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ORIGINAL ARTICLE

Clinical Characteristics, Predictors and Outcome of Children with Complicated Parapneumonic Effusion: A Single Centre Experience

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ABSTRAK

Jangkitan bakteria di paru-paru boleh menyebabkan pengumpulan cecair pada bahagian pleura, dikenali sebagai parapneumonia efusi (PPE). Faktor ramalan kepada tahap kerumitan PPE tidak di ketahui. Kajian ini dilakukan untuk mengenali ciri-ciri, faktor ramalan dan hasil rawatan kanak-kanak yang mengalami PPE di Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Data pesakit PPE kanak-kanak yang dimasukkan ke PPUKM dari Januari 2010 ke Disember 2017 dikaji secara retrospektif. Pesakit dibahagikan kepada dua kumpulan iaitu PPE tahap sederhana dan PPE tahap rumit. Dari 45 orang pesakit yang dikaji, 20 (44.4%) pesakit mempunyai PPE tahap sederhana, manakala 25 (55.6%) mengalami PPE tahap rumit. Median umur pesakit adalah 32 bulan (IQR 16-63). Jenis bakteria yang paling biasa di temui adalah Streptococcus pneumoniae (61.9%), diikuti oleh Mycoplasma pneumoniae (19.0%) dan Staphylococcus aureus (4.8%). Didapati hanya 11.1% pesakit kanak-kanak menerima suntikan vaksin pneumokokal. Tiada perbezaan yang ketara dalam perbandingan ciri-ciri klinikal antara pesakit PPE tahap sederhana dan rumit. Ujian ultrasound toraks hanya dilakukan ke atas 62.2% pesakit. Majoriti (95.0%) pesakit PPE tahap sederhana sembuh dengan hanya rawatan antibiotik. Manakala 60.0% dari pesakit PPE tahap rumit memerlukan rawatan intervensi surgeri. Purata jangkamasa pesakit menerima rawatan di hospital bagi PPE sederhana adalah 10 (4.0) hari, manakala bagi PPE rumit adalah 28 (16.5) hari. Kesimpulannya, ciri-ciri klinikal tidak dapat meramal tahap kerumitan PPE. Penggunaan ujian ultrasound toraks sebagai ujian utama dalam diagnosis dan tahap PPE perlu ditekankan. Rawatan antibiotik adalah berkesan untuk PPE tahap sederhana, manakala untuk PPE tahap rumit, kajian prospektif yang lebih besar diperlukan untuk menentukan kumpulan kanak-kanak yang bermanafaat untuk menerima rawatan intervensi lebih intensif.

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Kata kunci: *ciri-ciri, kanak-kanak, parapneumonia efusi*

ABSTRACT

Parapneumonic effusions (PPE) is a complication of bacterial pneumonia. Factors that contribute to complicated PPE remain uncertain. This study was aimed to describe the characteristics, clinical predictors and outcome of children with parapneumonic effusion (PPE) in Universiti Kebangsaan Malaysia Medical Centre (UKMMC). A retrospective study on children with PPE who were admitted to UKMMC between January 2010 to December 2017 was conducted. Patients were categorised into 2 groups: simple and complicated PPE. Of 45 patients recruited, 20 (44.4%) patients had simple PPE and 25 (55.6%) had complicated PPE. Their median age was 32 months (IQR 16-63). The most common isolated organism was *Streptococcus pneumoniae* (61.9%), followed by *Mycoplasma pneumoniae* (19.0%) and *Staphylococcus aureus* (4.8%). Only 11.1% of patients received pneumococcal vaccination. There was no statistical significant difference in clinical features between simple and complicated PPE. Only 62.2% patients had ultrasound thorax done. Majority (95.0%) of patients with simple PPE were successfully treated with intravenous antibiotics alone. Sixty percent of patients with complicated PPE needed surgical intervention. Mean length of hospital stay for simple PPE was 10 (4.0) days and complicated PPE was 28 (16.5) days. In conclusion, clinical features could not predict complicated PPE. Use of ultrasound thorax as the main investigation tool for diagnosis and staging should be emphasised. Antibiotics therapy alone is effective therapy for simple PPE, while in complicated PPE, larger prospective studies are required to investigate which children benefit significantly from more intensive intervention.

Keywords: children, clinical characteristics, parapneumonic effusion

INTRODUCTION

Parapneumonic pleural effusion (PPE) develops in about 40% of hospitalised children with bacteria pneumonia (Obando et al. 2008). *Streptococcal pneumoniae* is invariably the leading aetiological agent for PPE. Although the introduction of conjugate pneumococcal vaccine decreased the incidence of bacterial pneumonia, the rate of PPE was noted to have increased (Grijalva et al. 2010; Kaplan et al. 2004; Li & Tancredi 2010).

