Community-acquired pneumonia and parapneumonic effusions in developing countries

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SUMMARY: Seçmeer G, Çiftçi AÖ, Kanra G, Ceyhan M, Kara A, Cengiz AB, Kiper N, Haliloğlu M, Özçelik U, Çağdaş DN. Community-acquired pneumonia and parapneumonic effusions in developing countries. Turk J Pediatr 2008; 50: 51-57.

Ninety-eight patients with diagnosis of community-acquired pneumonia and parapneumonic effusion were retrospectively evaluated in order to determine the demographic properties of the patients, etiologic microorganism and the resistance patterns.

Ages of study groups were between 2 to 16 years (mean 6.5±3.5 years) and 56 of 98 patients (56%) were male. There were four groups: Pneumonia (Group 1, n: 57), pleural effusion-medical treatment (Group 2, n: 18), pleural effusion-tube thoracostomy (Group 3, n: 19), and pleural effusion-operative treatment (Group 4, n: 4). Pre-admission antibiotic use was up to 84% in study groups. Evaluation of seasonal dispersion revealed that 86.7% of patients were admitted to hospital in the October-May period. Blood cultures were positive in 4 of 98 patients (4%). Nine of 27 (33.3%) pleural effusion cultures were positive and 4 of them revealed *Streptococcus pneumoniae*. Intermediate penicillin resistance was found in 1/4 of *S. pneumoniae* isolates (25%).

Our study illustrates the problems in the diagnosis and management of pediatric respiratory tract infections in developing countries. Chest X-ray together with erythrocyte sedimentation rate (ESR) was also shown to be important in classifying lower respiratory tract infections. Increase in the usage of specific viral serologic studies will probably lower the percentage of antibiotic usage and lower the costs of cultures.

Key words: community-acquired pneumonia, parapneumonic effusions, lower respiratory infections, penicillin-resistant Streptococcus pneumoniae, seasonal dispersion.

Community-acquired pneumonia (CAP) is the presence of signs and symptoms of pneumonia in patients that acquired the infection outside the hospital. It remains a major cause of morbidity and mortality in developing countries and is estimated to cause the deaths of four million children under five years annually[1]. However, in industrialized countries, mortality is much lower and viruses primarily account for lower respiratory infections[2].

About 80% of all cases of pneumonia examined in hospitals in developing countries are caused by two types of bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Most other infections are of viral origin[3]. It is often impossible to distinguish clinically or radiologically between viral and bacterial pneumonia[4]. Current techniques have insufficient sensitivity to detect all relevant pathogens. Even in a research center, the approach to the investigation of pediatric CAP is inconsistent, with a diagnostic yield of only about 50%[5]. Hence, most cases are treated empirically without a causative agent being isolated.

Standardized antibiotic treatment can greatly reduce mortality due to pneumonia. The World Health Organization (WHO) developed simple guidelines for the treatment of pneumonia with

antibiotics. This antibiotic treatment regimen has shown a 55% reduction in pneumonia mortality[6]. However, inappropriate use of antibiotics has resulted in antibiotic resistance to many strains of bacteria.

Parapneumonic effusions occur in as many as 50-70% of patients admitted with a complicated pneumonia[7]. Classically, *Staphylococcus aureus* has accounted for the greatest proportion of cases with pediatric empyema[8]; however, *S. pneumoniae* is now the predominant pathogen[9].

There are some studies on pediatric CAP and parapneumonic effusions (PE) in developing countries[10-14]. In our study, CAP and PE in children were retrospectively evaluated in order to determine the microorganisms, the resistance patterns and the effects of preadmission antibiotic usage.

Material and Methods

Patients (2-16 years) who were hospitalized in the pediatric infectious disease unit of Hacettepe University İhsan Doğramacı Children's Hospital with the diagnosis of CAP and PE between 1 January 1999 and 1 June 2002 were retrospectively evaluated. This unit is an infectious diseases service for secondary and tertiary referrals with intensive care facilities. Patients with nosocomial infections were not evaluated.

Age, sex, status of preadmission antibiotic usage and predisposing disease(s) of patients were recorded.

All patients were evaluated with complete blood count (CBC); erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); biochemical, microbiological (blood cultures and aerobic and anaerobic cultures of pleural fluid sample) and radiological (chest X-ray, thoracal ultrasound and computerized tomography-CT) characteristics; treatment strategies; length of hospitalization; and complications. The microbiological data taken before the 72nd hour of hospitalization were evaluated in order to distinguish CAP and PE from nosocomial pneumonia and effusion. Pleural fluid characteristics were reviewed for Gram stain and culture, acid-fast stain and culture, pH, protein, glucose, lactate dehydrogenase (LDH) and cytology.

