Prevalence, Clinical Presentations and Complications among Hospitalized Children with Influenza Pneumonia

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SUMMARY: Viral respiratory tract infections are a major cause of hospitalization in children. Influenza is common but often not laboratory proven. We report a prospective study of children admitted with a clinical diagnosis of pneumonia. Infants and children (ages 1 month - 15 years) who were hospitalized with community-acquired pneumonia were enrolled in the study. Their nasopharyngeal aspirated samples were analyzed for common respiratory viruses, including influenza virus, by reverse transcription-polymerase chain reaction (RT-PCR) or PCR. Out of 257 patients, we identified 127 (49.4%) cases with respiratory viruses, and influenza was found in 32 of these cases (12.5%). Other common respiratory viruses included respiratory syncytial virus in 42 (16.3%), human metapneumovirus in 24 (9.3%), adenovirus in 17 (6.6%) and parainfluenza virus in 12 (4.7%). The median age of the influenza group was 2 years and 3 months, and 27 (84%) of children in this group were under the age of 5. Asthma was the most common co-morbidity (4/32, 12.5%). Common clinical presentations were fever and cough (100%) with crepitations (90%). The median length of hospitalization was 6 days. Three patients developed respiratory failure, with one mortality (3.1%). One child developed infection-associated hemophagocytic syndrome. Our study demonstrated that young children had a high risk of hospitalization due to influenza pneumonia, which contributed to a significant morbidity.

INTRODUCTION

Lower respiratory tract infection is a leading cause of morbidity and mortality in children worldwide (1,2). Community-acquired pneumonia (CAP) is associated with significant costs, including loss of school days, several health care visits and sometimes unnecessary antibiotics prescriptions. The etiologic agents of these common infections are respiratory syncytial virus (RSV), parainfluenza virus (PIV), influenza virus, coronavirus and rhinovirus (3). In addition, novel new respiratory viruses, associated with acute respiratory tract illness in humans, have been identified by the use of new molecular techniques. These include human metapneumovirus (hMPV) (3,4) and human coronavirus (5).

Influenza viruses are important causes of respiratory tract illness in infants and children (6,7). The World Health Organization (WHO) has estimated that approximately 3 to 5 million cases and 250,000 - 500,000 deaths are caused by influenza each year worldwide (8). Influenza-related deaths in children are infrequent but influenza-attributable hospitalization rates in young children or high-risk children are quite high. Previous studies found high incidences of admission among children less than 2 years old. The spectrum of influenza infection in children ranges from subclinical illness to complicated disease involving multiple organs (9,10), and pneumonia is one of the common presentations, although few studies have investigated its impact on clinical outcomes. The aim of our study was to explore the frequency, clinical presentations and impact of influenza and other viral pneumonias on hospitalized infants and children.

PATIENTS AND METHODS

Infants and children aged 1 month to 15 years who were hospitalized with a diagnosis of CAP were recruited in a prospective study (March 2006 - February 2007). Written informed consent for study participation was obtained from the legal guardians of the patients before recruitment. CAP was diagnosed using the following criteria (11): fever ≥37.8°C with abnormal respiration (tachypnea) according to age: less than 2 months old, respiratory rate (RR) >60/min; 2-12 months old, RR >50/min, 1-5 years old, RR >40/min, >5 years old, RR >30/min, plus one of the following criteria: abnormal lung auscultation (e.g., crackles, rhonchi, wheezing) or abnormal chest radiograph consistent with pneumonia (e.g., consolidation, perihilar infiltrates).

Patients were excluded if no formal consent was obtained or nasopharyngeal suction was not available.

The nasopharyngeal samples were analyzed for common respiratory viruses (RSV, PIV 1, 2, 3, adenovirus, hMPV), including influenza virus, by reverse transcription-polymerase chain reaction (RT-PCR) or PCR (4,12). Demographic, clinical and other laboratory data were recorded.

