Pediatric pleural effusions: etiological evaluation in 492 patients over 29 years

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SUMMARY: Ütine GE, Özçelik U, Kiper N, Doğru D, Yalçın E, Çobanoğlu N, Pekcan S, Kara A, Cengiz AB, Ceyhan M, Seçmeer G, Göçmen A. Pediatric pleural effusions: etiological evaluation in 492 patients over 29 years. Turk J Pediatr 2009; 51: 214-219.

Pediatric pleural effusions present a changing profile over time, both in terms of etiological subgroups and causative microorganisms in parapneumonic effusions. This retrospective study aimed to review pediatric pleural effusions in a large cohort over a 29-year period, with special emphasis on the etiological subgroups and microbiological causes of parapneumonic effusions. The medical records of 492 pediatric patients were reviewed for a comparison of subgroups of pleural effusions and microbiological causes of parapneumonic effusions between three decades. Parapneumonic effusions (381 patients) made up 77.4% of the group. Tuberculous pleurisy decreased, but malignant effusions doubled in number over time. A causative microorganism was identified in 34.6% overall, with *Staphylococcus aureus* and *Streptococcus pneumoniae* being the two most common. Relative frequency of *S. aureus* decreased, whereas pneumococci and *Haemophilus influenzae* were more frequent in recent years.

Key words: pediatric pleural effusion, parapneumonic, tuberculous, malignant effusion, empyema.

Pediatric pleural effusions present a changing profile over time, both in terms of etiological subgroups and causative microorganisms in parapneumonic effusions. The changing spectrum of causative agents in pediatric parapneumonic effusions is among the current topics on the subject[1,2]. The causative agent may be difficult to estimate empirically because of changes in frequency of microbial agents over years[1,2], incomplete sensitivity and specificity of different methods in detecting the agents[3-6], and increasing incidence of sterile empyemas as a result of wide utility of broad spectrum anti-microbial agents[2]. Reviews of causative agents over long periods of time help reveal this changing profile of causative microorganisms and would be clinically useful.

The current study was conducted to provide a general descriptive information on pediatric pleural effusions seen at Hacettepe University Children's Hospital between 1975 and 2003, with a main focus on frequencies of effusion subtypes and etiological causes.

Material and Methods

The medical records of 492 pediatric patients with pleural effusions admitted to Hacettepe University İhsan Doğramacı Children's Hospital

The study was accepted as a poster presentation at the 16th ERS Annual Congress, Munich, Germany, September 2-6, 2006: Utine GE, Özçelik U, Yalçın E, Doğru D, Çobanoğlu N, Pekcan S, Kiper N, Göçmen A. Pediatric pleural effusions: a retrospective review of 492 patients.

between 1975 and 2003 were available for review. These included patients in whom pleural effusions were the reason for referral as well as those with a clinical finding after admission for other presenting symptoms. Patients who developed pleural effusions during their follow-up for underlying diseases were also included in the study, if pleural sampling for diagnostic purposes was performed. Patients with low amounts of pleural fluid collections for whom diagnostic or therapeutic sampling was not required were excluded from the study. The study population did not include newborns or patients in whom pleural effusion was due to trauma or surgery.

History regarding symptoms, prior vaccination and types of previous treatments, findings on physical examination, and results of laboratory tests were evaluated. Laboratory tests included Gram-stained smears, pleural fluid cultures in ordinary media and blood culture media, blood cultures, pleural fluid cultures for *Mycobacterium tuberculosis*, and pleural fluid acido-resistant bacilli (ARB). Polymerase chain reaction (PCR) for *M. tuberculosis, Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae* was available for the last two years of the study period.

