ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Pediatric Parapneumonic Effusion/Empyema, an Unexpected Surge in the Season of Pneumonia: A Single-Center Experience

Elmira Hajiesmaeil Memar[1], Seyed Hossein Mirlohi[2]*, Rohollah Rohani[3], Rohollah Shirzadi[4], Mohammadreza Modarressi[4], Niloofar Ghanbari[5], Mohammadsadegh Talebi Kahdouei[6] and Fatemeh Aghaei[6]

[1]*Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

[2]*Assistant Professor and Pediatrician Pulmonology, Pediatric Respiratory and Sleep Medicine Research Center, Childrens Medical Center, Tehran University of Medical Science, Tehran, Iran*

[3]*Pediatric Pulmonology Fellowship, Pediatric Respiratory and Sleep Medicine Research Center, Childrens Medical Center, Tehran University of Medical Science, Tehran, Iran*

[4]*Pediatric Respiratory and Sleep Medicine Research Center, Childrens Medical Center, Tehran University of Medical Science, Tehran, Iran*

[5]*Pediarician, Emergency Division, Bahrami Hospital, Tehran University of Medical Science, Tehran, Iran*

[6]*Medical School of Tehran University of Medical Science, Tehran, Iran*

***Corresponding Author:** Seyed Hossein Mirlohi, Assistant Professor and Pediatrician Pulmonology, Pediatric Respiratory and Sleep Medicine Research Center, Childrens Medical Center, Tehran University of Medical Science, Tehran, Iran.

Received: April 27, 2023; **Published:** July 27, 2023

Abstract

Objective: In this study, we aimed to report a recent significant outbreak of pneumonia with an unexpectedly high rate of parapneumonic effusion/empyema in children.

Materials and Methods: This retrospective cross-sectional study was conducted in the Children's Medical Center of Tehran, Iran from September 23, 2022, to November 23, 2022. All children with pneumonia and parapneumonic effusion hospitalized at the emergency department of a tertiary referral hospital were reviewed. Medical records of patients eligible for the study were retrieved from the archives and the following parameters were recorded: age, gender, hematologic indices, blood culture, CXR findings, sonographic parameters, pleural fluid analysis parameters, and treatments. Statistical analysis was performed with SPSS.

Results: 36 children with pneumonia and parapneumonic effusion/empyema were reported in our study (mean age = 68.41 ± 32.54 months, 55.6% females). 20 patients (55.5%) developed empyema. The mean duration of admission was 11.41 ± 6.49 days. Except for a case with a positive influenza test (2.77%), all patients tested negative for influenza types A and B, RSV, and COVID-19. Blood culture was negative in 87.5% of patients without empyema and 80% of patients with empyema. Pleural fluid smear and culture were negative in 84.2% and 73.7% of cases, respectively. No significant difference was found between patients receiving and not receiving fibrinolytic therapy in terms of any study parameters.

Conclusion: An unexplained unexpected significant rise in parapneumonic effusion and empyema has been observed in recent weeks among children with pneumonia. Bacterial cultures and viral tests were negative in the majority of cases. Searching for a probable new viral infection with a high rate of parapneumonic effusion/empyema as the underlying cause of this phenomenon should be undertaken promptly.

Keywords: *Pediatric Parapneumonic Effusion; Empyema; Pneumonia*

Introduction

Parapneumonic effusion and empyema are well-characterized complications consequent to pneumonia [1]. Inflammatory and infectious involvement of pleura leads to the development of parapneumonic effusion. With the leakage of proteins, fluids, and cells. As the disease progresses, the effusion becomes invaded by the bacteria and grows fibrotic and thick which leads to the formation of empyema [2,3].

Reports have shown that parapneumonic effusion or empyema occurs in 2 - 12% of pediatric pneumonia patients. This prevalence increases to 28% in hospitalized patients [2,3]. Young children are more susceptible to these entities with a prevalence of approximately 4 cases per 100000 population age < 4 years [2]. Reports from different regions of the world have indicated a rising trend in the incidence of empyema in the at least last two decades [4-11]. The main cause of this epidemiological alteration has been theorized to be the introduction of PCV-7 followed by the PCV-13 (Prevnar 13) vaccine. This vaccine has reduced the incidence of pneumonia and its complications but since then, the incidence of parapneumonic effusion and empyema has continued to grow. Some authors have stated that the vaccine acts against some serotypes of pneumococcus but does not target some serotypes which strongly leads to empyema in pediatric patients [12-15]. Prevnar 13 vaccine is not included in the vaccination program of Iran, yet the anecdotal evidence and observations by authors in the routine daily practice show a significant increase in empyema in pediatric Iranian patients with pneumonia. Some studies have reported this increasing trend before the introduction of the PCV-7 vaccine. They have claimed that alterations in serotype distribution or changes in virulence of empyema-causing pathogens may lead to such findings [16,17].