General data is presented as percentage, median or mean ± SD. ANOVA was used for multiple comparisons. The chi-square test was used for categorical analysis. All statistical analyses were performed using SPSS software (version 13; Chicago, Ill., USA). P < 0.05 was considered statistically significant.

RESULTS

Out of 257 children enrolled in our study, 147 were boys
and 110 were girls (42.8%). Their median age was 1 year and 4 months (Table 1). Most were younger than 5 years old (239, 93%) (Fig. 1). We identified 127 cases (49.4%) of respiratory viruses. Influenza was found in 32 cases (12.5%). Other common respiratory viruses included RSV in 42 (16.3%), hMPV in 24 (9.3%), adenovirus in 17 (6.6%) and PIV in 12 (4.7%) (Fig. 2). In the influenza group, there were 14 males and 18 females. The median age was 2 years 3 months. Twenty-seven patients (84%) were younger than 5 years (Fig. 3). Patients with hMPV pneumonia had the longest hospitalization at 9.9 ± 15.8 days, followed by those with influenza at 9.5 ± 12.2 days (Fig. 4).

Clinical presentations of influenza pneumonia: In the influenza group, fever and cough were identified in every patient. Rhinorrhea was found in 27 (84.3%), vomiting was detected in 11 (34.4%) and diarrhea was seen in 3 (9.3%) (Fig. 5). Initial body temperature was 38.4 ± 1.2°C, and the duration of fever was 3.5 ± 2.7 days (range 1-10 days). Mean oxygen saturation at presentation was 94.6 ± 8.5%. Crackles were the most common abnormal lung sign (90.6%). This was significantly different (P < 0.05) when compared to the incidence in children with adenovirus (60%) and RSV (70%), respectively. Antibiotics had been administered to 18/32 influenza cases (56.2%). The median length of hospitalization was 6 days (range 2-57 days). Children with influenza and without influenza had common initial clinical presentations.

Laboratory findings in influenza group: The mean leukocyte count was 12.1 ± 5.7 × 10³ cell/mm³, hematocrit was

Table 1. Demographic data of patients enrolled in this study

<table>
<thead>
<tr>
<th>Patient characteristic (n = 257)</th>
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<tbody>
<tr>
<td>Male:Female</td>
<td>1:3</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>1 year 4 months (11 days - 14 years 10 months)</td>
</tr>
<tr>
<td>Patients with underlying diseases</td>
<td>82 (31.9%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>24 (9.3%)</td>
</tr>
<tr>
<td>Congenital heart diseases</td>
<td>21 (8.2%)</td>
</tr>
<tr>
<td>Chronic lung diseases</td>
<td>19 (8.2%)</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>13 (5.0%)</td>
</tr>
<tr>
<td>Cancer and immunocompromised</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (4.6%)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>43 (16.7%)</td>
</tr>
<tr>
<td>Environment related to smoking</td>
<td>81 (31.5%)</td>
</tr>
</tbody>
</table>

Fig. 1. Number of patients who diagnosed as community-acquired pneumonia enrolled in this study during March 2006 - February 2007 categorized by age in year (total number = 257). Ninety percent of patients were under the age of 4 and their peak was between 1-2 years.

Fig. 2. Distribution of respiratory virus identified in this study including influenza. Influenza was the second most common respiratory virus identified in this study. RSV, respiratory syncytial virus; hMPV, human metapneumovirus.

Fig. 3. Percentage of age distribution in patients diagnosed as influenza pneumonia (n = 32). Most of them were between 1-5 years old (62%).

Fig. 4. Duration of hospitalization comparing each respiratory virus identified in this study. There is no statistically significant difference between duration of hospitalization between influenza and non-influenza group (mean ± SD, 9.3 ± 11.9, 8.7 ± 14.6 days, P = 0.8). Each line (from left to right) represents adenovirus, parainfluenza, influenza, respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and negative.
land. However, the variation of influenza prevalence could differ from year to year, but the incidence was higher in June (21.9%) and July (16,17). We were able to detect influenza virus throughout the year, with the longer shedding period of the virus in these patients being 3 months. Younger children had an even higher incidence, with 93% of patients being less than 5 years old. This incidence is comparable to the findings in a recent study by Lahti et al. (14) and 15% reported by Wolf et al. (15) in this population. In our study, 93% of infants and children admitted with CAP, a finding comparable to the incidence reported by He et al. (16) and 15% reported by Peltora et al. (17) in which asthma was the underlying condition in 25% of influenza pneumonia patients. In our study, 18/32 patients had blood cultures drawn, of which three were positive (12%, coagulase-negative staphylococci in 2 and Salmonella choleraesuis in 1). These represented secondary infections.

