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Case Series of Pneumococcal Meningitis in the Post 13-valent Pneumococcal Conjugate Vaccine Era

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Abstract

Streptococcus pneumoniae is a leading cause of meningitis. Although rates of bacterial meningitis have decreased after pneumococcal conjugate vaccine introduction, pneumococcal meningitis has not been eliminated. In this case series, we describe the presentation, serotypes, and outcomes of 11 children with pneumococcal meningitis at a tertiary children's hospital after the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced, from 2011-2013. The median age of children with meningitis was 7 years. The majority of the isolates (82%) were susceptible to penicillin. Most isolates (73%) were serotyped and there was no evidence of disease caused by serotypes contained in PCV7. Only two patients had disease caused by serotypes contained in PCV13 and neither of these patients was eligible to receive PCV13. Significant findings from our study include: lack of documented fever in a portion of patients admitted with meningitis, older age of children with pneumococcal meningitis, and no evidence of PCV7 serotypes causing invasive disease.

Keywords: Meningitis; *Streptococcus pneumonia*; PCV-13

Abbreviations: PCV7: 7-valent pneumococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine; IPD: Invasive pneumococcal disease; CSF: Cerebrospinal fluid; WBC: White blood cell count

Introduction

Streptococcus pneumoniae causes significant morbidity and mortality in adults and children. In 2011, an estimated 36,850 cases and 4,250 deaths were attributed to invasive pneumococcal disease (IPD) in the United States [1]. Following introduction of the heptavalent pneumococcal vaccine (PCV7) in 2000, the incidence of pneumococcal meningitis declined by 54% in children less than two years of age [2]. The emergence of non-PCV7 serotypes, primarily 19A, was subsequently noted [2]. In February 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the Food and Drug Administration and recommended for routine vaccination of infants and high-risk individuals in the United States [3]. This vaccine includes PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) as well as six additional serotypes (1, 3, 5, 6A, 7F and 19A) [3]. In 2012, the CDC estimated that 94% of children aged two years of age had received three doses of PCV and over 80% had received four doses of PCV in Tennessee [4]. The full impact of this vaccine on IPD rates among children is unknown, but preliminary data from a 2011 multi-center pneumococcal surveillance study suggest an overall decrease in IPD cases post-PCV13 introduction [5]. However, serotype replacement may be a concern.

Previous pneumococcal case series describe the clinical presentation, laboratory features, and outcomes of children with pneumococcal meningitis in the pre-PCV13 era [6,7]. However, clinical data on pneumococcal meningitis cases post-PCV-13 introduction are lacking. Therefore, we sought to characterize pediatric patients admitted with pneumococcal meningitis to a tertiary care center from July 2011-July 2013, including outcomes, serotypes, and susceptibility patterns.

Methods

Chart review

A retrospective chart review of pediatric patients with pneumococcal meningitis admitted to Monroe Carell Jr. Children's Hospital at Vanderbilt during the period of July 2011-July 2013 was performed. Patients transferred from an outside facility were included. Patients were identified through microbiology laboratory records; ICD9 codes for "Streptococcus meningitis" (320.1) and "Pneumococcal meningitis" (320.2); and Pediatric Infectious Diseases service consultation database. Pneumococcal meningitis was defined as a cerebrospinal fluid (CSF) culture positive for *S. pneumoniae* or the presence of Gram-positive cocci on CSF Gram stain with a blood culture positive for *S. pneumoniae* in combination with a CSF white blood cell (WBC) count of >10/μL. Hospital

records of children with pneumococcal meningitis from our institution and the referring hospital were analyzed for demographic parameters, clinical features, laboratory findings, and outcomes. Data were anonymized and transcribed onto a standardized case report form. This study was approved by Vanderbilt University's Institutional Review Board.

Bacteriologic methods

Pneumococci were isolated from blood and/or CSF and identified according to standard laboratory procedures at both Vanderbilt University and the transfer hospitals. Blood was inoculated into Bactec Plus aerobic and anaerobic bottles and incubated at 37 °C with automated monitoring. When growth was detected, blood bottles were sub-cultured onto 5% sheep's blood BSA-agar and incubated at 37 °C under 5% CO_2. CSF specimens were inoculated directly onto sheep's blood BSA-agar in this manner. Organisms isolated underwent optochin-susceptibility and/or bile-solubility testing to identify pneumococci. Antimicrobial minimum inhibitory concentrations (MICs) were determined by clinically validated methodologies: Kirby Bauer and E-test gradient diffusion or micro-strep panel. Susceptibilities for penicillin, ceftriaxone and/or cefotaxime were assessed using breakpoints for pneumococcal CSF isolates established by the Clinical Laboratory Standards Institute [8]. Isolates were referred for serotyping to either Focus Diagnostics (Cyprus, CA) or to the Centers for Disease Control if the patient was a resident of a county included in the Active Bacterial Core Surveillance network [1].

