Pneumococcal Meningitis in the PCV13 Era: A Cluster of Cases With Increased Morbidity and Mortality

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Introduction

Pneumococcal meningitis is a rare but serious disease in infants and young children. In 2010, the Advisory Committee on Immunization Practices recommended the use of PCV13 (13-valent pneumococcal conjugate vaccine) in place of PCV7 for routine use in children. This occurred after a rise in invasive pneumococcal disease (IPD), including meningitis, caused by nonvaccine serotypes of Streptococcus pneumoniae. It was predicted that the inclusion of an additional 6 serotypes would decrease the incidence of IPD including meningitis in both immunized and underimmunized children as it did after PCV7.

In the state of Wisconsin, rates of pneumococcal meningitis have been consistently low since 2003 with 1 to 5 reported cases per year (personal communication: Jeffrey Davis, MD; Chief Medical Officer and State Epidemiologist). Our children’s hospital, which serves a large geographic area of both rural and urban patients in Wisconsin and northern Illinois, had infrequent admissions of children with pneumococcal meningitis over the past ten years. However, we observed a cluster of cases within a 17-month period during 2013 and 2014 with a severe degree of morbidity and 2 fatalities. The purpose of this case series is to alert health care providers who care for children to the ongoing and perhaps increasing need for a high degree of clinical suspicion for pneumococcal meningitis in infants and young children due to serotype replacement.

Methods

The 7 patients described in this series were identified through direct patient care provided by the authors and by a systematic search of medical records from January 2004 until December 2014 using ICD-9 (International Classification of Diseases, Ninth Revision) codes for pneumococcal meningitis (320.1), bacterial meningitis (320), and streptococcal meningitis (320.2). Diagnoses were verified by review of the medical record from which pertinent clinical information and laboratory data were abstracted. Meningitis was defined as pleocytosis in the cerebrospinal fluid (CSF) and a blood or CSF culture positive for S pneumoniae. The exception to this definition was a single patient with a positive blood culture for S pneumoniae who presented with clinical signs of meningitis and brain herniation in whom CSF was not obtained. The cluster of cases of pneumococcal meningitis occurred between September 2013 and December 2014.

To compare the number of cases of pneumococcal meningitis to cases of IPD other than meningitis, patients aged 0 to 18 years admitted to the children’s hospital over the past 10 years with culture proven IPD were identified through a retrospective search and review of medical records. To identify children with a diagnosis of IPD not including meningitis, the following diagnosis codes were used: pneumococcal septicemia (038.2), pleural effusion (511.1), pyogenic arthritis (711.0), pneumococcal peritonitis (567.1), pericarditis (420.99), and septic myocarditis (422.92). IPD was defined as isolation of S pneumoniae from a normally sterile body site (blood, pleural fluid, etc). The institutional review board of the University of Wisconsin approved this study.

Serotyping of pneumococcal isolates was performed at Focus Diagnostics (Cypress, CA). Colonies were serologically identified by type-specific antisera in a co-agglutination reaction.

Results

Fourteen cases of pneumococcal meningitis and 12 cases of IPD not including meningitis were identified during the study period (Figure 1). Between January 2004 and December 2012 there were 0 to 2 cases of
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pneumococcal meningitis each year. In contrast, we identified 7 cases of pneumococcal meningitis presenting in children aged 5 months to 6 years between July 2013 and December 2014 (Table 1). The duration of symptoms prior to presentation ranged from 2 to 5 days (mean 3.4 days). CSF analysis was remarkable for very modest pleocytosis observed in all but 1 child. Six children had a positive CSF Gram stain for Gram-positive diplococci with cultures positive for \textit{S pneumoniae}. The 6-year-old child who was moribund on presentation had a positive blood culture and brain imaging, which showed meningeal enhancement and herniation.

All 5 surviving children with meningitis experienced severe hearing loss and developmental impairment. In addition, 2 children developed seizures, 2 developed hemolytic uremic syndrome, 1 developed hydrocephalus requiring a shunt, 2 had transient cranial nerve palsy, 1 suffered persistent palsy of cranial nerve II, and 2 children died.

Two patients completed immunization with PCV13 and both were infected with nonvaccine serotype 23B. Two children were partially immunized with PCV13 and both were infected with nonvaccine strains (22F, 15B). Three infections resulted from serotypes contained within PCV13: A 5-month-old infant who received 2 doses of PCV13 and a 6-year old with an unknown immunization history were both infected with serotype 19A, and an unimmunized toddler was infected with serotype 18C. Immunological studies performed on the 5-month-old showed normal immunoglobulins and total hemolytic complement. The patient had no known conditions such as asplenia or sickle cell anemia that would predispose to a pneumococcal infection.

