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Original Article

Non-tuberculous Parapneumonic Effusion in Children and Adolescents Who Required Chest Tube Drainage: A 10-year Multi-centre Retrospective Study

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Abstract We retrospectively reviewed the records of all patients from 4 months to 18 years old with non-tuberculous parapneumonic effusion and empyema in 4 acute regional hospitals between 2011 and 2021, who underwent chest tube drainage as the first intervention. Of the 156 patients included, 77.6% had a pigtail catheter inserted as the first drainage, and 22.4% had a traditional drain. Thirty-eight (24.4%) required respiratory support other than low-flow oxygen. Thirty-four (27.8%) had thoracic surgery eventually (video-assisted thoracic surgery: 25, thoracotomy: 9). Five (3.2%) required extracorporeal membrane oxygenation. There were 5 cases of mortality (3.2%). Factors independently associated with a favourable clinical course (recovered, no invasive re-intervention, no respiratory support) were higher pleural fluid glucose content, longer duration of fever upon hospital admission, and longer duration between hospital admission and insertion of the first drain. Significant factors independently associated with longer hospitalisation were bacteraemia, pneumothorax, and lower pleural fluid glucose content.

Key words *Empyema; Paediatric; Pleural effusion; Pneumonia*

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Introduction

Parapneumonic effusion (PPE) and empyema (Em), together with necrotising pneumonia, lung abscess and respiratory failure, are well-recognised complications of bacterial pneumonia in children and adolescents, even in the era of widespread use of pneumococcal vaccines. Mortality can occur in a minority of cases, but the prognosis in previously healthy individuals is usually good without long-term sequelae. Nonetheless, the duration of hospitalisation is long comparing with other common paediatric infectious diseases.[1]

The basic definitions of simple (uncomplicated) and complicated parapneumonic effusion come from the features of various stages of parapneumonic effusion. In simple PPE, the pleural fluid has a low white cell count, with minimal septations and fibrin strands. In complicated PPE, there is deposition of fibrin and an increase in the cell count of the pleural fluid. Septations and fibrin strands appear.[2,3] The presence of septations does not necessarily mean the fluid does not flow freely.[2] In this way,

complicated PPE is not defined by the amount or the biochemical properties of the effusion, or the presence of respiratory compromise. However, in the literature, these features are often used to characterise whether a parapneumonic effusion is severe, entails complications, or requires invasive interventions. Some adult studies used the need of chest tube drainage to define failure of medical treatment and complicated parapneumonic effusion.[4-7]

In the context of parapneumonic effusion, empyema is a subset in which there is overt pus in the pleural space. In clinical practice, the diagnosis of empyema is based on the visualisation of the pleural collection obtained from thoracocentesis, chest tube drainage, or during thoracic surgery, but not the biochemical characteristics or the presence of pathogen in the pleural fluid. In our experience, it is rare to diagnose empyema in children and adolescents following the insertion of a chest drain, as very often the effusion fluid drained out is not overt pus.

There are recommendations for management of PPE/Em in children from the British Thoracic Society (BTS),[2] the American Pediatric Surgical Association (APSA),[3] and Pediatric Infectious Diseases Society (PIDS).[8] Systemic antibiotic therapy is the mainstay of treatment. An invasive intervention is required if the effusion is large, or there is moderate effusion with respiratory compromise. The invasive intervention can be chest tube drainage, with or without intrapleural fibrinolytic, or surgical drainage. In some cases, despite these interventions, the PPE/Em did not respond well and even deteriorated, and the patients required escalating respiratory support and additional interventions.

There are key differences in the recommendations on the use of diagnostic thoracocentesis and chest tube drainage between the adult and paediatric guidelines. In adults, diagnostic thoracocentesis is recommended at presentation to obtain pleural fluid for analysis, unless the procedure is deemed unsafe, or the effusion is too small. Not all cases require chest tube drainage initially. It depends on the appearance and the biochemical properties of the effusion fluid, the presence of a significantly large effusion, and whether respiratory function is compromised.[9,10]

In contrast, diagnostic thoracocentesis is not included in the management algorithm in the guidelines for parapneumonic effusion in children. It is recommended to put in a chest drain or proceed with video-assisted thoracic surgery (VATS), unless the effusion is small and there is no respiratory compromise.

In Hong Kong, there are recommendations for management of childhood community acquired pneumonia (CAP),[11] but not for PPE/Em. The practice of managing paediatric PPE/Em varies among different regional hospitals, depending on the experience and the expertise available in individual institutions. Dedicated cardiothoracic surgery or paediatric surgery service is not available in every regional hospital. Nonetheless, in addition to systemic antibiotic therapy, drainage with a traditional chest tube or a flexible pigtail catheter is often employed in indicated cases. The procedure of chest tube drainage is often performed under imaging guidance by a paediatric or radiology team. Intrapleural fibrinolytic is not universally used following an insertion of chest drain. If extracorporeal membrane oxygenation (ECMO) is required, they were managed in a specialised paediatric ECMO centre.

There is a gap of knowledge about the predictive factor of who will fail chest tube drainage, particularly in children. In the BTS 2005 guideline,[2] it is mentioned that more studies are recommended to find out the predictive factors of who will fail medical management.

