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Original Article

Complicated parapneumonic effusion and empyema in children

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Background and Purpose: Parapneumonic effusion and empyema are recognized complications of bacterial pneumonia. Optimal management in children, especially the duration of parenteral antibiotics and the role of surgery, is controversial. This study analyzed the clinical characteristics, management, outcome, and bacterial etiology of 59 patients with complicated parapneumonic effusion and empyema treated at a single medical center in Kaohsiung from January 1995 to March 2004.

Methods: The diagnosis of complicated parapneumonic effusion was based on the specific characteristics of pleural fluid, computed tomography or ultrasound findings, or direct visualization of loculations during the surgical procedure.

Results: Causative agents were culture-confirmed in 42% of the cases. *Streptococcus pneumoniae* was the leading pathogen in this series (20% of cases). None of the *S. pneumoniae* isolates were susceptible to penicillin. *Mycoplasma pneumoniae* accounted for 19% of cases based on immunoglobulin M assay.

Conclusions: An initial combination therapy regimen consisting of cefotaxime or ceftriaxone plus macrolide provided reasonable activity against 80% of the pathogens isolated in this series. This study also revealed that prolonged parenteral antibiotic treatment resulted in longer length of hospital stay.

Key words: Empyema, etiology, *Mycoplasma pneumoniae, Streptococcus pneumoniae,* treatment outcome

Introduction

Parapneumonic effusion and empyema are recognized complications of bacterial pneumonia. The incidence of empyema is increasing worldwide [1], but it is clear that most children recover irrespective of the treatment they receive. It is estimated that 0.6% of childhood pneumonias progress to empyema, affecting 3.3 per 100,000 children [2]. Although the incidence and mortality of empyema are low in children, pediatric empyema can be associated with considerable morbidity [3,4]. Treatment options include antibiotics alone or in combination with thoracocentesis [5,6], tube thoracostomy (chest drainage), intrapleural fibrinolytics [7,8], thoracoscopy [9-12], and open decortication [13-16].

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However, the recent publication of guidelines on the management of pleural infection in children by the British Thoracic Society [17] highlights the lack of grade A evidence available for best management practices [18]. The current treatment method for children is based on previous physician experience and local biases, as well as the availability of trained personnel and equipment. Variation in practice is partly due to the lack of randomized controlled trials, and because children virtually always recover, irrespective of the treatment they receive.

This study analyzed the clinical characteristics of patients, management, outcome, and bacterial etiology of 59 patients with pleural effusion treated at a single medical center in southern Taiwan from January 1995 through March 2004.

Methods

Children with a diagnosis of empyema were retrospectively identified by reviewing the charts of patients

Table 1. Classification of pleural empyema[a]

Classification	Characteristics
Acute	Pleural fluid is clear to slightly cloudy and serous Sterile fluid Has at least one of the following: pH <7.20 Glucose <40 mg/dL LDH >1000 IU/dL Protein >2.5 g/dL Specific gravity >1.018 WBC >500 cells/mm^3
Fibropurulent	Fluid is thicker and opaque, or positive culture
Chronic	A peel forms around the lung

Abbreviations: LDH = lactate dehydrogenase; WBC = white blood cell.
[a]Adapted from Chan et al [19].

admitted to the Chang Gung Memorial Hospital, Kaohsiung during the 10-year study period from January 1995 to March 2004.

The management of empyema was based on the results of diagnostic thoracentesis as acute, fibropurulent, or chronic as illustrated in Table 1 [19]. If the pleural empyema was classified as acute, a therapeutic tap or a tube thoracostomy was performed. Fibropurulent empyema was uniformly treated with tube thoracostomy. The lung was decorticated when the empyema was encased by a thick peel, multiloculated, refractory, had recurred, and the patient remained unwell, or had occurred as a complication of previous thoracostomy.

Data collected included age, gender, presenting symptoms and signs, findings of initial imaging studies, classification of empyema stage, culture results, drainage procedures, operative procedures, duration of fever, length of hospital stay, and duration of treatment with antibiotics.

Statistical significance of differences in study variables was analyzed using Student's *t* test, Fisher's exact test, or chi-squared analysis. Data were presented as mean ± standard deviation. Analyses were performed using the Statistical Package for the Social Sciences (SSPS) for Windows (Version 11.0; SPSS, Chicago, IL, USA) software. A p value <0.05 was considered statistically significant.

Results

During the study period, 81 children had a discharge International Classification of Diseases code indicative of complicated parapneumonic effusion. Of these children, 22 were excluded from this study — 14 due to pleural empyema that resulted from a process other than community-acquired pneumonia, 4 due to failure to fulfill the study criteria of empyema, and 4 due to empyema associated with tuberculosis. The remaining 59 children were included in the study.

