PREDICTIVE FACTORS, MICROBIOLOGY, AND TREATMENT OUTCOMES OF PEDIATRIC PLEURAL EMPYEMA

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ABSTRACT

Pediatric pleural empyema has increased substantially over the years and was a common issue in the pediatric intensive care unit (PICU), leading to prolonged hospital stays and rising mortality rates. However, this complex condition exhibits heterogeneous data regarding prognostic factors associated with severe outcomes. **Objectives:** This study aims to investigate microbiological findings, treatment outcomes and predictive factors related to pleural empyema in the PICU. **Participants and method**: A total of 70 children (33 boys and 37 girls) were admitted to Vietnam National Children's Hospital (VNCH) from January 2021 to October 2023. **Results:** The median age was 8 months (range 2–21), and about 17 patients (24.3) had comorbidities. The median PICU length of stay was 20.5 days [16-28]. Septic shock occurred in 61.4% of patients, and the overall mortality rate was 32.9% (23/70). Additionally, extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) were required in 8.6% and 17.1% of cases, respectively. We observed independent factors related to mortality outcome, including only the internal treatment and negative blood or fluid culture results with *Staphylococcus aureus* had a higher risk of death of 3.99 ($p < 0.05$, 95% CI: 1.004 – 15.84) and 5.64 ($p < 0.05$, 95% CI: 1.10 – 29.03). **In conclusion:** Despite the combination of medical and surgical treatments, pleural empyema remains associated with high mortality and prolonged hospital stays.

Keywords: *Children, Empyema, Microbiology, Predictive factors*

I. INTRODUCTION

A pleural empyema (PE) is the presence of purulent material, usually consisting of polymorphonuclear leukocytes and fibrin in the pleural space, and the incidence of pediatric PE has increased dramatically over the past several years in high-income countries, leading to considerable research focus on this medical condition(1). PE has become a significant challenge in Vietnam and the world, which is now a controversial issue in the field of research due to its protracted length of stay, nosocomially acquired infection, increased morbidity, and mortality, especially among patients in PICU (2). The rate of PE occurs in 0.6 - 25% of children with pneumonia and accounts for 28% of the causes leading to hospitalization (3). Despite the development of early diagnosis and treatment methods, PE still causes many complications such as respiratory failure, bronchopulmonary fistula, pleural thickening, septic shock, prolonged hospital stay, and increased rate of sequelae and death (6-24%), primarily focusing on children under two years old and children with underlying diseases (4). Although a variety of research shows that the predictive factor of the community-acquired pneumonia complicated (CAP) causes pleural empyema, limited data has been inspected on the predictive factor of PE associated with death

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outcomes and prolonged hospital stay (5). Meanwhile, treatment guidelines is inappropriate simply to extrapolate adult data to children, and only be applied partially to children due to significant differences in clinical manifestations, microbiological etiology, treatment methods, and prognosis (6, 7). Thus, we investigated predictive factors, microbiology, and treatment outcomes of pediatric pleural empyema.

II. PARTICIPANTS AND METHODS

2.1 Participants

During the study period, we included 70 children aged from 1 month to 15 years old who were diagnosed with PE, the criterion of the British Thoracic Society (8). We obtained written informed consent from all participants' parents or legal guardians, and the study was approved by the Vietnam National Children's Hospital Institutional Review Board (Approval no. VNCH-TRICH-2098). The study was conducted in accordance with the Declaration of Helsinki.

2.2 Methods

Study design

This prospective observational study was conducted from January 2021 to October 2023 at Vietnam National Children's Hospital (VNCH)—the country's largest referral tertiary children's hospital.

Statistical analysis

We used a convenient method for determining the sample size of our study. All statistical analyses were performed using SPSS software version 20.0. Categorical variables were described as frequencies and percentages, while continuous variables were described as the median and interquartile range (IQR). Results were described as odds ratio (OR) and 95% confidence intervals (CIs). Variables significantly associated with the outcomes in univariate analyses were selected for multivariate logistic progression to identify independent predictors. A two-sided p-value of less than 0.05 was considered statistically significant.

