Clinical Manifestations and Molecular Epidemiology of Necrotizing Pneumonia and Empyema Caused by Streptococcus pneumoniae in Children in Taiwan

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Recently, there have been increasing numbers of pneumococcal pneumonia cases, with their associated complications. We conducted a retrospective review to increase the understanding of childhood pneumococcal pneumonia. Seventy-one patients with pneumococcal pneumonia were identified. Forty (56.3%) of them developed complicated pneumonia. Multivariate analysis showed that presence of immature polymorphonuclear leukocytes in peripheral blood (odds ratio [OR], 3.67; 95% confidence interval [CI], 1.08–12.63), high C-reactive protein levels (>12 mg/dL) (OR, 5.24; 95% CI, 1.10–24.93), and no underlying disease at presentation (OR, 5.48; 95% CI, 1.06–28.25) were independent predictors of the occurrence of necrosis or/and abscess. Fourteen isolates (35%), which were genotypically identical and had the same pulsed-field gel electrophoresis pattern (serogroup 14, with MICs of penicillin of 0.1–0.5 μg/mL), were significantly associated with complicated pneumonia (P = .047). Whether the virulence of antibiotic-resistant pneumococci is evolving deserves further investigation.

Streptococcus pneumoniae is the most common pathogen of pyogenic pneumonia in children [1]. The critical issues concerning S. pneumoniae in recent decades are the global emergence of multidrug-resistant pneumococci and the high carriage rate of penicillin-non-susceptible S. pneumoniae (PNSP) among children [2–4]. There are many reports that address the impact of PNSP. The majority of these studies conclude that there is no difference in the clinical characteristics of and outcomes for pneumonic patients infected with penicillin-susceptible S. pneumoniae or PNSP [5, 6]. Only 1 retrospective study, which was performed in Atlanta, demonstrated a significant risk of supplicative complications among adults with pneumococcal pneumonia who were infected with PNSP strains [7].

We know from experience that pneumonia caused by S. pneumoniae uniquely preserves the pulmonary architecture, no matter how severe it is at the peak stage of disease. Since the introduction of penicillin into the treatment regimen, pneumonia has seldom evolved into empyema [8]. However, an increase in the prevalence of necrotizing pneumococcal pneumonia and pneumococcal empyema was observed among children, beginning in the 1990s [9–11]. In Taiwan—a geographic region in which there is a high prevalence of PNSP [12]—we observed pulmonary infection with S. pneumoniae in children usually progressing to necrosis or empyema along with the increase of PNSP in recent years. As a result, we conducted a retrospective study to evaluate the clinical epidemiology, microbiology, and course of pneumococcal pneumonia.

PATIENTS AND METHODS

Patients. We retrospectively identified patients <15 years old who received a diagnosis of pneumococcal pneumonia at the National Taiwan University Hospital (NTUH) between May 1995 and April 2003. NTUH is a 2000-bed medical center in northern Taiwan. Pneumococcal pneumonia was established on the basis of...
Childhood Necrotizing Pneumonia and Empyema

Figure 1. Annual number of cases (bars) and percentage of complicated cases of pneumonia (dots) caused by Streptococcus pneumoniae from May 1995 through April 2003. The annual percentages of penicillin-nonsusceptible S. pneumoniae (MIC, >0.06 μg/mL) among all available isolates were 50%, 85.7%, 100%, 100%, 100%, and 87.5%, respectively. A "study year" is defined as the 12-month interval from May through April (e.g., the study year 1995 is the interval from May 1995 through April 1996).
the referral rates for patients with pneumonia were stable during the study period. Forty of these patients had complicated pneumonia (1 case of necrotizing pneumonia, 27 cases of empyema, and 12 cases of empyema and necrotizing pneumonia; table 1). The mean age was 52.3 months (range, 9–144 months), and the female-to-male patient ratio was 6:5. Those with underlying diseases included 5 patients with asthma, 4 with heart disease, 2 with genetic disorders, 2 with malignancy, 1 with hemolytic anemia, and 1 with metabolic disease. No patient was receiving steroid or immunosuppressive therapy.