The steps that leads to the development of PPE and empyema are as the following: i.e. (i) stage 1, described as the early exudative phase, constitutes the collection of thin reactive fluid and few cells in the pleural space; (ii) stage 2, described as fibropurulent phase, involves the formation of loculations; and (iii) stage 3 is the organisation phase and it

involves the creation of a thick layer of fibrin that encloses the lung (Hamm & Light 1997).

Factors that contribute to the progression to complicated PPE remains uncertain (Roxburgh et al. 2008). Previous studies have suggested that children with complicated pneumonia or empyema tend to be from the older age group of 3 years old, had prolonged fever before hospitalisation and received ibuprofen or antibiotics prior to hospitalisation (Byington et al. 2002; François et al. 2010).

The treatment of thoracic empyema depends on the clinical presentation and the stage of the disease. The initial treatment of empyema is to begin empiric antibiotic therapy for prompt eradication of the causative organism; the second step is directed to drain the purulent fluid in order to restore pleural fluid circulation, allowing lung re-expansion and improvement of lung function (Jaffé & Balfour-Lynn 2005). The therapeutic management of paediatric PPE and the impact of initial therapeutic interventions on clinical outcome are the subject of controversial discussions with a striking lack of consensus on the treatment between centres (Hafen et al. 2016).

To the best of our knowledge, there is no local data pertaining to the management practices and outcome of PPE in children. Our experience in managing these group of children may help in preparing local guidelines for better management of childhood PPE. This study was aimed to describe the clinical characteristics, predictors for complicated PPE and outcome of children with simple and complicated PPE admitted to our centre.

MATERIALS AND METHODS

A retrospective study was conducted at Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, a tertiary referral university hospital in Kuala Lumpur which offers both paediatric medical and surgical services. Computerised medical records of eligible patients admitted from 1st January 2010 to 31st December 2017 (7 years) were reviewed. Inclusion criteria were all hospitalised children aged 1 month to 14 years old and diagnosed to have community- acquired pneumonia (CAP) complicated with PPE. Patients were recruited based on International Classification of Disease 10 (World Health Organization 2010) codes i.e. J86 (pleural empyema), J90 (parapneumonic effusion) and J91 (pleural effusion). Pleural effusion which occurred due to non-infective cause i.e. malignancy, trauma, congestive heart failure, nephrotic syndrome was excluded.

The study was approved by Research and Ethics committee of UKMMC (FF-2016-367).

Definitions

The diagnosis of PPE was based on signs and symptoms of lower respiratory tract infection with clinical features of pleural effusions i.e. stony dullness on percussion with reduced breath sounds. It was also supported by radiological findings of pleural

effusion on Chest X Ray (CXR) and / or Ultrasound (USG) Thorax.

For the purpose of this study, PPE was divided into 2 groups (Hamm & Light 1997) i.e. (i) Simple PPE: Patients with clinical and radiological evidence of pleural effusion. CXR with pleural effusion and/or Stage 1 PPE based on USG thorax. Pleural effusion which had resolved on subsequent CXR was categorised as simple PPE; (ii) Complicated PPE: Patients with clinical evidence of pleural effusion as radiological evidence stage 2 and/ or stage 3 PPE either from USG thorax or High-Resolution Computed Tomography (HRCT) thorax or based on any of these pleural fluid results either pH<7.20 or LDH>1000 IU.

Failure of medical treatment was defined as patients who were not successfully treated with antibiotics (with /without chest drain) and/ or fibrinolytic and needed surgical intervention.

Data Collection

Data extracted from medical records included demographics, co-morbidities, immunisation status based on Malaysian standard immunisation schedule and against *Streptococcus pneumoniae*, presenting symptoms (fever, cough, rapid breathing and abdominal pain), history of pre-hospitalised antibiotics as well as vital signs (respiratory rate, temperature and oxygen saturation under room air at presentation).

Laboratory results including haemoglobin, total white count (TWC), platelet count, C-reactive protein (CRP), total albumin and pleural fluid analysis were noted. Causative pathogens were documented based on bacterial culture from blood, sputum, nasopharyngeal aspirate and pleural fluids, if available. Urinary antigen positive for *S. pneumoniae* and Ig M positive for *Mycoplasma pneumoniae* (titre 1:160) were also documented.

The first CXR upon admission and USG thorax findings were verified by a paediatric radiologist and documented for presence of consolidation and stages of pleural effusion. HRCT thorax findings, if any, was also reviewed.