Groups were divided into CAP (Group 1) and pleural effusion groups. Pleural effusion groups were further divided into three groups according to the treatment modality: Pleural effusion-medical treatment (Group 2), pleural effusion-tube thoracostomy (Group 3), and pleural effusion-operative treatment (pleural debridement and formal thoracotomy and decortication) (Group 4).

The chest radiographs were classified as: alveolar and/or interstitial pneumonic appearance. When empyema was suspected, upright and decubitus radiographs and ultrasonography were used. Ultrasonography was used for characterizing the fluid density and detecting the presence of fronds, septations and loculations. Ultrasound was graded using a two-grade system[15] as low-grade (anechoic fluid, no evidence of fibrinous organization) and high-grade (evidence of fibrinous organization such as fronds, septations, loculations, or thickening of the visceral pleural surface). CT was used to evaluate pleural or parenchymal complications.

Cephalosporin, beta-lactamase antibiotics and macrolides were generally used in the treatment. If the suspected organism was *S. aureus* according to the clinical, radiological or microbiological data, vancomycin or teicoplanin was added to the treatment.

The group values were expressed as means and standard deviations. Contrasts between two and three groups were done by Mann-Whitney test and Kruskal Wallis, respectively. Differences between groups for categorical variables were determined by the χ^2-test. For all statistical tests, a two tailed p-value ≤ 0.05 was considered to be significant.

Results

A total of 98 cases aged 2 to 16 years (mean 6.5 ± 3.5 years) were enrolled; 56 (57.1%) were male, 42 (42.9%) female. Patients were placed into four categories according to the treatment scheme: Pneumonia group (n=57), pleural effusion-nonoperative treatment group (antibiotics) (n=18), pleural effusion-nonoperative treatment group (antibiotics and tube thoracostomy) (n=19), and pleural effusion-operative treatment group (pleural debridement and formal thoracotomy and decortication) (n=4).

The seasonal dispersion of all patients is seen in Figure 1; 86.7% of patients were admitted in the October-May period.

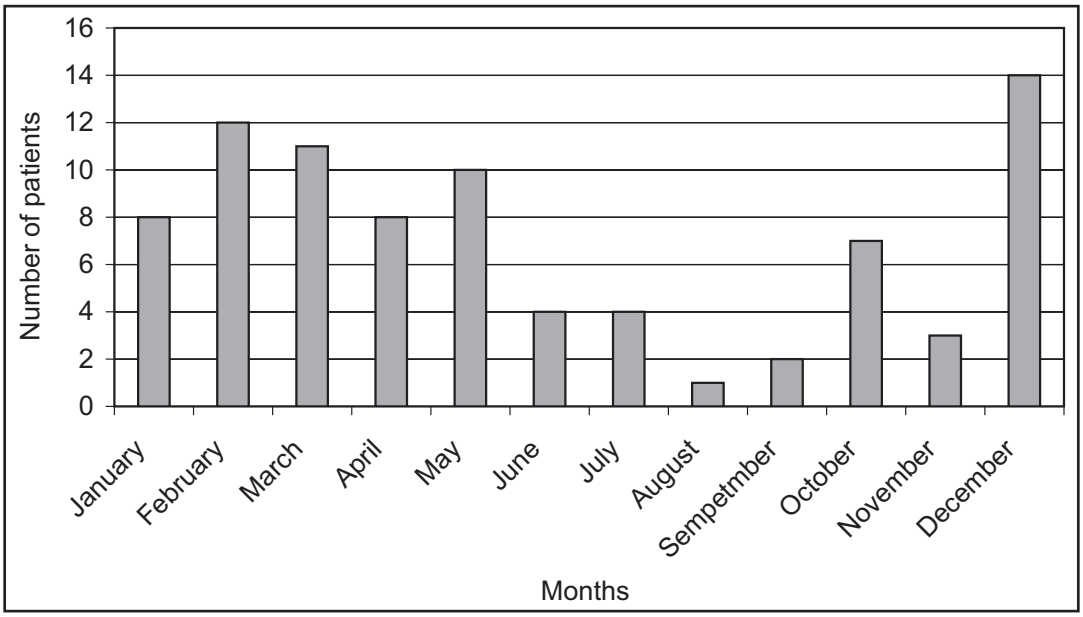

Fig. 1. Seasonal dispersion of the cases.

