An Epidemiological Investigation of a Sustained High Rate of Pediatric Parapneumonic Empyema: Risk Factors and Microbiological Associations

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We investigated the increasing incidence of pediatric empyema during the 1990s at Primary Children’s Medical Center in Salt Lake City. Of 540 children hospitalized with community-acquired bacterial pneumonia (CAP) who were discharged from 1 July 1993 through 1 July 1999, 153 (28.3%) had empyema. The annual population incidence of empyema increased during the study period from 1 to 5 cases per 100,000 population aged <19 years. Streptococcus pneumoniae was identified as the most common cause of CAP with or without empyema; serotype 1 accounted for 50% of the cases of pneumococcal empyema. Patients with empyema were more likely to be >3 years old, to have >7 days of fever, to have varicella, and to have received antibiotics and ibuprofen before admission to the hospital, compared with patients without empyema (P < .0001 for each factor). The increasing incidence of empyema was associated with infection due to S. pneumoniae serotype 1, outpatient treatment with certain antibiotics, ibuprofen use, and varicella.

Parapneumonic effusion and empyema are recognized complications of bacterial pneumonia. Empyema develops in ~5% of adults with bacterial pneumonia [1]. The incidence among children hospitalized for pneumonia has been reported to be ~0.6% [2]. A significant number of patients hospitalized with bacterial pneumonia at Primary Children’s Medical Center (PCMC) in Salt Lake City, Utah, in the mid-1990s were noted to have empyema, an observation that prompted an epidemiological investigation. The objectives of the investigation were (1) to determine the incidence of parapneumonic empyema among pediatric patients hospitalized with community-acquired bacterial pneumonia (CAP) in Utah; (2) to describe and compare the demographic characteristics and the clinical and microbiological findings for hospitalized patients with CAP who did and who did not have empyema; and (3) to determine if there are specific modifiable risk factors for the development of empyema in children.

PATIENTS AND METHODS

Patient ascertainment. The electronic medical record system at PCMC was searched for the period from 1 July 1993 to 1 July 1999 to identify all patients dis-
charged with ICD-9 (International Classification of Diseases, 9th revision) codes of 481–482.9 (bacterial pneumonia) and/or 510.0–510.9 (empyema, pleural effusion). The medical chart of each of these subjects was reviewed to confirm the diagnosis of CAP with or without empyema.

CAP was considered to be present if the chest radiograph demonstrated a focal infiltrate and if none of the exclusion criteria were present. Patients were excluded if the pneumonia was likely to have been viral in etiology (e.g., if there was a finding of a nonfocal infiltrate in a patient with respiratory syncytial virus infection), caused by aspiration, hospital acquired, associated with cystic fibrosis, or manifest at birth (in neonates).

Empyema was considered to be present if there was a finding of a pleural effusion on the chest radiograph coupled with any of the following additional findings: pleural fluid with a pH of ≤7.2, a lactate dehydrogenase level of ≥1000 IU/mL, a glucose level of ≤20 mg/dL, a protein level of ≥3000 mg/dL, and/or a WBC count of ≥50,000 cells/µL [3, 4]; culture or Gram staining of pleural fluid that was positive for bacteria; or need for surgical decortication. Surgical and pathology reports were reviewed to confirm the diagnosis of empyema.

Patients with a pleural effusion were excluded from the empyema group if there were no pleural fluid analysis results or if there were findings consistent with a transudate; however, these patients could be classified as having bacterial pneumonia if they fulfilled the inclusion criteria. Patients who had CAP and empyema were compared with patients who had CAP alone.

The study was reviewed and approved by the institutional review boards of both the University of Utah and Primary Children’s Medical Center in Salt Lake City.

Demographic and clinical evaluation. Demographic and clinical information obtained included the following: age; sex; race or ethnicity; date of admission to the hospital; length of hospital stay; signs and symptoms of infection at presentation; duration of symptoms; clinical outcome; and potential risk factors for the development of empyema, including antibiotic exposure before admission, ibuprofen or acetaminophen use before admission, immunization status, history of recent viral illness, immunodeficiency, chronic illness, tobacco use or exposure, and attendance at a daycare facility.

