RISK FACTORS FOR HOSPITALIZATION AMONG CHILDREN WITH INFLUENZA B INFECTION

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Abstract. Data regarding risk factors for hospitalization among children with influenza B infection are limited. We conducted a retrospective study of 184 children with influenza B infection during October 2011- September 2012 seen at Bamrasnaradura Infectious Diseases Institute, Thailand; clinical and laboratory data were compared between hospitalized and outpatient children. The numbers of hospitalized and outpatient children were 65 (35%) and 119 (65%), respectively. Most children (>80%) were aged ≥5 years. The median time from onset of symptoms to starting oseltamivir treatment was significantly longer among hospitalized than outpatient children (3 days *vs* 2 days, $p<0.05$). The significantly more hospitalized children received antibiotics than outpatient children (43% *vs* 7%, $p<0.05$). Complications were more common among hospitalized children than outpatient children (37% *vs* 2%, $p<0.05$). Pneumonia and rhinosinusitis were significantly more common among hospitalized children than outpatient children ($p<0.05$). Direct contact history, history of receiving an influenza vaccine, history of a previous influenza infection, body temperature, respiratory symptoms, gastrointestinal symptoms, headache and laboratory findings were not significantly different between the two groups ($p>0.05$). In conclusion, delay initiation of antiviral therapy and medical complications (pneumonia and rhinosinusitis) were more common among hospitalized children with influenza B than outpatient children with influenza B in the studied population.

Keywords: influenza B, hospitalization, children, Thailand

INTRODUCTION

Influenza is a major cause of morbidity and mortality among both adults and children (CDC, 2011). Most influenza infections are self-limited, but severe disease may occur, especially in children who may require hospitalization (WHO, 2004; Buchholz *et al*, 2010; Adamson *et al*, 2011). Three types of seasonal influenza have been described: influenza A, B and C *(*CDC, 2012a*)*. Influenza C occurs much less frequently than A and B (CDC, 2012a). Only influenza A and B viruses are included in seasonal influenza vaccines (WHO, 2004). Influenza virus can spread easily from country to country. Influenza A is usually the most common type but there has been an increase in the proportion of influenza B, which may be less patho-

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genic among adults, causing only mild respiratory infections (Kim *et al*, 2009; Aebi *et al*, 2010). Pneumonia, meningitis, encephalitis and febrile convulsions are all complications that occur among children with influenza (Tran *et al*, 2012). Severe illness and poor prognosis have been associated with bacterial co-infection, delayed treatment, co-infection, pregnancy and disease-related complications (Kim *et al*, 2009; Aebi *et al*, 2010; Christopher *et al*, 2013). Bacterial and viral co-infections are more common among patients with severe disease (Christopher *et al*, 2013).

A previous study of children hospitalized with influenza found 54% had underlying medical conditions, while among adults, 84% had underlying medical conditions such as cardiovascular disease, metabolic disorders, obesity and chronic lung disease, especially in patients aged greater than 45 years (Peralta *et al*, 2010; CDC, 2013a; Kusznierz *et al*, 2013).

To date, data regarding the clinical characteristics and treatment outcomes of children hospitalized with influenza B infection have mostly been about complications, such as pneumonia. Previous studies have found pneumonia in 2-20% (Peltola *et al*, 2003; Lahti *et al*, 2006; Liu *et al*, 2013). Administration of oseltamivir within 48 hours of the onset of flulike symptoms is recommended for children at high risk for influenza complications in order to reduce morbidity and mortality (Garg *et al*, 2012). However, information regarding the outcomes of children hospitalized with influenza B has rarely been reported in Thailand. Therefore, an objective of this study was to identify risk factors and outcomes among children admitted to hospital with influenza B infection at Bamrasnaradura Infectious Diseases Institute, Thailand.

MATERIALS AND METHODS

Study design

This retrospective study was conducted among children aged ≤15 years with influenza B infection at Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Thailand. The charts of all the children with confirmed influenza B infection seen between October 2011 and September 2012 were reviewed. Patients lost to follow-up or who could not be contacted by telephone were excluded. Subjects were divided into two groups: hospitalized and outpatient children. The history, physical examination, laboratory results, diagnoses and treatment were recorded. All patients were followed up until the infection was resolved.

Direct contact history was defined as direct contact with an influenza-infected person in their household or school within the previous 7 days. Pneumonia was defined clinically as having a cough or tachypnea and dyspnea or chest retractions (Thomas and Theodore, 2011). A central nervous system complication was defined as a deterioration in consciousness, seizures or encephalitis for which same other etiology could not be determined (Studahl, 2003). A complication was defined as developing pneumonia, diarrhea or seizures for which some other etiology could not be determined.

Laboratory testing

Influenza B infection was diagnosed with the Quidel QuickVue® Influenza A+B test (QuickVue, San Diego, CA). A complete blood count was obtained on all subjects.

Risk factors for hospitalization

Risk factors for hospitalization were obtained from the history, laboratory findings and outcomes.

