Original Article

Burden of respiratory support differs between critically ill children with severe bacterial and viral pneumonia

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Background: We hypothesized that children with viral pneumonia have higher severity of illness and higher mechanical ventilation (MV) requirement than children with bacterial pneumonia. We aim to compare respiratory support requirements of severe viral and bacterial pneumonia cases admitted to the pediatric intensive care unit (PICU).

Methods: This is a retrospective review of patients with microbiologically proven severe viral and bacterial pneumonia admitted to PICU in KK Women's and Children's Hospital, Singapore, from 2010 to 2014. Demographic, clinical and ventilatory data up to 14 days of PICU admission were extracted and analyzed.

Results: Forty-nine and 68 patients had sole viral and bacterial pathogens, respectively. Patients with viral pneumonia were more likely to be <2 years old (51.0% *vs.* 27.9%, P=0.011), to have underlying comorbidities (59.2% *vs.* 35.3%, P=0.010) and had higher pediatric index of mortality 2 (PIM2) score [3.0 (1.1, 8.0) *vs.* 1.6 (0.8, 3.0), P<0.001]. Patients with viral pneumonia were more likely to require alternative modes of MV (48.5% *vs.* 24.5%, P=0.008) and required longer duration of MV [7.0 (4.0, 10.0) *vs.* 4.0 (1.0, 10.8) days, P=0.031]. Oxygenation index (OI) of children with viral pneumonia was higher on day 1 [OI: 11.7 (6.6, 19.3) *vs.* 5.7 (3.7, 10.8), P=0.006] and 3 [OI: 8.0 (6.0, 20.0) *vs.* 5.0 (3.0, 8.0), P<0.001] of PICU admission. Acute respiratory distress syndrome (ARDS) was more common in children with viral pneumonia (22.4% *vs.* 0%, P<0.001).

Conclusions: Children with viral pneumonia were more likely to require alternative modes of MV and longer duration of MV.

Keywords: Airway-release pressure ventilation; pneumonia; viral

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Introduction

Pneumonia is one of the major causes of morbidity and mortality in children (1). Approximately 120 million new cases of community-acquired pneumonia (CAP) are reported each year with 1 million deaths among children aged <5 years (1). CAP is a global problem but it is especially prevalent in South-East Asia and sub-Saharan Africa (2). Severe pneumonia accounts for a significant number of pediatric intensive care unit (PICU) admissions and remains as one of the leading reasons for mechanical ventilation (MV) (3).

Accurate attribution of the causes of pneumonia is vital in estimating burden of disease and implementation

of targeted preventive or treatment strategies for better clinical outcomes in children who require MV. Several adult studies described increased mortality in patients with viral pneumonia, patients with multiple viruses and patients with secondary bacterial pneumonia (4,5). A pediatric study done in our center described a higher rate of acute respiratory distress syndrome (ARDS) in patients with viral pneumonia, attributing the difference to higher risk of direct lung injury hence oxygenation defects caused by viral pathogens (6). The same study also showed a higher rate of MV, and decreased ventilator and PICU free days in patients with co-detection of pathogens compared to those with single organism. Understanding MV requirements of patients with different primary pathogen can aid decision making in ventilation strategies for patients with severe pneumonia in PICU.

We embarked on this study to look at the difference in respiratory support requirement between children with sole viral and bacterial severe pneumonia in the subpopulation of our prior study. We hypothesized that children with viral pneumonia have higher severity of illness and higher MV requirement than children with bacterial pneumonia. The primary aim of this study is to compare respiratory support requirements of severe viral and bacterial pneumonia cases admitted to our PICU.

Methods

This is a retrospective study of all patients (1 month–18 years old) with sole bacterial or viral pneumonia admitted to PICU in KK Women's and Children's Hospital, Singapore, from January 2010 to December 2014. Our hospital is one of two tertiary and teaching pediatric hospitals in Singapore. The PICU is a 16-bedded multidisciplinary facility that admits general medical, oncology, general surgical, neurosurgical and cardiothoracic patients. For this study, approval was obtained from the SingHealth Centralized Institution Review Board (CIRB reference number: 201506-00083).