III. RESULTS

3.1 Baseline characteristics of the study population

Table 1. **Characteristics of patients hospitalized with PE in PICU**

Characteristics		Median	Value n (%)
Age(month), median (IQR)	Median	8 (2 – 21)	
	< 12 month	-	41 (58.6)
	12- 60 month	-	18 (25.7)
	> 60 month	-	11 (15.7)
Sex, n (%)	Male	-	33 (47.1)
	Female	-	37 (52.9)
Number of Organ failure	1 – 3	-	49 (70.0)
	> 3	-	21 (30.0)
Comorbidities		-	17 (24.3)
Illness duration (days)		4 (3 – 7)	-
VIS score 24 hours		37.5 (0 – 50)	-
PRISM III score		4 (3 – 17)	-
PELOD-2 score		6 (4 – 27)	-

Data are presented as median (25th–75th quartiles) or n (%), IQR: InterQuartile Range

Definition of abbreviation: VIS: Vasoactive-Inotropic Score, PRISM III: Pediatric Risk of Mortality III, PELOD-2: Pediatric Logistic Organ Dysfunction-2.

The average age of the participants is 8 months IQR (2 - 21). The group of children under 12 months old accounts for the highest proportion of 58.6% (41/70), and girls account for 52.9% (37/70). VIS score in the first 24 hours of administrated hospitalization was 37.5 IQR(0 – 50), PRISM III score 4 IQR (3 – 17), and PELOD-2 score 6 IQR(4 – 27).

3.2 Clinical and laboratory characteristics of patients hospitalized with PE in PICU

Table 2. **Clinical and laboratory characteristics within 24 hours of admission**

Characteristics		n	Proportion
Clinical characteristics (n=70)	Fever	63	90.0
	URTI	49	70.0
	Chest pain	6	8.6
	Respiratory failure	70	100
	Septic shock	43	61.4
	Simple PE	30	42.9
	Polymembrane effusion	40	57.1
Plasma laboratory characteristics (n=70)	Leukopenia with age	40	57.1
	Neutropenia with age	15	21.4
	Neutrophilia with age	39	55.7
	Thrombocytopenia	14	20.0
	Hemoglobin ≤ 10 g/dL	29	41.4
	Prothrombin > 15 seconds	33	47.1
	Plasma fibrinogen > 4 g/L	40	57.1
	aPTT > 56 seconds	40	57.1
	D-dimer > 400 ng/ml	67	95.7
	DIC	12	17.1
	CRP > 20 mg/L	59	84.3
	PCT > 2 ng/mL	37	52.9
	Increased LDH with age	49	70.0
	Hyperferritinemia with age	51	72.9
	Protein < 55 g/L	33	47.1
	Albumin < 30 g/L	42	60.0
	GOT > 40 U/L	24	34.3
	GPT > 40 U/L	16	22.9
	Increased plasma urea level with age	15	21.4
	Increased plasma creatinin level with age	23	32.9
Pleural fluid characteristics (n=56)	< 500 cells/mm^3	4	7.1
	500 – 1000 cells/mm^3	5	8.9
	> 1000 cells/mm^3	47	83.9
	Protein ≥ 30 g/L	55	98.2
	LDH ≥ 1000 IU/L	48	85.7
	The pleural fluid LDH/plasma LDH ratio simultaneously > 0,6	49	87.5
	Glucose < 40 mg/dl	56	100.0
CT measure of lung injury	Atelectasis	14	37.8
	Necrosis – abscess	3	8.1
	Condensation	24	64.9
	Ground-glass opacification	6	16.2
	Cystic lung lesion	9	24.3
	Pneumothorax	12	32.4
Pleural ultrasound (n=63)	Anechoic	9	14.3
	Complex nonseptation	14	22.2
	Complex septation	49	77.8

Data are presented as median (25th–75th quartiles) or n (%).

Definition of abbreviation: URTI: Upper respiratory tract infection, DIC: Disseminated intravascular coagulation, aPTT: activated partial thromboplastin time, CRP: C-reactive protein, PCT: Pro-calcitonin, LDH: Lactate dehydrogenase, GOT: glutamate oxaloacetate transaminase, GPT: glutamyl pyruvic transaminase. Thrombocytopenia: platelet count < 150 G/L, Hyperfibrinogenemia: plasma fibrinogen > 4 g/L, CT: Computed tomography.