Due to the COVID-19 pandemic in the last two years, schools were closed down and face masks were extensively used by the general population. Since the drops in COVID-19 cases and massive vaccination, schools were re-opened and children returned to schools. As well, using face masks was significantly decreased. Thus, the transmission of infections was facilitated in the recent autumn season. In this setting, we faced an unexpected huge increase in pediatric pneumonia cases presented to the emergency department with parapneumonic effusion or empyema. We assumed that this phenomenon might be attributed to the post-COVID-19 changes in patterns of respiratory infections and expected increases in influenza cases which might present as superinfection of bacterial pathogens over underlying influenza.

Aim of the Study

This study aimed to assess this hypothesis for the explanation of the surge in parapneumonic effusion/empyema cases.

Materials and Methods

This retrospective cross-sectional study was conducted in the Children's Medical Center of Tehran, Iran from September 23, 2022, to November 23, 2022. In this study, all children with pneumonia diagnosis on chest X-ray and confirmed parapneumonic effusion on sonography whose illness was so severe that needed hospitalization, were evaluated.

Criteria for diagnosis of empyema in our study included evidence of pus, positive culture, positive smear, pH < 7.2, leukocyte count > 50,000/mm^3, Protein > 3 g/dL, LDH > 200 IU/L or glucose < 60 mg/dL in the pleural fluid. Patients not meeting the criteria of empyema were assigned to the non-empyema group. Patients with a diagnosis of nosocomial pneumonia, aspiration pneumonia, cystic fibrosis, and other structural lung diseases were excluded from the study.

Medical records of patients eligible for the study were retrieved from the archives and the following parameters were recorded: age, gender, hematologic indices (WBC, neutrophil count, CRP, ESR), blood culture, CXR findings (consolidation, pleural effusion, hemithorax opacities, etc), sonographic parameters (pleural effusion volume and diameter, etc), pleural fluid analysis parameters (pH, LDH, glucose, culture, etc) and treatments (antibiotics, corticosteroid pulse, ICU admission, and fibrinolytic therapy). Fibrinolytic therapy used in our study was tPA with the following regimen: for patients over 10 kg, 0.1 mg/kg (maximum 6 mg) tPA was mixed with 1 mg/kg normal saline (maximum 5 ml), and then intrapleural injection was performed with drain clamp for 1 hour. This procedure was done daily for 3 consecutive days. For patients below 10 kg, 1 mg/kg tPA was mixed with 10 ml of normal saline and was then injected.

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive analysis is presented in the form of frequency and percentage or mean and standard deviation. Independent t-test and chi-square test were used for the comparison of continuous and categorical parameters. P-value ≤ 0.05 was considered as the statistical significance threshold.

Results

36 children with pneumonia and parapneumonic effusion/empyema were presented to the emergency department in the study period. The mean age of patients was 68.41 ± 32.54 months. 16 patients (44.4%) were males while 20 patients (55.6%) were females. 20 patients (55.5%) developed empyema. The mean duration of admission was 11.41 ± 6.49 days. Except for one case (2.77%) with a positive influenza test, all patients tested negative for influenza types A and B, RSV, and COVID-19.

Hematological indices, radiologic findings, and treatments in patients who did not develop empyema are presented in table 1.

Parameter	Patients without empyema	
Laboratory parameters on admission		
Leukopenia	1 (6.3%)	
Leukocytosis	8 (50%)	
Neutropenia	2 (12.5%)	
Elevated CRP	16 (100%)	
Elevated ESR	16 (100%)	
Blood culture		
Negative	14 (87.5%)	
Positive for *Streptococcus pneumoniae*	2 (12.5%)	
Positive for *Haemophilus influenzae*	0 (0%)	
Imaging findings		
CXR		
Pneumonia	Unilateral	8 (50%)
	Bilateral	4 (25%)
Pleural effusion	Unilateral	14 (87.5%)
	Bilateral	2 (12.5%)
Atelectasis	Unilateral	1 (6.3%)
	Bilateral	0 (0%)
Sonography		
Pleural effusion volume	116.66 ± 68.60	
Pleural effusion diameter	6.75 ± 2.62	
Treatments		
Antibiotic therapy		
Meropenem	0 (0%)	
Third-generation cephalosporins	15 (93.75%)	
Vancomycin	8 (57.1%)	
Clindamycin	6 (42.9%)	
Amikacin	0 (0%)	
Rifampin	0 (0%)	
Cloxacillin	0 (0%)	
Intubation	0 (0%)	
ICU admission	0 (0%)	
Non-invasive ventilation	1 (6.3%)	
Fibrinolytic therapy	0 (0%)	