The primary objectives of this retrospective study are to review the characteristics and clinical course of non-tuberculous PPE/Em in children and adolescents who required chest tube drainage in 4 acute regional hospitals in Hong Kong, and to find out the factors predictive of the clinical course, duration of hospitalisation and total drainage time. The information is important for anticipating the clinical course and making informed decisions on the management.

Method

We used our central electronic database (clinical data analysis and reporting system [CDARS]) to identify all patients under 18 years old with the discharge diagnosis (ICD9 code) of 'Pleurisy with effusion with a bacterial cause other than tuberculosis (511.1)', 'Other specified forms of pleural effusion except tuberculous (511.8)', 'Unspecified pleural effusion (511.9)' or 'Empyema thoracis (510.9)', admitted between 1 May 2011 and 30 April 2021 in the paediatric department or paediatric intensive care unit of the 4 public regional acute hospitals in Hong Kong (Caritas Medical Centre, Princess Margaret Hospital, Tuen Mun Hospital, and United Christian Hospital). We checked their medical records and excluded those: (1) did not undergo any chest tube drainage, (2) under 4 months old, (3) with confirmed or presumed

pulmonary tuberculosis for which they received anti-tuberculosis treatment, (4) with pleural effusion of non-infectious causes (such as nephrotic syndrome, heart failure, malignancies, and post-surgery complications), or (5) underwent thoracic surgical procedures before any chest tube drainage. Only those having chest tube drainage as the first intervention, apart from antibiotic therapy and diagnostic thoracocentesis, were included in this study. The information was collected retrospectively by reviewing their medical records.

For biochemical analysis of the pleural fluid (PF), we only used the results of the first sample taken during or after the insertion of the first chest drain. For microbiological analysis, we reviewed the results of all relevant specimens taken between the admission and two weeks after the insertion of the first chest drain.

Patients were regarded as having a favourable clinical course if they recovered, had only one chest tube drainage, and did not need surgery or respiratory support other than low-flow oxygen. Otherwise, the clinical course was defined as unfavourable. Low-flow oxygen is defined as oxygen supplementation of less than or equal to 5 litres per minute. Replacing a drain with a new one due to blockage, or having two separate drains for bilateral effusion, were regarded as an unfavourable course. For those who needed some oxygen supplement or respiratory support during their usual state, an escalation of the respiratory support during the disease course was regarded as an unfavourable clinical course.

The length of hospital stay was defined as the time between the first hospital admission for the PPE/Em and the final discharge from an acute care hospital, regardless of the number of inter-hospital transferral required. The total drainage time was defined as the time between the insertion of the first drainage and the removal of the last one, even if there was a period of no chest drain in situ for patients who needed more than one drainage.

Statistical Analysis

Demographic, clinical and laboratory variables were summarised by standard descriptive statistics. Mann-Whitney U test was used to compare the medians and ranges of the continuous variables between the two groups of different clinical course (favourable versus unfavourable). The odds ratios of favourable course were obtained by Pearson's chi-squared test for categorical variables, and univariate logistic regression for continuous variables. To obtain the mean differences of the duration of hospitalisation and the total drainage time, independent samples t-test and univariate linear regression were used for categorical and continuous variables respectively. Multivariate logistic regression was performed to identify variables independently predictive of favourable clinical course, while multivariate linear regression was used regarding the duration of hospitalisation and the total drainage time.

To find out whether the predictive factors of the use of respiratory support are different from those of invasive re-intervention or mortality, we performed two additional secondary analyses. First, those requiring invasive re-intervention (multiple chest drain insertions or thoracic surgery) or mortality were compared with those with none of these outcomes. Second, those requiring respiratory support, other than low-flow oxygen, but no invasive re-intervention or mortality were compared with those with a 'favourable' clinic course as defined in the primary analysis.

The variables being tested in the regression analyses are listed in Tables 4 and 5. A 2-tailed $P<0.05$ was considered statistically significant for all tests. Statistical analysis was conducted using the SPSS software package (Windows version 27.0; IBM Corp, Armonk [NY], US).

Results

One hundred and fifty-six patients were identified and included in the analysis. Around half of them were male (52.6%). The median age on admission was 4.9 years (interquartile range [IQR]: 0.4-17.7 years). Seventeen patients (10.9%) had significant underlying conditions that put them at increased risk of severe pneumonia, and they were placed in one group (M1). These conditions included neurological diseases with severe disability (9), syndromal diseases (4), congenital central hypoventilation syndrome (1), cardiomyopathy (1), and hypogammaglobulinaemia (2). Four had a tracheostomy, and 5 had a gastrostomy. The remaining 139 patients (89.1%) were placed in another group (M2), which included 136 patients with good past health and 3 with conditions that were not typically associated with an increased risk of pneumonia (mild-moderate intellectual disability, epilepsy, and low body weight respectively).

Almost all the patients (97.4%) had fever on or before the hospital admission. The median duration between the onset of fever and the day of hospital admission was 5 days

(IQR: 3-7 days).