Patients

A patient list was generated using International Classification of Disease [ICD9CM or ICD10AM (from 2012 onwards)] or the SNOMED Clinical Terminology (SCT) code for a primary or secondary discharge diagnosis of "pneumonia" in patients admitted to the PICU. Only patients with sole viral or bacterial pathogens were included. Electronic and paper clinical records were reviewed to include patients who fulfilled criteria for severe pneumonia. We excluded patients ≤1-month old as lung disease in this group may be due to congenital factors. Patients with mixed infection were also excluded as studies had shown that this group of patients had longer hospital and PICU length of stay and longer duration of MV (4,5,7).

Data collection

Data pertaining to demographic profile, clinical outcomes, complications, microbiological investigations and types of respiratory support were collected from case notes and electronic records. We recorded MV modes and settings on day of diagnosis and every alternate day up to day 14 of PICU admission. MV parameters such as fraction of inspired oxygen (FiO_2), peak inspiratory pressure (PIP), peak end expiratory pressure (PEEP), mean airway pressure (MAP) and tidal volume (TV) were collected at 06:00 hrs every day. The pediatric index of mortality 2 (PIM2) score was calculated on admission to PICU (8).

Definitions

Pneumonias were diagnosed by the presence of both clinical (i.e., febrile illness with lower respiratory tract signs) and radiological evidence. Examples of positive chest X-ray images included alveolar consolidation or pleural effusion (9,10). All radiographs were reported by in-house radiologists. Children with any general danger signs (e.g., desaturation, cyanosis, altered consciousness, convulsions) are classified as having severe pneumonia (11,12). Viral pneumonia was diagnosed by detection of a virus in respiratory fluids (e.g., nasopharyngeal aspirate, endotracheal tube aspirate or bronchoalveolar lavage) by multiplex polymerase chain reaction (PCR). Organisms tested in the multiplex PCR panel were influenza A and B, parainfluenza, respiratory syncytial virus (RSV), metapneumovirus, human coronavirus, adenovirus, *Bordetella pertussis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*. In our center, bacterial pneumonia was diagnosed by culture of bacteria in blood, pleural fluid, endotracheal aspirates or bronchoalveolar lavage fluid (13). Streptococcal pneumonia was also diagnosed if results were positive on latex agglutination of common bacterial antigens in pleural fluid, urine streptococcal antigen or anti-streptolysin O titer (≥1/200) (14). *Mycoplasma pneumoniae* was diagnosed by PCR of respiratory fluids or positive blood

mycoplasma serology (≥1/320) (15). Septic shock and multi-organ dysfunction were defined according to the International Pediatric Sepsis Consensus Conference (16). The definition of pediatric ARDS was based on the Pediatric Acute Lung Injury Consensus Conference (17).

MV in our unit was not protocolized at the time of data collection. In general, the most common mode of conventional MV in our center is pressure-synchronized intermittent mandatory ventilation (P-SIMV). Patients who had increased respiratory demands (i.e., increased work of breathing, hypoxia or hypercarbia) despite conventional MV would require escalation to alternative modes of MV such as airway pressure release ventilation (APRV) and high-frequency oscillatory ventilation (HFOV). Patients ventilated on at least 1 day of APRV or HFOV were considered to require alternative modes of MV. Blood gases were performed on capillary or arterial samples. The primary outcome was requirement for alternative modes of MV. Secondary outcomes were PICU mortality, length of PICU stay, length of hospital stay, changes in FiO_2, PIP, PEEP and MAP.

Statistical analysis

Patients were analyzed in two groups: viral and bacterial pneumonia groups. Categorical data were expressed as counts and percentages whereas continuous data were expressed as median and interquartile ranges (IQRs). Differences between categorical data were analyzed by chi-square tests or Fisher's exact test (when cell sizes were less than 5). Differences between continuous data were analyzed by Mann-Whitney test. We used multivariate logistic regression models to quantify the association between potential confounding factors and requirement for alternative modes of MV. All statistical tests were 2-tailed and P values of <0.050 were considered to be statistically significant. Statistical analysis was carried out using SPSS version 19 (IBM, Armonk, NY, USA).

