Pneumococcal Pleural Empyemas in Children

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Empyema rarely complicates pneumonia. In a 361-bed regional pediatric hospital, 50 pleural empyemas were identified from 1988 through 1994; 17 (34%) occurred in the last 12 months of this period, for which the incidence was 3.3 per 100,000 of the population aged ≤ 18 years (P < .05, χ² test). A significant seasonal prevalence was observed: 50% of cases occurred in the winter (P < .001, χ² test). In contrast with the findings of previous studies, in which empyemas predominantly occurred in infants, the median age of our patients was 7 years; underlying illnesses were present in only 10%, and all had community-acquired disease. Eighty-two percent had chest tubes inserted, 56% required a thoracotomy with pleural decortication, and 2% had a lobectomy. There were no deaths. Streptococcus pneumoniae was isolated in 40% of the cases; specimens in 44% of the cases were sterile. None of the empyemas were associated with Staphylococcus aureus or Haemophilus influenzae type b, and only one was caused by group A streptococcus. Among 13 S. pneumoniae isolates, the rate of resistance to penicillin was 15%; to erythromycin, 15%; to chloramphenicol, 31%; and to cefotaxime, 23%. The penicillin-resistance rate among blood and cerebrospinal fluid pneumococcal isolates was 17% during 1993–1994. Drug-resistant S. pneumoniae is now a recognized cause of pleural empyemas in children.

Bacterial pneumonia is a common childhood illness [1]. Over 40% of patients present with a parapneumonic effusion [2, 3]. Ineffective antibiotic therapy may be one factor that allows the effusion to progress to a pleural empyema. Although empyemas are rare, complicating 1%–2% of cases of pneumonia involving children, they are associated with considerable morbidity and mortality [4, 5].

In the 1940s, the most common etiologic agents of pleural empyema were Streptococcus pneumoniae and group A streptococcus [6]. With the widespread introduction of the sulfonamides and penicillin there was a notable decline in the suppurative complications of pneumonia [7]. In the 1950s, 92% of pleural empyemas were linked to Staphylococcus aureus [8]. With the introduction of the penicillinase-resistant penicillins in the 1960s, pneumonia due to S. aureus became rare [6]. In the early 1980s, Haemophilus influenzae type b emerged as a common cause of pleural empyema in children [9–12].

Presently, S. pneumoniae is the leading cause of pneumonia in all age groups except newborns [1, 6]. It is estimated to account for >500,000 cases of pneumonia each year in the United States [13]. Despite this era of rapidly emerging worldwide antimicrobial resistance to S. pneumoniae [14–16], we are unaware of any reports of pleural empyemas linked to drug-resistant S. pneumoniae [14–18]. Recently, however, we have observed an increase in the incidence of pleural empyemas in patients admitted to the Children's Hospital Medical Center (CHMC; Cincinnati), and some of the cases have been caused by antibiotic-resistant S. pneumoniae.

This case series describes the clinical epidemiology and microbiology of pleural empyemas in children that were identified and treated at CHMC during the period of July 1988 through June 1994. Antibiograms of patients with invasive pneumococcal infections were reviewed to identify rates of endemic antibiotic resistance among S. pneumoniae isolates recovered during 1993 and 1994. The etiologic trends with regard to cases of community-acquired bacteremia were also evaluated.

Patients and Methods

Hospital. CHMC is a 361-bed university hospital providing regional pediatric services to Greater Cincinnati, which has a referral population base of 1.7 million. More than 16,000 children are admitted annually to this tertiary care hospital, for an average stay of 5.1 days.

Criteria and patients. Cases involving a diagnosis of pleural effusion or empyema during the period of July 1988 through June 1994 were identified from the ICD-9 (International Classification of Diseases, ninth revision) codes in the CHMC Medical Records Department. A review of the medical records of these cases was performed. These children were routinely evaluated by means of detailed histories, physical examinations, chest radiography, complete blood cell counts, and blood cul-
tures. Pleural fluid aspirates were frequently examined for determination of pH, WBC count, and concentrations of glucose, protein, and lactate dehydrogenase. Appropriate bacterial stains and cultures were also performed. In addition, many cases were investigated with CT and ultrasonographic evaluations of the chest.