The microbiological findings are listed in Table 1. One hundred and five patients (67.3%) had positive evidence of bacterial infection. *Streptococcus pneumoniae* accounted for 77% of these and was mostly detected by PCR (polymerase chain reaction) test on the pleural fluid (65.4%). The rates of finding pneumococcus from the culture of blood, pleural fluid and the lower respiratory tract specimens in the pneumococcus-positive cases were 18.5%, 19.8% and 22.2% respectively. Other bacteria detected commonly included *Mycoplasma pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin-sensitive), and *Streptococcus pyogenes*. Bacterial-viral co-infection was not uncommon (46.7% of the bacteria-positive cases). In the 66 virus-positive cases, 17 (25.8%) had no positive evidence of bacterial infection.

One hundred and five patients (67.3%) had thorax computer tomography (CT). In these scans, necrotising pneumonia was detected in 75 patients, pneumothorax in 42, and lung abscess in 3.

Thirty-five patients (22.4%) had a traditional drain inserted as the first drainage. Three of these procedures were performed by surgeons. The remaining were by the paediatric teams. A pigtail catheter was inserted as the first drainage in 121 cases (77.6%). Sixty of the pigtail catheter insertions were performed by a paediatric team, and other 60 by a radiologist. All the pigtail catheter insertions were ultrasound-guided, except in two cases where CT guidance was employed.

Intrapleural fibrinolytic was given after the insertion of the first drainage (and before the second procedure, if present) in 118 cases (75.6%). Urokinase was used in most cases. Only 3 patients had streptokinase. The course of the intrapleural fibrinolytic ranged from 1 day to more than 3 days.

Thirty-eight patients (24.4%) required respiratory support other than low-flow oxygen during the hospitalisation, excluding the respiratory support given during the operation and early post-operative period for those who had surgery. The maximal degree of respiratory support given was high-flow nasal cannula oxygen therapy in 12 patients (7.7%), non-invasive continuous or bi-level positive airway pressure in 7 (4.5%), invasive mechanical ventilation in 14 (9.0%), and ECMO in 5 (3.2%).

Details about the clinical courses are listed in Table 2. Thirty-four patients underwent thoracic surgery (VATS in 25, thoracotomy in 9). In one case, following the insertion of a pigtail catheter as the first drainage procedure, the guidewire was retained in the pleural cavity, and thoracotomy was performed to remove the guidewire.

There were 5 cases of mortality (3.2%). Three of them had underlying medical conditions (severe neurological disability, hypogammaglobinaemia, and cardiomyopathy respectively). Two had no positive bacteriology and virology result, one had pneumococcal and *E. coli* coinfection, one had pneumococcal, adenovirus and parainfluenza virus coinfection, and the remaining one had adenovirus infection. Four received invasive mechanic ventilation, and among them two had ECMO. All did not have surgery for the parapneumonic effusion. The respective causes of death in 4 cases were: (1) severe necrotising haemorrhagic pneumonia, (2) hypoxic brain injury due to shock, (3) multiorgan failure (this case had haemolytic-uraemic syndrome and acute renal failure), and (4) intracranial haemorrhage and multi-organ failure. In one case, the cause of death was not well documented.

Excluding the mortality cases, the median duration of hospitalisation was 19 days (IQR: 15-27 days). Longer duration of hospitalisation was associated with surgery (median 23.5 versus 19 days, $P<0.001$) and respiratory support (median 29 versus 18 days, $P<0.001$). The median duration between the insertion of the first drain and the removal of the last drain was 9 days (IQR: 6-14 days). Long drain duration was also associated with surgery (median 13.5 versus 7 days, $P<0.001$) and respiratory support (median 14 versus 8 days, $P<0.001$).

For the 30 cases that required surgery (excluding those requiring ECMO and the one for removal of retained guidewire), the median duration between the insertion of the first drain and the surgery was 6 days (IQR: 3-10.75 days), and the median length of stay was 15.5 days (IQR: 10.5-23 days). For those 31 recovered cases requiring more than one chest drain but not surgery or ECMO, the median length of stay was 14.5 days (IQR: 10.25-24.5 days). It is not significantly different from the abovementioned surgery group (Mann-Whitney U test, $P=0.70$).

Seventy-four patients (47.4%) had a favourable clinical course. The group with favourable clinical course had significantly higher PF glucose (median: 3.85 versus 1.00 mmol/L, $P<0.05$) and lower PF lactate dehydrogenase (LDH, median: 1869 versus 3610 U/L, $P<0.05$) than the group with unfavourable course. There was no significant difference in the PF protein, pH and adenosine deaminase (ADA) level between the two groups, so as the age on admission. The time between the onset of fever and the hospital admission was significantly longer in the favourable course group (median: 6 versus 4 days, $P<0.05$). The favourable clinical course group also had