Pleural fluids were classified based on etiological cause of pleural fluid collection. Effusion fluids collected during the course of pneumonia are parapneumonic effusions. According to recent guidelines[7,8], empyemas include grossly purulent fluids, either free-flowing (simple empyema) or multiloculated (complex empyema). Complicated effusions include those with 1) a pH between 7.0 and 7.2 or an lactate dehydrogenase (LDH) level >1000, with glucose level above 40 mg/dl (borderline complicated), 2) a pH below 7.0 or glucose level lower than 40 mg/dl (simple complicated), 3) a pH below 7.0 or glucose level lower than 40 mg/dl, plus multiloculations in the pleural cavity (complex complicated). Uncomplicated parapneumonic effusions include those without these properties. Culture and/or Gram smear positivity may be present in simple complicated or complex complicated effusions, as well as in empyemas[7,8]. However, as measurements for pleural fluid pH, glucose and LDH were not uniformly available throughout the study period, fluids in which microorganisms were detected by either Gram-stained smears or cultures were classified as empyemas as suggested in earlier publications[5,9,10], for the purpose of simplicity in the present study. Others were classified as complicated parapneumonic effusions if the effusion fluid contained septae, had a pH below 7.2, glucose level lower than 40 mg/dl or an LDH level above 1000 U/L, and as uncomplicated parapneumonic effusions if these properties were absent.

Detection of malignant cells in the pleural fluid by cytological examination led to the diagnosis of malignant effusion[11]. Positive smears for ARB, PCR or culture detection of *M. tuberculosis* in the pleural fluid as well as an adenosine deaminase level greater than 40 U/L together with a pleural fluid cellular content of at least 50% lymphocytes were classified as tuberculous effusions[12]. Fluids not fulfilling these criteria were grouped as unclassified effusions.

Statistical analysis of data was performed using SPSS for Windows 12.0.

This study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine.

Results

Whole Group

Of 492 pediatric patients admitted to Hacettepe University Children's Hospital over the period 1975 to 2003, 304 (61.8%) were females and 188 (38.2%) were males. Median age was 4.0 years (range: 0-18; 1 20-year-old patient with tuberculous effusion was included in the group); 168 (34.1%) were aged 0-2 years, 117 (23.8%) 3-5 years, 112 (22.8%) 6-10 years and 95 (19.3%) were older than 10 years. The time period was arbitrarily divided into three decades (Table I).

Availability of laboratory tests showed changes throughout the 29 years. LDH analyses and cultivation of pleural samples in blood culture media were available during the last decade. PCR analysis of *M. tuberculosis* was available during the last decade and PCR analysis of *S. pneumoniae, S. aureus* and *H. influenzae* was done in 2001-2003.

Etiological classification of effusions revealed that parapneumonic effusions predominated in the whole group (77.4%) and in each of the three time periods (Table I). Frequencies of parapneumonic effusion subgroups and other groups are shown in Table I.

Table I. Distribution of Pleural Effusion Subtypes Over Years [in counts (%)]*

Subtypes of pleural effusions	Years			Total
	1975-1983	1984-1993	1994-2003	
Parapneumonic effusions	128 (78)	135 (79.9)	118 (74.2)	381 (77.4)
Empyema	81 (49.4)	91 (53.8)	63 (39.6)	235 (47.8)
Complicated parapneumonic effusions	4 (2.4)	2 (1.2)	32 (20.1)	38 (7.7)
Noncomplicated parapneumonic effusions	2 (1.2)	14 (8.3)	14 (8.8)	30 (6.1)
Unclassified parapneumonic effusions	41 (25)	28 (16.6)	9 (5.7)	78 (15.9)
Tuberculous effusions	27 (16.5)	22 (13)	13 (8.2)	62 (12.6)
Malignant effusions	2 (1.2)	5 (2.9)	12 (7.5)	19 (3.9)
Exudative effusions of unidentified etiology	5 (3.1)	4 (2.4)	9 (5.7)	18 (3.7)
Transudative effusions of unidentified etiology	0 (0)	1 (0.6)	3 (1.9)	4 (0.8)
Effusions due to congestive heart failure	2 (1.2)	1 (0.6)	4 (2.5)	7 (1.4)
Chylothorax due to lymphangiomatosis	0 (0)	1 (0.6)	0 (0)	1 (0.2)
Total	164 (100)	169 (100)	159 (100)	492 (100)

*Percentages are given for columns.

