Journal of Pediatric Surgery (2011) **46**, 452–457

ELSEVIER

Journal of Pediatric Surgery

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Impact of antibiotic therapy on laboratory analysis of parapneumonic pleural fluid in children ☆

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Received 18 December 2009; revised 8 September 2010; accepted 8 September 2010

Key words:
Empyema;
Parapneumonic pleural effusion;
Antibiotic therapy;
Children

Abstract

Objective: The therapeutic management of parapneumonic pleural effusions (PPE) is controversial in children. Decision-making often relies on parameters such as gross appearance of pleural fluid and on bacteriologic and biochemical analyses. Our goal was to describe the laboratory profile of PPE in children and to assess the influence of previous administration of antibacterial agents on culture and biochemical results.

Patients and methods: This was a prospective study including children (age, 1 month to 16 years) with a diagnosis of PPE. Two groups were evaluated: children with or without antibiotic treatment up to 48 hours before analysis of pleural fluid. Results were analyzed using the χ^2 or Mann-Whitney test ($\alpha = .05$). Odds ratio and 95% confidence intervals (95% CIs) were calculated, with control of previous antibiotic therapy using multivariate logistic regression analysis, to determine the risk of empyema associated with specific biochemical parameters.

Results: One hundred ten children were selected. Fifty percent had received antibiotics at least 48 hours before pleural fluid analysis. Differences were observed between the groups in terms of PPE gross appearance ($P = .033$) and identification of bacteriologic agent by culture or Gram stain ($P = .023$). Biochemical parameters (pH ≤7.1 and glucose ≤40 mg/dL) were associated with increased odds of receiving a more invasive treatment. For pH, the odds ratio was 9.614 (95% CI, 1.952-47.362; $P = .005$); and for glucose, 9.201 (95% CI, 1.333-63.496; $P = .024$).

Conclusions: Previous use of antibacterial agents affected the bacteriologic analysis of pleural fluid in this pediatric sample admitted for PPE. However, it did not interfere significantly with biochemical parameters of pleural fluid.

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0022-3468/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jpedsurg.2010.09.003

Acute respiratory infections are the main cause of morbidity and mortality from infectious diseases in children younger than 5 years in developing countries [1,2]. In these patients, the incidence of parapneumonic pleural effusions (PPE) varies widely, from 14.6% to 91%, evolving to empyema in 5% to 10% of the cases [1,3-5]. In the presence of PPE, the treatment to be followed depends on pleural fluid analysis [3,5-10]. A diagnosis of empyema (pus and/or bacteria in pleural fluid) is currently the only clearly accepted indication for surgical treatment of PPE (closed chest tube with or without fibrinolytics, video-assisted thoracic surgery, or thoracotomy) [5,9,11-14].

So far, the studies concerning predictors of the need for surgical treatment of PPE (biochemical analyses of pH, glucose, lactic dehydrogenase) have been conducted in adult populations [4,5,8,9], with results extrapolated to children. However, children with various disorders are often submitted to antibiotic therapy before laboratory testing. For example, 30% to 55% of children are treated with antibiotics before a laboratory diagnosis of bacterial meningitis is obtained. Cerebrospinal fluid (CSF) cultures have been observed to be sterile in 90% to 100% of patients receiving antibiotic therapy 14 to 48 hours before laboratory analysis [15]; therefore, it is reasonable to suppose that the previous use of antibiotics might delay or even prevent a diagnosis of meningitis [16]. Nevertheless, the effects of previous antibiotic therapy on pleural fluid analysis in pediatric patients have not been studied.

The objectives of the present study were to describe the biochemical and bacteriologic profile of a pediatric population with PPE and to determine whether previous antibiotic therapy affects the characteristics of the pleural fluid.