Results

Two hundred and forty-one patients were admitted to our PICU with the diagnosis of severe pneumonia, of which 117 patients had sole etiological agent identified. Forty-nine (41.9%) and 68 (58.1%) had sole viral and bacterial infections, respectively. In our cohort, the most common viral pathogens were RSV (n=13, 11.1%), influenza A virus (n=9, 7.7%) and adenovirus (n=7, 6.0%). The most common bacterial pathogens were *Streptococcus pneumoniae* (n=36, 30.8%), *Pseudomonas aeruginosa* (n=6, 5.1%) and *Klebsiella pneumoniae* (n=4, 3.4%).

Characteristics and outcomes of patients with viral or bacterial pneumonia were described in *Table 1*. Patients with viral pneumonia were more likely to be <2 years old (51.0% *vs.* 27.9%, P=0.011), to have underlying comorbidities (59.2% *vs.* 35.3%, P=0.010) and had higher PIM2 score [3.0 (1.1, 8.0) *vs.* 1.6 (0.8, 3.0), P<0.001]. Pediatric ARDS was more common in children with viral pneumonia compared to those with bacterial pneumonia (22.4% *vs.* 0%, P<0.001). However, children with bacterial pneumonia were more likely to get complications such as septic shock (27.9% *vs.* 12.2%, P=0.041), necrotising pneumonia (27.9% *vs.* 0%, P<0.001) and pleural effusion (66.2% *vs.* 26.5%, P<0.001) compared to children with viral pneumonia. Children with viral pneumonia required longer length of stay in PICU compared to those with bacterial pneumonia [7.0 (3.0, 11.5) *vs.* 3.0 (1.0, 8.0) days, P=0.018]. Mortality rates of children with severe viral and bacterial pneumonia were not significantly different.

Of all 117 patients, 85 (72.6%) patients required MV during their PICU stay. Forty-five/eighty-five (52.9%) were supported on P-SIMV, 31/85 (36.5%) on APRV and 9/85 (10.6%) on HFOV. Patients with viral pneumonia required longer duration of MV [7.0 (4.0, 10.0) *vs.* 4.0 (1.0, 10.8) days, P=0.031] and were more likely to require alternative modes of MV compared to those with bacterial pneumonia (48.5% *vs.* 24.5%, P=0.008). *Table 2* described the factors affecting the need for alternative MV using a multivariate regression model. The association between the need for alternative modes of MV and viral pneumonia remained significant after adjustment for age [adjusted odds ratio 3.32 (95% CI: 1.33–8.28)].

Figure 1 compared the need for alternative ventilation in the first 14 days of PICU stay. Seventeen (14.5%) patients remained intubated beyond day 14 of PICU stay. Higher percentage of intubated patients with viral pneumonia needed alternative ventilation on day 3 (60.7% *vs.* 34.4%, P=0.041) and day 7 of PICU stay (76.2% *vs.* 29.4%, P=0.004) compared to those with bacterial pneumonia. Among patients on conventional MV, there were no significant differences in ventilator settings (FiO_2, MAP, PIP, PEEP and TV) between viral and bacterial pneumonia in the first 14 days of PICU stay. Oxygenation index (OI) of children with viral pneumonia was significantly higher than that of bacterial pneumonia on day 1 [OI: 11.7 (6.6, 19.3) *vs.* 5.7 (3.7, 10.8), P=0.006] and 3 [OI: 8.0 (6.0, 20.0) *vs.*