The main signs of pleural empyema due to infection include fever in 90% (63/70), URTI in 70% (49/70), respiratory failure in 100%, septic shock accounts for 61.4% (43/70). Increased white blood cell count 57.1% (40/70), platelets <150 G/l 20% (14/70), DIC 17.1% (12/70). The number of pleural fluid cells was > 1000 cells/mm3, accounting for 83.9% (47/56). The most typical lesions on chest CT are lung consolidation 64.9% (24/37), pneumothorax 32.4% (12/37), lung necrosis, and abscess, accounting for a relatively high proportion of 8.1% (3/37).

3.3 Microbial characteristics of pediatric PE in PICU

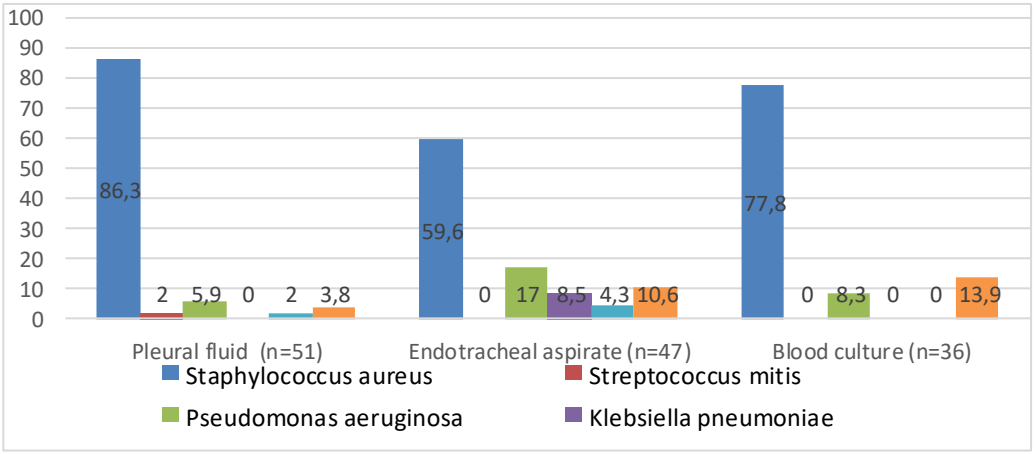

Figure 1. **The rate of some microbial pathogens isolated in specimens**

Table 3. **Antibiotic sensitivity levels of S.aureus in pediatric PE in PICU**

Antibiotics	Susceptible		Intermediate		Resistant	
	N	%	n	%	n	%
Vancomycin	42	95.5	0	0	2	4.5
Quinolone	42	95.5	0	0	2	4.5
Biseptol	36	81.8	1	2.3	7	15.9
Gentamycin	37	84.1	2	4.6	5	11.3
Oxacillin	1	2.3	0	0	43	97.7
Ceftriaxone	0	0	0	0	44	100.0

S. aureus, P. aeruginosa, and K. pneumoniae are the 3 most common causes. The isolation rate of *S. aureus* is highest in pleural fluid samples (Figure 1). *S.aureus* is also sensitive to the group's Vancomycin, Quinolone 95.5%, Gentamycin 84.1%, and Biseptol 81.8%, utterly resistant to Ceftriaxone (Table 3)

3.4 Evaluation of strategy and treatment results

Table 4. **The several strategies and treatment results**

Therapeutic intervention		Median (25%-75%)	Value n (%)
Assisted ventilation	Non-invasive ventilation	-	1 (1.4)
	Invasive ventilation	-	69 (98.6)
Inotropes		-	43 (61.4)
CRRT		-	12 (17.1)
ECMO		-	6 (8.6)
Pleural drainage		-	58 (82.9)
Failure of the initial antibiotic regimen		-	45 (64.3)
Surgical intervention (n = 40)	Endoscopic surgery	-	35 (87.5)
	Open thoracotomy decortication	-	5 (12.5)
Nosocomial infection		-	21 (30.0)
Treatment outcome	Life	-	47 (67.1)
	Mortality	-	23 (32.9)
Duration of MV (day)		12.5 [7-15.25]	-
PICU length of stay (day)		20.5 [16-28]	-
Length of hospital stay (day)		24.5 [17-32]	-

MV: Mechanical ventilation, ECMO: extracorporeal membrane oxygenation, CRRT: Continuous renal replacement therapy, failure of the initial antibiotic regimen: Antibiotics must be changed 48 hours after treatment from hospital admission. PICU: Pediatric Intensive Care Unit.

