

Influenza and Parainfluenza Associated Pediatric ICU Morbidity

Kam Lun Hon · Ting Fan Leung · Kam Lau Cheung ·
Pak Cheung Ng · Paul Kay Sheung Chan

Received: 16 March 2010 / Accepted: 17 June 2010 / Published online: 30 September 2010
© Dr. K C Chaudhuri Foundation 2010

Abstract

Objectives To investigate if morbidity in young children admitted to a pediatric intensive care unit (PICU with a laboratory proven diagnosis of influenza and parainfluenza infection) had increased.

Methods Retrospective study from January 2003 through December 2009 was carried out. Every child in the PICU with a laboratory-confirmed influenza or parainfluenza infection was included.

Results 18 influenza (influenza A=13 and influenza B=5) and 17 parainfluenza admissions were identified over the 7-year period. Parainfluenza type 3 ($n=9$) was the commonest subtype of parainfluenza infection. The median age of children admitted with influenza was higher than parainfluenza (4.5 vs 1.7 years, $p=0.044$). Admissions associated with proven influenza and parainfluenza infections accounted for 2% of PICU annual admissions. There was only one death in 2003. 51% of these patients required ventilatory support, 45% received systemic corticosteroids, and 91% received initial broad spectrum antibiotic coverage. Bacterial co-infections were identified in 25% of these patients. The incidence of influenza admissions had not

increased significantly in 2009 (H1N1 pandemic) when compared with 2003 (SARS epidemic) ($p=0.3$). There were only two PICU cases of pandemic H1N1 in 2009 and both survived. The annual incidence of severe PICU cases of influenza and parainfluenza were 0.94 and 0.88 per 100,000 children per annum, respectively.

Conclusions Pandemic H1N1, influenza and parainfluenza viruses may be associated with significant childhood morbidity and PICU admissions.

Keywords Influenza · Parainfluenza · PICU · H1N1 · Pediatric intensive care

Introduction

Respiratory viral infections cause significant morbidity and misery, affecting millions of children annually worldwide. Although most infections are self-limiting and managed by the general practitioners, some children are seriously affected and require hospitalization [1–4]. 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 [1–12]. Among these hospital admissions, a small percentage of children would require pediatric intensive care unit (PICU) support [13–17]. In 2003, there was extremely heightened awareness and surveillance of respiratory viral infections due to the epidemic of severe acute respiratory syndrome caused by a novel corona virus (SARS-CoV) [4, 18–20]. Heightened surveillance and stricter personal hygiene could result in a lowered interpersonal spread of all respiratory viruses. Nevertheless, there has been a global concern for an influenza pandemic that might result in dramatic increase

K. L. Hon (✉) · T. F. Leung · K. L. Cheung · P. C. Ng
Department of Pediatrics,
The Chinese University of Hong Kong, Prince of Wales Hospital,
6/F, Clinical Science Building,
Shatin, Hong Kong SAR, China
e-mail: ehon@hotmail.com

K. L. Hon
e-mail: ehon@cuhk.edu.hk

P. K. S. Chan
Department of Microbiology, Faculty of Medicine,
The Chinese University of Hong Kong, Prince of Wales Hospital,
Shatin, NT, Hong Kong SAR, China

in mortality and morbidity in recent years. Such a real and present concern is witnessed in 2009 with the pandemic H1N1. The purpose of this study was to investigate if morbidity in young children admitted to a pediatric intensive care unit (PICU) with a laboratory-proven diagnosis of influenza or parainfluenza infection had increased, and if the pandemic H1N1 in 2009 had resulted in a higher morbidity.

Material and Methods

Hong Kong, with a population of over seven million people, has a dual public and private system for both primary and secondary health care. Although there are ten government (Hospital Authority [HA]) and ten private hospitals providing general pediatric inpatient service, the HA system provides the majority of inpatient trauma care. The Prince of Wales Hospital (PWH) is a university teaching hospital situated in the Eastern part of the New Territories in Hong Kong. PWH provides tertiary pediatric intensive care unit (PICU) service for children <12 years of age to this region with a catchment population of over 1.1 million (approximately 25% were children <12 years of age). The criteria for PICU admissions include cardiopulmonary insufficiency/failure, neurological deterioration, and concerns of emergency care and/or general pediatric staff. Cases were identified from the hospital's computerized auditing system and from the PICU database of every admission to the unit. The PICU database was audited monthly. This retrospective study was carried out in the tertiary referral PICU. Every child in PICU with a proven influenza and parainfluenza virus infection from January 2003 through December 2009 was recruited. The respiratory viruses were identified using conventional diagnostic methods, including direct immunofluorescence testing (DIFT) on respiratory samples (e.g. nasopharyngeal aspirates–NPAs; bronchoalveolar lavages–BALs, tracheal aspirates–TAs, and oral swabs), with confirmation and typing by type-specific DIFT

and viral culture. In one case, a recent influenza A infection was confirmed by demonstrating a greater than four-fold rise in influenza A-specific antibodies using the complement fixation test. The results of all other (non-viral) bacterial cultures on respiratory specimens (including sputum) and blood cultures were evaluated. 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