Microbiological evaluation. The computerized microbiological records at PCMC were reviewed. Bacterial isolates from blood, pleural fluid, and surgical specimens were analyzed. Antimicrobial susceptibility profiles were collected for each bacterial isolate. For *Streptococcus pneumoniae*, penicillin susceptibility was defined according to the MIC of penicillin, as determined by use of the Etest (AB Biodisk) and with use of MIC break points established by the National Committee for Clinical Laboratory Standards [5].

The microbiology laboratory at PCMC routinely freezes specimens of pathogens isolated from blood and other normally sterile sites at −70°C. Viable isolates of *S. pneumoniae* recovered from patients with and without empyema were serotyped by means of the capsular swelling method with use of commercially available antiserum samples (Statens Serum Institut or Dako). The investigators who performed the analysis (E.O.M. and S.K.) were blinded to the sources of the pathogen samples.

Pulsed-field gel electrophoresis (PFGE) was done for all *S. pneumoniae* serotype 1 isolates by means of clamped homogeneous electric fields electrophoresis on a CHEF Mapper (Bio-Rad), as described elsewhere [6]. Genomic DNA in 2% IncCert agarose plugs (FMC BioProducts) was digested with *Smal*. DNA was subjected to electrophoresis in a 1.2% agarose gel with a voltage gradient of 6 V/cm and a switch time ramped linearly from 1 to 20 s over 21 h. Band patterns were interpreted according to the criteria established by Tenover et al. [7].

**Estimation of population incidence and statewide attack rate of empyema.** To estimate the population incidence of empyema, only data for case patients who resided in Utah were analyzed. Annual estimates of the pediatric population were obtained from the US Bureau of the Census [8]. To evaluate the statewide attack rate of empyema, discharge data were collected for all 55 licensed hospitals in Utah (Gulzar Shah, personal communication). Search criteria included age of <19 years, discharge from any hospital in Utah during the period from 1 July 1993 through 31 December 1998, and an ICD-9 diagnosis code of 481–482.9.

**Statistical analysis.** Stata, version 6.0 (Stata Corp.), and Epi Info 2000 (USD) were used for the statistical analysis. Categorical variables were analyzed by either the χ² test or Fisher’s exact test, and continuous variables were analyzed by either Student’s t test or nonparametric tests. For each potential risk factor for empyema, simple ORs and CIs were determined. A multivariate logistic regression model was constructed with use of historical, clinical, and microbiological variables to assess independent risk factors and calculate adjusted ORs. Variables were selected for testing in the model on the basis of clinical relevance and statistical significance in the crude analysis; P< .1 was considered significant. Confounding was evaluated by assessment of changes in β coefficients in models with and without putative confounding variables. By use of appropriate multiplicative terms, 2-way interactions were examined.

**RESULTS**

**Patient ascertainment.** Records were identified for 1093 patients with a discharge diagnosis of bacterial pneumonia with or without empyema; 540 (49%) of these patients fulfilled our criteria for a diagnosis of CAP. Of these 540 patients, 153 (28.3%) had CAP complicated by empyema. The rate of empyema among the patients with CAP was 28.3%, and the statewide attack rate of empyema was 28.3%.
Table 1. Pathogens isolated from pleural fluid or blood samples obtained from children aged <19 years with cases of bacterial pneumonia with or without empyema.

<table>
<thead>
<tr>
<th>Isolate, source of isolate</th>
<th>With empyema (n = 153)</th>
<th>Without empyema (n = 387)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>46 (72)</td>
<td>23 (92)</td>
<td>.04</td>
</tr>
<tr>
<td>Blood</td>
<td>26</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>Blood and pleural fluid</td>
<td>14</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>9 (14)</td>
<td>1 (4)</td>
<td>.18</td>
</tr>
<tr>
<td>Blood</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>7 (11)</td>
<td>1 (4)</td>
<td>.3</td>
</tr>
<tr>
<td>Blood</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>3 (4.6)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Total with positive culture result</td>
<td>64a (42)</td>
<td>25 (6.5)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NOTE. NA, not applicable.

* One patient had 2 organisms isolated (*S. pneumoniae* and *Enterococcus faecalis*).

Empyema in hospitalized patients with CAP ranged from 13% in 1994 to 41% in 1997.