1. Methods

This prospective, longitudinal, and observational study included patients between 1 month and 16 years of age with a diagnosis of PPE admitted to the Emergency Service at Hospital da Criança Santo Antônio, Porto Alegre, Brazil, from July 2001 to December 2005. Diagnosis was based on clinical and radiologic criteria (presence of fluid associated with ipsilateral lung infection). Every patient suspected to have PPE was submitted to anteroposterior and lateral chest x-ray, as well as horizontal x-ray of the affected side. The amount of fluid was determined by a chest x-ray with the side of the effusion down. When the distance between the outer border of the lung and inner border of the chest was more than 10 mm, a diagnostic thoracentesis was performed [7,17]. Ultrasound evaluation was indicated only in patients with clinical symptoms lasting for more than 5 days or if the presence of loculations was suspected on initial radiologic analysis.

Excluded from this study were patients with congenital or acquired immunodeficiency, pleural effusion associated with other clinical conditions (such as nephrotic syndrome, cardiopathy or tuberculosis), and those with insufficient pleural fluid for laboratory dosing or processing using established techniques. The study protocol was approved by the institution's research ethics committee (protocol no. 004/01), and the parents or guardians of the children enrolled signed an informed consent form.

All patients with PPE submitted to diagnostic thoracentesis were followed by the same investigator from the moment of fluid collection until discharge from the hospital. This investigator also examined and recorded the gross appearance of the pleural fluid. Demographic and laboratory data, as well as clinical outcome, were recorded in a standard form.

The patients were divided into 2 groups: with or without previous antibiotic treatment. Previous antibiotic treatment was defined as 2 doses of any antibacterial agent at least 48 hours before clinical evaluation/assessment and diagnostic thoracentesis. All the patients with previous antibiotic treatment had received oral antibiotics: 90% received amoxicillin, and 10% received cephalexin or erythromycin. The dose was established based on the child's weight in kilograms.

Following the routine of the emergency service, after thoracentesis was performed, pleural effusion specimens were sent for analysis of pH, glucose, lactic dehydrogenase (LDH), protein, bacterioscopy, and culture. Hemogram and hemoculture were simultaneously performed for all patients. Based on the physicochemical characteristics of the pleural fluid and on laboratory results, the initial therapeutic plan was established. Patients were then submitted to a new chest x-ray to detect post-thoracentesis complications and to assess the possibility of residual pleural effusion. The diagnosis of complications associated with the procedure was determined by the team in charge of the patient.

All laboratory analyses followed the institution's technical norms. The material for pH dosing was obtained in anaerobiosis with a heparinized syringe (1:1000 UI) and immediately sent to the laboratory sealed with a rubber stopper. Reading was performed by an ABL 5 gasometry device (Radiometer, Copenhagen, Denmark). Glucose measurements were made using the GOG-PAP (oxidase-peroxidase) assay with Merck reagents. Results were expressed in milligrams per deciliter [18].

Gram staining and optical microscopy were used for the bacterioscopic evaluation of pleural effusion. Blood agar medium was used to identify the pathogen involved in PPE. Pathogens identified as gram-negative and suggestive of *Haemophilus influenzae* were grown on chocolate agar. Other gram-negative pathogens were grown on MacConkey agar for differentiation of Enterobacteriaceae [19].

Clinical outcome was assessed based on the need for invasive procedures as judged by the medical team in charge of the child during admission. For analysis, clinical outcome was divided into 2 categories: requiring a simple thoracentesis or requiring a more invasive procedure (chest close

drainage or video-assisted thoracic surgery). As described in the literature, the performance of these procedures is used to distinguish noncomplicated parapneumonic pleural effusions from complicated parapneumonic pleural effusions (CPPEs) [3,8,9].

All the procedures were requested by the attending medical team based on institutional criteria without involvement of the investigators (because the purpose of the study was not to evaluate or compare specific treatments, but rather to assess the impact of previous antibiotic therapy on biochemical and bacteriologic parameters of the pleural fluid). The routines of the service were followed in all cases [3,11,20].

The initial sample size was determined based on previous studies [1,7]. For an estimated 40% frequency of positive pleural fluid cultures (patients without previous antibiotic treatment) and 10% (patients with previous antibiotic treatment), considering a 1:1 ratio, power of 80%, and 95% significance, 38 patients would be needed in each group (total of 76 patients). However, because the frequency of positive pleural fluid cultures was slightly different in this sample—35% in patients without and 12% in patients with previous antibiotic treatment—OpenEpi [21] was used to recalculate the sample size as 55 patients in each group to ensure a power of 80% with 95% significance.