Table 1 Microbiological findings

Bacteria detected in any of the following specimens*, n (%)	105/156 (67.3%)		
Streptococcus pneumoniae†		81	
Type 3			50
Type 19A			5
Miscellaneous types‡			8
Typing not available			18
Mycoplasma pneumoniae§		9	
Pseudomonas aeruginosa		7	
Staphylococcus aureus (methicillin-sensitive)		6	
Streptococcus pyogenes		4	
Moraxella catarrhalis		2	
Escherichia coli		2	
Haemophilus influenzae		2	
Miscellaneous¶		12	
Bacteraemia	17/105 (16.2%)		
Streptococcus pneumoniae		15	
Streptococcus pyogenes		1	
Salmonella group D		1	
Bacteria detected in culture of pleural fluid, n (%)	25/105 (23.8%)		
Streptococcus pneumoniae		16	
Streptococcus pyogenes		4	
Staphylococcus aureus (methicillin-sensitive)		4	
Parvimonas Micra		1	
In pneumococcus-positive cases:			
Pneumococcus DNA PCR positive in pleural fluid, n (%)	53/81 (65.4%)		
Pneumococcus antigen positive in pleural fluid, n (%)	1/81 (1.2%)		
Pneumococcus detected in sputum / tracheal aspirate / gastric aspirate (culture / PCR test), n (%)	18/81 (22.2%)		
Respiratory virus detected in the respiratory specimen, n (%)	66/156 (42.3%)		
Rhinovirus / enterovirus		30	
Influenza virus**		17	
Parainfluenza virus		15	
Adenovirus		7	
Respiratory syncytial virus		7	
Human metapneumovirus		1	
Coronavirus OC43		1	

Note:

* Nasopharygneal sample, sputum, tracheal aspirate, bronchoalveolar lavage fluid, blood, pleural fluid; test methods: culture, PCR, or antigen test

† Positive results in the following specimens are not regarded as evident of pneumococcal infection: urine pneumococcal antigen, throat swab culture.

‡ Type 15A: 3; Type 14: 2; Type 19F: 1; Type 33B/F: 1; Type 35B: 1

§ *Mycoplasma pneumoniae* PCR in respiratory specimen, or immunoglobulin M (IgM) against *Mycoplasma pneumoniae*

¶ One subject for each of the following: *Chlamydia pneumoniae* (by PCR in respiratory specimen), *Morganella Morganii, Proteus* species, *Achromobacter xylosoxidans, Providencia* species, Diphtheroids, Alpha-haemolytic streptococci, *Stenotrophomonas maltophilia, Acinetobacter* species, *Enterococcus faecalis, Parvimonas Micra, Salmonella* group D

** Influenza A: 9; Influenza B: 7; Influenza C: 1

longer time between the onset of fever and the insertion of the first drainage (median: 9 versus 7 days, $P<0.05$). The time of the insertion of the first drainage with respect to the admission day was not significantly different between the two groups (Table 3).

Multivariate analysis identified that only a higher PF glucose level, a longer time between onset of fever and hospital admission, a longer time between onset of fever and insertion of the first drainage, and the use of a pigtail catheter as the first drain were independently associated with a favourable clinical course. There was also a tendency, though statistically insignificant, of the association between bacteraemia and an unfavourable clinical course (Table 4). Longer hospitalisation and drainage time were both significantly associated with pneumothorax, bacteraemia, and lower PF glucose content (Table 5).

From the secondary analyses, it was found that low PF glucose level was associated with the need of invasive re-intervention or mortality (adjusted odds ratio of PF glucose

Table 2 Clinical course

	n (%)
Recovered, did not need a second (or more) drain / surgery / extracorporeal membrane oxygenation (ECMO) /respiratory support ('favourable' group, C1)	74 (47.4%)
Needed respiratory support, but did not need a second (or more) drain / surgery / ECMO; recovered	12 (7.7%)
Needed a second (or more) drain, but did not need surgery / ECMO; recovered	31 (19.9%)
Needed surgery, but did not need ECMO; recovered	31 (19.9%)
Video-assisted thoracoscopic surgery	25
Thoracotomy	6
Required ECMO; recovered	3 (1.9%) (all had thoracotomy)
Mortality	5 (3.2%) (all did not have surgery)
No ECMO	3
Had ECMO	2

Table 3 Comparison between the groups of favourable versus unfavourable clinical course

	Group C1 (favourable course) Median (IQR)	**Group C2 (unfavourable course) Median (IQR)**	***P* value***
Age, years	4.35 (3.25-7.65)	5.20 (2.97-8.15)	0.973
Pleural fluid (PF) Protein, g/L	42.0 (37.8-47.9)	41.6 (36.0-48.1)	0.645
PF Glucose, mmol/L	3.85 (0.68-5.23)	1.00 (0.30-3.38)	**<0.001**
PF lactate dehydrogenase, U/L	1869 (641-3870)	3610 (1456-10670)	**<0.001**
PF pH	7.47 (7.14-7.71)	7.31 (7.02-7.50)	0.155
PF adenosine deaminase, U/L	47.5 (29.8-83.8)	68.0 (31.8-154.3)	0.179
Time from the onset of fever to admission, days	6 (3-7)	4 (3-5)	**0.005**
Time from the admission to the insertion of the first drain, days	3 (1-6)	2 (1-5)	0.218
Time from the onset of fever to the insertion of the first drain, days	9 (7-13)	7 (5.3-10)	**0.002**
Duration of hospital stay (excluding mortality cases), days	16 (12.8-21.3)	24 (18-38)	**<0.001**
Duration between the insertion of the first drain and the removal of the last drain (excluding mortality cases), days	6 (4-9)	13 (8-23)	**<0.001**

Notes:

*Mann-Whitney U test; *P* value ≤ 0.05 is in **bold**.

for these outcomes: 0.670, $P<0.05$). For those not having any invasive re-intervention or mortality, bacteraemia (adjusted odds ratio: 84.95, $P<0.05$) and shorter duration between the onset of fever and the hospital admission (adjusted odds ratio: 0.625, $P<0.05$) were associated with the need of respiratory support.