Empyema complicating pneumonia was defined by the presence of one major criterion or two minor criteria. Major criteria included the following factors: the presence of pus (noted by visual inspection) in the pleural space; the performance of pleural decortication in association with a compatible clinical picture; and the positivity of a pleural fluid culture. Minor criteria included the following laboratory values or findings: pleural fluid pH, $\leq 7.2$; glucose, $\leq 40$ mg/dL; WBCs, $\geq 10,000$/mL; lactate dehydrogenase, $\geq 1,000$ U/L; and blood culture, positive.

Additional factors were evaluated for the patients who met these criteria for empyema. These factors included patient demographics; season and year of admission; concurrent antibiotic use; clinical presentation; reports concerning chest radiographs, CT scans, and ultrasonographic evaluations; sites of infection; antibiotic treatment; surgical management; and clinical outcome.

The criteria developed by the Centers for Diseases Control and Prevention (CDC) were utilized to distinguish nosocomial from community-acquired pneumonias and empyemas [19]. In brief, pneumonia was defined by a constellation of clinical, radiographic, and laboratory findings [19]. Pneumonia that was already present or in the incubation phase at the time of hospitalization was considered community-acquired [19]. All cases of pleural empyema that developed as an extension of pneumonia that was present on admission were designated as community-acquired [19].

**Microbiology.** Pleural fluid aspirates and blood were cultured by standard techniques [20]. Anaerobic cultures were performed when requested. Antibiotic susceptibility testing for *S. pneumoniae* was performed by the methods of the National Committee for Clinical Laboratory Standards [21, 22]. Antimicrobial susceptibility was defined with use of the following MIC breakpoints: penicillin, $\leq 0.06$ µg/mL; chloramphenicol, $\leq 4$ µg/mL; cefuroxime, $\leq 0.5$ µg/mL; erythromycin, $\leq 0.5$ µg/mL; cefotaxime, $\leq 0.5$ µg/mL; and ceftriaxone, $\leq 0.5$ µg/mL [22].

Pneumococci were stored on sheep blood at $-70^\circ$C. Pneumococci from empyema cases were later retrieved from the archival collection and restested by the Etest (AB BIODISK, Solna, Sweden) for antimicrobial susceptibility patterns, with use of 1994 criteria [22]. The isolates were then shipped to the CDC for serotyping in the laboratory of Richard Facklam, Ph.D., on the basis of capsular swelling with type-specific antisera (Quellung reaction) [23]. The concurrent etiologic trends with regard to cases of community-acquired bacteremia due to *S. aureus, S. pneumoniae*, and *H. influenzae* type b were also examined.

**Surgery.** Indications for chest tube placement included imminent respiratory failure, mediastinal shift, or large pleural effusions. Criteria for chest tube removal included the following findings: $<50$ mL of drainage over 24 hours, absence of bronchopleural fistulae, and reexpansion of the lung (as evidenced with repeated chest radiography). Decortication was performed in children who had persistent fever while receiving appropriate antibiotics, persistent respiratory difficulties, prolonged chest tube drainage, a thick pleural rind prohibiting lung reexpansion or chest tube drainage, and/or bronchopleural fistulae. The decortication procedure included thoracoscopy or muscle-sparing posterolateral thoracotomy with debridement of the involved visceral and parietal pleura, followed by closed chest tube drainage.

**Data analysis.** Data on the patient demographics and clinical and laboratory parameters were entered into the statistical program Epi-Info 5.1 [24] and analyzed by univariate methods.

**Results**

The hospital charts of 270 patients whose coded diagnosis was pleural effusion or empyema and who were treated during the period of July 1988 through June 1994 were reviewed. Two hundred and ten patients had pleural effusions; 50 met the criteria for empyema and inclusion in our study (figure 1).

**Patient demographics.** Among the 50 cases evaluated for pleural empyemas, 29 (58%) involved males. Their ages ranged from 1 year (in three cases) to 20 years ($\geq 15$ years in three cases). Median age was 7 years (first quartile, 3 years; third quartile, 11 years). All cases were community-acquired [19]. Although four patients were transferred from other hospitals, none of them had nosocomial disease. The duration of hospitalization ranged from 3 to 32 days (median, 12 days; mean, 13 days; first quartile, 8 days; third quartile, 15 days).