Relative frequency of tuberculous effusions decreased over the years (Table I). Median age in this group was 11 years (range: 2-20 years). Thirteen (21%) of patients with tuberculous effusions were not vaccinated against tuberculosis and for another 12 (19%), a history of vaccination was not recorded.

Malignant effusions constituted 1.2% (2 patients), 2.9% (5 patients) and 7.5% (12 patients) of all effusions, respectively, in the three time periods (Table I). Median age at diagnosis for malignant effusions was 11.0 years (range: 4 months-16 years). Pathologic diagnoses were as follows: non-Hodgkin lymphoma (7 patients), Burkitt lymphoma (2 patients), rhabdomyosarcoma (2 patients), neuroblastoma (2 patients), primitive neuroectodermal tumor (2 patients), chronic myelomonocytic leukemia (1 patient), yolk sac tumor (embryonal cell carcinoma) (1 patient), hemangioendothelio sarcoma (1 patient), and accelerated phase of Chédiak-Higashi syndrome (1 patient).

Parapneumonic Effusions Group

The median age of patients with parapneumonic effusions was 3.0 years (range: 0-18 years), with 68% younger than age 6 and 40.2% younger than age 3. Median age at admission was 3.0 years, for both genders (152 males, 229 females). Admissions during the three decades were 128 (33.6%), 135 (35.4%) and 118 (31.0%), respectively. No prior vaccination history against *H. influenzae* type b or *S. pneumoniae* was present. Parapneumonic effusion subtypes were determined as empyemas in 235 (61.7%), complicated in 38 (10%), uncomplicated in 30 (7.9%) and unclassified in 78 (20.5%) (Table I).

The majority (89.8%) had no underlying diseases. Fever (89.2%), cough (82.7%) and shortness of breath (39.4%) were the most frequent symptoms. Median preadmission time for symptoms overall was 10 days, and the difference between the three time periods (13.0, 7.5 and 9.0 days, respectively) was statistically significant ($p<0.001$). Prior to admission, 42 patients had undergone drainage and 258 had received antibacterial agents -- 51 orally, 145 parenterally and 62 via both routes. Data on previous antibiotic therapy was inadequate; thus, contribution of prior treatment to the yield of microbiological analyses and to clinical outcome could not be assessed. The most frequent findings in physical examination were decreased breath sounds (92.9%), retractions (46.7%) and rales (46.2%).

Microbiological analyses were not available for eight patients. Of the remaining 373 patients with parapneumonic effusions, microbiological analyses collectively enabled identification of a causative microorganism in 124 (34.6%) (Table II). A causative pathogen was detected in 30 (23%), 49 (36%) and 45 (38%) patients, respectively, over the three time periods. *S. aureus* was the causative agent in 57 patients (15%), pneumococci in 27 (7.1%) and *H. influenzae* (including nontypeable strains) in 4 (1%). Co-infection with pneumococci and *H. influenzae* was found in 2 patients (0.5%) and co-infection with *S. aureus* and *H. influenzae*

Table II. Causative Microorganisms in Parapneumonic Effusions [in counts (%)]♦ and Distribution Over the Three Time Periods

	Years			
Causative microorganisms	1975-1983	1984-1993	1994-2003	Total
Staphylococcus aureus	19 (63.4)	31 (63.3)	7 (15.6)	57 (46)
Streptococcus pneumoniae	3 (10)	8 (16.3)	16 (35.6)	27 (21.8)
Other streptococci*	4 (13.3)	3 (6.1)	3 (6.7)	10 (8)
Other staphylococci**	1 (3.3)	2 (4.1)	5 (11.1)	8 (6.5)
Haemophilus influenzae type b	0 (0)	0 (0)	4 (8.9)	4 (3.2)
Streptococcus pyogenes	0 (0)	1 (2)	2 (4.4)	3 (2.4)
Streptococcus pneumoniae + *Haemophilus influenzae* type b	0 (0)	0 (0)	2 (4.4)	2 (1.6)
Haemophilus influenzae + *Staphylococcus aureus*	0 (0)	0 (0)	1 (2.2)	1 (0.8)
Gram-negative bacteria***	3 (10)	4 (8.2)	5 (11.1)	12 (9.7)
Total	30 (100)	49 (100)	45 (100)	124 (100)

* α-hemolytic streptococci and streptococci of undetermined serotypes.

