

Premorbid Factors and Outcome Associated With Respiratory Virus Infections in a Pediatric Intensive Care Unit

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Summary. Objectives: The purpose of this study was to report the clinical features and outcome of all children with a laboratory proven diagnosis of respiratory virus infection admitted to a university Pediatric Intensive Care Unit (PICU). Methods: Retrospective study between January 2003 and April 2007 was carried out in the PICU. Every child with a laboratory-confirmed viral infection was included. Results: 54 viruses were identified in 49 children (27 M, 22 F) over a 52-month period. The three respiratory virus species, respiratory syncytial virus (RSV) ($n = 17$), influenza ($n = 13$) and parainfluenza ($n = 12$), accounted for 86% of these 49 cases. PICU admissions due to influenza A ($n = 10$) were more common than influenza B ($n = 3$), whereas parainfluenza type 3 ($n = 7$) was the commonest subtype of parainfluenza infection. Comparing these three common viruses, the mean age of children admitted with RSV was lower than with influenza or parainfluenza (1.2 years vs. 5.6 years vs. 2.4 years, $P = 0.003$). Pre-existing conditions such as prematurity and chronic lung disease were only present in children with RSV infection. These respiratory viruses caused both upper (croup) and lower respiratory tract diseases (bronchiolitis, pneumonia). Extrapulmonary presentations were less prevalent and included encephalitis, seizures, cardiac arrest, coexisting diabetes ketoacidosis and acute lymphoblastic leukemia. One patient with RSV and another with influenza A died during their PICU stay. Nearly half of these patients required ventilatory support or received systemic corticosteroids, and 88% received initial broad spectrum antibiotic coverage. Approximately one in five of them had nebulised adrenaline, airway endoscopies or bacterial co-infections. Adenovirus was isolated in four patients and two (both with adenovirus type 3) died during the PICU stay. Conclusions: In PICU, respiratory viral infections were associated with significant morbidity and life-threatening conditions. **Pediatr Pulmonol.** 2008; 43:275–280. © 2008 Wiley-Liss, Inc.

Key words: influenza; parainfluenza; adenovirus; PICU; respiratory syncytial virus; RSV; pediatric intensive care.

INTRODUCTION

Respiratory viral infections cause significant morbidity and misery, affecting millions of children annually worldwide. Although most infections are short-lived and managed by the general practitioners, some children are seriously affected and require hospitalization.^{1–3} These viruses account for a large workload in many of the pediatric departments in regional hospitals and are responsible for upper respiratory infections, croup, bronchiolitis, and pneumonia.^{1–11} Among these hospital admissions, a small percentage of children would require pediatric intensive care unit (PICU) support.^{12–15} In a Brazilian study of 261 children aged less than 7 years with a clinical diagnosis of pneumonia and/or bronchiolitis who were admitted to the PICU, a viral respiratory infection prevalence of 38.7% was found.¹³ 44.6% of bronchiolitis cases had viral infection, with respiratory syncytial virus responsible for more than one-third of cases. One quarter of pneumonia cases had viral infection. The overall case fatality rate was 2.7%, and adenovirus

showed a significantly higher case fatality rate than RSV. Injected antibiotics were often used in these infections. Risk factors such as prematurity, immunodeficiency and

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underlying cardiac disease are often implicated but rarely present. Of the patients who died from respiratory viral infection, only one patient had an underlying cardiac disease. In an Australian study, influenza infection was found to cause significant morbidity and mortality in young children admitted to a PICU, most of whom were not currently recommended for annual influenza vaccination.¹⁴ They reported that half of the children had some form of pre-existing morbidity. The purpose of this study was to report the clinical pattern and outcome of all children with a laboratory proven diagnosis of respiratory virus infection admitted to the PICU of a teaching hospital.