1.1. Statistical analysis

Data were recorded on Excel (Microsoft, Redmond, WA) spreadsheets and analyzed using the Statistical Package for the Social Sciences, version 10.0 (SPSS, Chicago, Ill). Quantitative variables with symmetrical distribution were expressed as means and standard deviation. Asymmetric variables were described as medians and 25% to 75% interquartile range. Categorical variables were expressed as absolute frequencies and percentages. The Mann-Whitney *U* test was used for comparison of asymmetric data. The χ^2 test was used for comparison of categorical variables. To assess empyema predictors and control for possible confounding factors, logistic regression analysis was used. A significance level of .05 was adopted.

Table 1 General characteristics of children with PPE

Characteristic	n = 110
Age (mo)	41.4 ± 30.7 [a]
	33 (19.7-56.2) [b]
Male sex [c]	58 (52.7)
Signs and symptoms [c, d]	
Fever	108 (98.2)
Cough	95 (86.4)
Dyspnea	49 (44.5)
Vomit	39 (35.5)
Loss of appetite	41 (37.3)
Moaning	37 (33.6)
Chest pain	24 (21.8)
Abdominal pain	25 (22.7)
Prostration	18 (16.4)
Effusion side [c]	
Right	59 (53.6)
Left	34 (30.9)
Bilateral	17 (15.5)
Biochemical analysis of pleural fluid	
pH [a]	7.42 ± 0.54
Glucose (mg/dL) [a]	45.55 ± 37.24
Proteins(g/dL) [a]	4.24 ± 0.89
LDH (IU/L) [b]	2.551.5 (1087.5- 8951.0)
Bacteriologic analysis of pleural fluid [c]	
Positive culture [e]	25 (22.7)
Streptococcus pneumoniae	22 (88.0)
Haemophilus sp [f]	1 (4.0)
Staphylococcus sp	1 (4.0)
Moraxella catarrhalis	1 (4.0)
Positive hemoculture [e]	19 (17.3)
Streptococcus pneumoniae	13 (68.4)
Haemophilus sp	2 (10.5)
Staphylococcus sp	2 (10.5)
Other pathogens [g]	2 (10.5)

[a] Data presented as mean ± SD.
[b] Data presented as median (25%-75% interquartile range).
[c] Data presented as absolute number (percentage).
[d] The same patient may present more than one sign or symptom.
[e] There was no difference or predominance in the identification of bacteria for different ages.
[f] The patient showed growth of 2 associated pathogens: *Haemophilus* sp and *Streptococcus pneumoniae*.
[g] Other pathogens were enterococcus in one patient and the association of *Streptococcus pneumoniae* and *Staphylococcus* sp in another.

2. Results

Between July 2001 and December 2005, 117 patients with PPE samples obtained by thoracentesis were selected for this study. Of those, 7 patients (6%) were excluded: in 5, pleural effusion (PE) was associated with tuberculosis rather than pneumonia, and in 2 the amount of pleural fluid was insufficient for analysis. Thus, 110 children with PPE were studied. Table 1 describes the main characteristics of the sample.

Mean time from the onset of symptoms until the performance of thoracentesis was 6.41 ± 3.33 days. All cases presented lobar pneumonia. In 5.5%, pneumatoceles were observed on radiologic assessment. In 59 (53.6%) children, the right lung was affected vs the left lung in 34 (30.9%). In 17 children (15.5%), both lungs were affected.