Results

Patient characteristics and clinical presentation

Eleven pediatric patients with pneumococcal meningitis were hospitalized at our hospital from July 2011-July 2013. Table 1 shows the baseline characteristics of the cases including race, age, gender and month of admission. The median age of the subjects was 7 years (range 6 weeks-14 years). Six (54%) had co-morbidities including: hereditary spherocytosis, obesity-related hypertension, asthma, pervasive developmental disorder, or craniofacial abnormality. None of the patients had a known immunodeficiency. Nine patients (82%) had concurrent illnesses, with sinusitis being the most common (Table 1).

Subject Admission Month/Year	Age (month and year)	Sex	Race/ Ethnicity	Vaccine History	Underlying Illness	Concurrent Illness	Days of Fever Prior to Admission	Temperature at admission (ºC)	Complications
1 2/2011	5mo	M	White	PCV13	None	Rhinorrhea	Yes (5d)	39	Mild unilateral hearing deficit
2 4/2011	12mo	F	White	PCV13	None	Acute otitis media	Yes (4d)	37.2	None
3 12/2011	14y6mo	M	White	PCV7	None	None	Yes (4d)	39	None
4 2/2012	1.5mo	F	White	None	None	None	Yes (5d)	39.2	Seizure (HD 4)
5 2/2012	12y5mo	F	Black	None	None	Sinusitis	Yes (2d)	37.9	Lateral gaze palsy (resolved by HD 4)
6 9/2012	9y6mo	M	White	PCV7	Pervasive developmental delay	Pharyngitis	None	36.9	Seizures (HD 1), herniation, expired (HD 2)
7 12/2012	6mo	M	White	PCV13	Mild hereditary spherocytosis	Acute otitis media	Yes (6d)	39.4	Seizure (HD 1)
8 12/2012	6y	M	Black	PCV7	Overweight, hypertension	Sinusitis	Yes (2d)	37	Psychiatric changes, bilateral hearing loss
9 12/2012	9y	F	Hispanic	PCV7	Asthma	Sinusitis	None	37.4	Herniation, expired (HD 2)
10 3/2013	6y	F	White	PCV7	Multiple facial fractures (orbital roof and R orbital floor) & encephalocele from motor vehicle accident one year prior to admission	Sinusitis	Yes (1d)	37.2	None
11 5/2013	13y	M	White	PCV7	None	Sinusitis	Yes (2d)	37.8	None

y: year, **mo:** Month
HD: Hospital day

Table 1: Demographics and Clinical Characteristics of 11 Cases of Pneumococcal Meningitis

At the time of admission to the hospital, only four (36%) patients had a documented fever (temperature ≥ 38.0 °C). Nine (82%) patients had fever at home, and two (18.2%) patients had no documented fever at home or on presentation. Vomiting was the most common symptom prior to admission (73%) (Table 1).

Laboratory studies

Median peripheral WBC count was $30x10^3$/µl ($8.6x10^3$/µl to $47x10^3$/µl), with higher mean WBC counts at admission in non-survivors compared to survivors (p=.03, Wilcoxon rank sum; Table 2). CSF WBC counts ranged from 125 x 10^3/mm3 to $9950x10^3$/mm^3 (median=$940x10^3$/mm^3) (Table 2). Seven cases (64%) had documented bacteremia and CSF cultures were positive in nine patients. The two patients with sterile CSF cultures received antibiotics prior to CSF evaluation but had Gram-positive diplococci on CSF Gram stain and blood cultures positive for *S.pneumoniae.*

Patient ID	Blood WBC	Initial CSF WBC (% neutrophil)	Initial CSF glucose	Initial CSF protein	Positive Culture and Serotype	Penicillin Sensitivity (MIC)	Ceftriaxone/ Cefotaxime Sensitivity (MIC)
1	$14.7x10^3$/µl	125/mm^3 (30%)	<1 mg/dL	239 mg/dL	Bld, CSF	S (0.016)	S (0.016)
2	10.4 $x10^3$/µl	180/mm^3 (86%)	0 mg/dL	185 mg/dL	CSF	S (0.016)	S (0.023)
3	13.6 $x10^3$/µl	2178/mm^3 (54%)	5 mg/dL	213 mg/dL	CSF	R (≥0.120)	U
4	8.6 $x10^3$/µl	1238/mm^3 (74%)	0 mg/dL	573 mg/dL	Bld, CSF 3^2	S (0.016	S (0.032)
5	30 $x10^3$/µl	3200/mm^3 (75%)	<1 mg/dL	519 mg/dL	CSF $17F^3$	S (≤0.030)	S (≤0.250)
6	46.8 $x10^3$/µl	9950/mm^3 (100%)	<5 mg/dL	270 mg/dL	Bld, CSF $23B^3$	R (0.190)	S (0.190)
7	15.7 $x10^3$/µl	940/mm^3 (86%)	0 mg/dL	162 mg/dL	Bld $12F^3$	S (0.047)	S (0.094)
8	29.6 $x10^3$/µl	807/mm^3 (84%)	<20 mg/dL	1313 mg/dL	CSF $19A^2$	S (0.032)	S (0.032)
9	11.7 $x10^3$/µl	219/mm^3 (89%)	33 mg/dL	352 mg/dL	Bld 34^3	S (0.016)	S (0.016)
10	31.6 $x10^3$/µl	2544/mm^3 (75%)	36 mg/dL	261 mg/dL	Bld, CSF $24F^3$	S (0.032)	S (0.032)
11	$9.96x10^3$/ µl	853/mm3 (100%)	65 mg/dL	58 mg/dL	Bld , CSF $11A^3$	S (0.016)	S (0.016)

[1]Indicates PCV7 serotype, [2]Indicates PCV13 serotype, [3]Indicates non-PCV serotype
S: Susceptible, **R:** Resistant, **U:** Unknown
MIC: Minimum inhibitory concentration.