** *Staphylococcus epidermidis* and undetermined staphylococcal species

*** Klebsiella, *Escherichia coli,* co-infection of *E. coli* and Klebsiella, coliform bacteria, pseudomonas, *Stenotrophomonas maltophilia.*

♦ Percentages are given for columns.

in 1 (0.3%). Other common pathogens were α-hemolytic streptococci (7 patients), *Staphylococcus epidermidis* (5 patients) and *Streptococcus pyogenes* (3 patients). In the last decade, the frequency of *S. aureus* was lower and of *S. pneumoniae* was higher than before. Overall, staphylococci were responsible in 66 patients and streptococci in 42 patients.

Of 58 patients in whom *S. aureus* was identified as a causative agent, 33 were younger than 3 years of age and 44 were younger than 6 years of age (Table III). Of 29 patients in whom *S. pneumoniae* was identified as a causative agent, 10 were younger than 3 years of age and 20 were younger than 6 years of age. Other streptococci, staphylococci and Gram-negative bacteria were also more frequently encountered in younger children.

In one patient, *S. aureus* detected in blood culture was considered pathogenic, while no pathogen could be detected in pleural fluid culture. *S. pneumoniae* was isolated in pleural fluid culture in 19 patients, but in pleural fluid cultivated in blood culture medium in only two patients and in blood cultures in only one patient. In one patient, the organism was isolated from a second pleural fluid culture. In the remaining five patients, the organism was detected by PCR in pleural fluid. Penicillin non-susceptibility was present in only three isolates, one being intermediate.

Discussion

Retrospective analysis of pediatric pleural effusions over a 29-year period demonstrated that parapneumonic effusions constituted the majority of effusions, with a decreasing relative frequency of tuberculous effusions and an increasing relative frequency of malignant effusions. Changes in the relative frequencies of causative microorganisms over the years imply a decrease in *S. aureus* pneumonia; however, *S. pneumoniae* and *S. aureus* continue to be major pathogenic organisms.

Parapneumonic effusions constituted the majority of pediatric pleural effusions, followed by congenital heart diseases and malignant effusions[1-3,6,9,13]. Parapneumonic effusions constituted 77.4% of the present group, which is higher than reports in the literature (50-60%)[1-3,6,9,13]; however, this is most probably because patients with congestive heart failure

Table III. Distribution of Microorganisms Among Age Groups in Patients with Parapneumonic Effusions [in counts (%)]♦

Causative microorganisms	Age in years				Total
	0-2	3-5	6-10	>10	
Staphylococcus aureus	33 (57.9)	10 (17.5)	5 (8.8)	9 (15.8)	57 (100)
Streptococcus pneumoniae	10 (37)	8 (29.7)	6 (22.2)	3 (11.1)	27 (100)
Other streptococci*	3 (30)	3 (30)	3 (30)	1 (10)	10 (100)
Other staphylococci**	5 (62.5)	2 (25)	1 (12.5)	0 (0)	8 (100)
Haemophilus influenzae type b	1 (25)	2 (50)	0 (0)	1 (25)	4 (100)
Streptococcus pyogenes	2 (66.7)	1 (33.3)	0 (0)	0 (0)	3 (100)
Streptococcus pneumoniae + *Haemophilus influenzae* type b	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)
Haemophilus influenzae + *Staphylococcus aureus*	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)
Gram-negative bacteria***	6 (50)	3 (25)	2 (16.7)	1 (8.3)	12 (100)
None	90 (36.2)	69 (27.7)	64 (25.7)	26 (10.4)	249 (100)
Total	150 (40.2)	101 (27.1)	81 (21.7)	41 (11)	373 (100)