Treatment modalities including medical management (antibiotics, chest drain and fibrinolytics) surgical interventions either video-assisted thoracoscopic surgery (VATS), decortication or open thoracotomy and its complications were studied. The treatment outcome such as length of stay, failure of medical treatment, requirement of intensive care and respiratory support were noted.

Statistical Analyses

Data was analysed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis was performed using frequencies and percentages for categorical data and median, as well as interquartile range (IQR) for continuous data, respectively. Categorical variables were analysed either by Chi-square or Fisher`s exact test while continuous variables were analysed using student t-test or non-parametric tests. Univariate analysis was used to analyse possible factors to predict complicated PPE. P-value of

<0.05 was considered as statistically significant.

RESULTS

Patient Characteristics

Within the 7 years' period, 1806 patients were admitted for CAP, of which 50 (2.8%) of them had PPE. As 5 of the 50 medical records were not found, only the remaining 45 patients with PPE were analysed.

Twenty (44.4%) patients had simple PPE, while another 25 (55.6%) patients had complicated PPE. Their characteristics was summarised in Table 1. The majority of children with PPE aged ≤24 months and there was no predominant sex. Although children with complicated PPE were older when compared to simple PPE, it was not statistically significant. More than 50.0% of patients had pre-existing co-morbidities; failure to thrive (33.0%), chronic respiratory illnesses (11.1%), prematurity (11.1%), cerebral palsy (4.4%), down syndrome (4.4%) and congenital heart disease (2.2%). About 18.0% of patients had incomplete immunisation and only 5 patients (11.1%) received pneumococcal vaccination.

There was no statistically significant

Table 1: Patient`s characteristics between simple and complicated PPE

	Simple n=20	Complicated n=25	P-value
Age (months), median (IQR)	27 (12.0 – 60.5)	38 (19.5 – 64.0)	0.86
≤24 months, n (%)	10 (50.0)	10 (40.0)	
25 - 60 months, n (%)	5 (25.0)	8 (32.0)	
>60 months, n (%)	5 (25.0)	7 (28.0)	
Male gender	10 (50.0)	14 (56.0)	0.84
Underlying comorbidities, n (%)	11 (52.4)	13 (54.2)	0.91
Incomplete immunization, n (%)	3 (15.0)	5 (20.0)	0.73
Pre-hospital antibiotics, n (%)	13 (65.0)	11 (44.0)	0.13
History of fever, n (%)	18 (90.0)	25 (100.0)	0.11
Duration of fever before admission (days), mean (SD)	6.2 (2.7)	6.0 (2.5)	0.99
Temperature >38.5°C, n (%)	15 (75.0)	15 (60.0)	0.29
Cough, n (%)	20 (100.0)	24 (96.0)	0.37
Rapid breathing, n (%)	12 (60.0)	17 (68.0)	0.58
WBC count (x 10^9 cells/mL), mean (SD)	20.76 (11.5)	17.10 (9.3)	0.43
Platelet (x 10^9/L), mean (SD)	378.5 (146.4)	340.7 (249.4)	0.54
Albumin (g/L), mean (SD)	37.5 (8.7)	29.2 (5.9)	0.09
C-reactive protein level (mg/dL), mean (SD)	14.40 (14.6)	20.20 (11.8)	0.23
Chest x-ray on admission Bilateral consolidation, n (%)	7 (33.3)	14 (58.3)	0.16

Table 2: Clinical predictors for complicated PPE

Factors	Simple Logistic Regression	
	Crude Odds Ratio (95% CI)	P-value
Male	1.13(0.35,3.67)	0.841
Age <60 months	2.00(0.45,8.84)	0.361
Presence of co-morbidity	1.25(0.36,4.36)	0.910
Incomplete immunization	1.48(0.31,7.21)	0.626
Pre - hospital antibiotics	0.29(0.08,1.00)	0.130
Duration of fever	1.08(0.85,1.36)	0.990
Temperature >38.5°C	0.50(0.14,1.82)	0.292
SPO^2< 92% under room air	0.99(0.89,1.11)	0.914
Anaemia Hb < 10 g/dL	0.41(0.09,1.98)	0.266
TWC	0.98(0.92,1.04)	0.439
CRP	1.03(0.98,1.08)	0.231
Albumin	0.89(0.77,1.02)	0.098
Platelet	1.00(1.00,1.00)	0.302
Positive organism	1.56(0.45,5.41)	0.487
Bilateral consolidation on CXR	2.37(0.70,7.94)	0.164

difference in demographic, clinical signs and symptoms as well as laboratory data between simple and complicated PPE patients. However, those in complicated PPE group had higher CRP, lower albumin level and higher percentage of having bilateral consolidation on CXR (Table 1).

