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Pneumonia due to 2009 Influenza A (H1N1) Infection in Thai children: Chulalongkorn experience

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Uppala R, Prapphal N, Deerojanawong J, Sritippayawan S, Samransamruajkit R, Pongsanon K. Pneumonia due to 2009 influenza A (H1N1) infection in Thai children: Chulalongkorn experience. Chula Med J 2012 Sep - Oct; 56(5): 533 - 43

Objective : *To study the clinical presentations and outcomes of 2009 influenza A (H1N1) pneumonia children at King Chulalongkorn Memorial Hospital.*

Setting : *Department of Pediatrics, King Chulalongkorn Memorial Hospital.*

Research design : *Descriptive study.*

Patients : *Pediatric patients aged 1 month - 18 years who were admitted due to H1N1 influenza pneumonia between June 2009 – March 2010.*

Methods : *All the pediatric patients with pneumonia who had laboratory confirmation of 2009 influenza A (H1N1) infection by positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay for H1N1 influenza A virus in their nasopharyngeal aspirates or combined nasal and throat swabs were studied. Their demographic data, clinical presentations, laboratory results, radiological findings and clinical outcomes were analyzed.*

Results : *There were 37 patients with confirmed 2009 influenza A (H1N1) pneumonia during the study period. Male: female was 1.3: 1. The mean age was 6.4 ± 4.7 years (ranged 2 months - 16 years). Twenty-one patients (56.8%) had underlying diseases. Chronic lung*

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disease and hematologic malignancy were the two most common underlying conditions. Only 43.2% of the patients (16/37 cases) had contact history and 7 cases got the infection while being in the hospital. The most common presenting symptoms were fever and cough (94.6%). Most of the patients had had fever with a mean temperature of 38.6 ± 0.9^{O}C (ranged 36.3 – 40.4^{O}C) for 50.0 ± 35.8 hours prior to hospitalization or diagnosis. The mean white blood cell count were 7,671 ± 623 cells/mm.^{3} The most common chest X-ray finding was perihilar interstitial infiltration (62.2%) while patchy infiltration was noted in 13.5% of the patients. Ten cases (27%) had hypoxemia and 4 cases (10.8%) with underlying conditions developed into acute respiratory failure. Two patients (5.4%) died due to ARDS and severe sepsis.

Conclusion : *Fever and cough with perihilar infiltrations were the most common clinical presentations of 2009 influenza A (H1N1) pneumonia in children admitted at King Chulalongkorn Memorial Hospital during the pandemic period. Respiratory failure occurred in patients with underlying diseases and accounted for 10.8% leading to a mortality rate of 5.4%. ARDS and superimposed bacterial infections were the major causes of death in this study.*

Keywords : *Pneumonia, 2009 influenza A (H1N1) infection, children.*

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รัฐพล อุปลา, นวลจันทร์ ปราบพาล, จิตลัดดา ดีโรจนวงศ์, สุชาดา ศรีทิพยวรรณ, รุจิภัตต์ สำราญสำรวจกิจ, เขมชาติ พงศานนท์. ปอดอักเสบจากการติดเชื้อไวรัสไข้หวัดใหญ่เอ 2009 (H1N1) ในผู้ป่วยเด็กที่รักษาในโรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2555 ก.ย. – ต.ค.; 56(5): 533 – 43

วัตถุประสงค์ : *เพื่อศึกษาลักษณะทางคลินิกและผลลัพธ์ของการรักษาในผู้ป่วยเด็กโรคปอดอักเสบจากการติดเชื้อไข้หวัดใหญ่เอ 2009 (H1N1) ที่รับการรักษาที่โรงพยาบาลจุฬาลงกรณ์*

สถานที่ทำการวิจัย : *หอผู้ป่วยกุมารเวชศาสตร์ โรงพยาบาลจุฬาลงกรณ์*

รูปแบบงานวิจัย : *การศึกษาแบบพรรณนา*

ผู้ป่วยที่ศึกษา : *ผู้ป่วยเด็กอายุ 1 เดือน ถึง 18 ปี ที่ได้รับการวินิจฉัยว่าเป็นโรคปอดอักเสบจากการติดเชื้อไวรัสไข้หวัดใหญ่เอ 2009 (H1N1) และเข้ารับการรักษาใน รพ. จุฬาลงกรณ์ ระหว่างที่มีการระบาดในช่วงมิถุนายน พ.ศ. 2552 - มีนาคม พ.ศ. 2553*

