of >7500 IU/L (P = .01). There were no significant differences noted in PF WBC count, glucose levels, protein levels, or pH values between the 2 groups. The mean duration of CT placement in the patients with complicated pneumococcal pneumonia was 8.44 days (median: 6 days; range: 1–56 days).

Table 3 shows a breakdown of the children with pneumonia (both complicated and uncomplicated) by age group. There is a significant increase in the percentage of children with complicated pneumonia in older children (>60 months of age; P < .001). Children older than 5 years also accounted for 48.2% of patients who subsequently underwent TD.

Analysis of the duration of illness before admission to the hospital in children with complicated pneumonia according to age group demonstrated that the mean number of days of illness before admission increased from 3.9 to 6.4 during the first 36 months of life (P = NS); however, no differences were observed beyond this time. Of the children who had complicated pneumonia and had received or were receiving antibiotics before admission, 44% were older than 61 months.

Antimicrobial Therapy

The most common antimicrobial regimen used in both complicated (22.6%) and uncomplicated (52.8%) patients was 1 or more doses of a parenteral second- or third-generation cephalosporin followed by an oral antimicrobial agent. Clindamycin was part of the treatment regimen in 16.5% of patients with complicated pneumonia versus 5.1% of patients with uncomplicated disease (P < .001). Twenty-nine percent (n = 38) of the patients with complicated disease received at least 1 day of intravenous vancomycin therapy (median: 3 days; mean: 7.1 day; range: 1–66 days) versus 15.7% (n = 37) of the patients with uncomplicated pneumonia (median: 3 days; mean: 4.8 days; range: 1–25 days; P = .003). The antibiotic susceptibility of the isolate was not the principal factor governing whether vancomycin was used as part of the therapeutic regimen; in both groups, the majority of patients (76.3% complicated, 67.6% uncomplicated) who received vancomycin as part of their therapy had penicillin-susceptible isolates. Nine patients in the complicated group and 12 patients in the uncomplicated group who received vancomycin had a penicillin-nonsusceptible isolate. Of the patients who received antibiotic therapy before

hospital admission, only 1 patient in the complicated group received discordant therapy. This patient received outpatient amoxicillin therapy (40 mg/kg/d divided 3 times a day) and on admission was found to have a pneumococcal isolate with a penicillin MIC of 16 μg/mL and a ceftriaxone MIC of 4 μg/mL. This patient underwent TD and completed a 21-day course of clindamycin with resolution of the pneumonia.

Ninety-eight percent of patients with both uncomplicated and complicated disease recovered from their episode of pneumonia; 7 patients in the uncomplicated group and 3 patients in the complicated group subsequently died; the death of 2 patients in the uncomplicated group and 1 patient in the complicated group was believed to be related to the pneumococcal infection. All 3 of these patients had penicillin-susceptible isolates. Both patients in the uncomplicated group died within 24 hours of admission. Each had an underlying illness; 1 had renal and pulmonary anomalies, and the other had a chromosomal abnormality.

Antimicrobial Susceptibility and Serotypes/Serogroups of the Isolates

Forty-seven (12.8%) of the 368 isolates were intermediate, and 37 (10.1%) were resistant to penicillin. Eighteen isolates (5%) were intermediate, and 9 (2.5%) were resistant to ceftriaxone. There was no difference found in the proportion of these isolates in the complicated versus uncomplicated groups. Figure 2 illustrates the most commonly recovered serotypes/serogroups for patients with complicated versus uncomplicated pneumonia. Serotype 1 caused a significantly larger percentage of infections in children with complicated pneumonia compared with patients with uncomplicated disease (24.4% vs 3.6%; P < .001). Serotype 3 caused 8.4% of disease in the complicated group versus 2.7% in the uncomplicated group (P = .02). The most common serotypes/serogroups that caused disease in both the complicated and uncomplicated groups were 6B, 14, and 19F, all of which are contained in the licensed heptavalent pneumococcal conjugate vaccine.
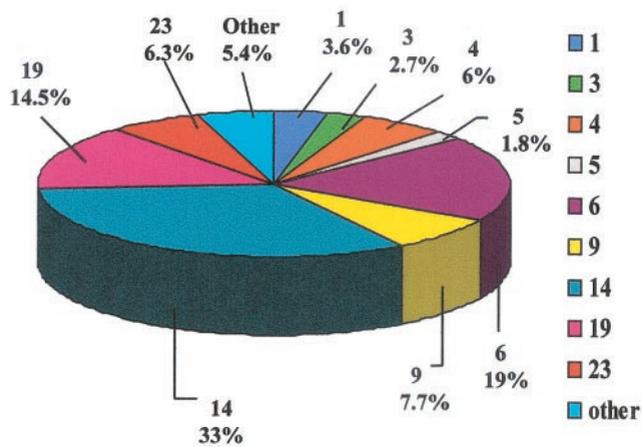
DISCUSSION