Statistic methods

The sample size was calculated by a proportion formula assuming the percentage of hospitalization due to influenza was 24% (Chan *et al*, 2013) and the minimum sample size for hospitalized patients was determined to be 70.

All continuous data were compared with the Mann-Whitney *U* test and categorical data were compared with the chi-square test. A p-value < 0.05 was considered statistically significant.

This study was approved by ethics committee for research on human subjects of the Department of Diseases Control, Ministry of Public Health and by the institutional review board.

RESULTS

From October 2011 to September 2012, 253 children were diagnosed as having infected with influenza B infection at our institution. Sixty-nine cases (27.3%) were excluded from the study because they were either lost to follow-up or could not be contacted by telephone. One hundred eighty-four subjects were included in the study. Of these, 65 (35.3%) were hospitalized children and 119 (64.7%) were treated as outpatients (Fig 1). None of the patients were admitted to the ICU or died.

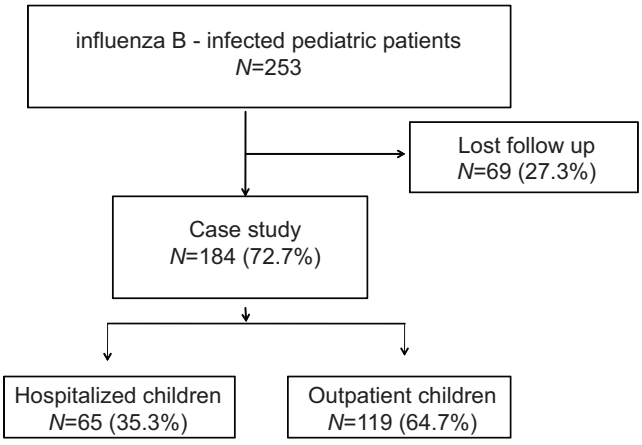

Fig 1–Schematic of study subjects.

The demographics of the hospitalized and outpatient children were not different from each other (p>0.05) (Table 1). More than 80% of the subjects in both groups were aged ≥5 years.

The baseline clinical characteristics of the patients are shown in Table 2. The median times from onset of symptoms to starting oseltamivir treatment in hospitalized and outpatient children were 3 and 2 days, respectively. Starting oseltamivir treatment among hospitalized children took significantly longer than among outpatient children. Direct contact history, prior history of receiving a seasonal influenza vaccine, prior history of having an influenza infection, body temperature, respiratory symptoms, gastrointestinal symptoms and headache were not significantly different between hospitalized and outpatient children (p>0.05). The clinical outcomes of the children are shown in Table 3. The duration between the onset of oseltamivir treatment until the fever subsided was not significantly different between hospitalized and outpatient children (p>0.05).

Complications were significantly more common among hospitalized than outpatient children (p>0.05). Pneumonia and rhinosinusitis were significantly more common among hospitalized than outpatient children p>0.05. The frequencies of diarrhea and febrile convulsions were not significantly different between hospitalized and outpatient children (p>0.05).

Of the 184 subjects, 28 hospitalized children (43.1%) and 8 outpatient children (6.7%) received antibiotics. Proportion of

Table 1
Demographics and characteristics of study subjects.

	Hospitalized children *N*=65	Outpatient children *N*=119	*p*-value
Age (years)			
<5	10 (15.4%)	20 (16.8%)	> 0.05
≥5	55 (84.6%)	99 (83.2%)	
Sex			
Male	36 (55.4%)	59 (49.6%)	> 0.05
Female	29 (44.6%)	60 (50.4%)	
Body weight (kilograms)	28.7±14.2	30.8±16.2	> 0.05

Table 2
Baseline clinical characteristics of study subjects.

Baseline clinical characteristic	Hospitalized children *N*=65	Outpatient children *N*=119	*p*-value
Direct contact history	12 (18.5%)	17 (14.3%)	> 0.05
History of receiving influenza vaccine within previous year	1 (1.5%)	5 (4.2%)	> 0.05
History of influenza infection	4 (6.2%)	8 (6.7%)	> 0.05
Time from onset of symptoms to initiating oseltamivir treatment in days, median (range)	3 (1-14)	2 (1-7)	< 0.05
Body temperature in ºC	38.23±1.09	38.27±0.86	> 0.05
Respiratory symptoms	64 (98.5%)	115 (96.6%)	> 0.05
Gastrointestinal symptoms	21 (32.3%)	32 (26.9%)	> 0.05
Headache	21 (32.3%)	39 (32.8%)	> 0.05

hospitalized children who received antibiotics was significantly greater than the proportion of outpatient children (p>0.05).

The laboratory findings are shown in Table 4. White blood cell counts, hematocrit levels , percent neutrophils and platelet counts did not differ significantly between hospitalized and outpatient children (p>0.05).

Risk factors associated with hospitalization in children with influenza B are shown in Tables 1-4. Our data suggest a delayed diagnosis, delayed initiation of antiviral therapy and medical complications (pneumonia and rhinosinusitis) were associated with hospitalization.