The majority of the children were previously healthy. Five (10%) had underlying illnesses (one case each of Bruton's agammaglobulinemia, trisomy 21 (Down's) syndrome, disseminated rhabdomyosarcoma, physical abuse, and cerebral palsy with seizures). None of the cases followed blunt or penetrating trauma, surgical procedures, spontaneous pneumothorax, esophageal perforation, thoracocentesis, or subdiaphragmatic infections.

**Clinical features.** The majority of the children had persistent symptoms despite antibiotic therapy for community-acquired pneumonia. Symptoms included spiking fevers in 47 cases (94%). The mean highest temperature was 103.6°F. Duration of fever ranged from 1 to 30 days (median, 5 days). Cough was reported in 34 cases (68%), dyspnea in 15 (30%), and pleuritic chest pain in 16 (32%). Forty-three patients (86%) had significantly elevated WBC counts (range, 12,000–58,000/ dL; median, 17,500/dL). The majority had neutrophilia.

**Chest radiology.** Some patients' initial chest radiographs did not suggest effusions, but later radiographic studies revealed them. Reports concerning chest radiographs (posterior-anterior
Figure 1. A flow chart describing the 210 cases of pleural effusions reviewed, of which 50 met the definition of empyema and were included in the study.

and lateral decubitus views) revealed pneumonic consolidation with effusion in all 50 cases. Thirty-two cases (64%) involved the right lung, while 18 (36%) involved the left lung. The most commonly affected consolidated lobes were the right middle and right lower lobes (in 14 cases each). Confirmatory CT of the chest was performed in 17 cases and revealed loculated empyemas in five. Reports concerning ultrasonograms of the chest for another 13 cases revealed multiple loculations in nine.

Microbiology. A bacterial etiology was confirmed for 28 empyemas (56%) (table 1). Twenty-one children (42%) had a positive pleural fluid culture, while 10 children (20%) had a positive blood culture. S. pneumoniae was the most common isolate (40%); seven of the 20 pneumococcal empyemas were identified within the last year studied. There were no cases due to S. aureus or H. influenzae type b. Only one polymicrobial case was identified (table 1). Coagulase-negative staphylococcus and viridans streptococcus were included as true pathogens, because they were isolated within 24-48 hours of culture and were associated with significant disease. Anaerobic bacteria were not isolated.

Serotyping of 13 pneumococci revealed type 14 (in 4 cases), type 1 (4 cases), and types 5, 6B, 9V, 19A, and 23F (1 case each). The etiologic trends associated with nonduplicate isolates of S. pneumoniae, S. aureus, and H. influenzae type b in the cases of bacteremia studied are compared in figure 2.

Antibiotic-resistant S. pneumoniae. The rate of resistance to penicillin among invasive S. pneumoniae isolates from CSF or blood was 17% (18 of 105 isolates) in 1993 and 17% (17 of 99) in 1994; the patterns of resistance to other antimicrobials are listed in table 2. Thirteen of the 20 (nonduplicate) pneumococcal isolates from our empyema cases were available for retesting of antibiotic susceptibility [22]. Two strains (15%) that were isolated in 1993 and 1994 were resistant to penicillin: one was intermediately resistant (MIC, 0.12 μg/mL), while the other was highly resistant (MIC, 4 μg/mL).

Previous antibiotic treatment. Thirty children (60%) were receiving 46 dosages of antibiotics (in various combinations) for community-acquired pneumonia at the time of the pleural fluid tap. Previous antibiotic treatment in the community (before thoracocentesis) was significantly associated with sterile empyemas (15 of 22) in comparison with pneumococcal empyemas (7 of 20; P = .03 per Fisher's exact test) (table 3). Duration of previous antibiotic therapy was longer for those with sterile empyemas (range, 2–14 days; median, 6 days) than for those with pneumococcal empyemas (1–2 days). Regarding previous antibiotic therapy in the community, cefuroxime (9), ceftriaxone (7), penicillin analogues (8), and erythromycin (7) were the most common antibiotic choices for all cases.