วิธีการศึกษา : *เก็บรวบรวมข้อมูลจากเวชระเบียนของผู้ป่วยเด็กทุกรายอายุ 1 เดือน ถึง 18 ปี ที่ได้รับการวินิจฉัยว่าเป็นโรคปอดอักเสบจากการติดเชื้อไวรัสไข้หวัดใหญ่เอ 2009 (H1N1) โดยยืนยันการวินิจฉัยด้วยวิธี RT-PCR และทำการวิเคราะห์ในเรื่องของข้อมูลทั่วไป อาการและอาการแสดง ผลการตรวจทางห้องปฏิบัติ ภาพถ่ายทางรังสีทรวงอก และผลการรักษา*

ผลการศึกษา : *ผู้ป่วยทั้งหมด 37 ราย อายุเฉลี่ยเท่ากับ 6.4 ± 4.7 ปี (range 2 เดือน – 16 ปี) ชาย : หญิง 1.3: 1 ร้อยละ 56.8 ของผู้ป่วยมีโรคประจำตัว ที่พบมากที่สุด คือ chronic lung disease และ hematologic malignancy มีเพียงร้อยละ 43.2 (16 ราย) เท่านั้นที่มีประวัติการสัมผัสกับผู้ป่วยที่เป็นไข้หวัดใหญ่ และมีผู้ป่วยที่มีการติดเชื้อขณะอยู่รับการรักษาในโรงพยาบาล 7 ราย (ร้อยละ18.9) อาการนำที่พบบ่อยที่สุดคือไข้และไอ และผู้ป่วยส่วนใหญ่มีไข้สูง อุณหภูมิเฉลี่ย 38.6 ± 0.9^{o}C (range 36.3 - 40.4) ระยะเวลาเฉลี่ยที่มีไข้ก่อนรับไว้ในโรงพยาบาลหรือได้รับการวินิจฉัยเท่ากับ 50.0 ± 35.8 ชั่วโมง ผลการตรวจทางห้องปฏิบัติการพบว่าค่า white blood cells count เท่ากับ 7,671 ± 623 เซลล์/ลบ.มม. ความผิดปกติของภาพถ่ายรังสีปอดที่พบมากที่สุดคือ perihilar interstitial infiltration (ร้อยละ 62.2) รองลงมา*

คือ patchy infiltration (ร้อยละ13.5) ผู้ป่วย 10 ราย (ร้อยละ 27) มีภาวะ hypoxemia ซึ่งทุกรายมีโรคประจำตัว ผู้ป่วย 4 ราย (ร้อยละ 10.8) มีภาวะ acute respiratory failure และ 2 ราย (ร้อยละ 5.4) เสียชีวิตจากภาวะ ARDS และติดเชื้อรุนแรงในกระแสเลือด

สรุป : *ลักษณะทางคลินิกที่พบบ่อยสุดในผู้ป่วยโรคปอดอักเสบจากการติดเชื้อไข้หวัดใหญ่เอ 2009 (H1N1) คือไข้และไอ ร่วมกับ perihilar infiltration ในภาพรังสีปอด ผู้ป่วยที่มีภาวะพร่องออกซิเจน และมีภาวะหายใจล้มเหลวมีโอกาสเสียชีวิตได้จากภาวะ ARDS และ ติดเชื้อแบคทีเรียในกระแสเลือด ดังนั้นควรป้องกันและให้การรักษาที่มีประสิทธิภาพสำหรับภาวะดังกล่าวเพื่อลดอัตราการเสียชีวิตของผู้ป่วย*

คำสำคัญ : *โรคปอดอักเสบ, ไข้หวัดใหญ่เอ 2009 (H1N1), เด็ก.*

The influenza pandemic was a concerned issue due to the historical record of 675,000 deaths in the United States and at least 40 million deaths worldwide in 1918.[1,2] An outbreak of 2009 influenza A (H1N1) during the period of early 2009 generated a worldwide panic especially in the outbreak countries. After the announcement of initial pandemic in Mexico, some studies reported high mortality especially in young adults.[3,4] The disease also invaded the United States, with more severity of the disease reported.[5,6] After a rapid spread of the emerging pathogen, many countries worldwide had protective strategies to prevent overseas transmission. The 2009 influenza A (H1N1) still crossed the barrier rapidly into Argentina, and spread to Asian countries like Hong Kong and Thailand.[7] In June 2009, the World Health Organization (WHO) declared the first influenza pandemic in 41 years.[8] Thailand announced the pandemic of 2009 influenza A (H1N1) in early April 2009 and the transmission rate increased rapidly.