Univariate analysis revealed that no underlying disease, age >36 months, presence of immature polymorphonuclear leukocytes (PMNs) in the peripheral blood, thrombocytopenia, and C-reactive protein (CRP) levels ≥12 mg/dL were significantly associated with the occurrence of necrosis or empyema (table 1). In the multivariate analysis, no underlying disease (OR, 5.48; 95% CI, 1.06–28.25; P = .04), immature PMNs in the peripheral blood (OR, 3.67; 95% CI, 1.08–12.63; P = .037), and high CRP levels (>12 mg/dL) (OR, 5.24; 95% CI, 1.64–20.70; P = .037) were independent predictors of complicated pneumonia. Children who were >36 months old accounted for 62% of all patients, and age was a significant predictor of pneumonia complications in the univariate analysis only (P = .038). The occurrence of complicated pneumonia was associated with longer durations of fever and hospital stays (P < .001). Twenty-four (60%) of the 40 patients with complicated pneumonia received a thoracotomy. The mortality rate in this group was 7.5% (3 of 40 patients), compared with a rate of 3.2% (1 of 31 patients) among those with lobar pneumonia (P = .627).

All but 4 patients with pneumococcal pneumonia were empirically treated with parenteral second- or third-generation cephalosporins or with a combination of amoxicillin plus clavulanic acid. After culture results and antimicrobial susceptibility reports were made available, the antimicrobial regimen was adjusted according to the patients’ clinical response. Two patients were empirically treated with a first-generation cephalosporin; 1 had lobar pneumonia due to S. pneumoniae (MIC of penicillin, 2 µg/mL), and the other had empyema due to S. pneumoniae (MIC, 0.38 µg/mL). Two other patients were empirically treated with high-dose penicillin (400,000 U/kg per day); 1 had lobar pneumonia due to S. pneumoniae (MIC of penicillin, 2 µg/mL), and the other had empyema due to S. pneumoniae (MIC, 3 µg/mL).

MIC testing was performed for 50 bacterial isolates. The prevalences of infection with S. pneumoniae immediately susceptible or resistant to penicillin were higher and lower, respectively, among patients with complicated pneumonia than among patients with lobar pneumonia (table 2). Five isolates had an MIC of penicillin of 4 µg/mL; 2 isolates were from patients with complicated pneumonia, and 3 isolates were from patients with lobar pneumonia. No isolate had an MIC of penicillin that was >4 µg/mL. The prevalence of ceftriaxone-nonsusceptible S. pneumoniae was 40% (10 of 25) among patients with complicated pneumonia and 64% (16 of 25) among patients with lobar pneumonia. There was no statistically significant difference between the prevalences of PNSP and ceftriaxone-nonsusceptible S. pneumoniae in these 2 groups.

The serogroup of 38 bacterial isolates was determined. Infection with S. pneumoniae from serogroup 14 was most prevalent among children with pneumococcal pneumonia. Isolates from serogroups 23, 19, and 6 were also recovered from these