METHODS

A retrospective study was carried out in the tertiary referral PICU. Every child in PICU with a proven virus infection between January 2003 and April 2007 was recruited. Of these viral infections (including those in the serum, CSF and urine that were identified by molecular polymerase chain reaction testing), a subgroup of all respiratory viruses were identified using conventional diagnostic methods, including direct immunofluorescence testing (DIFT) on respiratory samples (e.g., nasopharyngeal aspirates—NPAs; broncho-alveolar lavages—BALs, tracheal aspirates—TAs, and oral swabs), with confirmation and typing by type-specific DIFT and viral culture with neutralization studies. In one case, recent influenza A infection was only identified by testing paired acute and convalescent sera for a greater than fourfold rise in influenza A-specific antibodies (using the complement fixation test). The results of all other (nonviral) bacterial cultures on respiratory specimens (including sputum), blood cultures, hematological and biochemical serial blood tests, and imaging studies were evaluated. Children admitted for respiratory infection in the PICU during the study period who had negative viral studies were also analyzed for comparison. Enteric viruses such as rotavirus or norovirus were not included for analysis. Numerical data were compared with student *t*-test and categorical data with χ^2 -test. All comparisons were made two-tailed, and *P* values less than 0.05 considered statistically significant.

RESULTS

In total, 54 viruses were identified in 49 children (27 M, 22 F) admitted to PICU at the Prince of Wales Hospital in Hong Kong between January 2003 and April 2007 (Fig. 1). Of these, 50 were associated with respiratory infection. Three respiratory viruses: respiratory syncytial virus (RSV, *n* = 17), influenza (*n* = 13) and parainfluenza (*n* = 12), accounted for 86% of these 49 cases, and 7% of 580 PICU admissions. The other viruses isolated were

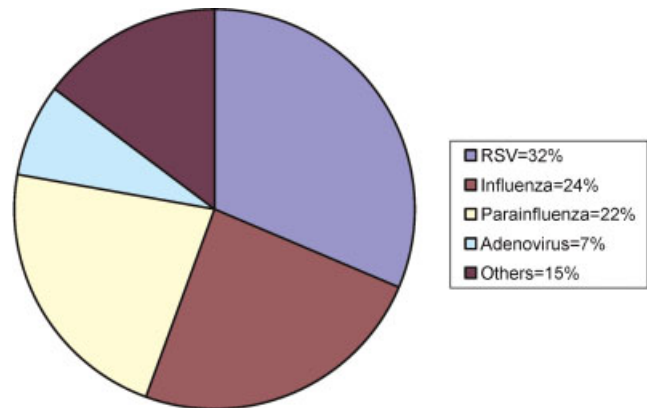


Fig. 1. The distribution of 54 viruses isolated in respiratory or other sample types in 49 patients.

adenovirus (*n* = 4), herpes (herpes simple virus type 1, *n* = 2 in one oral swab and one CSF; human herpes virus type 7, *n* = 1 in one CSF), Epstein–Bar virus (EBV, *n* = 1 in one serum), coxsackie B3 (*n* = 1), and BK virus (*n* = 2 both in urine). Viral co-infections occurred in four patients: one with parainfluenza type 1 and adenovirus (untyped), one with EBV DNA in the serum, HSV 1 in an oral swab and BK virus in the urine, one with human herpes virus 7 (HHV7) DNA in the CSF and BK virus in the urine, and one with enterovirus RNA in a TA and HSV 1 DNA in the CSF.

The focus of the present study was on respiratory viruses. Comparing the three common respiratory viruses (influenza, parainfluenza, RSV), there was no gender difference among these admissions but the mean age of children admitted with RSV was lower than with influenza or parainfluenza (1.2 years vs. 5.6 years vs. 2.4 years, *P* = 0.004) (Table 1). PICU admissions due to influenza A (*n* = 10) were more common than influenza B (*n* = 3), whereas parainfluenza type 3 (*n* = 7) was the commonest subtype of parainfluenza infection. Pre-existing conditions such as prematurity and chronic lung disease were only present in children with RSV infection. Asthma did not appear to be a significant risk factor and occurred only in one patient with influenza A infection. These viruses caused both upper respiratory (croup) and lower respiratory diseases (bronchiolitis, pneumonia). Extrapulmonary presentations such as encephalitis (*n* = 1), seizures (*n* = 6), cardiac arrest (*n* = 1), coexisting diabetes (IDDM or type 1 diabetes) ketoacidosis (*n* = 1) and acute lymphoblastic leukemia (*n* = 1) and septic shock (*n* = 1) also occurred in the presence of these viral infections. The case of acute leukemia was incidentally discovered in the complete blood counts of a 1-year old girl with RSV bronchiolitis. The patients with influenza B infection (*n* = 3) were generally older (2.3, 8, and 11 years, respectively) and all had extrapulmonary symptoms. One patient with RSV and another with influenza A died

TABLE 1—Clinical Data of Patients With Influenza, Parainfluenza and Respiratory Syncytial Virus Infection