Age, gender, preadmission antibiotic usage, predisposing diseases, length of hospitalization, and laboratory and radiologic data are shown in Table I. Group 4 was not involved in the statistical analysis as there were only four patients in this group. Mean age was 7.5, 5.7 and 5 for Groups 1, 2 and 3, respectively. There was a statistically significant difference between Group 1 and Groups 2 and 3 ($p<0.05$). CAP was seen in about 7.5 years of age and pleural effusion in about 5 years of age in our series.

The white blood cell (WBC) count and CRP were not different in the three groups. ESR in Group 1 was lower than in Groups 2 and 3 ($p<0.05$).

Eighteen of 25 pleural fluid samples were classified as empyema according to biochemical criteria given above (4 patients from Group 2, 12 patients from Group 3, 2 patients from Group 4).

When pleural effusion groups (Groups 2 and 3) were compared with the CAP group (Group 1), interstitial infiltration ratio in the chest radiographs of Group 1 was higher with respect to alveolar infiltration ($p<0.05$).

The grade of the chest ultrasounds was compared in Groups 2 and 3, and more cases with high-grade chest ultrasounds were determined in Group 3 ($p<0.05$).

In the present study, CT was used especially in patients having predisposing disease. CT was used in 8 of Group 1 patients, 8 of Group 2 patients, 12 of Group 3 patients and all of Group 4 patients. Pulmonary abscess was found in 2 of Group 2 patients, 7 of Group 3 patients and 4 of Group 4 patients.

The hospitalization periods were 9.2, 11.2 and 19.2 days for Groups 1, 2 and 3, respectively. The hospitalization periods were longer when tube drainage was used ($p<0.05$).

The ratios of patients with predisposing diseases were 40.3% in Group 1, 16.6% in Group 2 and 5.3% in Group 3 (22 cases in the CAP group, 2 cases in pleural effusion-nonoperative treatment [antibiotics] group, 1 case in pleural effusion-nonoperative treatment [antibiotics/tube thoracostomy] group, 2 cases in pleural effusion-operative treatment group). Underlying diseases included neuromuscular disorders (cerebral palsy, congenital muscular dystrophy, Duchenne muscular dystrophy, infantile spasm, epilepsia), cystic fibrosis, immunodeficiency syndromes (ataxia-telangiectasia, Chédiak-Higashi disease, cyclic neutropenia, chronic granulomatous disease, hyper IgE syndrome), congenital heart disease, and bronchial asthma.

The pneumonia group (CAP) was further divided into two groups according to predisposing disease: CAP without predisposing disease

Table I. Clinical, Radiological and Laboratory Data of 94* Patients with CAP and PE

		Group 1 (n=57)	Group 2 (n=18)	Group 3 (n=19)
Age (year)		7.5±4	5.7±4.4	5±2
Gender (Female / Male)		20/37	8/10	9/10
Pre–admission antibiotic use (%)		54.4	77.8	84
Predisposing disease (%)		40	16.6	5
Length of hospitalization (day)		9±8	11±6.5	19±10
WBC (/mm^3)		13205±8300	17239±14828	16168±5787
Sedimentation (mm/hour)		49±28	76±20	76±20
CRP (mg/dl)		11±11	14±14	14±12
Pleural effusion	pH	–	7.2±0.3	7.3±0.5
	Protein (g/dl)	–	4. 8±0. 8	4.6±1
	Glucose (mg/dl)	–	70.5±12	36.7±33.3
	LDH (IU/L)	–	1433±1557	1173±1055
	Specific gravity	–	1027±10	1021.9±10
	Protein effusion/blood	–	0.68±0.1	0.7±0.1
	LDH effusion/blood	–	3.2±3.3	2.2±2.2
Chest X–ray	Interstitial	18	1	0
USG	Alveolar	39	17	19
	Low grade	–	9	2
	High grade	–	1	12

*4 patients in Group 4 not included in evaluations.
CAP: Community-acquired pneumonia. PE: Complicated parapneumonic effusions. WBC: White blood cell. CRP: C-reactive protein. LDH: Lactate dehydrogenase. USG: Ultrasonography.

(n=22) and CAP with predisposing disease (n=35) (Table II). Age, gender and antibiotic usage before admission to hospital were not different between the two CAP groups. There were also no differences between the groups with respect to WBC, CRP and ESR. The hospitalization period was longer in the CAP group with predisposing disease ($p<0.05$).