Antibiotic therapy. Empirical broad-spectrum parenteral antibiotic therapy for pleural empyemas was commenced after the appropriate cultures were performed. Antibiotic regimens

### Table 1. Bacterial etiology of 28 of the 50 evaluated pleural empyemas involving children at CHMC (1989–1994).

<table>
<thead>
<tr>
<th>Isolate(s)</th>
<th>No. of cases with positive cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strepoccoccus pneumoniae</td>
<td>20*</td>
</tr>
<tr>
<td>Coagulase-negative staphylococcus</td>
<td>2</td>
</tr>
<tr>
<td>Viridans streptococcus</td>
<td>2</td>
</tr>
<tr>
<td>Group A streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Alpha-hemolytic streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Actinomyces species</td>
<td>1</td>
</tr>
<tr>
<td>Xanthomonas maltophilia, Enterococcus species, and coagulase-negative staphylococcus</td>
<td>1</td>
</tr>
<tr>
<td>Total (% of 50 cases)</td>
<td>28 (56) 10 (20) 21 (42)</td>
</tr>
</tbody>
</table>

* In three cases, both blood and pleural fluid cultures were positive.
were later modified when culture and susceptibility reports were available. Initial antibiotic therapies (on admission) were compared for pneumococcal (20) and sterile empyemas (22) (table 3). Cefuroxime was used in 95% of those cases due to pneumococci, whereas the semisynthetic penicillins (40%) and cefuroxime (41%) were most frequently prescribed for sterile empyemas. Ceftriaxone and cefotaxime were used only in the patients with sterile empyemas, possibly in anticipation of penicillin-resistant pneumococcal strains.

**Outcome.** Forty-one children (82%) required surgical interventions. In all 41, chest tubes were placed on admission (before antibiotic therapy commenced) or during the course of hospitalization. All 17 patients presenting during the last year studied had chest tubes inserted. The total duration of chest tube drainage was 2–30 days (median, 6 days; mean, 7 days). Two cases required repeated chest tube placement or aspiration thoracoscopy. Twenty-eight (56% of 50) were severe enough to require a thoracotomy with pleural decortication. A thick pleural rind was reported in all of the cases.

Changes in incidence as related to season and geography. The incidence of pleural empyemas in children varied from 0.6 to 3.3 per 100,000 of the pediatric population in Greater Cincinnati during the period of 1988 to 1994. Seventeen (34%) of the 50 empyema cases were diagnosed in the last year of the study, compared with 10 in each of the previous 5 years (figure 3). A \( \chi^2 \) test for linear trend showed that this apparent increase was significant (\( \chi^2 = 4.64, 1 \) df, \( P < .05 \)).

A significant seasonal prevalence was also observed: 25 (50%) of the cases were identified during the winter, 12 (24%) in spring, 11 (22%) in autumn, and 2 (4%) in summer. A \( \chi^2 \) test revealed that the seasonal frequencies were not the same (\( \chi^2 = 21, 3 \) df, \( P < .001 \)). Mapping of the empyema cases by Greater Cincinnati zip codes revealed no evidence of temporal-spatial clustering (Atlas Geographic Information Systems, Strategic Mapping, San Jose, CA).

**Discussion**

This study suggests a significant recent increase in the incidence of pleural empyemas in children in Cincinnati. Among 50 cases identified in the 6-year study period, 34% were diagnosed in the last year, yielding an incidence of 3.3 cases per 100,000 children. Although the definition of empyema can be difficult, we believe these results represent a true increase, as
our indications for diagnostic thoracocentesis have not changed in recent years.

Forty percent of our bacterial isolates were \textit{S. pneumoniae}. Only one isolate of group A streptococcus was recovered, and there was a notable absence of \textit{H. influenzae} type b and \textit{S. aureus}. This contrasts with previously published reports of pediatric investigations in which these organisms were predominant isolates. Fourteen pooled studies of pleural empyemases in children over the past decade, representing 1,142 diagnostic thoracocenteses, demonstrated \textit{S. aureus} to be the primary isolate in 25\% of the cases; other bacteria included \textit{S. pneumoniae} (14\%), \textit{H. influenzae} type b (7\%), anaerobes (6\%), other streptococcal species (7\%), and other bacteria (9\%); the remaining cultures were sterile (32\%) [10, 11, 17, 25–35].

The absence of \textit{H. influenzae} type b isolates from empyemases may be partly explained by the recent widespread use of the effective \textit{H. influenzae} type b vaccine, administered at 2, 4, and 6 months of age. A recent report noted that >70\% of 227 children with parapneumonic effusions and empyema were <2 years of age [10], and their pleural fluid yielded \textit{S. aureus} or \textit{H. influenzae} type b. Previous reports have emphasized the occurrence of pleural empyemases in infants and young children; the older age (median, 7 years) in our empyema cases is consistent with the predominantly pneumococcal etiology observed.