Case	Influenza (n = 13)	Parainfluenza (n = 12)	RSV (n = 17)	P
Median (IQR) age (year)	4.8 (1.6–9.1)	1.6 (0.7–3.1)	0.9 (0.1–2.1)	0.012
Male (%)	8 (62)	6 (50)	8 (47)	0.720
Virus	Influenza A = 10, influenza B = 3	Subtype 1 = 4, subtype 2 = 1, subtype 3 = 7		
Laboratory				
Median (IQR) white cell count $\times 10^9/L$	8.8 (5.9–19.0)	8.7 (6.3–10.5)	9.2 (7.8–11.1)	0.343
Median (IQR) C-reactive protein, $\mu g/L$	16.9 (3.6–31.2)	73.8 (17.4–125.5)	27.6 (10.3–90.8)	0.053
C-reactive protein $>10 \mu g/L$	6	9	13	0.168
Abnormal lung fields by chest radiography	3	8	12	0.022
Diagnosis ¹				
Bronchiolitis	0	1	9	0.001
Viral pneumonia	2	5	4	0.311
Croup	5	4	2	0.206
Central nervous system (encephalitis/seizures)	2	3	3	0.814
Miscellaneous	4	1	2	0.252
Relevant risk factors				
Prematurity <36 weeks	0	0	3	0.093
Cleft palate	2	0	1	0.317
Neurodevelopmental condition (mental retardation, cerebral palsy, neuromuscular disease)	2	2	3	0.987
Seizure disorders	1	0	2	0.478
Malignancy	0	1	1	0.596
Chronic lung disease	0	0	3	0.093
Bacterial co-infection	2	3	3	0.776
Treatment				
Ventilation	7	6	7	0.774
Systemic antibiotics	10	11	16	0.320
Systemic corticosteroids	6	8	6	0.248
Airway endoscopies	4	4	1	0.127
Neb adrenaline	3	3	3	0.880
Median (IQR) PICU stay (days)	3 (2–4)	10 (1–12)	3 (2–8)	0.403
Died in PICU	1	0	1	0.640

IQR, interquartile range.

A 7-day course of oseltamivir was used in one patient with croup who was subsequently diagnosed to have parainfluenza subtype 2 and tracheitis with *Staphylococcus aureus* co-infection.

Inotrope (intravenous adrenaline) was given to one patient with influenza A, who presented with cardiac arrest.

Only include risk factors that have occurred ≥ 2 times.

¹Some patients have more than one diagnosis. Bronchiolitis is a clinical diagnosis made in children under 2 years of age with typical presentation of acute onset of lower respiratory symptoms including tachypnea, cough, or expiratory wheezing, and chest radiography showing hyperinflation, interstitial infiltrates, or atelectasis.

during their PICU stay. Nearly half of these 42 patients required ventilatory support or received systemic corticosteroids, and 88% received broad initial antibiotic coverage. Approximately one in five of them had nebulised adrenaline, airway endoscopies (Table 1) or bacterial co-infections (Table 2). We had no documented evidence that any of the children had received influenza vaccination. Chest radiography was important to rule out lung parenchymal involvement, and was often abnormal in parainfluenza and RSV but rarely in influenza infections (Table 1).

Adenovirus was isolated in four patients and two of them (with adenovirus serotype 3) died during the PICU stay (Table 3). A 6-month-old boy had co-infection with both adenovirus (untyped) and parainfluenza type 1. He presented with ileocolic intussusception, colonic perforation, hyponatremic seizure, and pneumonia.

During the study period, there was no metapneumovirus, measles, dengue fever, avian influenza or severe acute respiratory syndrome (SARS)-associated coronavirus isolated in patients admitted to the PICU. In the year 2003, young children with SARS were isolated in a separate ward and none required PICU admission at our hospital.^{16,17}

During the study period, viral investigations were also performed on 134 patients but no virus was found. Data from those children were compared with the 49 children with proven viral diagnosis (Table 4). There was no difference in gender, age, deaths, days of ICU stay, and days of ICU stay before death between the two groups. Bacterial isolates were found in 23 of the 134 children with negative viral isolation, whereas 9 of the 49 patients with viral isolation had positive bacterial isolations (*P* not significant; Tables 2 and 4).