The antibiotic use before admission to hospital was 54.4% in Group 1, 77.8% in Group 2 and 84.2% in Group 3. The preadmission antibiotic usage of Group 1 was less than of Groups 2 and 3, but there was no significant difference in preadmission antibiotic usage between Groups 2 and 3 ($p<0.05$) (Fig. 2).

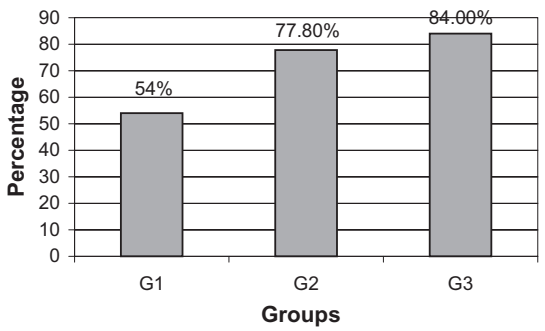

Fig. 2. Antibiotic usage before admission to hospital.

Blood culture was taken from 96 of 98 patients. Four of the blood cultures (4%) were positive (1 *S. pneumoniae*, 1 *Staphylococcus*

Table II. Comparison of CAP Cases According to Existence of Predisposing Diseases

CAP patients		Predisposing disease (–)	Predisposing disease (+)
Number of cases		34	23
Age (year)		6.4±3.7	9±4.2
Gender (F/M)		12/22	8/15
Preadmission antibiotic use (%)		62.8	40.9
Length-hospitalization (day)		6.8±4	12.7±11
WBC (/mm^3)		14744±8382	10827±7763
Sedimentation (mm/hour)		49±24	48±34
CRP (mg/dl)		10.6±11.6	10.8±12
Chest X-ray	Interstitial	9	9
	Alveolar	25	14

CAP: Community-acquired pneumonia. WBC: White blood cell. CRP: C-reactive protein.

hominis, 1 *Staphylococcus haemolyticus* and 1 *Stenotrophomonas maltophilia* and none of them was correlated with the pleural culture). All cases having positive blood cultures were patients with pleural effusion.

A sample was taken from 27 of 41 patients with pleural effusion. The culture positivity was 9/27 (33.3%): 4 patients with *S. pneumoniae* positivity, 1 each with *Staphylococcus epidermidis*, *H. influenzae, Streptococcus pyogenes, S. aureus* and *Staphylococcus simulans*. There was intermediate penicillin resistance in one of the S. pneumoniae isolates (25%). Acid- fast stains and cultures of pleural effusions were negative for tuberculosis in 27 patients with pleural effusion.

Bronchoscopy was performed in four patients (microorganisms were isolated by lavage culture in 2 - alpha hemolytic streptococcus and *H. influenzae*).

Tube drainage was applied in 20 (19 patients in Group 3, 1 patient in Group 4) (48%) patients. Streptokinase was given only in one patient who had pneumatocele and thick pleural septations (Group 3).

Decortication was performed in 4 (9%) (Group 4) of 41 patients with effusion. There was no mortality, recurrence or sequela in the patients over a six-month follow-up.

Discussion

Community-acquired pneumonia (CAP) is a common disease and the most frequent cause of mortality among children in the developing world. It is accompanied by pleural effusion in 10-57% of cases[16,17]. A pathogen is not identified in 15-60% of patients with CAP[18]. However, several generalizations are possible with respect to age. In younger children, viruses (especially respiratory syncytial virus-RSV) are most commonly found as a cause[19]. In older children (over 5 years of age), the causes are most commonly S. pneumoniae followed by mycoplasma and Chlamydia pneumoniae[20]. Viruses may initiate infection, but the death from pneumonia in developing countries is bacterial[11]. In the study of Juven et al.[19], a potential causative agent was detected in 85% of patients; 62% of patients had viral, 53% had bacterial and 30% had concomitant infection.

In our study, the onset of diseases in 86.7% of cases began in the October-May period. In the literature, the seasonal relation is also common especially with viruses. Epidemics usually begin in the rainy season and winter[21,22].

The usefulness of acute phase reactants in distinguishing bacterial from viral pneumonia was examined in a study by Nohynek et al.[23]. In that study, the cut-off points for ESR, CBC, and CRP values that would reliably distinguish bacterial from viral infections or bacterial from mixed infections could not be identified. We found that the ESR level was higher in the pleural effusion groups (Groups 2 and 3) compared to the CAP group.