All cases of empyema were clinically and radiographically manifest at admission to the hospital. Pleural fluid samples obtained from 53 (35%) of 153 patients with empyema were analyzed. All had results consistent with the definition of empyema, and 31 patients required decortication. Overall, decortication was done for 118 (77%) of 153 patients with empyema. Surgical reports confirmed the diagnosis of empyema for all 118 patients. Intraoperative specimens from 31 (26%) of 118 patients were submitted for pathological review, and the diagnosis of empyema was substantiated for all 31.

**Demographic and clinical evaluation.** Children with empyema were significantly older than those with CAP alone (71 months vs. 47 months; P < .0001). The majority (70%) of the patients in each group were white, and there were no significant differences between groups with respect to sex or race/ethnicity. Fever was the most common presenting feature in both groups. Patients with empyema had a longer duration of fever before hospitalization than did children with CAP alone (8 days vs. 4.6 days; P < .001), and they were more likely to have chest pain (P < .0001), abdominal pain (P = .0005), or dyspnea (P = .0021).

Patients with empyema experienced significantly more morbidity than did patients with CAP alone. They were more likely to require chest tube thoracostomy, treatment in the intensive care unit, longer hospital stays, and longer duration of antibiotic therapy (P < .0001 for each factor). Decortication was required for the majority of patients with empyema secondary to loculated fluid collections associated with poor chest-tube drainage and ongoing signs of illness. Despite the serious nature of the illness, there was no mortality associated with empyema.

**Microbiological evaluation.** Pathogenic bacteria were recovered from blood or pleural fluid samples obtained from 64 patients (42%) with empyema and 25 patients (6.5%) with pneumonia (P < .0001; table 1). For 9 additional patients with empyema, gram-positive cocci were revealed by Gram staining of pleural fluid samples. Seventy-nine patients with empyema had blood cultures done and 21 (26.5%) had culture results positive for a pathogen, compared with 25 (11.4%) of 220 patients with pneumonia (P = .001). *S. pneumoniae* was the most commonly identified cause of CAP with or without empyema.

Of the 69 patients from whom *S. pneumoniae* had been isolated, 40 (60%) had viable isolates that were recovered and serotyped (table 2). Of pneumococcal isolates recovered from patients with empyema, 50% were serotype 1, compared with 7% of those recovered from patients with pneumonia (P = .007). Results of PFGE indicated that all *S. pneumoniae* serotype 1 isolates were indistinguishable or closely related (1–2 band differences), according to the criteria of Tenover et al. [7]. These isolates were obtained from patients treated in 1993 (1 isolate), 1995 (4), 1996 (2), 1997 (3), 1998 (2), and 1999 (2). All patients were from 3 contiguous counties; Salt Lake County (10 patients), Tooele County (2), and Davis County (2). These 3 counties contain 50% of Utah’s population but accounted for 65% of all cases of empyema reported.

Patients with empyema due to *S. pneumoniae* were less likely to be infected with penicillin-nonsusceptible organisms than were patients with uncomplicated pneumococcal pneumonia (16% vs. 48%; P = .0021). All serotype 1 pneumococcal isolates...
were susceptible to penicillin. In addition, 14 (70%) of the 20 pneumococcal isolates from patients with empyema that were identified but not recovered for serotyping were susceptible to penicillin.

**Nonmicrobiological factors associated with empyema.**

Univariate analysis of variables potentially associated with empyema formation was done (table 3). Empyema was significantly associated with outpatient treatment with the following drugs: ceftriaxone (OR, 4.1; 95% CI, 2.0–8.3; \( P < .0001 \)), azithromycin (OR, 3.2; 95% CI, 1.3–8.1; \( P = .013 \)), cefaclor (OR, 3.5; 95% CI, 1.1–11.5; \( P = .031 \)), and ibuprofen (OR, 7.8; 95% CI, 2.2–32.8; \( P < .0001 \)). Varicella-zoster virus infection in the month before hospitalization was also associated with empyema (OR, 6.23; 95% CI, 1.06–46.09; \( P = .023 \)). The proportion of patients who attended a day-care facility, were exposed to tobacco, or had immunodeficiency or chronic illness were similar for the 2 groups, as were patient’s immunization histories.