TABLE 2—Bacteria Isolated From Tracheal Aspirates, Sputum, Urine or Blood

Patient	Virus	Underlying condition	Tracheal aspirate (TA)/sputum/urine	Blood culture
Male 5.9 years	Influenza A	Asthma, <i>Pseudomonas aeruginosa</i> UTI recently	Sputum: <i>Enterococcus</i> , <i>S. pneumoniae</i>	Negative
Male 4.8 years	Influenza A	Cleft palate	TA: <i>S. pneumoniae</i>	Negative
Male 1.5 years	Parainfluenza 3	Healthy	TA: <i>H. influenzae</i>	
Female 6.2 years	Parainfluenza 1	Congenital syphilis, global delays, epilepsy	TA: <i>S. pneumoniae</i> , later <i>C. albicans</i>	Negative
Male 8.1 years	Parainfluenza 2	Healthy	TA; <i>S. aureus</i>	Negative
Female 1.1 years	RSV	Recent herpes simplex-1 encephalitis and epilepsy	Urine: <i>E. coli</i>	Negative
Female 0.1 year	RSV	Caesarean section at 34 weeks for maternal fever	TA: <i>Enterococcus</i>	Negative
Male 1.9 years ¹	RSV	Healthy	Nil	<i>P. aeruginosa</i>
Male 9.3 years	Herpes simplex -1	Adrenoleukodystrophy, post bone marrow transplant	Nil	<i>Micrococcus</i>

¹Patient had septic shock and disseminated intravascular coagulopathy and succumbed in PICU 2 days later.

DISCUSSION

Respiratory infections are exceedingly common among children. Most infections are trivial and often present as upper respiratory tract infection with fever, rhinitis, and cough. Occasionally, children are sick enough to be admitted to the general wards for observation and treatment.^{2,3,6} Some children may develop febrile convulsion.⁷ These infections can readily spread among children in daycare centers, schools and within families, resulting in school absence and parental loss of workdays to care for their sick children at home. Severe forms of respiratory viral infections are rare in children but may lead to life-threatening conditions, necessitating PICU admission and resulting in death.

One of the clinical problems facing pediatric intensivists is the differentiation between viral and bacterial infections when an acutely ill child, with or without respiratory manifestations, is admitted. Empirical course of antibiotics were often used in the initial management in order to avoid missing any treatable bacterial co-infections. A low threshold for negative-pressure reverse isolation should be considered whenever possible so that other critically ill patients would not be put at risk. Rapid diagnosis of respiratory viral infections in children is important and it has been shown that prompt diagnosis results in significantly reduced hospital stays, antibiotic

use, and laboratory utilization compared with those of a matched group of patients from the previous year who were diagnosed by virus culture. Woo et al.¹⁸ demonstrate that rapid diagnosis of respiratory infections in children is a cost-effective procedure.

Upper airway obstruction in croup is usually caused by the parainfluenza virus. In our series, however, influenza is more common than parainfluenza in causing croup in the PICU. In lower respiratory disease such as bronchiolitis and pneumonia,¹⁰ radiographic abnormalities are often present, rendering differentiation from bacterial infections and co-infections difficult. We found that parenchymal involvement as evidenced by abnormal radiography is more common with RSV than influenza infection. As it is often difficult to delineate viral from bacterial infection in the acute setting, broad-spectrum antibiotics were used in nearly 90% of the study patients to cover for pneumonia and sepsis. Our findings were in agreement with those reported by other investigators.^{19,20} Antibiotics were often discontinued when positive viral studies and negative bacterial cultures were subsequently obtained and the patients became more stable.

The mortality potentially attributable to the four respiratory viruses (RSV, influenza, parainfluenza, and adenovirus) was 8% during PICU stay. Adenovirus was notorious in its preponderance in causing severe diseases like encephalitis, bronchiolitis obliterans, and myocarditis.