In the study of Virkki et al.[24], children diagnosed as CAP were retrospectively evaluated. Most children with alveolar pneumonia, especially those with lobar infiltrates, had laboratory evidence of a bacterial infection and the interstitial infiltrates were seen in both viral and bacterial pneumonias. It was concluded that children with radiologically confirmed pneumonia should be treated with antibiotics as it is virtually impossible to distinguish exclusively between viral and bacterial pneumonia in clinical practice. We also classified the chest radiographs of all cases as interstitial and alveolar, and treated the radiologically confirmed pneumonias with antibiotics. The ratio of interstitial over alveolar infiltrates in chest radiographs was 39/18 in the CAP group and 1/17 and 0/19 in the PE groups.

According to our study and some other studies[24], higher ESR value together with alveolar infiltrate or pleural effusion in chest radiograph suggests mostly bacterial etiology.

In the present study, blood cultures were positive in 4 of 96 cases (4%). All cases having positive blood cultures were patients with pleural effusion (Groups 2 and 3). In the study by Falade et al.[25], blood culture alone yielded a bacterial pathogen in 18% of childhood cases of lobar pneumonia and empyema. The low ratios seem to be due to the high rate of antibiotic use (up to 84.2%) before hospitalization or to the low ratio of bacteremia in bacterial pneumonias.

Pneumonia may lead to more severe morbidity and mortality in predisposing diseases[2]. Our study showed that the hospitalization periods were longer in the patients with CAP who had predisposing diseases.

Four of the patients who failed to respond to broad spectrum antibiotics underwent bronchoscopy to obtain bronchoalveolar lavage (BAL) fluid. One of these patients was immunosuppressive (chronic granulomatous disease). Two of the four patients had BAL culture positivity.

A persisting pyrexia despite adequate antibiotic treatment should always lead the clinician to suspect the development of an empyema. Chan et al.[26] reviewed their experience of treating 47 children with empyema. Thirty-nine children with fibropurulent effusions were treated successfully with chest tube, and only seven of them required decortication for persistent loculation. In our study, 20 of 41 (48%) patients with pleural effusion were treated with chest tube. Four of 41 patients (9%) underwent surgical intervention. Persistent fever, worsening parenchymal disease, insufficient drainage of pleural empyema and residual pleural cavities were the main indications for surgery. In our study, streptokinase was applied in a patient having pneumatocele and thick pleural septations, and video-assisted thoracic surgery (VATS) was not used.

After the introduction of penicillinase-resistant penicillins and ensuing development of other antimicrobials effective against *S. aureus*, the incidence of *S. aureus* pneumonia and complicated PE decreased[27]. Recent reports now again describe *S. pneumoniae* as the principal bacterial pathogen in complicated PE[28]. In Hardie's[28] series of 64 children with complicated PE, 26 (40%) had positive cultures (88% were *S. pneumoniae*). Twenty-six percent of the *S. pneumoniae* were penicillin-resistant. Pleural effusion culture was often found to be sterile because of the prior use of antibiotics. In our study, the pleural effusion culture positivity was 9/27 (33.3%). Four samples were positive for *S. pneumoniae* (4/9) and one of them was penicillin-resistant (1/4).

Because of uncontrolled and frequent use of antibiotics, resistance to drugs is an emerging problem. In the study of Gur et al.[13], penicillin resistance in *S. pneumoniae* was observed in 10 of 40 (25%) strains from children. However, these strains were not isolated from only respiratory sites and 7 of 10 penicillin-resistant strains were from children having cystic fibrosis, lymphoma and immunodeficiency syndrome. In the study of Sener et al.[29], *S. pneumoniae* isolates were moderately resistant to penicillin in 39.9% and highly resistant in 3.5% (minimum inhibitory concentration-MIC>1). In the study of Yurdakul et al.[30], a total of 548 strains of *S. pneumoniae* were isolated from respiratory specimens in adults. Low-level resistance to penicillin was found in 16 isolates (3.0%), while no isolates were highly resistant.

Our study illustrates the problems in the diagnosis and management of pediatric respiratory tract infections in developing countries. The chest X-ray together with ESR was also shown to be important in classifying lower respiratory tract infections. Increase in the usage of specific viral serologic studies will probably lower the percentage of antibiotic usage and lower the costs of cultures.

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