Baseline characteristics

The average age of the patients was 4.0 years (range, 3 days to 13 years). The male-to-female ratio was 1:1 (30 boys and 29 girls). The mean value of blood leukocyte count was 17,017 ± 8817/mm^3; hemoglobin, 10.1 ± 1.4 g/dL; platelet count, 332,519 ± 201,440/mm^3, and C-reactive protein, 239.1 ± 115.0 mg/L.

The majority of patients (52 patients, 88%) presented primarily with respiratory symptoms of cough (52 patients), dyspnea (12 patients), and chest pain (5 patients); 49 patients (83%) presented with fever. Twenty seven patients (46%) developed gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain. The median duration of fever before admission was 6.7 days.

Pleural fluid samples were obtained from 57 patients (97%). Decortication was performed in 10 patients (17%) with empyema. Of the 59 patients, 8 patients (14%) had predisposing factors, including cerebral palsy (3 patients), chickenpox (1 patient), very young age (2 patients), and immunocompromised state (2 patients).

Annual and seasonal distribution

The number of cases of pleural empyema showed a gradual increase in the first 5 years of the study period, then dropped suddenly in 2000 for unknown reasons (Fig. 1). More than half (63%) of the cases were diagnosed during the winter months between October and February (Fig. 2).

Etiologic agents

Causative agents were confirmed in 42% (25 patients) of the patients by isolation of bacteria from blood (12 patients), pleural fluid (16 patients), or both (5 patients), and bronchial wash (2 patients). The isolated pathogens included *Streptococcus pneumoniae* in 12 patients (1 confirmed by the referring hospital), *Pseudomonas aeruginosa* in 5, viridans streptococcus in 2, *Prevotella* spp. in 2, *Staphylococcus aureus* in 2, *Salmonella* serogroup B in 1, enterococcus in 1, and *Haemophilus influenzae* b (Hib) in 1. *Mycoplasma pneumoniae*

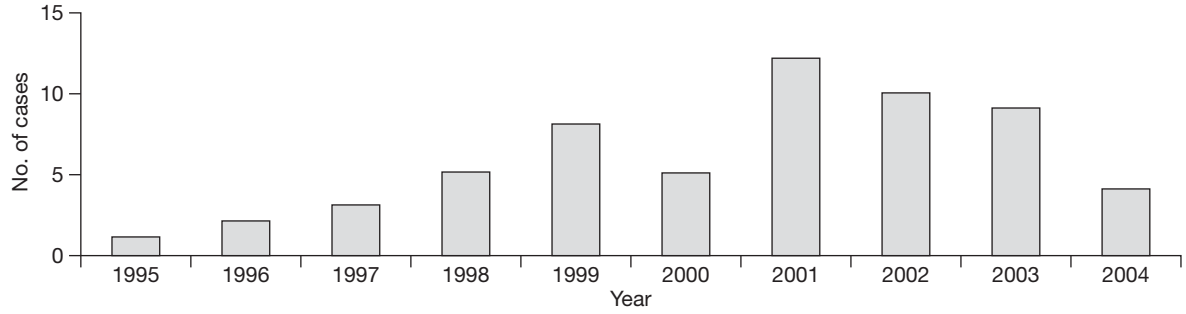

Fig. 1. Annual distribution of cases of complicated parapneumonic effusion at Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

serum immunoglobulin M assay (enzyme-linked immunosorbent assay, cut-off index: 9.999 BU/mL) was positive in 11 patients. Fig. 3 shows the percentage of cases for each of the isolated pathogens. Gram-positive diplococci were isolated from a pleural fluid specimen in 1 patient; urine was positive for Hib antigen in 1; and endotip culture was positive for *P. aeruginosa* in 1. Culture was negative in 25 patients (36%). Mixed infection was found only in 2 patients — one with *S. pneumoniae* and *Prevotella malani*, and the other with *Salmonella* serogroup B and viridans streptococcus.

In summary, the culture-positive rate was 42% (25 of 59 cases). If mycoplasma infection and other possible causative organisms are included, then the pathogens of pleural effusion could be identified in 35 cases (59%).

According to the National Committee for Clinical Laboratory Standards, penicillin-resistant pneumococci from sites other than cerebrospinal fluid are either intermediately resistant, with minimal inhibitory concentrations (MICs) of 1-2 μg/mL, or highly resistant, with MICs of 4 μg/mL or greater. Of the 14 *S. pneumoniae* isolates that were susceptible to third-generation cephalosporins, 8 (57%) were intermediately susceptible to penicillin and 6 were highly resistant to penicillin.

Of the 5 patients with *P. aeruginosa* infection, 3 showed normal immune function. Four of the five patients were less than 1 year in age. Review of medical records in these 5 patients revealed no evidence of superimposed infection before admission or during hospitalization that might have been responsible for *P. aeruginosa* infection.