Table 1: *Hematological laboratory indices, imaging findings, and treatments in patients without empyema.*

The hematologic indices, imaging findings, and treatment of patients who developed empyema are also summarized in table 2.

Parameter	Patients with empyema	
Laboratory parameters		
Leukopenia	2 (10%)	
Leukocytosis	12 (60%)	
Neutropenia	1 (5%)	
Elevated CRP	19 (95%)	
Elevated ESR	20 (100%)	
Blood culture		
Negative	16 (80%)	
Positive for *Streptococcus pneumoniae*	3 (15%)	
Positive for *Haemophilus influenzae*	1 (5%)	
Imaging findings		
CXR		
Pneumonia	Unilateral	13 (65%)
	Bilateral	4 (20%)
Pleural effusion	Unilateral	15 (75%)
	Bilateral	5 (25%)
Atelectasis	Unilateral	0 (0%)
	Bilateral	0 (0%)
Cavity	Unilateral	1 (5%)
	Bilateral	0 (0%)
Sonography		
Pleural effusion volume	418.57 ± 228.57	
Pleural effusion diameter	13.12 ± 8.33	
Treatments		
Antibiotic therapy		
Meropenem	11 (55%)	
Third-generation cephalosporins	9	
Vancomycin	17 (85%)	
Clindamycin	3 (15%)	
Amikacin	2 (10%)	
Rifampin	3 (15%)	
Cloxacillin	2 (10%)	
Intubation	4 (20%)	
ICU admission	3 (15%)	
Non-invasive ventilation	1 (5%)	
Fibrinolytic therapy	19 (95%)	

Table 2: *Hematological laboratory indices, imaging findings, and treatments in patients with empyema.*

Pleural fluid analysis was also performed in patients with empyema. The culture was negative for 14 cases (38.9%). *Streptococcus pneumonia, Streptococcus viridans*, and *Haemophilus influenza* were responsible for culture positivity in 3 (15.8%), 1 (5.3%), and 1 (5.3%) patients, respectively.

The details are presented in table 3.

Parameter	Mean ± SD/frequency (%)
WBC	7824.7 ± 10931.2 (range = 79-37760)
Neutrophils	6124.5 ± 9426.0 (range = 47-29160)
Protein	2771.2 ± 1476.3 (range = 200-4100)
The ratio of pleural fluid/serum protein	0.78 ± 0.28 (range = 0.56-1.10)
Glucose	30.3 ± 23.75 (range = 5-63)
pH	6.85 ± 0.37 (range = 6-7)
LDH	12794.5 ± 11663.5 (range = 491-36040)
Ratio of pleural fluid/serum LDH	19.52 ± 21.78 (range = 0.68-73)
Pleural fluid smear	
Negative	17 (85%)
Streptococcus pneumoniae	3 (15%)
Pleural fluid culture	
Negative	15 (75%)
Streptococcus pneumoniae	3 (15%)
Streptococcus viridans	1 (5%)
Haemophilus influenza	1 (5%)

Table 3: *Results of pleural fluid analysis in patients with empyema.*

Study parameters were compared between patients who needed fibrinolytic therapy and patients not undergoing fibrinolytic therapy. Only admission duration (15.77 ± 6.14 days for patients undergoing fibrinolytic therapy and 7.05 ± 2.97 days for patients not requiring fibrinolytic therapy, p = 0.000) and pleural effusion volume on sonography (418.57 ± 228.57 mm vs 116.66 ± 68.60 mm in patients requiring and not requiring fibrinolytic therapy, respectively; p = 0.010). These variables were analyzed in the multivariate logistic regression model and the significant differences between groups did not remain significant (OR = 1.28, p = 0.147 for admission duration and OR = 1.01, p = 0.280 for pleural effusion volume).