A total of 18 influenza (influenza A=13 and influenza B=5) and 17 parainfluenza admissions were identified over the 7-year period (Tables 1 and 2). Parainfluenza type 3 (*n*=9) was the commonest subtype of parainfluenza infection. The median age of children admitted with influenza was higher than parainfluenza (4.5 vs >1.7 years, *p*=0.044). There was no significant gender predilection in the two categories. Admissions associated with proven influenza and parainfluenza infections accounted for 2% of PICU annual admissions. There was only one death associated with influenza A in 2003. The duration of ICU stay was generally brief (median 3 days). Influenza affected older children than parainfluenza but there was no difference between the two groups of viruses in terms of morbidity. These respiratory viruses caused both upper (croup) and lower respiratory tract diseases (bronchiolitis, pneumonia). Extrapulmonary presentations such as seizures and encephalitis were less prevalent. 51% of these patients required ventilatory support, 45% received systemic corticosteroids for airway obstruction such as croup, and 91% received initial broad spectrum antibiotic coverage pending cultures. Bacterial co-infections were identified in 25% of these patients. The incidence of influenza PICU admissions had not increased significantly in 2009 (H1N1 pandemic) when compared with 2003 (SARS epidemic) (Table 2, Fig. 1; *p*=0.3). Using the catchment population of over 1.1 million (approximately

Table 1 Clinical data of patients with influenza and parainfluenza virus infection

Case	Influenza (<i>n</i> =18)	Parainfluenza (<i>n</i> =17)	<i>p</i>
Median age (yr)	4.5	1.7	0.044
Male (%)	10	8	0.44
Bacterial Co-infection	6	3	0.25
Ventilation	10	8	0.37
Systemic antibiotics	16	16	0.40
Systemic corticosteroids	7	9	0.19
Median (IQR) PICU stay (days)	3.0	3.0	0.35
Died in PICU	1	0	0.51

Table 2 PICU admissions associated with proven influenza and parainfluenza infections as a percentage of the annual PICU admissions

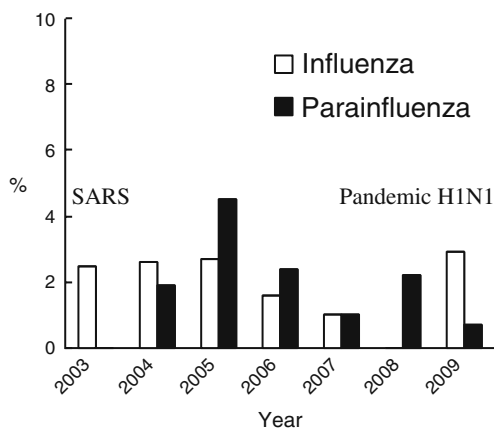
PICU admissions	Total	Influenza A + B (%)	Parainfluenza (%)	Mortality
2003	122	3+0 (2.5)	0 (0)	1
2004	155	3+1 (2.6)	3 (1.9)	0
2005	111	2+1 (2.7)	5 (4.5)	0
2006	127	2+0 (1.6)	3 (2.4)	0
2007	144	0+2 (1.0)	2 (1.0)	0
2008	138	0+0 (0)	3 (2.2)	0
2009	140	3+1 (2.9)	1 (0.7)	0
Total	937	18 (1.9)	17 (1.8)	1

25% were children <12 years of age), the annual incidence of severe PICU cases of influenza and parainfluenza were 0.94 and 0.88 per 100,000 children per annum, respectively.