Table 1 Characteristics and outcomes of patients

Characteristics and outcomes	Viral pneumonia, n=49	Bacterial pneumonia, n=68	P value
Characteristics			
Age, years	1.5 (0.5, 6.9)	3.4 (1.7, 6.6)	0.154
Age category, n (%)			
<2 years old	25 (51.0)	19 (27.9)	0.011
≥2 years old	24 (49.0)	49 (72.1)	
Weight, kg	10.0 (5.1, 17.5)	13.9 (10.2, 19.7)	0.050
Male gender, n (%)	28 (57.1)	28 (41.2)	0.088
Prematurity, n (%)	11 (22.4)	7 (10.3)	0.072
Comorbidities, n (%)	29 (59.2)	24 (35.3)	0.010
Neuromuscular	10	10	
Cardiovascular	2	2	
Respiratory	6	4	
Gastrointestinal	0	3	
Hematology-oncology	4	0	
Others	7	5	
PIM2 score	3.0 (1.1, 8.0)	1.6 (0.8, 3.0)	<0.001
VATS decortication, n (%)	1 (2.0)	31 (45.6)	<0.001
Outcomes			
ARDS, n (%)	11 (22.4)	0 (0)	<0.001
Septic shock, n (%)	6 (12.2)	19 (27.9)	0.041
Multi-organ dysfunction, n (%)	5 (10.2)	7 (10.3)	1.000
Pleural effusion, n (%)	13 (26.5)	45 (66.2)	<0.001
Air leaks, n (%)	5 (10.2)	12 (17.6)	0.299
Lung abscess, n (%)	0 (0)	4 (5.9)	0.138
Necrotizing pneumonia, n (%)	0 (0)	19 (27.9)	<0.001
Day 1 OI	11.7 (6.6, 19.3)	5.7 (3.7, 10.8)	0.006
Day 3 OI	8.0 (6.0, 20.0)	5.0 (3.0, 8.0)	<0.001
Length of stay in hospital, days	18.0 (11.5, 38.0)	16.0 (10.0, 27.8)	0.203
Length of stay in PICU, days	7.0 (3.0, 11.5)	3.0 (1.0, 8.0)	0.018
Mortality, n (%)	8 (16.3)	7 (10.3)	0.336
Treatment and Respiratory support			
Corticosteroids use, n (%)	21 (42.9)	5 (7.4)	<0.001
Non-invasive ventilation, n (%)*	41 (83.7)	40 (58.8)	0.005
MV, n (%)	34 (69.4)	51 (75.0)	0.502
Maximum MV requirement, n (%)			0.008
P-SIMV	12 (24.5)	33 (48.5)	
Alternative MV (APRV or HFOV)	22 (44.9)	18 (26.5)	
Duration of MV, days	7.0 (4.0, 10.0)	4.0 (1.0, 10.8)	0.031

Continuous variables summarized in medians (IQRs). *, patients who received any form of non-invasive ventilation during their PICU stay. PICU, pediatric intensive care unit; IQRs, interquartile ranges; PIM2, pediatric index of mortality 2; VATS, video-assisted thoracoscopic surgery; ARDS, acute respiratory distress syndrome; OI, oxygenation index; MV, mechanical ventilation; P-SIMV, pressure-synchronized intermittent mandatory ventilation; APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation.

Table 2 Factors affecting the need for alternative MV

Characteristics	Alternative MV, n=40	No alternative MV, n=45	P value
Age, years	2.5 (0.4, 4.8)	3.1 (1.2, 6.2)	0.324
Age category, n (%)			
<2 years old	17 (42.5)	16 (35.6)	0.512
≥2 years old	23 (57.5)	29 (64.4)	
Weight, kg	12.0 (5.2, 18.0)	13.3 (8.7, 18.3)	0.315
Male gender, n (%)	18 (45.0)	23 (51.1)	0.574
Prematurity, n (%)	7 (17.5)	7 (15.6)	0.809
Comorbidities, n (%)	18 (45.0)	20 (44.4)	0.959
Neuromuscular	6	8	
Cardiovascular	1	1	
Respiratory	4	3	
Gastrointestinal	2	1	
Hematology-oncology	0	2	
Others	5	5	
Viral pneumonia, n (%)	22 (55.0)	12 (26.7)	0.008
PIM2 score	3.0 (1.1, 8.2)	2.4 (1.3, 5.9)	0.376
Corticosteroids use, n (%)	13 (32.5)	9 (20.0)	0.189

Alternative ventilation: patients ventilated on at least 1 day of APRV or HFOV. MV, mechanical ventilation; PIM2, pediatric index of mortality 2; APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation.