Discussion

The current study was conducted to report an abrupt increase in pediatric pleural empyema among patients hospitalized with the diagnosis of pneumonia. The diagnosis of 36 patients in just two months (equivalent to the number of patients with this diagnosis in several years), that too in only one hospital, indicates an unexpected event. Although, empyema is recognized as a serious complication of pneumonia, its incidence and rate of progression from pleural effusion to empyema is generally much lower than what we have observed in recent weeks. In our study, an extraordinarily high rate of 55.5% was found for empyema incidence among pediatric patients admitted with pneumonia and parapneumonic effusion in the emergency department of a referral hospital. A previous report on Iranian children with pneumonia has revealed that 41.2% of pediatric patients with pleural effusion develop empyema [18]. Grisaru-Soen., *et al.* also reported a rate of 24.9% for empyema among pneumonia patients [19]. Another study has stated that 2 - 12% of children with pneumonia develop parapneumonic effusion or empyema while in the patients hospitalized due to pneumonia, this rate reaches 28% [2]. The

incidence rate of empyema reported in the current study is remarkably higher than other available reports but reviewing the literature reveals that the rate of parapneumonic effusion and empyema are following an increasing trend in recent decades and our findings can be interpreted as another piece of evidence confirming this ongoing continuous rise in the rate of empyema. For instance, a study by Eslami., *et al*. [20] in the north of Iran has shown that the incidence of empyema in pneumonia patients has grown from 6% to 14% over 12 years. A report from New Zealand has demonstrated that rates of pleural empyema have experienced a 10-fold increase from 1 in 100000 children to 10 in 100000 children from 1998 to 2012 [21]. Similar statistics have been published from the province of Quebec in which rates of empyema reached from 0.23 to 4.01 per 100000 person-years between 1990 to 2007 [22]. Several mechanisms and risk factor for this increasing trend has been suggested and evaluated in the literature. In our study, we found no significant difference between cases requiring fibrinolytic therapy and patients not undergoing fibrinolytic therapy (~empyema versus non-empyema) (p-values of 0.147 and 0.280 for admission duration and pleural effusion volume on multivariate analysis). Byington., *et al*. reported that ages over 36 months, infection with varicella zoster, pneumococcal serotype 1 infection, longer duration of fever, and receiving antibiotics and ibuprofen before hospitalization are among the risk factors of empyema development [9]. Another report has nominated serotype 19A of *Streptococcus pneumonia* as the pathogen responsible for empyema [14]. Francois., *et al*. also revealed that longer duration of disease, higher wages, and frequent receiving of antibiotics and ibuprofen before admission were the risk factor for empyema development in children suffering from pneumonia [23]. From the risk factors mentioned in the former studies, the duration of hospitalization was significantly longer for the empyema group in our study ($p = 0.000$).

The majority of patients in our study had negative blood and pleural fluid cultures but among pathogens isolated from these specimens, we found *Streptococcus pneumonia* responsible for around 15% of the cases. As an example, Grisaru-Soen., *et al*. have reported positive culture of *S. pneumoniae* in 61% of patients with empyema which is significantly higher than our culture positivity rate [19]. So, the rate of positive culture in our study is significantly lower than in previous reports. This low rate of positive culture can be probably due to irrationally high consumption of oral and intravenous antibiotics before hospitalization which leads to the negativity of cultures. We assumed that maybe predilection of a specific pneumococcal serotype with a higher chance of empyema formation in the recent autumn and its coinfection with typical influenza pneumonia may be responsible for such a surge in the incidence of empyema among our pneumonia patients. Except for one case (2.77%), viral tests for influenza A and B, RSV, and COVID-19 were negative in all patients. Thus, the assumption of bacterial superinfection on viral involvement is ruled out. So, this unexplained surge in parapneumonic effusion and empyema in recent weeks among children might be due to a new viral infection that cannot be detected by routine viral assessments. In addition, technical problems with sampling and methods of obtaining specimens can partly contribute to the negativity of culture results. Search for the underlying cause of this phenomenon should be rapidly prompted.

All patients had to receive antibiotics for their treatment plan. ICU admission, fibrinolytic therapy, and intubation were only seen in patients with empyema. No case of mortality had occurred among our patients.

At last, we should point out that the patients reported in this article were limited to hospitalizations of only 2 months in this center and the presentation of patients with the condition explained was continued as we were preparing this manuscript.

The main limitation of our study was the lack of previous years' data for a more accurate understanding of the trend of empyema incidence. Also, PCR tests for the evaluation of specimens were not performed in our study. The sample size of the study was relatively low which should be extended in future studies.