Pneumonia is second only to bacteremia as a manifestation of invasive systemic disease attributable to *S pneumoniae* in children and accounts for 19% of all systemic pneumococcal illnesses.[14] In this age of antibiotic resistance, the clinical presentation and outcome of patients with pneumococcal pneumonia attributable to isolates with any degree of penicillin resistance does not seem to differ significantly from patients with susceptible isolates; however, the data are very limited on the impact that high-level resistance (MIC >4.0 μg/mL) may have on the outcome of these infections.[9,15] Previous studies suggested that patients with systemic infections outside the central nervous system caused by pneumococcal isolates that are intermediate as well as some that are resistant to penicillin may respond adequately to penicillin and other β-lactam agents.[15–17] Therapy with the advanced-generation cephalosporins or

TABLE 3. Hospitalized Children With Pneumonia Caused by *S pneumoniae* Divided by Age Groups (N = 368)

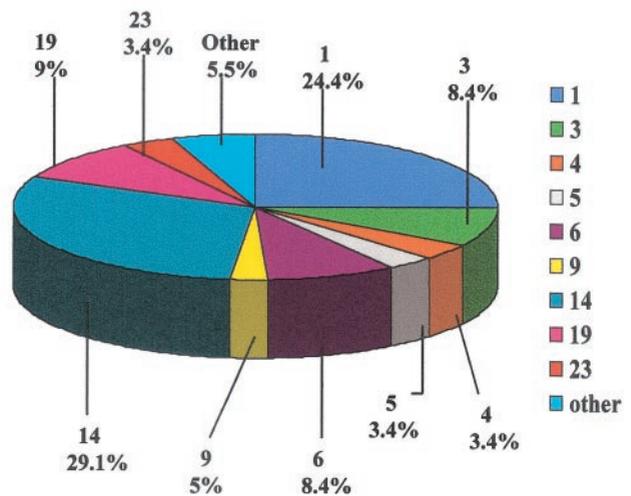| Age Group	N	No. With CP	% of All CP (n = 133)	TD (n = 56)
0–12 mo	72	19 (26.4%)	14.3	7 (12.5%)
13–24 mo	77	22 (28.6%)	16.5	10 (17.9%)
25–36 mo	57	16 (28.1%)	12	6 (10.7%)
37–48 mo	38	11 (29%)	8.3	3 (5.4%)
49–60 mo	18	9 (50%)	6.8	3 (5.4%)
≥61 mo	106	56 (53%)	42.1	27 (48.2%)

CP indicates complicated pneumonia.

Fig 2. Percentage of pneumococcal serotypes/serogroups that cause disease in children with complicated versus uncomplicated pneumonia.

non–β-lactam agents (eg, vancomycin, clindamycin, linezolid) is usually recommended for patients with isolates of pneumococci that have a high level of resistance to penicillin, and patients who are immunocompromised or critically ill. Therapeutic changes historically have been based on the susceptibility of the isolate and not so much on the clinical response of the patient. In contrast to these studies, a recent study in adult patients with bacteremic pneumococcal pneumonia demonstrated that the penicillin susceptibility of the isolate seems to play a role in the outcome of patients. Patients who were infected with penicillin-nonsusceptible isolates were found to be at significantly higher risk for suppurative complications. The majority of these patients had intermediate-resistance isolates; however, the antimicrobial regimens used for treatment and the pneumococcal serotypes that caused disease were not discussed.[18] In another study of patients with invasive pneumococcal pneumonia, investigators found that mortality was increased after the fourth hospital day in patients whose isolate had a penicillin MIC ≥ 4.0 μg/mL or a cefotaxime MIC ≥ 2.0 μg/mL.[19] In our study, the presence of an antibiotic-resistant pneumococcal isolate was not found to be a risk factor for the development of a complicated pneumonia; however, the number of patients with high-level penicillin and cephalosporin resistance was limited. Discordant therapy occurred in only 1 patient with complicated pneumonia; the isolate had high-level penicillin and cephalosporin resistance. It is not known at this time what impact discordant therapy in the presence of a pneumococcal isolate with high-level antibiotic resistance has on the risk of developing a complicated pneumonia.