Discussion

Parapneumonic effusion and empyema are important conditions in paediatrics as they can cause mortality, and often entail invasive procedures and long hospitalisation. They affect not only those with chronic medical conditions, but also children and adolescents with good past health, even in the era of widespread use of pneumococcal vaccines. Our study involved paediatric patients with non-tuberculous PPE/Em who required chest drain. It did not include milder cases, in which chest drain was not required. Those having thoracic surgeries straightaway after diagnosis, and those having severe suppurative complications of pneumonia but not PPE/Em were not included. Nonetheless, it still represents a significant proportion of our paediatric patients who developed moderate-to-severe complications of pneumonia and required invasive interventions. Although we did not include the information about the size of the effusion, it should be of considerable amount in all cases, which made the drainage insertion feasible.

The management of paediatric PPE/Em in the 4 centres was mostly in keeping with the recommendations from BTS (2005) and APSA (2012). All these cases were managed with systemic antibiotics and chest tube drainage. Small bore (8-12 FG) percutaneous drains, like pigtail

Table 4 Odds ratios of favourable clinical course for different variables

Variable *	Crude odds ratio of favourable course (95% confidence interval)	*P* value †	Adjusted odds ratio of favourable course (95% confidence interval)	*P* value ‡
Group M1 (significant underlying medical conditions), comparing with group M2	0.570 (0.200-1.626)	0.288	0.730 (0.158-3.383)	0.688
Traditional chest drain as the first drain inserted, comparing with pigtail catheter	0.356 (0.158-0.805)	**0.011**	0.167 (0.041-0.678)	**0.012**
Use of intrapleural fibrinolytic after the insertion of the first chest drain (and before the second procedure, if any)	1.467 (0.694-3.102)	0.315	1.072 (0.347-3.315)	0.904
Positive bacterial culture in PF	0.371 (0.145-0.949)	**0.034**	2.265 (0.476-10.787)	0.304
Bacteraemia	0.217 (0.060-0.791)	**0.013**	0.168 (0.027-1.062)	0.058
Evidence of influenza virus infection	1.678 (0.603-4.666)	0.317	3.052 (0.380-24.507)	0.294
PF glucose ≥ 3.4 mmol/L	3.900 (1.751-8.686)	**0.001**		
PF LDH ≥ 7000 U/L	0.278 (0.110-0.701)	**0.005**		
PF ADA ≥ 100 U/L	0.323 (0.106-0.986)	**0.042**		
PF glucose (mmol/L)	1.379 (1.141-1.666)	**0.001**	1.483 (1.145-1.921)	**0.003**
PF LDH x 1000 (U/L)	0.969 (0.934-1.004)	0.078	0.980 (0.940-1.023)	0.361
Time from the onset of fever to the admission (days)	1.155 (1.037-1.287)	**0.009**	1.298 (1.087-1.548)	**0.004**
Time from the admission to the insertion of the first drain (days)	1.042 (0.950-1.144)	0.381	1.163 (1.003-1.350)	**0.046**
Time from the onset of fever to the insertion of the first drain (days)	1.138 (1.043-1.242)	**0.004**		

Notes:

* Other variables that were not significantly associated with a favourable / unfavourable clinical course (*P* value >0.05 in the Chi-square test or univariate logistic regression) were: age, male sex, fever on or before admission, right PPE/Em (comparing with left; unilateral cases only), bilateral PPE/Em (comparing with unilateral), 'the first drain being inserted by a non-radiologist (comparing with by a radiologist)', bacteria detected in any microbiological specimen, pneumococcus detected in any microbiological specimen, positive pleural fluid pneumococcus DNA PCR or antigen test, respiratory virus detected in the upper respiratory specimen, bacterial and viral co-infection, necrotising pneumonia, lung abscess, pneumothorax, PF protein (g/L), PF pH, PF ADA (U/L). They were not put into the multivariate logistic regression.

† Chi-Square test for categorical variables, and univariate logistic regression for continuous variables. *P* value ≤0.05 is in **bold**.