Conclusion

An unexplained unexpected significant rise in parapneumonic effusion and empyema has been observed in recent weeks among children with pneumonia. Bacterial cultures were negative in the majority of cases and viral tests were all negative. Searching for a probable new viral infection with a high rate of parapneumonic effusion/empyema as the underlying cause of this phenomenon should be undertaken promptly.

Bibliography

1. Light RW., *et al*. "Parapneumonic effusions". *The American Journal of Medicine* 69 (1980): 507Y512.
2. Byington CL., *et al*. "An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations". *Clinical Infectious Diseases* 34.4 (2002): 434-440.
3. Bradley JS., *et al*. "Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of communityacquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America". *Clinical Infectious Diseases* 53.7 (2011): e25-e76.
4. Rees JHM., *et al*. "Increase in the incidence of childhood empyema in West Midlands, UK". *Lancet* 349 (1997): 402.
5. Gupta R and Crowley S. "Increasing pediatric empyema admissions". *Thorax* 61 (2006): 179-180.
6. Eastham KM., *et al*. "Clinical features, etiology and outcome of empyema in children in the north east of England". *Thorax* 59 (2004): 522-525.
7. Roxburgh CS., *et al*. "Trends in pneumonia and empyema in Scottish children in the past 25 years". *Archives of Disease in Childhood* 93 (2008): 316-318.
8. Hendrickson DJ., *et al*. "Five-fold increase in pediatric parapneumonic empyema since the introduction of the pneumococcal conjugate vaccine". *The Pediatric Infectious Disease Journal* 27 (2008): 1030-1032.
9. Byington CL., *et al*. "An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: Risk factors and microbiological associations". *Clinical Infectious Diseases* 34 (2002): 434-440.
10. Obando I., *et al*. "Pediatric parapneumonic empyema Spain". *Emerging Infectious Diseases* 14 (2008): 1390-1397.
11. Strachan R and Jaffé A. "Assessment of the burden of pediatric empyema in Australia". *Journal of Paediatrics and Child Health* 45 (2009): 431-436.
12. Muñoz-Almagro C., *et al*. "Influence of pneumococcal vaccine on the incidence of empyema". *Current Opinion in Pulmonary Medicine* 16 (2010): 394-398.
13. Vogel AM., *et al*. "Impact of pneumococcal vaccine on hospital admission with lower respiratory tract infection in children resident in South Auckland, New Zealand". *The New Zealand Medical Journal* 126 (2013): 26-35.
14. Thomas MF., *et al*. "The emergence of pneumococcal 19A empyema in UK children". *Archives of Disease in Childhood* 97 (2012): 1070-1072.
15. Strachan RE., *et al*. "Bacterial causes of empyema in children in Australia 2007-2009". *Emerging Infectious Diseases* 17 (2011): 1839-4185.
16. Buckingham SC., *et al*. "Incidence and etiologies of complicated parapneumonic effusions in children, 1996 to 2001". *The Pediatric Infectious Disease Journal* 22 (2003): 499-504.
17. Koshy E., *et al*. "Impact of the seven valent pneumococcal conjugate vaccination (PCV7) program on childhood hospital admissions for bacterial pneumonia and empyema in England: National time-trends study, 1997-2008". *Thorax* 65 (2010): 770-774.
18. Bilan N., *et al*. "Evaluation of Predictive Factors of Empyema in Children with Parapneumonic Pleural Effusion". *International Journal of Pediatrics* 8.10 (2020): 12297-12304.

19. Grisaru-Soen G., *et al*. "Pediatric parapneumonic empyema: risk factors, clinical characteristics, microbiology, and management". *Pediatric Emergency Care* 29.4 (2013): 425-429.

20. Eslami G., *et al*. "The Survey of Pediatric Pleural Empyema in North of Iran (from 2004 to 2016)". *International Journal of Pediatrics* 6.3 (2018): 7421-7432.

21. Mahon C., *et al*. "Incidence, etiology and outcome of pleural empyema and parapneumonic effusion from 1998 to 2012 in a population of New Zealand children". *Journal of Paediatrics and Child Health* 52.6 (2016): 662-668.

22. Deceuninck G., *et al*. "Pediatric Pleural Empyema in the Province of Quebec: Analysis of a 10-Fold Increase Between 1990 and 2007". *Journal of the Pediatric Infectious Diseases Society* 3.2 (2014): 119-126.

23. Francois P., *et al*. "Prevalence and risk factors of suppurative complications in children with pneumonia". *Acta Paediatrica* 99 (2010): 861-866.

Volume 12 Issue 8 August 2023