S. aureus was isolated from 2 patients — one was 8 months old and the other was 2 years old. Both isolates were resistant to semisynthetic penicillin. Neither of these patients had associated risk factors, such as previous hospitalization, previous surgery, presence of central venous catheters, residence at a day-care center, or hemodialysis.

Viridans streptococci were associated with aspiration pneumonia in 2 patients; one of these patients had cerebral palsy, a predisposing factor for aspiration pneumonia, and the other had no obvious risk factors. Both these patients received chest tube drainage.

In this study, diagnosis of mycoplasma infection required that routine bacterial cultures from throat swabs, pleural fluid, and/or blood, and serological examinations were negative for other bacterial or viral pathogens tested, accompanied with a positive serological result for mycoplasma. Based on this definition, *Mycoplasma pneumoniae* was considered the most likely causative

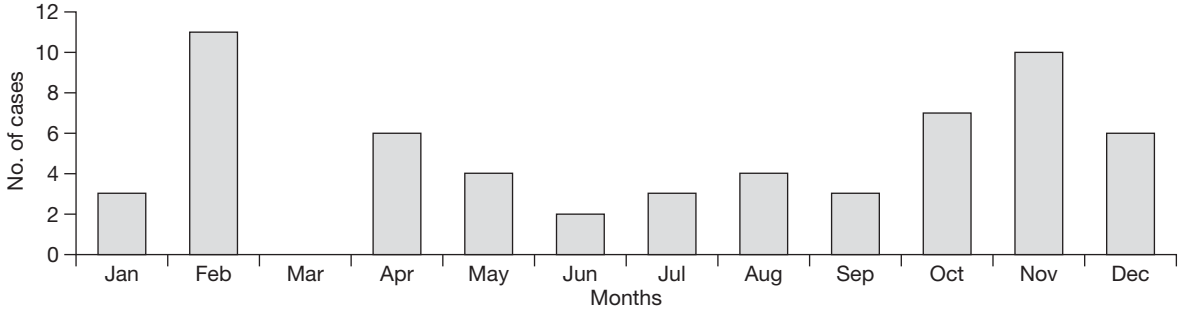

Fig. 2. Seasonal distribution of cases of complicated parapneumonic effusion (1995-2004) at Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

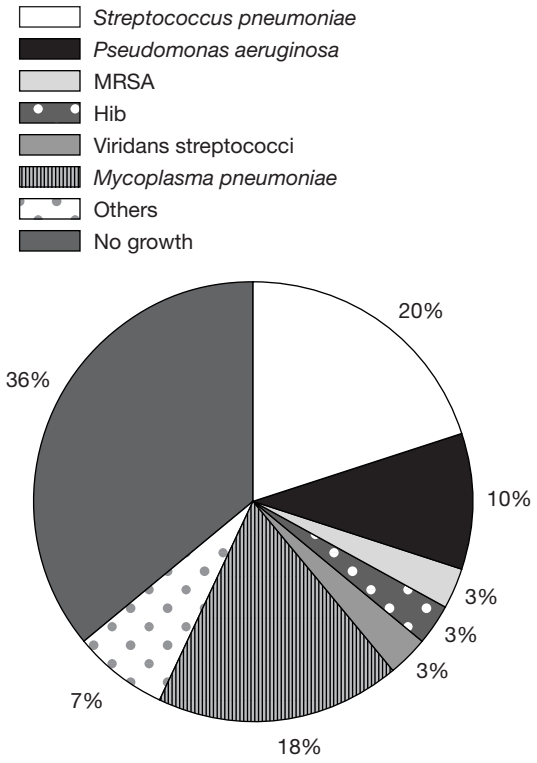

Fig. 3. Spectrum of causative pathogens identified in this series. MRSA = methicillin-resistant *Staphylococcus aureus;* Hib = *Haemophilus influenzae* b.

pathogen in 8 patients (3 patients were excluded because of the presence of other bacteria).

Treatment

Based on the characteristics of pleural effusion, empyema was categorized as acute in 42 patients, and as fibropurulent in 17 patients. None of the patients met the criteria for classification of chronic stage empyema.

Acute empyema responded to antibiotics alone or in combination with simple chest tube drainage in 81% of patients (34 of 42). Decortication was performed in 8 patients with acute empyema that was due to persistent fever in 1, pericardial effusion in 1, and progressive clinical deterioration in 4. In addition, 2 of these procedures were performed at the referring hospital without recording specific indications. The median duration of hospitalization was 22.4 ± 6.6 days, the median duration of fever after drainage was 9.2 ± 6.6 days, and the median duration of tube insertion was 7.6 ± 5.6 days.

Fibropurulent empyema responded to antibiotics and thoracostomy drainage in 88% of patients (15 of 17). The median duration of hospitalization of patients with fibropurulent empyema was 30.1 ± 11.5 days. Fever persisted post-drainage for 10.0 ± 4.0 days, and the median duration of tube insertion was 12.8 ± 9.3 days. The median duration of hospitalization and tube insertion were significantly longer in the fibropurulent group than those in the acute empyema group ($p<0.05$).