From April to December 2009, 2,519 patients under 12 years of age were tested for the pandemic H1N1 influenza A, and 553 (56% males) were laboratory-confirmed to be infected with the virus. Of these 553 patients, 58 were <1 year, 93 were between 1 and 2 years, 144 were between 3 and 5 years of age, and 258 were between 6 and 12 years. Only two cases required PICU admission and both survived. A 10-yr-old boy from a special residential school was transferred from a regional hospital to the PICU with septic shock, acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulopathy. He was a mentally retarded abandoned child. His roommate was also hospitalized with confirmed pandemic H1N1 infection. The boy presented with fever, chills and rigors but no apparent coughs or running nose. His past history also included bilateral sensori-neural hearing impairment, epilepsy (on valproate and clobazem), urinary tract infections, left pelvi-ureteric junction obstruction, orchidopexy, left pyeloplasty, chronic hepatitis B carrier state, iron deficiency anemia, and chronic renal failure.

The child was intubated and ventilated (FiO₂ up to 0.65 for 24 days). Hypotension was treated with saline boluses, dopamine (up to 20 mcg/kg/min) and norepinephrine (up to 0.1 mcg/kg/min) infusions. Tracheal aspirate yielded heavy growth of burkholderia cepacia (sensitive to ceftazidime). The child was treated with intravenous cefotaxime and cloxacillin initially, and vancomycin and ceftazidime subsequently. He gradually recovered from the septic episode and inotropes and ventilation were weaned off (total PICU stay 25 days).

An 8-yr-old previously healthy girl was admitted via the emergency department to the PICU with generalized purpura and thrombocytopenia (lowest platelet count of $3 \times 10^9/L$) despite repeated platelet transfusions (Fig. 2). The presumptive diagnosis was meningococemia and intravenous cefotaxime was given. Shortly after admission, however, nasopharyngeal aspirate came back positive for pandemic H1N1 virus. The child was transferred to an isolation ward for further monitoring and management. She remained well. A 5-day course of oseltamivir was given. The thrombocytopenia was also treated with a dose of intravenous immunoglobulin. Blood culture was positive for *Streptococcus pyogenes* sensitive to penicillin. Hence, this is a case of co-infection with H1N1 and *Streptococcus pyogenes*.

**Fig. 1** Influenza and parainfluenza PICU admissions

Discussion

Infections by the “flu viruses” are exceedingly common among children [4]. In recent years, there have been global concerns that the next influenza pandemic might result in increased mortality and morbidity. Flu 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 [4, 17]. Despite massive global and



Fig. 2 A child with alarming thrombocytopenic purpura, co-infection with pandemic H1N1 and *streptococcus pyogenes*

media concerns in their locality, the authors have not witnessed a significant increase in mortality or severe PICU morbidity in recent years. Even with the 2009 H1N1 pandemic, only two children with the H1N1 were admitted and there was no mortality. Similar phenomenon was observed in other PICUs in Hong Kong. There was no redirection of known H1N1 cases to other units and underestimation of the incidence was unlikely.

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 [4, 17]. As previously described, these respiratory viruses caused both upper (croup) and lower respiratory tract diseases (bronchiolitis, pneumonia). Extrapulmonary presentations were less prevalent. Empirical course of antibiotics was often used in the initial management in order to avoid missing any treatable bacterial co-infections [17]. Corticosteroids were often used empirically for airway obstruction such as croup. 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. These principals are well illustrated in the two H1N1 cases

in 2009. The first case demonstrated that institutionalized children with chronic illnesses are at high risk whereas the second case demonstrated previously well children are not spared. The clinical course was complicated by heavy growth of *burkholderia cepacia* in the tracheal aspirate. The second case was initially treated as presumed meningococemia but was promptly confirmed to be a case of H1N1. The antibiotic was rightly continued as subsequent blood culture confirmed septicemia with *S. pyogenes* co-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. The present findings were in agreement with those reported by other investigators [21, 22].

The use of influenza vaccine could prevent hospitalizations and cases of influenza-related diseases [12, 15]. Universal influenza vaccination of children older than 6 months of age has become available in Hong Kong since 2008. Starting in December 2009, vaccination for the pandemic H1N1 has also become available. It remains the doctors' responsibility to explain to the parents that adverse and side effect profiles of these vaccines are generally acceptable.

This study also illustrates the important fact that the parainfluenza viruses cause an equal magnitude of PICU morbidity. In contrast to the influenza viruses, the parainfluenza viruses affect younger children. Worse still, there is no vaccine available and the antiviral agents for influenza are generally not efficacious for the parainfluenza viruses. Respiratory syncytial virus (RSV) infection is also an important cause of PICU admissions that we previously described [17]. Clinical presentation and management in the PICU is similar except that the virus affects infants and younger children.