Ultrasound evaluation was performed in 57 (51.8%) patients, with the initial examination showing septations in 61.4%. Pleural fluid was clear in 33 patients (30%), turbid in 46 (41.8%), and purulent in 23 (20.9%). The presence of bacteria was demonstrated by Gram stain in 27 cases (24.5%) and by culture in 25 (22.7%). Culture results were positively correlated with Gram staining. Pneumothorax and subcutaneous emphysema were the most frequent

Table 2 Comparison of children with or without previous use of antibiotic therapy

Characteristic	Previous use of antibiotics (n = 55)	Without previous antibiotics (n = 55)	*P*
Demographic data			
Age (mo) [a, b]	27 (15-61)	37 (24-52)	.152
Male sex [c, d]	31 (56.4)	27 (49.1)	.567
Gross appearance of PE [c, d]			
Purulent	6 (12)	17 (32.7)	.033
Septations on chest ultrasound	21 (65.6)	14 (56)	.641
Biochemical analysis			
pH ≤7.1 [c, d]	11 (23.4)	20 (41.7)	.093
Glucose ≤40 mg/dL [c, d]	19 (36.5)	30 (56.6)	.062
LDH ≥1.000 UI/L [c, d]	37 (78.7)	29 (74.4)	.825
Microbiological analysis			
Gram-positive [c, d]	8 (14.5)	19 (34.5)	.027
Positive PE culture [c, d]	7 (12.7)	18 (32.7)	.023
Positive hemoculture [c, d]	5 (9.4)	15 (27.3)	.033
WBC count (cells/mm^3) [a, b]			
Blood	15.190 (11.530-20.367)	16.460 (9.400-22.200)	.964
PE	4.500 (1.082-9.370)	5.400 (563-20.590)	.568
Outcome			
Complicated PPE [c, d, e]	34 (61.8)	42 (76.4)	.149
Length of admission (d) [a, b]	13 (10-18)	15 (12-20)	.143

WBC indicates white blood cell.
[a] Mann-Whitney test.
[b] Data presented as median (25%-75% interquartile range).
[c] χ^2.
[d] Data presented as absolute number (percentage).
[e] Complicated PPE: need for any surgical procedure (chest drainage and/or videolaparoscopy).

complications associated with thoracentesis, occurring in 11.8% of the patients. In 76 (69%) patients, additional surgical interventions were required. In all these cases, the pleural effusion was characterized as complicated (CPPE). Closed chest drainage was performed in 36 patients (32.72%) as an adjunct treatment. Thirty-four patients (30.9%) required videothoracoscopy.

In 55 patients (50%), there was a record of previous use of antibacterial agents for at least 48 hours before admission. The groups with or without previous use of antibacterial agents were similar in terms of clinical characteristics ($P > .05$; Table 1).

Previous antibacterial use did influence the incidence of positive bacterial culture but did not significantly influence the biochemical parameters of pleural fluid: the groups with and without prior treatment were different in terms of gross pleural fluid appearance ($P = .033$) and the ability of culture to identify the pathogen ($P = .023$). Hemoculture was also statistically different ($P = .033$) (Table 2). There was no difference concerning biochemical parameters when the groups with or without previous antibiotic treatment were compared. However, considering the biochemical parameters of pleural effusion, we observed that pH ≤7.1 and glucose ≤40 mg/dL increased the odds of receiving a more invasive treatment. For pH, the odds ratio (OR) was 11.139 (95% confidence interval [CI], 2.28-54.4; $P = .003$). For glucose, the OR was 8.351 (95% CI, 1.20-58.12; $P = .032$). Lactic dehydrogenase increase was not associated with empyema (OR, 0.53; 95% CI, 0.54-5.22; $P = .58$). There was a trend (OR, 9.614; 95% CI, 1.952-47.362; $P = .005$) for pH to be lower after antibacterial treatment.

3. Discussion

Despite the high prevalence of PPE, especially in developing countries, management of this condition is still controversial [1,2,10,12-14,22-25]. Pleural fluid analysis is the main tool to guide the need for adjunct surgical treatment and antibiotic therapy in these patients. However, previous use of antibiotic therapy, a frequent situation in children, might impact the results of pleural fluid analysis, potentially affecting therapeutic decision-making. Nevertheless, no study so far has assessed the influence of antibiotic therapy before PPE analysis on aspects such as biochemical behavior of pleural effusions.