The local etiologic trends associated with bacteremia in children also mimic this etiologic finding. The significant occurrence of pleural empyemases in the influenza/winter season (50\%) would also support a pneumococcal etiology [36]. Some of the sterile empyemases may have been linked to anaerobic organisms. While anaerobic pleural empyema is less common in children than in adults, Fajardo and Chang isolated anaerobes in 7\% of 71 cases involving children [11].

Although a few case reports have demonstrated \textit{S. pneumoniae} as a primary isolate from pleural fluid [29, 34], none of the cases were associated with drug-resistant organisms. At CHMC, among 13 pneumococcal empyema isolates, the rate of resistance to penicillin was 15\%; to chloramphenicol, 31\%; to erythromycin, 15\%; and to cefotaxime, 23\%. Cases of pneumonia involving a prolonged, complicated course and sterile empyema and blood cultures may also have been caused by drug-resistant pneumococci; duration of antibiotic therapy preceding thoracocentesis was longer in cases of sterile vs. pneumococcal empyemases, and cefuroxime or ceftriaxone may have been effective in eradicating such strains.

During 1993–1994, the endemic rate of penicillin resistance was 17\% among pneumococcal isolates from blood or CSF. Within the same period, resistance rates were 2\%–10\% for cefuroxime and zero to 5\% for ceftriaxone. Comparatively (also during 1993–1994), the prevalence of penicillin resistance among 406 invasive pneumococcal isolates was zero to 35\% (mean, 14\%) at nine other children’s hospitals in the United States; cephalosporin resistance was observed in 4\% of the isolates [37].

Only two of our cases were severe enough to require intensive care (without thoracotomy), and there were no deaths. In contrast, the high mortality rates among infants (which previously approached 50\% [38]) have declined over the past 4 decades of the antibiotic era, although recent death rates remain significant at 4\%–12\% [4, 11]. The zero mortality rate among our cases may be related to the significant absence of (1) infants among the patients studied [39]; (2) nosocomial infections, which are associated with a death rate of 33\% [11]; (3) disease caused by \textit{S. aureus} [10]; (4) polymicrobial infection [11, 18]; and (5) underlying immunodeficiency [4, 10, 18, 28, 40].
A recent report from Barcelona and data from South Africa showed mortality was not linked to in vitro antibiotic resistance in cases of pneumococcal pneumonia and other invasive infections outside of the CNS [14, 16, 18]. Although controversial [29, 31–34], another factor is the early and aggressive surgical intervention with tube thoracostomies and pleural decortication, which may hasten recovery from severe empyema [29]. The decortication rate was high (56% of 50 cases), but our criteria for surgical intervention to prevent “trapped lung” syndrome were not different. These cases may represent a more aggressive form of the disease. Nosocomial acquisition of pneumococcal pneumonia in patients with underlying disease was a risk factor for pneumococcal infection in Barcelona [18], but this was not observed in our series.

In summary, our data suggest an increase in the incidence of pleural empyemas in children. Most were linked to pneumococci, of which some were multiply drug-resistant. Simultaneously, 17% of invasive blood and CSF pneumococcal isolates were also resistant to penicillin, our first-line therapy for bronchopulmonary pneumonia.

Interim recommendations might include judicious selection of an antibiotic with the narrowest possible spectrum for the outpatient management of community illnesses, especially pneumonia, and to control the problem of pneumococcal resistance. Careful follow-up is needed for consideration of the necessity of diagnostic lung punctures [39] or bronchoalveolar lavage [41]. Identification of empyema in its early stages also enables the use of thoracentesis for efficient isolation of the appropriate bacteria, to define resistance patterns, and to guide drug therapy for the best outcomes.

High-dose penicillin, clindamycin, third-generation cephalosporins, or vancomycin may be considered for the effective treatment of drug-resistant pneumococcal empyemas. Most of the serotypes encountered in pneumococcal empyemas are included in the 23-valent pneumococcal vaccine, which prevents invasive complications in at-risk children. Newer antimicrobials and acceleration of the licensing of new conjugate pneumococcal vaccines [42, 43] may be needed.

Physicians should be aware of this possible change in the epidemiology of pleural empyema in children, especially in this era of rapidly emerging worldwide antibiotic resistance to \textit{S. pneumoniae}.

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