‡ Multivariate logistic regression. *P* value ≤0.05 is in **bold.**

PF: Pleural fluid; LDH: lactate dehydrogenase; ADA: adenosine deaminase

Table 5 Mean differences of the duration of hospitalisation and the drain duration for different variables

Variable *	Duration of hospitalisation (days)				Drain duration (days)			
	Crude mean difference	*P* value†	Adjusted mean difference	*P* value‡	Crude mean difference	*P* value†	Adjusted mean difference	*P* value‡
Group M1 (significant underlying medical conditions), comparing with group M2	6.662 (-3.906-17.229)	0.215	8.764 (-1.012 – 18.539)	0.078	5.517 (-1.674 – 12.708)	0.132	6.676 (-0.479 – 13.830)	0.067
Traditional chest drain as the first drain inserted, comparing with pigtail catheter	-0.274 (-7.650 – 7.102)	0.942	0.149 (-6.650 – 6.948)	0.966	-1.788 (-6.811 – 3.236)	0.483	-0.735 (-5.711 – 4.241)	0.771
Use of intrapleural fibrinolytic after the insertion of the first chest drain (and before the second procedure, if any)	-0.832 (-8.165 – 6.500)	0.823	-3.291 (-9.857 – 3.275)	0.323	2.814 (-2.168 – 7.795)	0.266	1.632 (-3.174 – 6.437)	0.503
Bacteria detected in any of the following specimens §	6.524 (-0.008 – 13.055)	0.050			2.780 (-1.711 – 7.271)	0.223		
Positive bacterial culture in PF	10.941 (2.647 – 19.234)	**0.010**	3.215 (-5.547 – 11.977)	0.469	5.197 (-0.529 – 10.923)	0.075	-0.842 (-7.255 – 5.570)	0.795
Bacteraemia	26.029 (16.535 – 35.523)	**<0.001**	26.036 (17.103 – 34.969)	**<0.001**	6.952 (-0.061 – 13.964)	0.052	6.926 (0.388 – 13.464)	**0.038**
Respiratory virus detected in the upper respiratory specimen	-0.847 (-7.116 – 5.422)	0.790	-2.653 (-8.279 – 2.972)	0.353	-1.879 (-6.145 – 2.387)	0.386	-2.320 (-6.438 – 1.797)	0.267
PF glucose ≥ 3.4 mmol/L	-9.821 (-17.128 – -2.515)	**0.009**			-8.169 (-13.377 – -2.962)	**0.002**		
Pleural fluid LDH ≥ 7000 U/L	7.448 (-0.431 – 15.328)	0.064			6.671 (1.336 – 12.005)	**0.015**		
Pneumothorax in CT	12.261 (4.469 – 20.052)	**0.002**	11.143 (3.983 – 18.303)	**0.003**	9.597 (3.935 – 15.260)	**0.001**	7.557 (2.316 – 12.797)	**0.005**
PF glucose (mmol/L)	-2.536 (-4.235 – -0.836)	**0.004**	-2.312 (-3.939 – -0.685)	**0.006**	-1.984 (-3.200 – -0.768)	**0.002**	-1.548 (-2.739 – -0.357)	**0.011**
PF LDH x 1000 (U/L)	0.208 (-0.037 – 0.454)	0.096	0.023 (-0.212 – 0.259)	0.846	0.190 (0.023 – 0.356)	**0.026**	0.109 (-0.063 – 0.281)	0.214
PF pH	-0.672 (-6.183 – 4.838)	0.808	3.118 (-2.471 – 8.706)	0.272	-1.389 (-4.559 – 1.782)	0.385	1.707 (-2.383 – 5.798)	0.411
Time from the onset of fever to the admission (days)	-1.059 (-2.007 – -0.111)	**0.029**	-0.994 (-1.912 – -0.076)	**0.034**	-0.443 (-1.097 – 0.211)	0.183	-0.629 (-1.301 – 0.043)	0.06
Time from the admission to the insertion of the first drain (days)	0.133 (-0.771 – 1.037)	0.771	0.301 (-0.532 – 1.134)	0.476	-0.645 (-1.253 – -0.037)	**0.038**	-0.606 (-1.216 – 0.003)	0.051
Time from the onset of fever to the insertion of the first drain (days)	-0.599 (-1.368 – 0.170)	0.126			-0.753 (-1.268 – -0.238)	**0.004**		

Notes:

* Other variables that were not associated with significant mean differences of the duration of hospitalisation and the drain duration (*P* value > 0.05 in the independent samples t-test or univariate linear regression) were: age, male sex, fever on or before admission, right PPE/Em (comparing with left; unilateral cases only), bilateral PPE/Em (comparing with unilateral), 'the first drain being inserted by a non-radiologist (comparing with by a radiologist)', pneumococcus detected in any microbiological specimen, positive pleural fluid pneumococcus DNA PCR or antigen test, influenza virus infection, bacterial and viral co-infection, necrotising pneumonia, lung abscess, PF protein (g/L), PF ADA (U/L). They were not put into the multivariate linear regressions.

† Independent samples t-test for categorical variables, and univariate linear regression for continuous variables. *P* value ≤ 0.05 is in **bold**.

‡ Multivariate linear regression. *P* value ≤ 0.05 is in **bold**.