Complications seen with pneumococcal pneumonia include progression to necrotizing pneumonia, pleural or parapneumonic effusion, pleural empyema, pneumatocele formation, and lung abscess.[6–8] In adults, the incidence of parapneumonic effusions in pneumococcal pneumonia is reported to be up to 57%,[7,20] with the occurrence of pleural empyema having an incidence ranging from 2% to 8%.[12,20] The development of necrotizing or cavitating pneumonia and the occurrence of lung abscess have been reported as being infrequent.[2,21] In a previous study, we found that 13.8% of hospitalized children with bacteremic pneumococcal pneumonia had PF parameters indicative of a pleural empyema[11]; in the current study, 36% of the patients had an episode of complicated pneumonia as evidenced by presenting symptoms, radiographic studies, and/or PF parameters. Our current study demonstrated a significant increase in the relative frequency of complicated bacteremic pneumococcal pneumonia in hospitalized patients throughout the study period from 22.6% in 1994 to 53% in 1999. Other investigators have also reported an apparent increase in the frequency of complicated pneumonias.[10,11]

The reasons for this increase are not clear and may be related to yet unknown host, environmental, and/or microbial factors. Patients who had complicated disease were older than patients who had uncomplicated disease (median age: 45 vs 27 months, respectively), with a larger percentage having received antibiotics before diagnosis. Older children may have been more likely to present with complicated disease if the antibiotic therapy that they were receiving before diagnosis was able to suppress partially the infection for a period of time but was insufficient to prevent progression to a complicated pneumonia. Children of Native American, Alaskan Native, and black origin are recognized to have a high incidence of severe invasive pneumococcal disease. Rates among the black population are 2 to 3 times higher than in the white population, with even higher rates reported in the Native American and Alaskan Native populations.[22] The reason for this increased risk is not known. It is interesting that in our study we found that children who had complicated pneumonia were significantly more likely to be of white ethnicity.

The recently licensed heptavalent pneumococcal conjugate vaccine contains pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which account for between 80% and 90% of serotypes that cause disease in children younger than 5 years in the United States.[23] In a double-blind efficacy trial performed in the Kaiser Permanente system, the pneumococcal conjugate vaccine demonstrated a 73% efficacy (intent-to-treat group) in the prevention of consolidative pneumonia (consolidation on CXR 2.5 cm or greater). On the basis of these data, it seems that the heptavalent conjugate vaccine may prevent up to three fourths of the episodes of pneumococcal pneumonia in children.[24–26] In our study, 56% of patients with complicated disease versus 77% of patients with uncomplicated disease (69.4% overall) had serotypes that are included in the currently licensed heptavalent pneumococcal conjugate vaccine. In our series of patients (both complicated and uncomplicated), serotypes 1 and 3 accounted overall for 28% and 11%, respectively, of the pneumonia cases and were more common in the patients with complicated pneumonia. As these serotypes are not included in the currently licensed vaccine, the impact of the vaccine on the incidence of complicated pneumonia may be predictably less compared with other forms of invasive pneumococcal disease.

The ongoing surveillance of pneumococcal antimicrobial susceptibility and the serotypes that cause disease remains important now that a pneumococcal conjugate vaccine is available. Continued surveillance will provide crucial data to help determine vaccine efficacy for the general pediatric population as well as the effect that the vaccine may have on the frequency of infections caused by pneumococcal isolates with antibiotic resistance and/or serotypes not included in the heptavalent pneumococcal conjugate vaccine.

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