TABLE 3—Adenovirus Infection

Patient	Diagnosis	Underlying condition	Outcome
Female 5.6 years	Status epilepticus	Inactive seizure disorder	PICU for 1 day
Male 4.5 years	Pneumonia, pleural effusion, left lower lobe abscess, lobectomy left lower lobe	Asthma for 2 years	Ventilated. Died in PICU 5 days later
Female 9.7 years	Encephalitis	Chronic myeloid leukemia, post bone marrow transplant	Ventilated. Died on day of PICU admission
Male 6 months	Ileocolic intussusception and colonic perforation, hyponatremic seizure and pneumonia	Healthy	Ventilated. PICU for 12 days, then general ward Co-infection with parainfluenza type 1

TABLE 4—Comparing Patients With Negative Viral Isolation (n = 134) With the 49 Patients With Positive Viral Isolation During the Same Study Period

	Negative viral isolation (n = 134)	Positive viral isolation (n = 49)	P
Median (IQR) age in years	2.4 (0.8–5.4)	2 (0.6–5.3)	0.58
Male (%)	84 (63)	27 (55)	0.45
Positive bacterial isolations tracheal aspirate/sputum, blood or urine cultures for bacteriology	23	9	0.98
Median (IQR) PICU stay (days)	3 (2–6) ¹	3 (2–9)	0.57
Median (IQR) PICU days before death	4 (2–12)	1 (0–4)	0.14
Died in PICU	13	4	1.00

IQR, interquartile range.

The common respiratory diagnoses in the negative-isolation group were: pneumonia (n = 25), asthma (n = 13), croup (n = 6), bronchiolitis (n = 4) whereas the common diagnoses in the positive isolation group were pneumonia (n = 11), croup (n = 11) and bronchiolitis (n = 10).

¹One patient is still in the PICU and has been excluded for calculation.

Two of the four patients with adenovirus died during their PICU stay. Three of the patients had the serotype 3 which is known to be able to cause severe respiratory infection.^{21–24} Bacterial co-infections were present in 9 of the 49 patients (18%) and included various Gram positive and Gram negative bacteria cultured in the tracheal aspirate, urine, or blood (Table 2). The most common organism was *Streptococcus pneumoniae* (n = 3). Extrapulmonary manifestations of viral infection are important cause of morbidity and range from seizures to cardiac arrest.

Age is an important demographic factor. Among the three respiratory viruses, RSV infections particularly can cause significant morbidity and mortality in young children. Chronic lung disease and prematurity have been found to be associated with infection with the RSV virus.^{25–28} In our series, the mean age of children infected with influenza (A and B) and RSV was 5.3 years and 1.2 years respectively.

Most of the children in Hong Kong are not currently receiving annual influenza vaccination, and we have no documented evidence that any of the studied patients had received influenza vaccination. The use of influenza vaccine in high-risk children could prevent hospitalizations and cases of influenza-related diseases.^{11,14} Monthly intramuscular injection of Palivizumab has been advocated in patients vulnerable to RSV infections.^{5,29,30} None of our patients had received Palivizumab or influenza vaccination for prevention. Universal influenza vaccination of children older than 6 months of age may help prevent infection by influenza but is not currently routine practice in Hong Kong. Starting in 2007, selective immunization will be offered to children with chronic respiratory and cardiac diseases. The status of Palivizumab prophylaxis in at-risk infants in Hong Kong is still unclear. As influenza vaccination and Palivizumab prophylaxis were not offered to children in Hong Kong at the time of the study, the results of the present study might not be generalizable.

During the study period, nearly one-third of children and infants admitted to our PICU were screened for viral infections as indicated by suspicion of an underlying viral etiology. Of the screened patients, more than one-quarter were positive for a respiratory virus. The yield was comparable with studies reported in other centres.^{13–14} Similar to the Australian study, pre-existing morbidity was present in some of our patients with respiratory virus infection.¹⁴ Our data are also in agreement with the Brazilian findings that adenovirus infection with resultant ICU admission carries a higher mortality than with other respiratory virus infection. Serotypes 3, 4, and 7 are the most common causes of lower respiratory tract disease in children. Fatal cases of adenovirus and pneumonia can occur even in previously healthy young infants.^{13,21–24} In RSV infection, it was reported that higher mortality and greater severity with prolonged symptoms occur in infants and children with underlying cardiopulmonary disease, prematurity, and immunocompromised state.^{1–6,25–30} Parainfluenza virus (types 1 and 2) is often associated with laryngotracheobronchitis and croup than with pneumonia (usually type 3). PICU admissions with parainfluenza virus occur as frequently as those with influenza infections in our locality, and bacterial co-infections and super-infections can be present in any of these infections.

In summary, respiratory viral infections leading to PICU admissions may be associated with significant morbidity and mortality. Presentation can be pulmonary and extrapulmonary. Prompt diagnosis will ensure that the appropriate treatment (such as corticosteroid for croup) can be instituted as soon as possible. Vaccination of the high risk groups may help preventing infection and ICU admission.

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