Table 2: Lab characteristics

Clinical course and outcomes

All patients were empirically treated with vancomycin and ceftriaxone or cefotaxime at meningitic dosing. In the nine cases where an isolate was susceptible to penicillin, vancomycin was discontinued. Of two patients with penicillin-resistant *S. pneumoniae* meningitis, only one survived. The survivor was treated with 10 days of combination therapy with ceftriaxone and vancomycin because ceftriaxone susceptibilities were not performed due to poor growth of the isolate.

Four (36%) patients required mechanical ventilation due to profoundly altered mental status. Two (18%) of these patients required vasopressors and both died within one day of presentation. Four (36%) patients had seizures during hospitalization. Duration of follow up ranged from 10 days to 1 year. Serious complications included hearing loss in two (18%) patients, with one patient requiring bilateral cochlear implants. This patient also developed hallucinations and delirium and required psychiatric medications. Other patient complications are listed in Table 1.

Penicillin susceptibility and serotype information

Only two isolates were resistant to penicillin (Table 2). Serotype information was available for eight (72%) of the isolates. Three isolates were not sent for serotyping. In those sent for testing, none were PCV7 serotypes; however two (25%) of the serotypes were PCV13 serotypes (Table 2). Notably these two patients had not received any doses of PCV13.

Discussion

Despite the reported declines in IPD after the introduction of PCV7 and PCV13, our institution had 11 cases of pneumococcal meningitis during a two-year period in the post-PCV13 era. None of the cases were PCV7 serotypes but two subjects had meningitis due to PCV13 serotypes (3 and 19A). One was a 6 week old infant who had not yet received PCV-13 and the other was a 6 year-old previously vaccinated with PCV7 who did not meet criteria for PCV13 administration. These data are consistent with our group's prior publication documenting elimination of IPD due to PCV7 serotypes in children <12 years of age from 2005-2008, with nearly half of IPD cases due to PCV13 serotypes, predominantly 19A [9].

A surprising finding of our study was that the median age of our patients was 7 years. In a larger study conducted by Hsu et al. pre-PCV13, the median age of pediatric patients with pneumococcal meningitis was 15 months [10]. Another interesting finding is that our cases had meningitis due to pneumococcal serotypes that have been thought to be less virulent in prior studies, specifically 24F, 34, 17F and 23B; some of which have infrequently caused IPD [10,11]. Larger case series and population surveillance will help further elucidate whether or not these trends are seen on a national scale post-PCV13.

Although our sample size was small, our study shares similarities with pre-PCV13 pneumococcal meningitis reports. For instance, our case fatality rate and seizure rate are similar to those published in other, larger case series [6,7]. Our study suggests that the morbidity and mortality of pneumococcal meningitis cases post-PCV13 is similar to that pre-PCV13. Patients in our case series had higher frequency of concomitant sinusitis (45%) compared to a series of pediatric meningitis cases by Ostergaard et al. which reported only 2% of cases having sinusitis [7]. Otitis media was less frequent in our study as compared to the Ostergaard study [7].

Interestingly, only 36% of our patients had documented fever in the hospital at admission. Unfortunately we do not have documentation of whether or not anti-pyretics were administered at home. However, only 82% of our patients had a history of fever at home. Of the two patients who were afebrile prior to admission, both presented with altered mental status and headache, and both subsequently died. One was initially diagnosed with a migraine and the other with a possible cerebrovascular accident. Therefore, this case series highlights the need for thorough history taking and for CSF evaluation in patients with altered mental status, even in the era of PCV13 usage.

The main limitations of our study are the small sample size and variable duration of follow-up. Not all isolates were serotyped. Since patients were not followed for a fixed amount of time it is possible that some patients developed complications after hospital discharge that were not included in their medical record. In addition, since we are not using molecular diagnostics such as PCR, we are only capturing culture positive meningitis cases and may be underestimating the burden of disease.

Conclusions

Our case series indicates that in the post-PCV13 era, *S. pneumoniae* meningitis continues to be a significant concern, especially when 75% of the cases with confirmed serotypes were due to non-PCV13 serotypes. Furthermore, these children were older, healthy children and not considered high risk for IPD. This study emphasizes the need for heightened awareness of pneumococcal meningitis in children with meningismus or altered mental status of all ages even if they are afebrile. In addition, continued surveillance of IPD is imperative; especially to document which non-vaccine serotypes are causing IPD. These data can have implications for future immunization policy and vaccine targets.

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