Seasonal influenza virus infection was an important cause of hospitalized pneumonia in Thailand. The incidence was highest in children less than 5 years of age as well as in adults over 60 years of age. [9] The severity of 2009 influenza A (H1N1) had been noticed as higher than seasonal influenza. The overall rate of death was 1.1 per 100,000 children in 2009 influenza A (H1N1) as compared to 0.1 per 100,000 children for seasonal influenza.[10]

Objectives

We collected the data of 2009 influenza A (H1N1) infections in hospitalized children in order to study the clinical presentations and the outcomes of 2009 influenza A (H1N1) pneumonia in pediatric patients during the period of pandemic between June 2009 - March 2010 at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Material and Methods

Population

All the pediatric patients aged 1 month - 18 years who were hospitalized due to pneumonia and had been confirmed of 2009 influenza A (H1N1) infection between June 2009 and March 2010 were studied. The H1N1 influenza infection was confirmed by positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay for H1N1 influenza A virus in their nasopharyngeal aspirates or combined nasal and throat swabs which were performed at the regional laboratories according to the protocol recommended by the Center for Disease Control and Prevention (CDC) of the US.[11]

The demographic data, clinical presentations, laboratory results, radiological findings, and clinical outcomes of the studied patients were reviewed. Hypoxemia was defined as having oxygen saturation (SpO_2) of less than 93% while the patients were breathing ambient air.[12]

Statistical analysis

All statistical analysis was performed by SPSS for Windows version 17.0 and Chi-square test was used for comparison between groups. A *p*-value of less than 0.05 indicated statistical significance.

Results

Characters of the patients:

Thirty-seven patients with confirmed 2009

influenza A (H1N1) pneumonia were included in the study. The mean age of the patients was 6.4 ± 4.7 years (range 2 months – 16 years). 56.8% (21 cases) had underlying diseases in which chronic lung disease was the most common one (9 cases) followed by hematologic malignancies (Table 1). Twenty-four point three percent of the patients had history of contact with H1N1 patients in the community while 7 patients acquired H1N1 pneumonia at the hospital. All of the patients with nosocomial infections were in the immune-compromised ward.

Clinical presentations:

The two most common clinical presentations were fever and cough (noted in 94.6% of all the studied patients). The majority of the patients had high fever with a maximal temperature of 40.1°C (38.6 ± 0.9°C) and a mean duration of 50.0 ± 35.8 hours prior to admission (Table 2). Cough was mostly initially presented as non-productive. Chest retractions indicating respiratory distress were found in 10 cases (27%). Crepitation which was the most common adventitious breath sound was noted in 12 patients (32.4%) and expiratory wheezing was found in 21.6% (8 cases). Bronchodilator was given to those who had wheezing or severe respiratory distress without detectable adventitious sound and positive response was noted in 11 cases (29.7%). Coryza, headache and myalgia were found in 24 cases (64.9%), 8 cases (21.6%) and 8 cases (21.6%) respectively. Diarrhea was also reported in 3 cases (8.1%).

Laboratory and chest X-ray findings:

The initial laboratory findings were summarized in Table 3. Their average white blood cells count was 7,671.3 ± 623.8/mm.^{3} Perihilar interstitial infiltration was the most common chest X-ray finding (62.2%) while patchy infiltrations occurred in 5 cases (13.5%). *Streptococcus pneumoniae* was found in tracheal aspiration in one case who developed respiratory failure requiring mechanical ventilation upon admission.

Table 1. Demographic data and underlying diseases (N = 37).

