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Pneumococcal Necrotizing Pneumonia in Utah: Does Serotype Matter?

Jeffrey M. Bender[1], **Krow Ampofo**[1], **Kent Korgenski**[2], **Judy Daly**[1,2], **Andrew T. Pavia**[1], **Edward O. Mason**[3], and **Carrie L. Byington**[1]

[1]Department of Pediatrics, Division of Infectious Diseases, University of Utah, Salt Lake City, Utah

[2]Department of Microbiology, Primary Children's Medical Center, Salt Lake City, Utah

[3]Department of Pediatrics, Division of Infectious Diseases, Baylor College of Medicine, Houston, Texas

Abstract

Background—*Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children. Despite the use of the 7-valent pneumococcal conjugate vaccine, the incidence of pneumococcal necrotizing pneumonia (PNP) has been increasing. Our objectives were to describe temporal trends in PNP and to evaluate pneumococcal serotypes associated with PNP in Utah.

Methods—We performed a retrospective review of all children <18 years of age who were cared for at a tertiary care children's hospital and who had blood, lung tissue, broncheoalveolar lavage, or pleural fluid cultures that grew *S. pneumoniae,* as well as radiographic evidence of pneumonia, from January 1997 through March 2006. All *S. pneumoniae* isolates were typed.

Results—A total of 124 children with pneumococcal pneumonia were identified, and 33 (27%) of these children had radiographic evidence of PNP. During the period 1997–2000, 5 (13%) of 39 cases of culture-confirmed pneumococcal pneumonia were associated with PNP. In contrast, during the period 2001–2006, 28 (33%) of 85 pneumococcal pneumonia cases were complicated by PNP (odds ratio, 3.34; 95% confidence interval, 1.11–12.03). Non–7-valent pneumococcal conjugate vaccine serotypes comprised 49% of the isolates during 1997–2000 and 88% of isolates during 2001–2006 (odds ratio, 7.89; 95% confidence interval, 2.91–21.90). Pneumonia due to serotype 3 was most often associated with PNP. Eleven (79%) of 14 cases of serotype 3–associated pneumonia were associated with PNP. When compared with all other serotypes, serotype 3 was strongly associated with necrosis (odds ratio, 14.67; 95% confidence interval, 3.39–86.25).

Conclusions—PNP is a serious and increasingly common complication of *S. pneumoniae* pneumonia in Utah. Infection with serotype 3 is associated with an increased risk of developing PNP. The increase in the incidence of infection due to nonvaccine serotypes reported worldwide and the changing epidemiology of invasive pneumococcal disease should be considered when developing vaccine strategies.

Reprints or correspondence: Dr. Jeffrey Bender, University of Utah, Div. of Pediatric Infectious Diseases, Dept. of Pediatrics, 30 North 1900 East, Salt Lake City, Utah 84132 (Jeffrey.Bender@hsc.utah.edu).

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Over the previous decade, there has been a marked increase in the number of cases of pediatric parapneumonic empyema (PPE) in the United States, Europe, and Asia [1–11]. In 2000, the 7-valent pneumococcal conjugate vaccine (PCV-7; Prevnar; Wyeth Lederle Vaccine) was licensed in the United States, and its use was recommended for all children <5 years of age [12]. Significant decreases in pediatric invasive pneumococcal disease (IPD) have since been reported, including a 69% decrease in the overall incidence of IPD and a 96% decrease in the incidence of IPD due to the serotypes of *Streptococcus pneumoniae* included in PCV-7 [13]. Despite the overall reduction in IPD, PPE due to nonvaccine serotypes of *S. pneumoniae* is a serious and increasing problem in the pediatric population.

The incidence of pediatric IPD in Utah decreased by 27% during the first 3 years of PCV-7 use [14]. Although this is a significant decrease, it is less than the decrease observed in other regions of the United States and was attributable, in part, to increased rates of complicated pneumonia and PPE [14]. In the decade from 1993 through 2003, the rate of pediatric PPE in Utah increased from 1 case per 100,000 children in 1993 [1] to 14 cases per 100,000 children in 2003 [14]. In Utah, PPE in children is most often a result of infection with *S. pneumoniae* serotype 1 [1, 14]. In Utah, during 1993–2003, every child from whom *S. pneumoniae* serotype 1 was isolated experienced complicated pneumonia or PPE.