All patient had CXR done on admission. Initial USG thorax was done in 28 (62.2%) of the patients with median of 3 days (range 1-17) of admission. HRCT thorax was done in one patient with simple PPE to exclude congenital lung anomaly which was suspected on the CXR. However, it was found to be negative. Fifteen of the 25 patients (60.0%) in the complicated PPE group had HRCT thorax done, all of them requiring surgical intervention.

Microbiological Data

Twenty-one of the 45 patients (46.7%) had positive micro-organisms identified from at least one sample. The commonest bacteria isolated was *Streptococcus pneumoniae* (61.9%), followed by *Mycoplasma pneumonia* (19.0%) and *Staphylococcus aureus* (4.8%). It is noteworthy that all isolated *Streptococcus pneumoniae* were sensitive to penicillin (MIC between 0.016-0.064 ug/mL). All patients with positive blood culture for *Streptococcus pneumoniae* were from the complicated PPE group. Viruses (adenovirus and Influenza A) were positive in 3 patients (14.3%).

Predictors of Complicated PPE

Univariate analyses showed that there were no significant clinical, biochemical or radiological factors to

Table 3: Clinical outcome between simple and complicated PPE

Outcome	Simple n=20	Complicated n=25	P-value
PICU admission, n ((%)	5 (25.0)	15 (60.0)	0.020
Respiratory assistance, n (%)	17 (85.0)	22 (88.0)	
Oxygen support, n (%)	11 (55.0)	10 (40.0)	0.290
Non-invasive ventilation, n (%)	5 (25.0)	10 (40.0)	0.200
Invasive ventilation, n (%)	2 (10.0)	12 (48.0)	0.003
LOS, mean (SD)	10 (4.0)	28(16.5)	<0.001

predict the progression from simple to complicated PPE (Table 2).

Treatment Modalities for Simple and Complicated PPE

A majority of patients (93.3%) were treated with at least 2 intravenous antibiotics; mainly benzylpenicillin and second or third generation cephalosporins. Only 3 patients received a single antibiotics of benzylpenicillin. About 20.0% of patients received macrolides.

Nineteen of 20 (95.0%) patients with simple PPE were successfully treated with intravenous antibiotics alone. One patient required a chest drain, had bilateral pleural effusion and was admitted to intensive care unit for an invasive ventilation.

Ten of the 25 patients (40.0%) with complicated PPE were managed with medical therapy; 3 received intravenous antibiotics only, 6 patients received antibiotics and required chest drains, while 1 patient required antibiotics, chest drains and fibrinolytic therapy.

Fifteen of the 25 patients (60.0%) with complicated PPE failed medical therapy and required surgical procedure. VATS was performed in 10 patients (40.0%), VATS with decortication performed in 3 patients (12.0%) and VATS with open thoracotomy and decortication performed in 2 patients (8.0%). VATS was done at mean duration of 22 days (range 12-45 days) of illness.

Treatment Outcome

Overall, the median length of hospital stay (LOS) for children with PPE was 16 days (IQR 9-27 days). Patients with simple PPE had a mean LOS of 10 (4) days while those with complicated PPE had a longer mean LOS of 28 (16.5) days, mainly due to surgical intervention that needed ventilator support post-operatively while a few had nosocomial pneumonia (Table 3). Five patients with simple PPE group required the Paediatric Intensive Care Unit (PICU), of which 2 had severe bronchopneumonia with septic shock at presentation and needed invasive ventilation, while 3 patients had nosocomial pneumonia resulting in escalation of respiratory support.

DISCUSSION

The prevalence rate of PPE in our

centre was 2.8%, almost similar to reported prevalence rate of PPE in other Asian countries, 1-3% (Nyambat et al. 2008). Our cohort showed that the majority of PPE cases were in young children below 5 years of age while complicated PPE tends to occur in older children, > 3 years old. These findings were consistent with several previous studies (François et al. 2010; Grijalva et al. 2010; Islam et al. 2012; Nyambat et al. 2008).

The main organism found in our study was *Streptococcus pneumoniae*, similar to other studies (Gayretli-Aydın et al. 2016; Krenke et al. 2016; Liese et al. 2019). The second most common organism was *Mycoplasma pneumonia.* The majority of our patients received intravenous penicillin and cephalosporin, while 20% of them received macrolide, consistent with the main organisms cultured. We noted that very small percentage (11.1%) of children received pneumococcal vaccine and 18.0% of them had incomplete standard immunisation. These findings reflect the need for more effort in improving public awareness on the importance of immunisation. A recent move by the Malaysian government to include pneumococcal vaccine in the standard immunisation may improve the rate of children who received the pneumococcal vaccine in future. Detection rate for positive organisms in our centre was 46.7%, slightly lower compared to study by Elemraid et al. (2015), 61.0% and (Yu et al. 2014), 59.6%. Diagnostic techniques used in both of these studies were superior, utilising molecular techniques of real time polymerase chain reaction and amplifications of specific genes.