Characteristics	Results
Age (yrs)	
Mean ± SD.	6.4 ± 4.7
Male: Female	1.3:1
Underlying diseases : cases (%)	21 (56.8)
Chronic lung disease	9 (24.3)
Hematologic malignancy	6 (16.2)
Chronic liver disease	2 (5.4)
Others	4 (10.8)
History of contact with H1N1 patients	9 (24.3)

Table 2. Clinical signs and symptoms (N = 37)

Clinical symptoms & signs	Cases (%)
Fever	35 (94.6)
- Duration (hours) : mean (range)	50 (3 - 144)
- Body temperature (^{O}C) : mean ± SD	38.6 ± 0.9
Breath sound	
- normal	17 (45.9)
- crepitations	12 (32.4)
- wheezing	8 (21.6)
Bronchodilator responsiveness	11 (29.7)
Chest retraction	10 (27)
Cough	35 (94.6)
Coryza	24 (64.9)
Myalgia	8 (21.6)
Headache	2 (5.4)
Diarrhea	3 (8.1)

Table 3. Initial laboratory and radiological findings (N = 37)

Laboratory parameters	Results
Leukocyte count (cells/mm^3) : mean ± SD	7,671.3 ± 623.8
Chest X-ray findings: cases (%)	
- perihilar interstitial infiltration	23 (62.2)
- peribronchial thickening, no definite pulmonary infiltration	9 (24.3)
- patchy infiltration	5 (13.5)
Positive culture (tracheal suction culture) : case (%)	
- *Streptococcal pneumoniae*	1 (2.7)

Clinical outcomes:

Of the 37 cases, 10 (27%) had hypoxemia (SpO_2 < 93%) in which 4 cases (10.8%) developed acute respiratory failure. Two patients (5.4%) died, both of them had underlying diseases with their clinical information were summarized in Table 4.

Oseltamivir was given to 31 patients who recovered and was also empirically given within 24 hours after admission to both of the patients who died. The remaining 4 patients who did not receive oseltamivir were previously healthy and were clinically not severe. They rapidly recovered after receiving supportive treatment.

Concerning factors associated with severe pneumonia or pneumonia with hypoxemia, we found that the initial laboratory parameters including white

blood cell count and hematocrit level were not significantly related to the severity of the patients. However, patchy infiltration on the initial chest X-ray was significantly related to hypoxemia in our studied patients (10.8% *vs*. 2.7%; $p = 0.04$) as shown in Table 5. None of the patients who had only peribronchial thickening without definite pulmonary infiltrations had hypoxemia.

Table 4. Characteristics of the 2 patients with 2009 H1N1 influenza pneumonia who died.

No.	Age	Sex	Preexisting conditions	Length of hospital stay (d)	Complications	Cause of death
1	2 yr	M	Chronic lung disease with pulmonary hypertension	6	ARDS with septic shock	ARDS and septic shock (*A.baumanii*)
2	15 yr	M	Acute myeloid leukemia (AML)	12	ARDS	ARDS, end stage - AML

Table 5. Factors associated with hypoxemia in 2009 - H1N1 influenza pneumonia.

Parameters	No Hypoxemia N =27	Hypoxemia* N =10	*p*-value
Leukocyte count (cells/mm^3) : mean ± SD.	7520.4 ± 3750.4	8079.0 ± 4087.1	0.69
Hematocrit (%)	33.8 ± 5.1	33.5 ± 7.4	0.90
Fever prior to admission (hours) : mean ± SD	44.6 ± 33.6	64.8 ± 39.3	0.12
Chest X-ray: cases (%)			
- perihilar interstitial infiltration	17 (45.69)	6 (16.2)	0.99
- peribronchial thickening, no definite pulmonary infiltration	9 (24.3)	0	0.01
- patchy infiltration	1 (2.7)	4 (10.8)	0.04

Discussion

In our study, we found that the prominent clinical presentations of 2009 influenza A (H1N1) pneumonia were fever and cough. Wheezing was found in about 21%. Most of our patients had chronic lung disease and hematologic malignancies as their underlying diseases. Nosocomial infection also occurred among our immune-compromised patients.

The chest radiological findings in our patiens were mainly perihilar interstitial infiltrations and peribronchial thickening which were similar to previous reports in which unilateral or bilateral ground glass opacities with or without associated focal or multifocal areas of consolidation, predominantly peribronchovascular and subpleural distribution were the major findings on chest X-ray or CT scan.[13] Patchy infiltration was significantly associated with hypoxemia in our patients with H1N1 infection. However, we could not demonstrate whether or not all of them had co-infection with bacteria or had secondary bacterial infection.