Concomitant with this increase in the incidence of PPE, Utah has experienced an observed increase in pneumococcal necrotizing pneumonia (PNP). We hypothesized that, similar to PPE, pneumococcal serotype is an important factor in the development of necrotizing pneumonia. Our objectives were to (1) describe the temporal trends in PNP and (2) evaluate whether individual pneumococcal serotypes were associated with necrotizing pneumonia.

PATIENTS AND METHODS

Human subjects protection

The institutional review boards for both the University of Utah and Intermountain Healthcare reviewed and approved this study. Informed consent was waived.

Setting

The study was conducted at Primary Children's Medical Center (PCMC) in Salt Lake City, Utah. PCMC is a 250-bed children's hospital that serves both as the community hospital for Salt Lake County, Utah, and as a tertiary referral center for 5 states in the intermountain West (Utah, Idaho, Wyoming, Nevada, and Montana).

Identification of children with necrotizing pneumonia

All isolates of *S. pneumoniae* recovered from normally sterile sites from children cared for at PCMC have been archived and serotyped since1996. Using archive of isolates and computerized medical records, children <18 years of age who were treated at PCMC for culture-confirmed pneumococcal pneumonia from January 1997 through March 2006 were identified. All positive culture results were from blood or pleural fluid specimens. Patients who received a diagnosis of pneumonia and/or PPE, defined by the *International Classification of Diseases, Ninth Revision,* were included using codes 481 and 510.9, respectively. The diagnosis of PPE was confirmed by physician (C.L.B. and J.B.) review of the medical record and pleural fluid characteristics using the criteria established by Light [15]. These criteria included an effusion occupying >50% of the hemi-thorax or an effusion that was loculated, positive results of Gram staining or culture of the pleural fluid, and a purulent pleural fluid with a pH <7.20 or a glucose level <60 or a lactic acid dehydrogenase level of >3 times the upper limit of normal for serum.

The diagnosis of PNP was defined as culture-confirmed pneumococcal pneumonia and radiographic evidence of necrotic pneumonia. Radiographic evidence of necrosis was determined on the basis of the reading of necrotic lung parenchyma, lung abscess, or pneumatocele on chest radiograph or CT by a board-certified pediatric radiologist. Radiologists were not aware of microbiologic test results.

Microbiologic evaluation

Bacterial cultures included for analysis were blood, lung tissue, bronchioalveolar lavage, or pleural fluid. Isolates were serotyped by means of the capsular swelling method with the use of commercially available type-specific antiserum samples. The investigator performing the analyses (E.O.M.) was blinded to the sources of the pathogen samples.

Demographic evaluation

Demographic characteristics evaluated included sex, age in months, preexisting medical condition, ethnicity, and vaccination status. Documentation of PCV-7 vaccination was obtained through the electronic medical record or by direct review of the child's vaccination card (C.L.B.).

Outcomes evaluation

Outcomes examined included those that reflected disease severity and morbidity. These included evidence of PNP or PPE, need for chest tube placement, need for intensive care, need for surgical intervention, length of hospital stay, hospital cost, hospital charges, and death.

Comparisons

We divided the study period into the years prior to the licensing of and introduction of PCV-7 (period 1; 1 January 1997 through 31 December 2000) and the years after licensing of introduction of PCV-7 (period 2; 1 January 2001 through 31 March 2006). To examine the importance of serotype in PNP, we evaluated our cases in a step-wise fashion. First, we reviewed all PNP cases that occurred during the study period. We then evaluated all serotypes individually to document whether any individual pneumococcal serotype was associated with PNP. We next compared patients with PNP with those patients without evidence of necrosis to evaluate whether PNP was associated with increased morbidity or mortality.

Statistical analysis

Stata statistical software, version 10.0 (Stata), was used for the statistical analysis. Data were analyzed using Fisher's exact test for categorical outcomes and the Mann-Whitney *U* test or Wilcoxon 2-sample test for continuous outcomes. For each demographic and outcome variable, *P* values and ORs with 95% CIs were calculated.

RESULTS

Identification of PNP

During the study period, 319 cases of pediatric IPD were identified. Of these, 124 involved children with culture-confirmed *S. pneumoniae* pneumonia, and 33 (27%) of these children had radiographic evidence of PNP. All isolates were susceptible to penicillin. During study period 1, 5 (13%) of 39 cases of culture-confirmed pneumococcal pneumonia were associated with PNP (tables 1 and 2). During study period 2, 28 (33%) of 85 pneumococcal pneumonia cases were complicated by PNP (OR, 3.34; 95% CI, 1.11–12.03).