Our study demonstrated that there was no difference in clinical characteristics between simple and complicated PPE. We did not find any significant clinical, biochemical and radiological factors that could predict complicated PPE. Other studies have also reported that initial common presenting symptoms such as fever and cough were not significantly different between simple and complicated PPE, while some reported that dyspnoea, chest pain and abdominal pain were more frequently observed in complicated PPE (Byington et al. 2002; Gayretli-Aydın et al. 2016; Krenke et al. 2016). Lin et al. (2006) retrospectively studied 131 Taiwanese children hospitalised with bacterial pneumonia and found elevated CRP count (>12 mg/dL) was an independent predictor for complicated lobar pneumonia resulting in empyema and necrotising pneumonia, OR 3.51 (CI 1.04-1.26). In our study, patients with complicated PPE were noted to have higher mean CRP count (14 vs 20 mg/dL) and lower mean albumin (37.5 vs 29.2 g/L); although not statistically significant but may be clinically significant. All of our patients with positive blood culture for *Streptococcus pneumoniae* were from the complicated PPE group. Elemraid et al. (2015), prospectively studied risk factors of complicated PPE in hospitalised children aged ≤ 16 years old in England, also found that patients with confirmed bacterial infection were associated with development of complicated PPE.

Diagnostic imaging methods plays an important role in the diagnosis and

management of PPE. Although CXR is frequently used as the first investigation method to detect the presence of PPE, it could not determine the complexities of the pleural effusion. Chest USG is the primary choice of imaging in PPE (Balfour-Lynn et al. 2005; Gayretli-Aydın et al. 2016). Chest USG helps to confirm the presence of pleural fluid, estimate the amount of fluid and determine PPE staging. It is safe, radiation-free and an inexpensive mode of imaging. The usage of USG thorax in our study was relatively low (62% of PPE cases) compared to European studies by Sakran et al. (2014) (83%) and Proesmans et al. (2014) (90%). Chest CT is not done routinely and should be used for distinguishing parenchymal abscesses or necrotising pneumonia from empyema or to detect broncho-pleural fistulae as a complication of empyema (Balfour-Lynn et al. 2005; Gayretli-Aydın et al. 2016; Sakran et al. 2014).

Sixty percent of our patients with complicated pneumonia required surgical procedure, of which VATS was performed in 40% of them. Only 1 patient received fibrinolytic therapy. Previous paediatric studies showed that fibrinolytic therapy and VATS were equally effective and had no significant difference in LOS after intervention, total LOS or radiologic outcomes (Kurian et al. 2009; Shah et al. 2010, Sonnappa et al. 2006). Our cohort showed that patients with complicated PPE had mean LOS of 28 (16.5) days. A Polish study by Krenke et al. (2016), which had more patients treated with chest tube drainage and intrapleural fibrinolytic (75%), reported shorter median LOS of 19.5 days (IQR 15-25.5 days) for patients with complicated PPE. However, a recent study by Segerer et al. (2017) showed that initial treatment with intrapleural fibrinolytic therapy or surgical procedure did not result in shorter LOS than initial pleural puncture alone (Segerer et al. 2017). The decision on treatment options also depends on local expertise, facilities e.g. operation theatre time, paediatric intensive care beds and financial resources. Nosocomial pneumonia or hospital-acquired infection may also contribute to prolonged LOS. Precautionary measures to minimise this complication include emphasising on hand hygiene among medical staff and preventive plan to avoid medical equipment contamination. Recent study showed *Staphylococcal epidermidis,* a commensal bacterium of human skin recognised as emerging problem contributing to hospital-acquired infection and antibiotics resistance (Abu Zarrin et al. 2020).

This study provides local data on our experience in managing children with PPE. However, it is limited by the small sample size and retrospective design that makes it lack in standardised treatment protocol, especially in the complicated PPE group.

CONCLUSION

Clinical, biochemical and radiological features could not predict complicated PPE. Use of USG thorax as the main investigation tool for diagnosis and staging should be emphasised. Antibiotics therapy alone is an effective therapy in simple PPE, while for

children with complicated PPE, larger prospective studies are required to investigate which group would benefit significantly from more intensive intervention.

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