One of our patients had co-infection with *Streptococcus pneumoniae* which progressed to respiratory failure. Some previous studies demonstrated the increased risk of secondary bacterial infections especially from *Staphylococcus aureus* and *Streptococcus pneumoniae* in H1N1 infected patients. If the patients had progressive worsening signs and symptoms of respiratory system, it was appropriate to start empirical treatment to ward off the possible secondary bacterial infections.[14]

Concerning the mortality rate among our patients with H1N1 influenza pneumonia, two patients out of 37 died (mortality rate 5.4%), both of them had underlying diseases (chronic lung disease with pulmonary hypertension and end-stage acute myeloid leukemia) that developed into severe respiratory failure and ARDS. The 2-year-old patients with preexisting chronic lung disease (bronchopulmonary dysplasia), reactive airway disease and pulmonary hypertension were rapidly deteriorated after contracting 2009 influenza A (H1N1) infection. One of them developed respiratory failure and ARDS one day after the onset of the disease despite having received oseltamivir on the first day of admission. Alveolar infiltration was found on his initial chest X-ray (Fig. 1). His clinical course was complicated with secondary bacterial infection and developed septic shock. His hemoculture and tracheal cultures grew *Acenetobacter baumanii*. No significant improvement was observed after antibiotic treatment together with hemodynamic and ventilatory support. Moreover, tension pneumothorax occurred and he finally expired on the 6th day of hospitalization (Fig. 2). The pathological findings among the patients who died of influenza infection which had been reported included tracheitis, bronchiolitis and diffuse alveolar damage. Influenza viral antigens were observed in the epithelium of the tracheobronchial tree, alveolar epithelial cells and macrophages. The histologic and microbiologic autopsy evidence of bacterial pneumonia were detected in 55% of the cases.[14] Unfortunately, the autopsy was not done and their pathological findings could not be disclosed in both of our patients who died.

Conclusion

This study shows that clinical presentations of the pandemic 2009 influenza A (H1N1) infection in children who were hospitalized at King Chulalongkorn Memorial Hospital between June 2009 and March

2010 were high fever and cough. Perihilar interstitial infiltration was the most common chest X-ray findings and the presence of patchy infiltrations was associated with hypoxemia which might progress to respiratory failure. Secondary bacterial infection and severe diseases with fatal outcomes should be aware of in children with pneumonia especially in those with chronic lung disease and immune-compromised conditions.

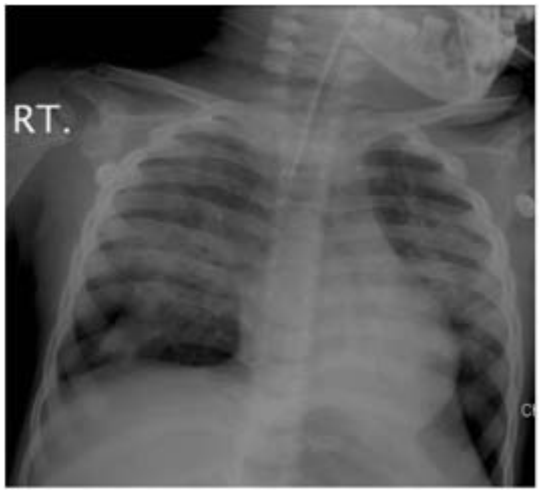

Figure 1. Chest X-ray of the 2-year-old boy with H1N1 influenza pneumonia upon admission.

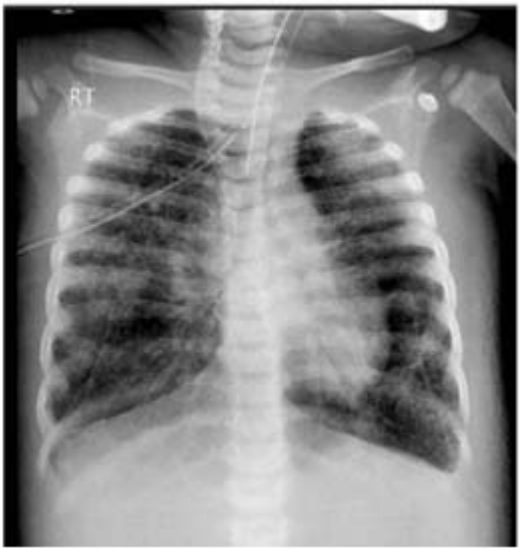

Figure 2. Tension pneumothorax on D6 of admission.

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