The initial antibiotic failure rate was 64.3% (45/70), and surgical intervention was 57.1% (40/70), of which laparoscopic surgery was 87.5% (35/40). Patients required MV, ECMO, and CRRT, 98.6% (69/70), 8.6% (6/70), and 17.1% (12/70), respectively. The average MV time is 12.5 IQR [7 -15.25] days. PICU length of stay and length of hospital stay were 20.5 IQR(16 – 28) and 24.5 IQR(17 – 32) days, and the mortality rate was 32.9% (23/70).

3.5 Prognostic independent factors related to death outcome factors of mortality outcome in pediatric PE

Table 5. **Univariate logistic regression for predictors of mortality pediatric PE in PICU**

Factors	Survivor (n = 47)		Mortality (n = 23)		p*	OR	95%CI
	N	%	n	%			
Age ≥ 12 months	15	31.9	14	60.9	**0.024**	3.32	1.18 – 9.37
Comorbidities	8	17.0	9	39.1	**0.048**	3.13	1.01 – 9.71
Septic shock	24	51.1	19	82.6	**0.015**	4.55	1.34 – 15.43
Polymembrane effusion	24	51.1	15	65.2	0.265	1.80	0.64 – 5.04
Organ failure ≥ 3	25	53.2	17	73.9	0.101	2.49	0.84 – 7.44
Leukopenia with age	32	68.1	8	34.8	0.063	3.05	0.94 – 9.87
CRP > 20 mg/l	41	87.2	18	78.3	0.338	0.53	0.14 – 1.95
PCT > 2 ng/ml	26	55.3	11	47.8	0.556	0.74	0.27 – 2.01
Hyperferritinemia	33	70.2	18	78.3	0.479	1.52	0.47 – 4.93
Increase the level of LDH	31	66.0	18	78.3	0.295	1.86	0.58 – 5.93

Factors	Survivor (n = 47)		Mortality (n = 23)		p*	OR	95%CI
	N	%	n	%			
DIC	7	14.9	5	21.7	0.478	1.59	0.44 – 5.68
Serum albumin < 30 g/L	30	63.8	12	52.2	0.351	0.62	0.22 – 1.70
Blood and fluid cultures were negative for *S.aureus*	6	12.8	12	52.2	**0.001**	7.45	2.28 – 24.37
Internal treatment	14	29.8	16	69.6	**0.002**	5.39	1.81 – 15.96
Failure of the initial antibiotic regimen	28	59.6	17	73.9	0.243	1.92	0.64 – 5.76
Inotropes	24	51.1	19	82.6	**0.015**	4.55	1.34 – 15.43
Nosocomial infection	8	17.0	13	56.5	**0.001**	6.33	2.06 – 19.46

Through univariate regression analysis (Table 5), the group of children over 12 months old, comorbidities and septic shock had a higher risk of mortality by 3.32 (95% CI: 1.18 - 9.37), 3.13 (95% CI: 1.18 - 9.37), 3.13 (95% CI: 1.01 – 9.71) and 4.55 (95% CI: 1.34 – 15.43) in the remaining group. The group of participants who required inotropes, only internal treatment, and hospital-acquired infections had a higher risk of mortality by 4.55 (95% CI: 1.34 - 15.43), 5.39 (95% CI: 1.34 - 15.43). CI: 1.81 – 15.96) and 6.33 (95% CI: 2.06 – 19.46).