**DISCUSSION**

Viruses are the leading cause of lower respiratory infections in young children, as demonstrated in our study, with RSV as the most common virus followed by influenza viruses. The clinical spectrum of influenza in children could range from subclinical illness to complicated disease that can affect multiple organs. It can present as croup, bronchiolitis or acute febrile illness mimicking bacterial sepsis. Pneumonia is the most common clinical manifestation. Influenza and other viral pneumonias can cause severe illness in preschool children, school-age children, adolescents and adults (13). In our study, influenza pneumonia was seen in 12.5% of infants and children admitted with CAP, a finding comparable to the 14% recently reported by Lahti et al. (14) and 15% reported by Wolf et al. (15) in this population. In our study, 93% of patients were less than 5 years old. Younger children had an increased risk of hospitalization. This may be explained by the longer shedding period of the virus in these patients (16,17). We were able to detect influenza virus throughout the year, but the incidence was higher in June (21.9%) and August (15.6%), which represent the rainy season in Thailand. However, the variation of influenza prevalence could vary from year to year.

Fever, cough and rhinorrhea were among the most common clinical presentations of influenza pneumonia in our study. Interestingly, wheezing was found in only nine patients (28%). This was significantly different compared to adenovirus or RSV. Previous investigators suggested that the presence of expiratory wheezing distinguished RSV from influenza (18), but another study was reported that 19% of infants with acute bronchiolitis had influenza (A or B) and that 56% of infants presenting with only wheezing had influenza (13). Clinical presentations alone cannot reliably predict which virus is responsible, and specific antiviral therapy should not be initiated without laboratory studies. Viruses as a cause of lower respiratory tract infection are common in children with negative diagnostic tests. We did not look for rhinovirus or coronaviruses in our study (7,13). There are almost certainly many other as yet unidentified agents responsible for respiratory illnesses in children and adults.

Many children infected with influenza viruses had at least one underlying disease. Asthma was the most common underlying condition associated with influenza pneumonia, documented in 4/32 (12.5%) of our study cases. This number was lower than that reported in a previous study by Peltora et al. (2003) (17) in which asthma was the underlying condition in 25% of influenza pneumonia patients. In our study, 18/32 patients received antibiotics because of the clinical severity of illness which mimicked bacterial disease. Three had respiratory failure and required mechanical ventilation. One of our patients developed the rare and fatal complication of hemophagocytic syndrome, which could have been the primary illness or a complication of influenza infection (19).

The overall mortality of influenza pneumonia is low (3.1%), but it can be a life-threatening disease and deaths from influenza pneumonia do occur, as demonstrated in our study. This is in agreement with other recent reports (16,20-22). The cost of hospitalization is high. We estimated the expense of the average hospitalization as approximately 1,800 USD/case, which is quite low when compared to other studies whose authors estimated the cost of pediatric hospitalization for influenza as 3,000 - 4,000 USD/case (16,23) or even 13,000 USD/case from a recent study in the United States (24). Influenza pneumonia is the only vaccine-preventable viral-associated respiratory tract illness. Modern vaccines and antiviral drugs offer new approaches for the prevention and treatment of influenza. In Thailand, influenza vaccination is not yet scheduled as a routine health maintenance program for children; it is supported only for the elderly. In addition, most children who have asthma and other immunocompromised individuals do not receive an annual influenza vaccination. Our study results indicate that this immunization practice may prevent morbidity in these young children.

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**REFERENCES**