5.0 (3.0, 8.0), P<0.001] of PICU admission PICU stay. OI between the 2 groups was however not significant from day 5 to 14 of PICU stay.

All our patients were started on empirical antibiotics. The most common types of empirical antibiotics prescribed in our cohort were intravenous penicillin {e.g., ampicillin or Augmentin [68/117 (58.1%)]}, followed by intravenous cephalosporin {e.g., ceftriaxone [34/117 (29.1%)]}. Most of the patients with viral pneumonia received supportive treatment only; 2/13 (15.4%) patients with RSV pneumonia and 6/9 (66.7%) patients with influenza A pneumonia received 10-day course of intravenous ribavirin and 5-day course of oral oseltamivir, respectively. Patients with viral pneumonia were more likely to receive steroids compared to those with bacterial pneumonia (42.9% *vs.* 7.4%, P<0.001).

Discussion

Our study demonstrated that patients with viral pneumonia were more likely to require alternative modes and longer duration of MV. Pediatric ARDS was also more common in children with viral pneumonia. Patients with viral pneumonia required longer length of stay in PICU but there was no significant difference in overall length of stay in hospital. Despite these differences, we did not find any difference in mortality rate between patients with severe viral and bacterial pneumonia in our cohort.

Patients with viral pneumonia were more likely to require alternative modes of MV such as APRV and HFOV around day 3–7 of PICU stay compared to those with bacterial pneumonia. This requirement seemed to mirror the increased OI in patients with viral pneumonia, especially around day 3. One possible explanation of increased OI in viral infection is the increased epithelial sloughing associated with epithelial and interstitial inflammation leading to ventilation-perfusion mismatch, typically seen in children with RSV infection (18). Disruption of the alveolar-capillary barrier also impairs surfactant production via the leakage of plasma proteins into the alveoli, resulting in lung collapse (19). During our study period, escalation to

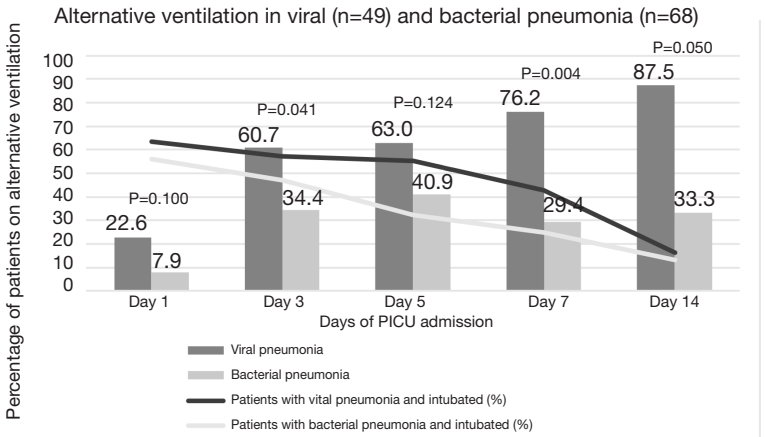

Figure 1 Alternative ventilation in viral and bacterial pneumonia. PICU, pediatric intensive care unit.

APRV was deemed reasonable for patients with ARDS who did not improve with conventional MV as APRV allows spontaneous breathing with higher MAP and prevents collapse of unstable alveoli units. However, a recent RCT was terminated early as the study revealed higher mortality in children with ARDS ventilated on APRV compared to the conventional low TV ventilation (20). HFOV, as a strategy to deliver low TV at high flow rate, is thought to facilitate lung recruitment and prevent lung collapse. Studies have shown that HFOV could safely improve hypercarbia and hypoxia in children with severe ARDS (21,22). The Pediatric Acute Lung Injury Consensus Conference has recommended the use of HFOV in pediatric patients with ARDS when conventional MV fails (23). This knowledge can aid the clinical team to anticipate more severe oxygenation problems in patients with viral pneumonia and consider early escalation to alternative modes of MV.