Serotype distribution

A total of 23 different pneumococcal serotypes were identified among isolates obtained from the children with pneumococcal pneumonia (table 2). The majority (77%) of the *S. pneumoniae* isolates were non–PCV-7 vaccine serotypes. Nonvaccine serotypes comprised 49% of the isolates from 1997–2000 and 88% of isolates from 2001–2006 (OR, 7.89; 95% CI, 2.91–21.90).

Twelve unique serotypes were identified among isolates obtained from patients with PNP (table 1). Overall, 28 (85%) of 33 cases of PNP were due to infection with nonvaccine serotypes, but the frequency of PNP due to infection with non-vaccine serotypes differed significantly between the 2 study periods: 2 (40%) of 5 isolates in period 1, compared with 27 (96%) of 28 isolates in period 2 ($P < .005$). Pneumonia due to serotype 3 was most often associated with PNP, with 11 (79%) of 14 patients developing necrosis. When compared with all other serotypes, serotype 3 was almost 15 times more likely to be associated with radiographic evidence of lung necrosis (OR, 14.67; 95% CI, 3.39–86.25).

PNP

Age, sex, and ethnicity did not differ between children with and children without PNP or between children with infection due to serotype 3 and children with infection due to all other serotypes (tables 3 and 4). Most (94%) of the children with PNP were previously healthy. In contrast, 20% of the children with nonnecrotizing pneumonia had an underlying medical condition, including chromosomal and anatomic abnormalities, prematurity, malignancy, and immunodeficiency ($P = .07$). PCV-7 vaccination history was not different between children with and children without evidence of necrotizing pneumonia. However, more children with serotype 3 pneumonia had documentation of vaccination with at least 1 dose of PCV-7 (21%), compared with children with pneumonia due to other serotypes (6%) ($P = .05$).

Children with PNP and those with pneumonia due to serotype 3 strains demonstrated a statistically significant increase in morbidity, compared with children who had pneumococcal pneumonia without evidence of necrosis or pneumonia due to other serotypes (Tables 3 and 4). Children with PNP or serotype 3 infection were more likely to have associated PPE, require chest tube placement, and undergo surgical procedures. These children also had longer hospital stays and higher hospital costs and charges. There was no difference between the groups with respect to the need for hospitalization in the pediatric intensive care unit or mortality.

DISCUSSION

In this study, we document a marked increase in the incidence of necrotizing pneumonia due to *S. pneumoniae.* The incidence of PNP has been increasing in Utah since 2001 and is associated with nonvaccine pneumococcal serotypes, especially type 3. PNP is associated with a significant increase in morbidity and hospital costs. New vaccine strategies need to be considered to protect US children from PNP.

Although the introduction of PCV-7 has greatly reduced the incidence of IPD across the United States [13], nonvaccine serotypes of *S. pneumoniae* are increasingly reported as the cause of complicated pneumonia, including parapneumonic empyema and necrosis. Recently, Singelton et al. [10] demonstrated an increase in the incidence of IPD caused by non–PCV-7 *S. pneumoniae* serotypes in Alaskan native children. In that study, there was a significant increase in the proportion of cases involving empyema. A study from the United Kingdom identified 75 children with pneumococcal pneumonia over a 7-year period using culture and molecular techniques [16]. Fifteen (20%) of the cases had evidence of necrosis.

Ramphul et al. [16] concluded that *S. pneumonia* may replace *Staphylococcus aureus* as the most common cause of necrotizing pneumonia in children. In another study involving adults and children, infection with serotype 3 *S. pneumonia* was the most common cause of fatality in Spain and the United States [17]. Other studies have demonstrated the emergence of nonvaccine *S. pneumonia* serotypes, such as 1, 15, 19A, and 33, in the post–PCV-7 era [4, 18–21]. Kaplan et al. [22] showed an increase in the median number of serotype 3 isolates per year in 8 children's hospitals. The recent case-control study looking at IPD in the Active Bacterial Core (ABC) surveillance sites did not look at serotype 3–associated disease specifically but demonstrated an overall decrease in the incidence of IPD [18].

PNP is associated with increased severity and morbidity, compared with pneumonia without necrosis. A case series describing 4 patients with PNP in Israel showed that all of the patients had prolonged hospital courses, and 2 patients required chest tube drainage [23]. In our study, patients with PNP had more-complicated hospital stays with increased morbidity and higher hospital costs.