§ Nasopharygneal sample, sputum, tracheal aspirate, bronchoalveolar lavage fluid, blood, pleural fluid; test methods: culture, PCR, or antigen test

PF: Pleural fluid; LDH: lactate dehydrogenase; CT: computer tomography

catheters, were commonly used at the first place, very often inserted under ultrasound guidance. The documentation of the ultrasound findings of the effusion (fluid mobility, fibrin strands and septations, loculations, echogenicity, and surrogate parameters of the size of the effusion) by the non-radiologists was often not adequate. Intrapleural fibrinolytics were not universally used in some centres, since there was a concern that if a surgical drainage would ultimately be required, intrapleural fibrinolytics would make it technically more difficult to perform. In some cases, even the response to systemic antibiotics and chest tube drainage was not optimal after a certain period, the management approach remained non-surgical. These patients had prolonged chest tube drainage, with or without additional chest drain inserted or multiple courses of intrapleural fibrinolytic. In some other cases, surgery was only performed after a prolonged period. This practice is not in accordance with the BTS and APSA guidelines. Having said that, there was no significant difference in the length of hospitalisation between the subgroup with surgery and those without surgery but multiple chest drains.

Almost all the cases involved CAP rather than hospital-acquired pneumonia, as they were in the community before the disease onset. Pneumococcal infection accounted for half of the cases, while some other common bacterial pathogens in previously healthy children were *Mycoplasma pneumoniae, Staphylococcus aureus* and *Streptococcus pyogenes*. In our cohort, those with pneumococcal infection had similar clinical course as those with non-pneumococcal infections. The presence of viral infection, including influenza, did not affect the clinical course or the time-related outcomes.

Bacteraemia was independently associated with a longer hospitalisation and drain duration. On average, if bacteraemia was present, the hospitalisation and drain durations were 26 days and 7 days longer respectively. It was also possibly associated with higher adjusted odds of an unfavourable clinical course, particularly with respect to the need of respiratory support. On the other hand, a positive bacterial culture in PF was associated with an unfavourable clinical course and longer hospitalisation in the univariate analysis, but not in the multivariate regression models. Our results echo the findings by Picard et al that in children with PPE, a positive blood or PF culture was significantly associated with a prolonged fever.[12]

PF Biochemical Analysis

The PIDS guideline stated that biochemical analysis of the PF is not recommended as it rarely changes patient management, despite 'very low-quality evidence'.[8] The BTS recommendations are in keeping with PIDS.[2] There was no mention about these tests in the Hong Kong childhood CAP management recommendation.[11]

In our study, we found that PF glucose level is a strong prognostic factor in paediatric PPE/Em. Those with PF glucose below 3.4 mmol/L were 3.9 times more likely to have an unfavourable clinical course. A higher PF glucose level was independently associated with lower odds of invasive re-intervention or mortality, shorter hospitalisation, and shorter drain duration.

PF LDH of above 7000 U/L was associated with a 3.6-time higher chance of an unfavourable clinical course. Nonetheless, it was not a significant independent associating factor in the multivariate regression models. One possible reason is that it was confounded by the PF glucose level, which has a moderate correlation with it (Pearson correlation: -0.351, $P<0.01$). PF protein, pH and ADA levels were not associated with the clinical course or the time-related outcomes in our study.

Our findings agree with those from a retrospective study by Chiu et al about PPE/Em in children. They found that a pleural fluid acidosis with low PF glucose level and increased LDH level was associated with the progression of the stages of parapneumonic effusion in children.[13] Some other studies found that various biochemical parameters had an association with the clinical course in paediatric PPE/Em, which includes the need of invasive re-intervention and prolonged hospitalisation.[14-17] Moreover, the PF biochemical parameters were not influenced by the previous administration of antibiotics.[17]

In adults, biochemical analysis of the effusion fluid obtained by diagnostic thoracocentesis helps to identify which patient requires invasive intervention in addition to antibiotic treatment. Also, certain changes in the biochemical properties (low pH, low glucose, high LDH) of the effusion fluid are associated with more advanced stages of parapneumonic effusion. Contrastingly, according to the BTS[2] and APSA[3] guidelines for children, the decision of chest tube drainage or early thoracic surgery does not hinge on the biochemical properties of the effusion fluid. However, we found that it indeed helps us to predict who would have invasive re-intervention, prolonged hospitalisation, or mortality.

CT Findings

Necrotising pneumonia and pneumothorax were commonly detected in CT thorax in these patients. There was no association between these pathologies and an unfavourable clinical course. However, patients with pneumothorax had longer hospitalisation and drain duration. Complications of PPE/Em include bronchopleural fistula, pyopneumothorax, and lung entrapment (non-expandable lung).[18] All these conditions require longer drain duration and thereby longer hospitalisation. They may also need surgical intervention.

Chest Drainage and Use of Intrapleural Fibrinolysis

In this patient group, pigtail catheters were more commonly used in the first drainage. It was independently associated with higher odds of a favourable clinical course, comparing with traditional chest drain. It was not associated with the length of hospitalisation and the drain duration. In the secondary analyses, pigtail catheter was not significantly associated with the need of invasive re-intervention or mortality. But in the subgroup without invasive re-intervention or mortality, it was associated with a fewer use of respiratory support. It is possible that those having respiratory distress had a larger effusion or severe lung parenchymal disease, hence more likely to have a traditional chest drain inserted at the first place, rather than a pigtail catheter. We cannot draw any conclusion on whether pigtail catheter is superior to traditional chest drain in managing paediatric PPE/Em. Prospective controlled studies are required. Nonetheless, our findings support the recommendations from BTS[2] and APSA[3] that small drains, including pigtail catheters, should be used whenever possible. A small drain can cause less discomfort on the patients. Our findings also support that the procedure of chest drain insertion can be performed under sonographic guidance by not only radiologists, but also trained medical professionals (including paediatricians) at bedside, without an increase in the chance of an unfavourable clinical course.