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**Table 1. Univariate analysis of demographic data and clinical characteristics for children with complicated or lobar pneumonia caused by Streptococcus pneumoniae.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complicated (n = 40)</th>
<th>Lobar (n = 31)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months (range)</td>
<td>52.3 ± 28.8 (9–144)</td>
<td>41.8 ± 21.7 (10–97)</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Age &gt;36 months</td>
<td>72.5</td>
<td>48.4</td>
<td>2.81 (1.05–7.56)</td>
<td>.038</td>
</tr>
<tr>
<td>Female sex</td>
<td>62.5</td>
<td>51.6</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>No underlying disease</td>
<td>92.5</td>
<td>61.3</td>
<td>7.79 (1.96–30.99)</td>
<td>.001</td>
</tr>
<tr>
<td>WBC count, ×10⁶ cells/µL</td>
<td>13.3 ± 8.7</td>
<td>17.4 ± 9.5</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of immature PMNs in peripheral blooda</td>
<td>60</td>
<td>22.6</td>
<td>5.14 (1.79–14.74)</td>
<td>.002</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;10,000 platelets/mm³)</td>
<td>22.5</td>
<td>3.2</td>
<td>8.71 (1.04–73)</td>
<td>.035</td>
</tr>
<tr>
<td>C-reactive protein level &gt;12 mg/dL</td>
<td>87.5</td>
<td>60</td>
<td>5.83 (1.64–20.70)</td>
<td>.004</td>
</tr>
<tr>
<td>Time to fever clearance after hospital admission, days</td>
<td>13.5 ± 8.2</td>
<td>5.0 ± 4.8</td>
<td>...</td>
<td>.000</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>60</td>
<td>0</td>
<td>...</td>
<td>.000</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>25.2 ± 12.0</td>
<td>12.6 ± 6.8</td>
<td>...</td>
<td>.000</td>
</tr>
<tr>
<td>Mortality</td>
<td>7.5</td>
<td>3.2</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of patients or mean values ± SD. NS, not significant.

*a Defined as presence of bands, myelocytes, metamyelocytes, or promyelocytes.
patients (table 2). The distribution of serogroups was not statistically significantly different among patients with complicated pneumococcal pneumonia and those with lobar pneumonia.

PFGE analysis of 40 invasive isolates revealed 17 PFGE types (figure 2). There were 8 PFGE types among the 20 isolates associated with complicated pneumonia and 11 PFGE types among the 20 isolates associated with lobar pneumonia. Fourteen (35%) of 40 isolates had a major PFGE type (serogroup 14, with an MIC of penicillin of 0.1–0.5 μg/mL). These 14 strains were indistinguishable; 10 were from a group of 20 isolates associated with complicated pneumonia, and 4 were from a group of 20 isolates associated with lobar pneumonia (P = .047). Eight (20%) of 40 isolates had another PFGE type (serogroup 14, with an MIC of penicillin of 1 μg/mL) accounted for 20% (8 of 40). These 8 strains were closely related; 3 were from a group of 20 isolates associated with complicated pneumonia, and 5 were from a group of 20 isolates associated with lobar pneumonia. Two isolates collected consecutively from siblings with pneumococcal empyema were identical and belonged to the major PFGE type (serogroup 14, with penicillin MICs of 0.1–0.5 μg/mL). One serogroup 14 isolate and 1 serogroup 23 isolate were closely related, according to results of PFGE typing (figure 2).

DISCUSSION

This 8-year retrospective study in a university hospital setting revealed that the number of cases of complicated pneumococcal pneumonia has increased significantly. Although our study was limited to observations in a tertiary care hospital, we believe it reflects the increasing number of complicated pulmonary infections caused by *S. pneumoniae* in the community at large, because our hospital has been a medical center for >17 years and serves a steady population of referred patients.

We showed that the absence of an underlying disease, the presence of immature PMNs in the peripheral blood, and a high CRP level (>12 mg/dL) were significant predictors for necrosis or empyema complications in the multivariate analysis. The host inflammatory response to the pneumococcal components is the major element that causes tissue injury [18]. This may explain why immunocompetent children without underlying disease are at an increased risk for complicated pneumonia. CRP, an acute-phase protein, plays an important role in innate immunity by binding to the C-polysaccharide of pneumococci to increase the rate at which the invading pneumococci are cleared [19]. PMNs, even in immature form, have been shown to mediate microbial killing during invasive pneumococcal infection [20]. Thus, the presence of immature PMNs and a high CRP level in children with complicated pneumonia may imply a higher bacterial burden. Taking note of these signs can help in predicting severe pneumococcal infection at an early stage.