As displayed in table 4, clinical correlates of empyema determined by logistic regression analysis were as follows: history of varicella (OR, 14; 95% CI, 2.3–86.5; \( P < .0001 \)), \( \geq 7 \) days of fever prior to hospitalization (OR, 6.4; 95% CI, 2.9–13.9; \( P < .0001 \)), age \( \geq 3 \) years (OR, 4.0; 95% CI, 1.9–8.2; \( P < .0001 \)), and presence of chest pain (OR, 2.4; 95% CI, 1.2–4.7; \( P = .01 \)). Also correlated with empyema were use of ibuprofen (OR, 4.0; 95% CI, 2.5–6.5; \( P < .0001 \)) and receipt of ceftriaxone prior to hospitalization (OR, 3.3; 95% CI, 1.5–7.1; \( P < .0001 \)).

**Estimation of population incidence and statewide attack rate of empyema.**

Statewide discharge data identified 1197 hospitalizations for bacterial pneumonia from 1 July 1993 through 31 December 1998. During this period, 123 patients from Utah with empyema were cared for at PCMC. The minimum attack rate for empyema in Utah children hospitalized with CAP during this period was 123 (10.3%) of 1197. The annual population incidence for empyema in Utah increased from 1 per 100,000 population aged \(< 19\) years in 1994 to 5 per 100,000 in 1999 \( (P = .0002; \text{figure 1}) \).

**DISCUSSION**

During the past decade, investigators at our institution and others noted an increase in the number of cases of complicated pneumonia and empyema \([9–12]\). Almost 30% of pediatric patients hospitalized for CAP at PCMC during 1993–1999 had empyema as a complication of their illness. The minimum occurrence of empyema in the Utah pediatric population hospitalized with CAP was 10.3%. This attack rate for empyema is much higher than has been reported previously for either children or adults \([1, 2]\). The pathogen most commonly identified was \( S. pneumoniae \). Children with empyema in our series had a median age of \( \sim 6 \) years. One possibility to explain the increased occurrence of pneumococcal empyema in older children in Utah is the appearance of a new virulent serotype in the community. Pneumococcal serotype 1 is highly virulent and accounts for 15%–20% of invasive pneumococcal disease in Latin America, Asia, Africa, and some European countries \([13]\). The fact that \( S. pneumoniae \) serotype 1 was isolated from 50% of patients with documented pneumococcal empyema supports this hypothesis, as does the fact that 65% of cases of empyema reported were from the 3 counties in which pneumococcal serotype 1 was found. All serotype 1 isolates available for analysis by means of PFGE were either identical or closely related, further substantiating the hypothesis of clonal spread.

\( S. pneumoniae \) serotype 1, which is generally considered a pathogen of the developing world, has been reported to account for 1%–2.4% of cases of invasive pneumococcal disease in the United States \([13–16]\). The surveillance areas reported for the United States do not include intermountain western states such as Utah \([14–16]\). \( S. pneumoniae \) serotype 1 may be an emerging pathogen in the United States in certain geographic areas \([9, 10, 12]\). Others have documented significant variations in the distribution of serotype 1 in different ethnic and cultural groups and have suggested that outbreaks of serotype 1 disease may occur in underprivileged populations living in impoverished conditions \([17, 18]\). In contrast, the Utah population with empyema were members of the majority population, were well nourished, and were living in a setting that, by global standards, would be considered affluent; these observations suggest that either serotype 1 virulence factors, host factors, or environmental factors other than poverty contributed to the observed increase in empyema.

In an era when vaccines against pneumococcal disease are available, it is important to understand the epidemiology of serious pneumococcal infection in order to plan strategies that

<table>
<thead>
<tr>
<th>Serotype</th>
<th>With empyema (n = 28)</th>
<th>Without empyema (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>13 (50)</td>
<td>1 (7)a</td>
</tr>
<tr>
<td>Type 14</td>
<td>4 (15)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Type 9</td>
<td>4 (15)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Type 19</td>
<td>1 (4)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Type 18</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Type 12</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Type 29</td>
<td>1 (4)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Nontypeable</td>
<td>1 (4)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Type 24</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Type 6</td>
<td>0</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Type 7</td>
<td>0</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

* \( P = .007 \).
will help prevent invasive disease and to remain vigilant for changes in serotype distribution. The recently licensed 7-valent pneumococcal conjugate vaccine (Prevnar; Wyeth-Lederle Vaccines) that is recommended for universal use in children ≤23 months of age does not contain serotype 1 [19]. However, the licensed 23-valent polysaccharide vaccines and both the investigational 9-valent and 11-valent pneumococcal conjugate vaccines contain serotype 1 [13].