There were no deaths in the study group. All patients showed complete clinical resolution during follow-up.

Discussion

Identification of the causative agents in children with empyema is often difficult. Reported diagnostic yield from pleural and/or blood cultures ranged from 60% to 70% [20]. Only 42% of pediatric patients in this series had a cause established by either blood or pleural cultures. The most common pathogens that cause effusions or empyema associated with community-acquired pneumonia in children are *S. pneumoniae*, *S. aureus*, and group A streptococcus [21], is contrast to the findings in this study. Due to the implementation of vaccination, especially in the United States, the incidence of empyema due to *S. pneumoniae* has significantly decreased [22].

Pleural effusion is a well-recognized complication of mycoplasma infection [23]. Based on the definition, *M. pneumoniae* was considered the most likely causative pathogen in 8 patients in this study. Among these patients (age ranging from 3-13 years), 2 underwent surgery due to persistently abnormal radiologic findings, one at 15 days and the other at 18 days after chest tube drainage. Histological examination of pleural peel in both patients showed suppuration and fibrinoleukocytic exudate. The others had a benign course as compared to patients infected by other causative pathogens. Narita et al found that positive polymerase chain reaction (PCR) results of pleural fluid samples of children with mycoplasma pleuritis were strongly associated with residual radiographic abnormalities [24]. As PCR for mycoplasma was not available in our hospital during the study period, we could not confirm these findings. Nevertheless, PCR from a single acute phase specimen may have predictive value for persistent radiographic abnormalities.

Because the etiology of empyema is difficult to identify in a timely manner, treatment of empyema is usually empirical. Another factor complicating empirical antibiotic selection is the increase in drug-resistant organisms, especially *S. pneumoniae* [25]. The selection of empirical antimicrobial therapy should ideally be based on local epidemiologic data. Our sensitivity test

results indicated that an initial combination therapy regimen consisting of cefotaxime or ceftriaxone plus azithromycin would provide appropriate activity against 80% (28 of 35 cases) of pathogens isolated in southern Taiwan.

The length of hospital stay in this series was longer (average, 24 days) than that reported in previous studies (range, 9-17 days) [22]. A short length of hospital stay significantly reduces the cost of care. Steps that have been reported to shorten the length of hospital stay include shifting to oral form antibiotics earlier [26], early surgery [22,27,28], and fibrinolytic therapy [28].

Information on optimal duration of parenteral antibiotics therapy is lacking [7]. However, prolonged parenteral therapy would result in the selection of resistant organisms and thereby an increase in the therapeutic cost. Our patients received longer duration (23.7 days) of parenteral antibiotic treatment though defervescence was 9.27 days post-parenteral antibiotic treatment. Baranwal et al [26] suggested that antibiotics be administered orally after patients became afebrile, respiratory distress subsided, and significant lobulation was ruled out.

Patients with persistent pleural sepsis should be treated surgically. Huang et al [27] demonstrated the advantages of pleural decortication, including low morbidity and mortality rates with rapid defervescence, and showed its safety and effectiveness for children with thoracic empyema in central Taiwan. Baranwal et al [26] suggested that surgery was indicated for debridement of the pleural space if tube drainage failed after a 10-day trial. Karaman et al [29] compared 30 children with empyema who were randomized prospectively to receive open thoracostomy or chest tube. Average length of stay in the open decortication group was 9.5 days as compared to 15.4 days in the chest tube group. In this series, none underwent surgery as primary purpose and secondary surgery was delayed by an average of 18.5 days after chest tube drainage failed.

Due to difficulties in persuading patients about the need to undergo surgery in southern Taiwan, intrapleural fibrinolytics have become an alternative treatment for complicated parapneumonic effusion or empyema. Fibrinolytic drugs may lyse the fibrinous strands in loculated empyemas. Thomson et al [30] reported a multicenter randomized controlled trial showing that intrapleural urokinase was effective in treating empyema in children and significantly shortened hospital stay. The value of intrapleural fibrinolytics in decreasing the duration of parenteral antibiotics and shortening hospital stay in Taiwanese children with parapneumonic effusion, however, remains to be established.

In conclusion, *S. pneumoniae* (especially penicillin non-susceptible strains) is the leading causative pathogen of complicated parapneumonic effusion in southern Taiwan. An initial combination therapy regimen consisting of cefotaxime or ceftriaxone plus azithromycin provided reasonable activity against 80% of the pathogens isolated in patients with complicated parapneumonic effusion in this series. The results of this study revealed that prolonged parenteral antibiotic treatment (average, 23.7 days) resulted in a longer length of hospital stay.

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