Table 6. **Multivariate logistic regression for predictors of mortality pediatric PE in PICU**

Factors	p*	OR	95% CI
Age ≥ 12 months	0.261	2.13	0.57 – 7.95
Inotropes	0.079	3.84	0.86 – 17.24
Internal treatment	**0.049**	3.99	1.004 – 15.84
Nosocomial infection	0.754	1.29	0.27 – 6.23
Comorbidities	0.699	1.34	0.31 – 5.86
Blood and fluid cultures were negative for *S.aureus*	**0.038**	5.64	1.10 – 29.03

From the multivariate regression analysis, the group of patients only receiving internal treatment had a higher risk of mortality by 3.99 ($p < 0.05$, 95% CI: 1.004 - 15.84) compared to the group that integrated surgical intervention. Group of negative blood or fluid culture results, *S.aureus* had a higher risk of death at 5.64 ($p < 0.05$, 95% CI: 1.10 – 29.03) with the blood or fluid culture group positive for *S.aureus*

IV. DISCUSSION

Children with infected pleural effusion often require a combination of multiple treatment methods, which tends to prolong treatment time in the PICU and increase hospital stay. The median age was 8 (range 2 – 21) months, and only 17 (24.3) patients had comorbidities. These score findings within 24 hours of admission, VIS score 37.5 IQR (0 – 50), PRISM III score 4 IQR (3 – 17) and PELOD-2 score 6 IQR (4 – 27), number of children with organs failure > 3 accounts for 30% (21/74). (23) **(Table 1)**. The reported rate of identifying an infectious organism from pleural fluid varies markedly, < 60% in most studies, because of different pleural specimen sampling rates, culture, and

identification techniques. Pleural fluid culture is often negative, because poor detection rates are most likely due to a combination of prior antimicrobial therapy before obtaining pleural fluid samples for culture, low microbial concentration in pleural effusion, and possibly causal agents that are difficult to isolate in the laboratory due to stringent requirements. Even using newer molecular techniques, for instance Polymerase chain reaction (PCR) to amplify and detect the 16S ribosomal RNA gene, with results generally available within hours, although difficulty with micro-organisms identified with PCR is to determine if the microbe is a bystander or genuine causative agent (9). The most common positive culture rate in patient samples is pleural fluid at 85% (51/70), and the positive endotracheal fluid culture rate and blood culture are 83%, respectively. 9% (47/70) and 72% (36/70). Agent *S. aureus, P. aeruginosa, and K. pneumoniae* are the 3 most common causes, and *S. aureus* is the most frequently isolated microbial pathogen in all patient samples **(Figure 1)**. *S. aureus* is sensitive to the group's Vancomycin and Quinolone (95.5%), Gentamycin (84.1%), and Biseptol (81.8%), completely resistant to Ceftriaxone **(Table 3)**. Author X. Zhang et al. (10) researched 63 children and found the 3 most common factors *S.aureus* 23.8%, *S.pneumoniae* 15.9%, *P.aeruginosa* 11.1%. Research by author J.G Liese et al. in 2019 (11) pointed out that *S.pneumoniae* is the most common cause of infectious pleural effusion (44.8%), of which mainly serotype 1 (30.8%) and 19A (7.7%), the rate of pleural fluid culture is positive with *S. pneumoniae, S. pyogenes* and *S. aureus* 72%, 14%, and 11% respectively. The above difference may be because our study subjects were seriously ill patients who needed treatment at the PICU. In contrast, other authors' research subjects were mainly CAP and were treated at respiratory centers.

Regarding clinical presentations, the most frequent symptoms were fever 90% (63/70), followed by URTI 70% (49/70), chest pain 8.6% (6/70), septic shock developed in 61.4% (43/70) patients ***(Table 2)***. In our study, the age group under 12 months old had the highest incidence, while chest pain symptoms manifested in older children. The results of our study are similar to others: fever symptoms and URTI are the two most common symptoms, and chest pain symptoms have a lower rate (12).