In addition to infection with S. pneumoniae serotype 1, several other risk factors for empyema were revealed by this study. Recent varicella-zoster virus infection was strongly associated with development of empyema. Universal immunization with varicella vaccine, which is currently recommended by the American Academy of Pediatrics, has the potential to decrease the occurrence of empyema. In addition, early recognition of pneumonia may be an important factor in the prevention of empyema [20]. Children with empyema were older and were more likely to present to the hospital with a history of prolonged fever and outpatient treatment with antibiotics and ibuprofen use. The antibiotics found to be associated with the development of empyema were azithromycin, cefaclor, and ceftriaxone. Resistance of S. pneumoniae to the oral agents has been reported in vitro, and both azithromycin and cefaclor have been associated with pneumococcal treatment failures in vivo [21–25]. Although ceftriaxone is effective against even drug-resistant S. pneumoniae, it is likely to be given as a single low dose when administered intramuscularly. Treatment with these antibiotics might lead to inadequate drug levels in the pleural space and contribute to empyema formation.

Ibuprofen use by outpatients was also associated with empyema. Our data cannot identify whether ibuprofen was given

### Table 3. Univariate analysis of variables potentially associated with empyema formation in children aged <19 years with cases of bacterial pneumonia with or without empyema.

<table>
<thead>
<tr>
<th>Variable</th>
<th>With empyema (n = 153)</th>
<th>Without empyema (n = 387)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication received before hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>77 (50)</td>
<td>264 (68)</td>
<td>.0001</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>23 (15)</td>
<td>16 (4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>12 (8)</td>
<td>10 (3)</td>
<td>.013</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>8 (5)</td>
<td>6 (1.6)</td>
<td>.031</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>14 (9)</td>
<td>32 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>14 (9)</td>
<td>18 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>7 (4.6)</td>
<td>6 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Antipyretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen only</td>
<td>31 (20)</td>
<td>188 (49)</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen with or without acetaminophen</td>
<td>118 (77)</td>
<td>166 (43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>None</td>
<td>3 (2)</td>
<td>33 (9)</td>
<td></td>
</tr>
<tr>
<td>Coinfections or comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>3 (2)</td>
<td>16 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Varicella</td>
<td>5 (3)</td>
<td>2 (0.5)</td>
<td>.023</td>
</tr>
</tbody>
</table>

**NOTE.** NS, not significant.

* For factors divided into multiple mutually exclusive categories, a single P value (determined by Fisher’s exact test) is given.
before or after the development of empyema. Therefore, it is not possible to state whether ibuprofen use caused empyema to develop. Ibuprofen use might allow children with significant disease to be managed more comfortably at home, delaying definitive treatment. It is also possible that use of ibuprofen directly contributed to the development of empyema. Low dosages of ibuprofen, such as those given for antipyresis, have been shown to be proinflammatory, encouraging the influx of neutrophils and increasing the levels of cytokines in the lungs of animals and humans with cystic fibrosis [26–28]. Ibuprofen use has also been implicated as a risk factor in the development of necrotizing fasciitis in children with *Streptococcus pyogenes* infections [29–31]. Further investigation is needed regarding the immunomodulating properties of ibuprofen in children, especially in those with streptococcal infections.

This study examined the occurrence of empyema in children hospitalized with CAP. The study was limited by its retrospective design and by an inability to confirm a bacterial etiology of pneumonia for all patients. However, positive blood culture results were obtained for 11.4% of children with simple bacterial pneumonia in this study. This exceeds rates reported in recent series of hospitalized pediatric patients with CAP [32–37] and is similar to rates reported in adult series [38, 39]. If patients with nonbacterial pneumonia were inadvertently included in the data set, the percentage of patients found to have empyema would only be more significant.

In summary, empyema as a complication of CAP is a serious and increasing public health problem in Utah. The population incidence of pediatric parapneumonic empyema in Utah increased 5-fold during the study period. The increasing incidence of empyema was related to the appearance of a clone of *S. pneumoniae* serotype 1, but other factors, including outpatient treatment with certain antibiotics, ibuprofen use, and varicella, were also associated with empyema. Immunization and modification of outpatient treatment may affect the incidence of empyema in children and should be studied prospectively. Surveillance for the appearance of pneumococcal serotype 1 in other communities is warranted because of the direct impact it will have on pneumococcal vaccine choice.

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