DISCUSSION

The majority of children in this study were aged ≥ 5 years. Children this age typically have the highest attack rates

Table 3
Clinical outcomes of study subjects.

Clinical outcomes	Hospitalized children *N*=65	Outpatient children *N*=119	*p*-value
Duration of hospitalization in days, median (range)	4 (2-8)	NA	NA
Duration from onset of oseltamivir treatment until fever subsided in days, median (range)	2 (1-6)	2 (1-7)	> 0.05
Concurrent antibiotic treatment	28 (43.1%)	8 (6.7%)	< 0.05
Complications	24 (36.9%)	2 (1.7%)	< 0.05
Pneumonia	18 (27.7%)	0	< 0.05
Diarrhea	2 (3.1%)	2 (1.7%)	> 0.05
Rhinosinusitis	4 (6.2%)	0	< 0.05
Febrile convulsions	2 (3.1%)	0	> 0.05

NA, not analyzed.

Table 4
Laboratory results among study subjects.

Laboratory results	Hospitalized children *N*=64	Outpatient children *N*=34	*p*-value
Complete blood counts			
WBC x10^3 in cells/ l, median (range)	5.4 (1.1-12.5)	5.2 (3.1 -10.7)	> 0.05
Hematocrit in mg%, median (range)	37.0 (26-51)	36.5 (30-43)	> 0.05
Neutrophil count in cells/ l, median (range)	3,519 (418-11,250)	2,928 (884-6,527)	> 0.05
Platelet count x10^5 in cells/ l, median (range)	2.20 (0.99-4.21)	2.12 (1.27-3.17)	> 0.05

NA, not analyzed.

during community outbreaks of influenza (CDC, 2012a). Children this age also serve as a major source of transmission of influenza within communities (CDC, 2012a). Influenza has a substantial impact on school-aged children and their contacts (CDC, 2012a).

The rate of hospitalization among children aged ≥5 years was significantly higher than among children aged < 5 years. It was similar to other studies that reported a substantial increase in admission rates among school-aged children. There was an 80% increase in number of influenza related hospital admissions in this age group (Molbak *et al*, 2011; Chen *et al*, 2012). Our study differed from 2 previous studies that found the highest risk of hospitalization was among children aged < 5 years (Simmerman *et al*,

2009; Van *et al*, 2011). Several studies have found young children are at higher risk for serious illness and hospitalization due to influenza virus infection (Dawood *et al*, 2010; Fiore *et al*, 2010).

Studies have shown treatment with oseltamivir has clinical and virological benefit for patients with uncomplicated influenza when it is administered within 48 hours of the onset of symptoms (Nicholson *et al*, 2000; Treanor *et al*, 2000; Whitley *et al*, 2001; Hernan and Lipsitch, 2011). In this study, oseltamivir was started more slowly among hospitalized children (3 days) than among outpatient children (2 days). Severity of symptoms has been associated with a delay in administration of antiviral therapy among patients infected with influenza B (Gutiérrez-Pizarraya *et al*, 2012). Delay onset in antiviral therapy among children is associated with a higher risk for a poor outcome among influenza A infected patients (Jain *et al*, 2009; Chen *et al*, 2012).

In this study, the complication rate was significantly higher among hospitalized children than outpatient children. Pneumonia was the most frequent complication in our study similar to a previous study (Gutiérrez-Pizarraya *et al*, 2012). Febrile convulsions occurred in 3.1% of hospitalized children in our study, similar to the previous study (4.3%) (Lin *et al*, 2006). Seizures are found less frequently among patients with influenza B infection than influenza A infection (19.5%) (Chiu *et al*, 2001). Because higher complication rates were seen among hospitalized children, antibiotics were significantly more commonly used among hospitalized children than among outpatient children.

Influenza vaccination is important to prevent influenza infection and is recommend annually for all children aged ≥6 months by Advisory Committee on Immunization Practices (ACIP) (CDC, 2012b). However a history of influenza vaccination does not rule out the possibility of influenza virus infection (CDC, 2013a,b). The history of influenza vaccination rate was low in this study because influenza vaccination is not routine in Thailand.

This study has several limitations. The study was conducted retrospectively and there was missing information. Heights and underlying medical conditions were not recorded completely, preventing evaluation of the BMI. It is difficult to distinguish between complications and co-infections because hemocultures and viral testing are not routine tests here. In our study, we could not determine the incidence of co-infections because of limited data. None of the patients were severe, so they did not have a detained investigation. In clinical practice, respiratory illness caused by influenza is difficult to distinguish from respiratory illness caused by other pathogens on the basis of symptoms alone. Rapid influenza testing is required to detected influenza B infection. Early detection and initiation of antiviral therapy is need.

In conclusion, hospitalization was associated with a delay in initiation of antiviral therapy, antibiotic use and complications, such as pneumonia and rhinosinusitis. Timely diagnosis and antiviral therapy initiated within the first 2 days of symptom onset may reduce hospitalizations and unnecessary antibiotics.

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