Patients had an increased WBC count of 57.1% (40/70) and a decreased PLT count of 21.4% (15/70). The most common coagulation disorder is increased D-dimer 95.7% (67/70) and DIC 17.1% (12/70). Author Pourcyrous M et al.(13) found that PCT index ≥ 2 ng/mL and CRP > 20 mg/L play an essential role in diagnosing and treating children with sepsis. In our study, inflammation biomarkers increased, CRP > 20 mg/L and PCT > 2 ng/mL accounting for 84.3% (59/70) and 52.9% (37/70) ***(Table 2)***. There are no data to suggest that the biochemical characteristics of pleural fluid in children are any different from adults, Protein, LDH and Glucose levels or Light's criteria differentiate exudates from transudates, PE is associated with raised protein, LDH and low glucose levels (14). Patients with pleural fluid cell count > 1000 cells/mm^3 accounted for 83.9% (47/56), Protein ≥ 30 g/L was 100% (56/56) and 98.2% (55/56), and the ratio of pleural fluid LDH/blood LDH was > 0.6 accounting for 87.5% (49/56) ***(Table 2)***. Lung-pleural ultrasound helps detect the quantity and character of pleural fluid and guide

thoracocentesis or drain placement (7). Patients showing residual foci or septations on chest ultrasonography was very high, 77.8% (49/63). Besides, ultrasound can be performed many times with little impact on the children, especially as no sedation and radiation. The most common lesions on chest CT are lung consolidation 64.9% (24/37), pneumothorax 32.4% (12/37), necrosis, and lung abscess, accounting for a relatively high rate of 8.1% (3/37) ***(Table 2)***. Chest CT can also detect airway, parenchymal lung abnormalities (endobronchial obstruction or a lung abscess), mediastinal pathology. However, it is unnecessary for most cases of paediatric empyema (7). Saleem Islam et al. (15) suggests chest CT should only be performed when it is necessary to evaluate the type and extent of parenchymal damage as suspected in patients with complications of necrotizing pneumonia and lung abscess or to rule out other causes of pleural effusion if clinically indicated. Surgeons will require a chest CT and ultrasound before indicating open thoracotomy or thoracoscopy.

Pediatric PE should be treated with intravenous antibiotics, and empirical antibiotics must cover *S. pneumoniae, S. pyogenes,* and *S. aureus*. If the blood and pleural fluid cultures are positive, antibiotics take into account antibiotic sensitivities (7). In our study, the initial antibiotic failure rate was 64.3% (45/70), and surgical intervention was 57.1% (40/70), of which laparoscopic surgery was 87.5% (35/40). Patients required MV, ECMO, and CRRT, 98.6% (69/70), 8.6% (6/70), and 17.1% (12/70), respectively. The average MV time is 12.5 IQR [7 -15.25] days. PICU length of stay and length of hospital stay were 20.5 (range 16 – 28) and 24.5 (range 17 – 32) days, respectively, and mortality was 32.9% **(Table 4).** PE was associated with longer hospital stays and higher in-hospital mortality in PICU. To decrease the rate of mortality, physicians should make a reasonable and instantaneous diagnosis, implement efficacious treatment, as well as analyze and eradicate risk factors in mortality outcome (16). Through univariate and multivariate regression analysis, independent factors related to mortality outcomes in children with PE, such as children over 12 months old, comorbidities, septic shock, only the medical treatment, and negative blood or fluid culture results with S.aureus **(Table 5-6)**. The group of patients with negative blood or endotracheal fluid, or pleural fluid culture results with *S.aureus* had a higher risk of death by 5.64 (95% CI: 1.10 – 29.03, $p < 0.05$) compared to the blood or fluid culture group positive for *S.aureus*. Patients negative for *S. aureus* were the majority of patients with hospital-acquired infections, often with positive culture results for gram-negative bacteria, especially multi-resistant gram-negative bacteria, thus prolonged MV time and increased mortality.

Participants who received only internal treatment had a higher 3.99 (95% CI: 1.004 - 15.84, $p < 0.05$) risk of death compared to the group receiving the surgical intervention. Author Carrie L. Byington et al.(17) studied 1,093 children with infected pleural effusion treated at Salt Lake City Pediatric Center, Utah, USA, for 6 years and identified risk factors. The risk of increasing the patient's risk of death through multivariable regression analysis includes age over 3 years old, having a fever for over 7 days, having chickenpox, and having received antibiotics or ibuprofen before admission to the hospital.

V. CONCLUSIONS

Independent prognostic factors related to mortality outcomes related to children > 12 months old, comorbidities, septic shock, only internal treatment, and culture-negative microbiological etiology *S.aureus*. Although combining multiple internal and surgical treatment methods, PE has a high mortality rate and protracted length of stay.

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