Since the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic, definitions, terminologies and abbreviations proliferate in Hong Kong to describe infections associated with respiratory viruses, such as ILI for influenza-like illness, "ARDS" for acute respiratory diseases, URTI for upper respiratory tract illness, HSI for human swine influenza, and nH1N1 for novel H1N1. In essence, all these viral infections are characterized by a contact history + fever + respiratory symptoms. The clinical definitions are very similar to that for SARS [20]. These definitions serve no good purposes and possibly confuse the public. They should not be confused with the influenza and the parainfluenza infections.

In conclusion, pandemic H1N1, influenza and parainfluenza viruses may be associated with significant childhood morbidity and PICU admissions. Further investigations are required to explore if vaccination may help prevent influenza infection and ICU admissions.

References

1. Sung RY, Chan RC, Tam JS, Cheng AF, Murray HG. Epidemiology and aetiology of acute bronchiolitis in Hong Kong infants. *Epidemiol Infect.* 1992;108:147–54.
2. Hon KL, Nelson EA. Gender disparity in paediatric hospital admissions. *Ann Acad Med Singap.* 2006;35:882–8.
3. Nelson EAS, Tam JS, Yu LM, Li AM, Chan PKS, Sung RYT. Assessing disease burden of respiratory disorders in Hong Kong children with hospital discharge data and linked laboratory data. *Hong Kong Med J.* 2007;13:114–21.
4. Hon KL, Leung AK. Severe childhood respiratory viral infections. *Adv Pediatr.* 2009;56:47–73.
5. O’Kelly EA, Hillary IB. Epidemiology of respiratory syncytial virus infection among infants over three winter seasons. *Irish J Med Sci.* 1991;160:12–6.
6. Kristensen K, Dahm T, Frederiksen PS, et al. Epidemiology of respiratory syncytial virus infection requiring hospitalization in East Denmark. *Pediatr Infect Dis J.* 1998;17:996–1000.
7. Chan PK, Sung RY, Fung KS, et al. Epidemiology of respiratory syncytial virus infection among paediatric patients in Hong Kong: seasonality and disease impact. *Epidemiol Infect.* 1999;123:257–62.
8. Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. *Pediatrics.* 2001;108:E63.
9. Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. *New Engl J Med.* 2002;347:2097–103.
10. Nicholson KG, McNally T, Silverman M, Simons P, Zambon MC. Influenza-related hospitalizations among young children in Leicestershire. *Pediatr Infect Dis J.* 2003;22:S228–30.
11. van Woensel JB, van Aalderen WM, Kimpen JL. Viral lower respiratory tract infection in infants and young children. *BMJ.* 2003;327:36–40.
12. Rojo JC, Ruiz-Contreras J, Fernandez MB, Marin MA, Folgueira L. Influenza-related hospitalizations in children younger than three years of age. *Pediatr Infect Dis J.* 2006;25:596–601.
13. Keren R, Zaoutis TE, Saddlemire S, Luan XQ, Coffin SE. Direct medical cost of influenza-related hospitalizations in children. *Pediatrics.* 2006;118:e1321–7.
14. Straliootto SM, Siqueira MM, Machado V, Maia TM. Respiratory viruses in the pediatric intensive care unit: prevalence and clinical aspects. *Mem Inst Oswaldo Cruz.* 2004;99:883–7.
15. Milne BG, Williams S, May ML, Kesson AM, Gillis J, Burgess MA. Influenza A associated morbidity and mortality in a Paediatric Intensive Care Unit. *Commun Dis Intell.* 2004;28:504–9.
16. Richard N, Hackme C, Stamm D, Floret D. Influenza in pediatric intensive care unit [French]. *Arch Pediatr.* 2004;11:879–84.
17. Hon KL, Hung E, Tang J, et al. Premorbid factors and outcome associated with respiratory virus infections in a pediatric intensive care unit. *Pediatr Pulmonol.* 2008;43:275–80.
18. Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet.* 2003;361:1701–3.
19. Hon KL, Li AM, Cheng FW, Leung TF, Ng PC. Personal view of SARS: confusing definition, confusing diagnoses. *Lancet.* 2003;361:1984–5.
20. Hon KL. Just like SARS. *Pediatr Pulmonol.* 2009;44:1048–9.
21. van Woensel JB, von Rosenstiel IA, Kimpen JL, Spanjaard L, van Aalderen WM. Antibiotic use in pediatric intensive care patients with lower respiratory tract infection due to respiratory syncytial virus. *Intens Care Med.* 2001;27:1436.
22. Bloomfield P, Dalton D, Karleka A, Kesson A, Duncan G, Isaacs D. Bacteraemia and antibiotic use in respiratory syncytial virus infections. *Arch Dis Child.* 2004;89:363–7.