**Discussion**

We report a cluster of cases of pneumococcal meningitis in young infants and children in the PCV13 era associated with a very high degree of morbidity and mortality. All patients in this cluster experienced neurologic sequelae in contrast to rates of 40% to 63% reported in the recent literature.\textsuperscript{4,6} In addition, all our surviving patients had profound hearing loss compared to 29% to 30% reported in the series from Utah and Nationwide Children’s Hospital.\textsuperscript{4,6} Also surprising was the modest CSF pleocytosis (in 5 children) despite high levels of bacterial burden as demonstrated by the positive Gram stains. The mortality rate in children with pneumococcal meningitis is expected to be in the range of 8% to 13% in well-resourced health care settings;\textsuperscript{5,4} however, the mortality rate in this small series was 29%.

Data have begun to appear regarding the effectiveness and impact of PCV13 on IPD. While 2 early reports showed a decrease in the number of cases of IPD in 2010 and 2011,\textsuperscript{7,8} a report from Spain showed no change in the rate of pneumococcal meningitis after introduction of PCV13.\textsuperscript{9} Our cluster of cases is consistent with reports from Kaplan and colleagues, which also shows that rates of pneumococcal meningitis are not decreasing as rapidly as other manifestations of IPD following PCV13.\textsuperscript{8,10} The recent retrospective surveillance study from New York City, documents the decreasing incidence of IPD but does not comment on meningitis in particular.\textsuperscript{11} An explanation for persisting rates of meningitis may be a serotype shift with increased propensity for central nervous system invasion by some serotypes not included in PCV13. Four of our 7 cases were infected with nonvaccine serotypes, including 1 infant who died.

There are several possible explanations for the poor outcomes in these cases. The decreasing incidence of meningitis in general may lower practitioners’ suspicion for bacterial meningitis, which may lead to delayed diagnosis. The modest pleocytosis observed in 5 patients may reflect a less robust inflammatory reaction which in turn may be associated with fewer early symptoms, also leading to delayed diagnosis. Poorer outcomes may in part be explained by increased virulence (19A, 15B) for some serotypes.\textsuperscript{12} Finally, several children were younger than 1 year, which in itself may portend poorer prognosis.\textsuperscript{13} Although patients with underlying medical conditions have an associated higher degree of morbidity, all of our patients were previously healthy.\textsuperscript{7}

The main limitation to this brief report is that it is not population-based, and we are thus not able to comment on incidence rates. Accordingly, the high degree of observed morbidity and mortality, in addition to the clustering of cases, may simply be a chance event. Nonetheless, it is alarming that 7 of 14 cases occurring during a 10-year period were observed during 17 months.

In conclusion, we report a cluster of severe cases of \textit{S pneumoniae} meningitis in 2013 and 2014. We highlight these cases to alert pediatric health care providers to the
## Table 1. Cases of Pneumococcal Meningitis From July 2013 to December 2014.

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Presenting Symptoms</th>
<th>Duration of Symptoms Before Diagnosis</th>
<th>Doses of PCV13</th>
<th>Blood Culture Results</th>
<th>Initial CSF Results</th>
<th>Complications Observed in Hospital</th>
<th>Duration of Follow-up After Admission</th>
<th>Subacute Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 months</td>
<td>Fever, lethargy, low tone, unilateral esotropia</td>
<td>3 days</td>
<td>3</td>
<td>Positive</td>
<td>196</td>
<td>N/A</td>
<td>130</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5 months</td>
<td>Fever, poor feeding, grunting with lethargy on day of admission</td>
<td>36 hours</td>
<td>2</td>
<td>Positive</td>
<td>46</td>
<td>166</td>
<td>135</td>
<td>15</td>
</tr>
<tr>
<td>15 months</td>
<td>Fever, emesis, irritability</td>
<td>2 days</td>
<td>4</td>
<td>Positive</td>
<td>85</td>
<td>32</td>
<td>U</td>
<td>&lt;1</td>
</tr>
<tr>
<td>18 months</td>
<td>Fever, ear pain, emesis, lethargy, right lateral gaze palsy</td>
<td>5 days</td>
<td>0</td>
<td>Negative</td>
<td>201</td>
<td>29</td>
<td>86</td>
<td>19</td>
</tr>
<tr>
<td>9 months</td>
<td>Fever, emesis, rhinorrhea, congestion with decreased oral intake and lethargy on day of admission</td>
<td>5 days</td>
<td>3</td>
<td>Negative</td>
<td>93</td>
<td>171</td>
<td>1370</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5 months</td>
<td>Fever, poor feeding, irritability with seizure on day of admission</td>
<td>2 days</td>
<td>2</td>
<td>Positive</td>
<td>632</td>
<td>35</td>
<td>474</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6 years</td>
<td>Rhinorrhea, cough, seizure</td>
<td>3 days</td>
<td>U</td>
<td>Positive</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cells; NA, not applicable; U, unavailable.

*PCV13 serotype.
ongoing need for considerable suspicion for bacterial meningitis in the PCV13 era and hypothesize that this cluster may reflect ongoing serotype shift with increased central nervous system propensity by serotypes not included in PCV13. This study supports the need for ongoing population-based surveillance for invasive pneumococcal disease.

**Author Contributions**
SW conceived the idea for manuscript, performed chart review, and authored manuscript. GC performed chart review and authored manuscript. ERW reviewed and edited manuscript and discussed format. GDM reviewed and edited manuscript and discussed format.

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**References**