Another recommendation from BTS[2] and APSA[3] is that intrapleural fibrinolytics should be given for any complicated PPE/Em because of the benefit of shortened hospital stay. Contrastingly, we found that it did not affect the clinical course and the time-related outcomes, even after adjusting for other factors, including PF biochemical parameters. One possible reason is that we included respiratory support and additional chest tube drainage as the definition of unfavourable clinical course. Similar results were found in another retrospective study by Aydogan et al. They found that in paediatric patients with empyema, intrapleural streptokinase did not significantly reduce the duration of chest tube drainage and hospital stay, and the need for surgery, regardless of the stage of the disease, compared to simple tube drainage.[19] A Cochrane review on surgical versus non-surgical management for empyema for all age groups stated that there was insufficient evidence to assess the impact of fibrinolytic therapy.[20] Another Cochrane review on intrapleural fibrinolytic therapy versus conservative management in the treatment of adult PPE/Em found heterogeneous results from different trials in terms of the benefit in reducing the requirement for surgical intervention.[21,22]

Timing of Hospitalisation and Drainage Insertion

We observed a paradox that patients who were admitted to hospital later from the onset of fever, and those having later drainage insertion since the hospital admission or the onset of fever, were more likely to have a favourable clinical course. We do not know the exact reason of this phenomenon. It was possible that those having an unfavourable clinical course tended to have more aggressive disease, presented to hospital earlier, and developed significant PPE/Em early on. It is in keeping with the findings of a study on intrapleural fibrinolysis for empyema in children, which shows that immediate admission to intensive care is a risk factor of treatment failure, defined as repeated pleural drainage or total length of stay greater than 2 weeks.[23] After all, in our cohort an unfavourable clinical course was not associated with a delayed presentation to hospital, or a delayed insertion of chest drainage.

Limitation

Some important factors, which might affect or associate with the clinical course and the outcome, were not analysed. It is because the documentations about the following information were incomplete in many cases: the vaccination status of pneumococcus and seasonal influenza, the amount and radiological characteristics of

the pleural effusion in ultrasound and CT, the size of the traditional chest tube or pigtail catheter used, and the number of doses of intrapleural fibrinolytic given. The analysis of the effect of the size of the pleural effusion was also hindered by the fact that there is no simple standardised way to accurately measure the size of the pleural effusion in ultrasound and CT, especially in children. Although we were not able to study the association of sonographic appearance with the clinical course, it is shown from the retrospective study in children by Chiu et al that the successful rate of tube drainage decreases with the advancement of stages of parapneumonic effusion, based on the sonographic appearance.[13] We could not study the effect of different regimens of antibiotic treatment, as the retrieval and analysis of the corresponding information was technically quite complicated. Examination on the effect of antibiotic susceptibility was not possible even in the bacteria-positive cases, as many of the bacteria were detected by molecular studies but not culture. We did not analyse the PF cell count, as very often the PF was thick and deemed unsuitable for this analysis.

Second, the expertise available in the 4 centres participating in this study differed, which led to variation in the practice of managing paediatric PPE/Em in different centres. Dedicated cardiothoracic or paediatric surgery services are only available in some centres. It could be a confounding factor as these centres might be more ready to perform surgical interventions because of the availability of the surgical expertise. Lastly, this study is of a non-randomised and retrospective design, which might have resulted in patient selection bias.

Clinical Implications

During the management of paediatric parapneumonic effusion, it is important to take into consideration the effusion size, the presence of septation and loculation, and the respiratory status. Having said that, biochemical analysis of the PF can be beneficial. It is inexpensive and can be readily performed after obtaining PF from chest tube drainage. It may give valuable information for assessing the stage and the severity of the parapneumonic effusion, predicting the clinical course and guiding decision-making on the management. Further prospective studies are warranted to confirm the usefulness of biochemical analysis of pleural fluid in managing paediatric parapneumonic effusion.

Other studies have shown that early surgical interventions improve the clinical outcomes by reducing the chance of re-intervention and hospital duration.[20,24-27] These interventions can be especially beneficial in cases with adverse features, such as adverse PF profile, bacteraemia, early hospitalisation, and certain sonographic appearances of the pleural effusion.[13] Further local prospective studies are warranted to assess the efficacy of early surgical interventions over chest tube drainage for paediatric PPE/Em in our population.

Conclusion

This study is the first multi-centre review of PPE/Em in children and adolescents in Hong Kong. PF glucose level is a strong prognostic factor in paediatric PPE/Em. Bacteraemia and pneumothorax are the other factors predictive of longer hospitalisation. When these factors are present, we need to be more cautious if a conservative approach is adopted.

Conflicts of Interest

All authors have disclosed no conflicts of interest.

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Ethics Approval

This study was approved by the Central Institutional Review Board, Hospital Authority Hong Kong (Ref: CIRB-2021-014-4). The requirement for patient informed consent was waived.

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