Likewise, serotype 3 PNP led to increased morbidity, as well. The increased morbidity associated with serotype 3 infection is probably associated with its propensity to cause PNP. Although the relationship between serotype 3 *S. pneumoniae* and necrotic pneumonia was described in the early literature among adults, it has not, to our knowledge, been addressed in children [24–26]. A recent study from the United Kingdom showed that 3 of 15 cases of necrotizing pneumonia were due to serotype 3 [16]. Another study from Taiwan looking at 15 cases of PNP in children identified 2 cases caused by serotype 3 [27]. The mechanism for *S. pneumoniae* serotype 3 leading to necrosis has been hypothesized to be related to the rapid accumulation of capsular polysaccharides leading to a large antigenic load and possible reduced humoral immune responses [24]. Although the mechanism is not clearly defined, we have shown that *S. pneumoniae* serotype 3 is significantly associated with necrotizing pneumonia and, thus, leads to increased morbidity and hospital costs.

The epidemiology of IPD in children in Utah appears to differ significantly from that documented by the ABC surveillance system [1, 2, 14, 18]. However, similar trends have been reported from non-ABC sites in the United States, as well as from Canada and Europe [4, 8, 10, 19, 20, 28–30].

Many factors have likely played a role in the epidemiology of IPD in Utah. One likely contributor is the distribution of serotypes before the introduction of PCV-7. In the pre–PCV-7 era, the seroepidemiology of IPD in Utah was different from that seen in the ABC sites, with serotype 1 being the most common [1]. This included high rates of pneumonia and PPE mainly caused by non–PCV-7 serotypes. Mathematical models predicted that the determinants of serotype replacement would include the prevalence of nonvaccine serotypes before vaccine introduction and the tendency of nonvaccine strains to cause colonization and invasive disease [31].

In the post–PCV-7 era, although ABC sentinel sites and other investigators have reported an overall dramatic decrease in the incidence of all pediatric IPD [13], Utah has seen only a modest decrease in total IPD [2, 14]. This is likely to be secondary to significant increases in PPE caused by nonvaccine serotypes, especially 1, 3, and 19A. In a recent case-control study of IPD in Utah, the factors associated with IPD were similar to those reported from other geographic regions, although children ≥2 years of age were 2.2 times more likely (95% CI, 1.3–3.7 times more likely) to have IPD caused by infection with nonvaccine serotypes, compared with younger children [32].

The demographic characteristics of Utah itself may also be a factor in the epidemiology of IPD. Utah has the highest rates of household crowding and the greatest number of

households with children in the United States [33]. Utah children with IPD due to infection with nonvaccine serotypes tended to be from larger households [32]. The temporal trends in IPD in Utah occur against the background of a PCV-7 vaccination rate of 80% for 3 doses, compared with a national rate of 87%, and thus, it is unlikely that differences in vaccine use played a major role [34].

In combination, the above factors may have allowed for more-rapid emergence of serotype replacement disease and further explain why the epidemiology of IPD in Utah is different from that reported by the ABC surveillance sites. This further highlights the importance of regional surveillance.

This study was limited by its retrospective design. We used radiographic evidence of necrotizing pneumonia as a surrogate for the pathologic diagnosis of lung necrosis. There was no significant difference in the number of CTs performed between the prevaccine and postvaccine study periods.

Furthermore, our study examined the occurrence of necrotizing pneumonia due to culture-confirmed *S. pneumoniae* infection in children. The proportion of children with culture-positive pneumonia is relatively low. In an earlier study performed at PCMC, we found that 11.4% of children with uncomplicated bacterial pneumonia had a positive bacterial culture result [1]. Molecular techniques for the detection of bacteria in pleural fluid will, in the future, allow for a more complete understanding of necrotic pneumonia in children [16].

In conclusion, *S. pneumoniae* infection leading to necrotizing pneumonia is a growing and significant problem. PNP is associated with increased morbidity and hospital costs. Infection with serotype 3 *S. pneumoniae* is a significant contributor to PNP. The increase in infection due to nonvaccine serotypes reported worldwide and the changing epidemiology of IPD should be considered when developing vaccine strategies.

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Table 1

No. (%) of *Streptococcus pneumoniae* isolates associated with necrotizing pneumonia before (period 1; 1 January 1997–31 December 2000) and after (period 2; 1 January 2001–31 March 2006) the introduction of the 7-valent pneumococcal conjugate vaccine, by serotype.