Previous studies have demonstrated that the ability of bacteriologic analysis to identify pathogens is decreased in the blood and pleural fluid of patients treated with antibiotics before hospitalization [26]. As a result, the development of alternative, more sensitive laboratory techniques has been

encouraged (polymerase chain reaction, detection of capsular antigens) [9,27,28]. Our study confirms that previous antibiotic therapy may significantly influence culture results in pleural fluid and blood: bacteria were more easily identified in the absence of previous antibacterial treatment. This supports the notion that use of antibacterial agents before pleural fluid analysis may compromise identification of the etiologic agent in PE, and consequently influence subsequent therapeutic decision. In addition, previous antibiotic treatment might influence the development of lung infection, measured in this study in terms of length of admission and presence of complicated PPE. However, we did not observe an increase in hospitalization time or a greater number of additional surgical procedures in the pretreated group.

Harper and colleagues [26] were unable to identify the etiologic agent in the hemoculture of patients diagnosed with bacteremia in the presence of previous antibiotic therapy. When analyzing the CSF of patients with meningitis, Kanegaye and colleagues [29] verified that the previous use of antibacterial agents could lead to CSF sterilization after 1 hour from the beginning of endovenous treatment. Other investigators have reported similar results, with CSF sterilization 48 to 72 hours after the beginning of treatment with antibiotics in up to 99% of the cases [30-32].

Although it is adopted by many institutions, the classification of PPE and empyema proposed by Light and colleagues [20] is still controversial [33-36]. Berger and Morganroth [35] showed a favorable outcome with antibacterial agents only (no surgical treatment) in a series of patients with PPE categorized according to the Light criteria as CPPE. Poe and colleagues [36] have concluded that the sensitivity of the Light classification is low, despite its high specificity to detect PPE. An international clinical consensus statement concerning management of PPE in the pediatric population does not mention biochemical analyses of pleural fluid as important for therapeutic decision-making [6]. Lower sensitivity of biochemical parameters for early identification of patients who may benefit from thoracic drainage (pH $\leq$7.10, glucose $\leq$40 mg/dL, LDH $\geq$1000 U/L) [9,11,33,37,38] has also been reported in the literature [34-36,39,40].

Although the primary goal of our study was not to assess the accuracy of biochemical parameters for recommending the most appropriate therapy, we observed that pH, glucose, and LDH are not significantly influenced by previous use of antibacterial agents. This finding is important given the significant number of patients who seek medical care for PE and who are already using antibacterial agents. Rothrock and colleagues [16] concluded that biochemical CSF parameters (glucose and protein) are not significantly altered by previous use of antibacterial agents in patients with bacterial meningitis. Similar results were shown by Blazer and colleagues [32] in the assessment of cellularity, glucose, proteins, and the percentage of polymorphonuclear cells in CSF.

We observed that pH $\leq$7.1 and glucose $\leq$40 mg/dL were associated with increased risk of receiving a more invasive treatment. The importance of this finding is underscored by the fact that risk rates barely changed after adjustment for previous use of antibacterial agents. Therefore, unlike bacteriologic parameters, biochemical parameters do not seem to be influenced by the previous administration of antibacterial agents.

Our study, which is one of the largest involving pediatric patients with PPE, has several limitations. As expected, taking into consideration the prior use of antibacterials by half the sample, identification of the etiologic agent in the overall group was low (22.7%). Also, previous use of antibiotic therapy was higher in our patients than in previous studies. Davies and colleagues [41] described previous use of antibiotics in 39% of PPE patients vs 50% in the present study.

The characterization of previous antibiotic therapy (administration of at least 2 doses of any antibacterial at least 48 hours before diagnostic thoracentesis) also has limitations. We had no control over serum antibiotic levels and could not establish whether or not the medication had been correctly administered. In addition, we cannot rule out the possibility that the absence of impact on biochemical parameters may have resulted from an inadequate prescription of antibacterial agents, that is, absence of clinical effect. However, this is unlikely, because we were able to determine an effect on bacteriologic analysis.

In conclusion, in this study, previous use of antibacterial agents in children with parapneumonic pleural effusion did impact the results of Gram, culture, and hemoculture tests. Nevertheless, it did not interfere significantly with biochemical parameters of pleural fluid (pH, glucose, and LDH). This information is useful to guide decisions on the need for surgical treatment in children with PPE.

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