*α-hemolytic streptococci and streptococci of undetermined serotypes.
**_Staphylococcus epidermidis_ and undetermined staphylococcal species.
***Klebsiella, _Escherichia coli_, co-infection of _E. coli_ and Klebsiella, coliform bacteria, pseudomonas, _Stenotrophomonas maltophilia_.
♦Percentages are given for rows.

are underrepresented in the group. The effusion subgroups changed slightly over the years, although parapneumonic effusions comprised the majority in all decades. Subgroups of parapneumonic effusions were determined more commonly in later years, as availability of laboratory tests, particularly the LDH test, increased. Frequency of tuberculous effusions has decreased gradually, in keeping with general improvement in health and decrease in tuberculosis incidence in Turkey over this time period[14].

Parapneumonic pleural effusions are encountered more frequently in young children, particularly during the first two years of life[15] and accordingly, 34.1% of the current patients were aged 0-2 years and 57.9% were younger than 6 years.

Causative pathogens remain unidentified in 20-50% of patients with pleural empyemas[5,6], although pathogen detection rates as variable as 8-76% have been reported[3,4]. The detection rate in the present study was 34.6% over the 29-year period, with the lowest rate in the first decade.

The most frequent organisms encountered in children are *S. aureus*, *S. pneumoniae*, *H. influenzae* and *S. pyogenes, Pseudomonas aeruginosa, Mycoplasma pneumoniae* and anaerobes[6,9,15,16]. However, the relative frequencies of the major pathogens responsible for pleural infections have shown some changes over the years[1,2,4,5,9,17]. Recently, it has been reported that *H. influenzae* is almost never observed in children as a major pathogen[2], that *S. pneumoniae* is being isolated more frequently as a more virulent and penicillin-resistant microorganism in pleural effusions and that *S. aureus* is responsible for less than 10% of patients[2,18]. In more recent reports, *S. pneumoniae* appears to be responsible for the majority of pediatric effusions, particularly where more effective control against *S. aureus* has been achieved[6,19]. However, *S. aureus* continues to be the most common organism in children from South Asia[19]. A review in 2002 reported that *S. aureus* is still responsible for 29-35% of pediatric empyemas, particularly in children younger than 2 years, and *S. pneumoniae* is responsible for 25% of empyema cases[1]. *H. influenzae,* although less frequent than the other two, is still an important cause of parapneumonic effusions in children younger than 5 years[1].

The current study revealed a decreasing relative frequency of *S. aureus* and an increasing relative frequency of *S. pneumoniae* in pediatric parapneumonic effusions, and the frequencies of *S. aureus* and *S. pneumoniae* were higher in patients younger than 2 years of age (Table III). No decrease in the relative frequency of *H. influenzae* was observed. The decrease in the frequency of *H. influenzae* type b in developed countries is usually explained by effective vaccination of children against this microorganism, which was not routinely performed in Turkey during the period of the present study. Vaccination against *S. pneumoniae* was also not routine, and no history of prior immunization against this microorganism was present in this group. These two factors may account for the increase in relative frequency of *S. pneumoniae*, as emergence of penicillin-resistant strains was not detected. PCR detection of these microorganisms also may account for the increase in the frequencies of *H. influenzae* type b and *S. pneumoniae* in the last decade.

The current study demonstrates that parapneumonic effusions constitute the majority of the pediatric pleural effusions. Causative microorganisms were identified in 34.6% overall, with *S. aureus* and *S. pneumoniae* determined as the two most common. A changing profile of the causative agents in Turkey over this 29-year period was evident, with a decrease in tuberculous effusions and an increase in malignant effusions. The relative frequency of *S. aureus* decreased, whereas pneumococci and *H. influenzae* were more frequent in recent years.

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