In our study, patients with viral pneumonia had a more severe clinical course with higher rate of ARDS and greater hypoxemia [day 1 median OI: 11.7 (6.6, 19.3) *vs.* 5.7 (3.7, 10.8), P=0.006]. Similarly, a recent pediatric observational study reported that one-third of children with human metapneumovirus or RSV and respiratory failure developed ARDS (24). A prospective, multicenter, observational study in Spain (n=146) reported that one-fifth of patients with ARDS and requirement of MV in PICU had RSV infection, with reported mortality of approximately 15% (25). Pathologic mechanisms implicated in the development of ARDS caused by respiratory viruses are not completely understood. Reports on molecular pathology of influenza virus and coronavirus infections describe a complex interaction between viral pathogenicity and host immune response leading to endothelial injury, cytokines release and finally a common end pathway of diffuse alveolar damage (26,27). In RSV and influenza A infection, studies have reported that viral load is independently associated with increased risk of respiratory failure and need for MV (28,29). Despite higher incidence of ARDS in the viral pneumonia group, we did not find any difference in mortality rate between patients with viral and bacterial pneumonia.

A more severe clinical course induced by viral pneumonia with higher ventilatory demands, as shown in our study, have several implications. Firstly, identification of viral pathogens could potentially allow clinicians to choose specific ventilator strategies for patients. Secondly, anti-viral treatment should be considered in the management of severe viral pneumonia. In our cohort, only 2/13 (15.4%) patients with RSV pneumonia received a 10-day course of intravenous ribavirin. A meta-analysis of 12 pediatric trials reported shorter days of MV and hospitalization when aerosolized ribavirin was administered to critically ill children who had RSV infection and required MV (30). In contrary to aerosolized ribavirin, there is a paucity of studies on the safety and use of intravenous ribavirin in the pediatric population. A case series of 6 pediatric hematopoietic stem cell transplant recipients who received intravenous ribavirin for RSV infection showed resolution of infection without associated side effects (31). In our center, ribavirin was only available in the intravenous form and its use was limited for immunocompromised patients. Six/nine (66.7%) patients with influenza A pneumonia received a 5 days course of oral oseltamivir. Studies have shown improved survival, shorter days of MV and length of stay in hospital in patients treated

with oseltamivir, especially when initiated in the first 4 days of illness (32,33). Future prospective controlled studies are needed to evaluate the long-term efficacy of anti-viral treatment in the pediatric population.

Besides antiviral medications, clinicians should also be mindful of potential impact of other pharmacological treatments in modulating illness severity and need for MV in children with severe pneumonia. In our institution, all our patients were started on empirical antibiotics. Several studies have shown that empirical antibiotic therapy was associated with lower intensive care unit (ICU) mortality, especially in patients with septic shock and who required MV (34,35). Our study also showed that patients with viral pneumonia were likely to have received corticosteroids compared to those with bacterial pneumonia (42.9% *vs.* 7.4%, P<0.001). A recent meta-analysis (n=528) showed that adjunctive corticosteroids significantly reduced mortality and need for MV in adult patients with severe pneumonia (36).

The main strength of the study is the complete identification of all patients with severe pneumonia who required PICU admission. The list of patients was generated from diagnostic codes as well as via a manual search. Accuracy was enhanced by reviewing clinical and radiological findings from charts. The main limitation of our study is the correct classification of the infective etiologies. Both viral and bacterial microbiological diagnostic tests have their limitations (13-15). As such, we expect certain degree of misclassification in our study. Other limitations include the small retrospective and single-centered nature of the study. In addition, we did not collect data pertaining to socioeconomic status and vaccination status which might affect severity of pneumonia.

In conclusion, our study showed patients with viral and bacterial pneumonia have varying needs for respiratory support. Critically ill children with viral pneumonia were more likely to require alternative modes of ventilation and longer duration of MV. Although the clinical course of severe viral and bacterial pneumonia was different, there was no difference in mortality between the two groups.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. For this study, approval was obtained from the SingHealth Centralized Institution Review Board (CIRB reference number: 201506-00083).

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