Antibiotic resistance is frequently seen in serogroups 6, 14, 19, and 23, which have the good ability to colonize the nasopharynxes of children [21]. Some clinical and epidemiological investigations showed that invasive isolates were more likely to be susceptible to antibiotics, whereas less-invasive isolates were more likely to be resistant to antibiotics [22, 23]. In Taiwan, the nasopharyngeal carriage of PNSP was highly prevalent among children [3]. We confirmed that the common invasive

**Table 2. Results of penicillin-resistance testing and serogroup analysis of *Staphylococcus pneumoniae* isolates from children with complicated or lobar pneumonia.**

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>Complicated</th>
<th>Lobar</th>
<th>P</th>
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<tbody>
<tr>
<td>Penicillin resistance (MIC)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible (0.06)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediately susceptible (0.1–1)</td>
<td>18 (72)</td>
<td>11 (44)</td>
<td></td>
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<tr>
<td>Resistant (≥2)</td>
<td>6 (24)</td>
<td>13 (52)</td>
<td></td>
</tr>
<tr>
<td>Serogroup&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4 (21.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0 (0)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>13 (68.4)</td>
<td>12 (63.1)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0 (0)</td>
<td>2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>2 (10.5)</td>
<td>4 (21.1)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** NS, not significant.

<sup>a</sup> Penicillin-resistance testing was performed on 25 isolates from patients with complicated pneumonia and 25 isolates from patients with lobar pneumonia. MICs are expressed as μg/mL.

<sup>b</sup> Serogroup analysis was performed on 19 isolates from patients with complicated pneumonia and 19 isolates from patients with lobar pneumonia.

Figure 2. PFGE analysis revealing 17 PFGE types among 40 isolates of *Streptococcus pneumoniae* from patients with pneumonia. The numbers in parentheses indicate the total number of isolates belonging to each PFGE type. Lane M, λ ladder; lane A, major PFGE type serogroup 14 (MIC of penicillin, 0.1–0.5 μg/mL); lane B, PFGE type serogroup 14 (MIC of penicillin, 1 μg/mL); lanes C–H, PFGE types related to complicated pneumonia; lanes I–S, PFGE types related to lobar pneumonia; lanes P and Q, an identical PFGE type; lane P, serogroup 14 (MIC of penicillin, 1.5 μg/mL); and lane Q, serogroup 23 (MIC of penicillin, 1.5 μg/mL).
isolates in Taiwan were penicillin-resistant serogroups 6, 14, 19, and 23. The distribution of serogroups 6, 9, 14, 19, and 23 did not differ much between the group with and the group without complications.

All patients (in both groups) were empirically treated with β-lactam antimicrobial agents, which have been suggested to be appropriate therapies for pneumonia caused by PNSP [24]. Therefore, complicated pneumococcal pneumonia was not the result of ineffective antimicrobial treatment. A PFGE analysis revealed that 35% of patients with pneumococcal pneumonia were infected with S. pneumonia from 1 major PFGE type (serogroup 14, with an MIC of penicillin of 0.1–0.5 μg/mL). One-half of the cases of complicated pneumonia were caused by bacteria from this major PFGE type. These results suggest that spread of S. pneumonia from this major PFGE type caused pneumonia among children in Taiwan. Surprisingly, we found that 2 closely related strains belonging to 1 PFGE type were associated with different capsular serogroups (serogroups 14 and 23). It suggested the mechanism of capsular transformation among pneumococcal isolates and has been previously described [25].

International dissemination of a limited number of clones by human-to-human spread is thought to have contributed to the rapid emergence of PNSP throughout the world. Examples include the spread of Spain23F-1 to the United States, Spain9V-3 to France, Taiwan19F-14 and Taiwan6B clones to Hong Kong [19]. The rapid emergence of PNSP throughout the world has acquired not only a high transmission rate, but also high clinical virulence. On the other hand, the currently licensed heptavalent pneumococcal conjugate vaccine is documented to be effective in reducing pneumococcal pneumonia among children [33]. In our study, this vaccine could cover at least 25 (66%) of 38 serogroups causing pneumonia. We believe the administration of conjugate vaccines will substantially reduce pneumococcal pneumonia among children in Taiwan.

Acknowledgment

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