Serotype	Period 1 (*n* = 5)	Period 2 (*n* = 33)
Vaccine		
6B	2 (40)	…
19F	1 (20)	…
4	…	1 (3)
Nonvaccine		
1	1 (20)	…
6A	1 (20)	…
3	…	2 (6)
7	…	11 (33)
8	…	1 (3)
17	…	1 (3)
19	…	4 (3)
19A	…	4 (12)
NG	…	1 (12)
NT	…	2 (6)

NOTE. NG, no growth during serotyping; NT, nontypeable.

Table 2

Streptococcus pneumoniae serotypes leading to pneumonia and pneumococcal necrotizing pneumonia (PNP), January 1997–March 2006.

Serotype	No. of children with pneumonia due to the specified serotype	No. (%)of children with PNP due to the specified serotype
All serotypes	124	38 (23)
1	28	3 (11)
3	14	11 (79)
4	**2**	**1 (50)**
6A	2	1 (50)
6B	**6**	**2 (33)**
7	7	1 (4)
9	3	0
9N	2	0
9V	**5**	**0**
14	**7**	**0**
18C	**0**	NA
19	8	4 (50)
19A	13	4 (31)
19F	**6**	**1 (17)**
22	2	0
23F	**2**	**0**
NG	2	1 (50)
Other[a]	6	2 (33)
NT	9	2 (22)

NOTE. Serotypes included in the 7-valent pneumococcal conjugatevaccine are in boldface type. NA, not applicable; NG, no growth during serotyping; NT, nontypeable.

[a]Other serotypes include 1 of each of the following serotypes: 6, 8, 17, 18, 28, and 29/38/42.

Table 3

Comparison of demographic characteristics and outcomes of patients with necrotizing pneumonia due to *Streptococcus pneumoniae* and patients with nonnecrotizing pneumonia due to *S. pneumoniae.*

Variable	Patients with necrotizing pneumonia (*n* = 33)	Patients with nonnecrotizing pneumonia (*n* = 91)	*P*	OR (95% CI)
Demographic characteristic				
Male sex	18 (55)	51 (56)	.88	0.94 (0.39–2.28)
Age, mean months	40	41	.44	…
Vaccination	3 (9)	7 (8)	.80	1.20 (0.19–5.67)
Preexisting condition	2 (6)	18 (20)	.07	0.26 (0.03–1.21)
Outcome				
Empyema	32 (97)	39 (43)	<.005	42.67 (6.39–1769.45)
Required chest tube	30 (91)	42 (46)	<.005	11.67 (3.22–62.85)
LOS, mean days	10.4	7.1	.03	…
Underwent surgical procedure	11 (33)	14 (15)	.028	2.75 (0.97–7.56)
Hospitalization in PICU	18 (55)	37 (41)	.17	1.75 (0.73– 4.24)
Death	1 (3)	4 (4)	.73	0.68 (0.01–7.23)
Hospital costs, mean value	$27,505	$14,086	<.005	…
Hospital charges, mean value	$39,310	$21,060	<.005	…

NOTE. Data are no. (%) of patients, unless otherwise indicated. LOS, length of stay; PICU, pediatric intensive care unit.

Table 4

Comparison of demographic characteristics and outcomes of patients with pneumonia due to *Streptococcus pneumoniae* serotype 3 and other serotypes.

Variable	Patients with pneumonia due to serotype 3 (*n* = 14)	Patients with pneumonia due to other serotypes (*n* = 110)	*P*	OR (95% CI)
Demographic characteristic				
Male sex	8 (57)	61 (55)	.90	…
Age, mean months	27.4	42.3	.51	…
Vaccinated	3 (21)	7 (6)	.05	4.01 (0.58–20.71)
Preexisting condition	2 (14)	18 (16)	.84	…
Outcome				
Necrotizing pneumonia	11 (79)	22 (20)	<.005	14.67 (3.39–86.25)
Empyema	12 (86)	58 (52)	.019	5.38 (1.11–51.14)
Required chest tube	12 (86)	60 (55)	.026	5.00 (1.03–47.57)
LOS, mean days	8.9	7.5	.53	…
Underwent surgical procedure	6 (43)	19 (17)	.025	3.59 (0.90–13.28)
Admitted to PICU	7 (50)	47 (43)	.61	…
Death	0 (0)	5 (4)	NS	…
Hospital costs, mean value	$21,473	$17,640	.03	…
Hospital charges, mean value	$32,442	$25,685	.022	…

NOTE. Data are no. (%) of patients, unless otherwise indicated. LOS, length of stay; PICU, pediatric intensive care unit.