The purpose of this study is to clarify the incidence of bacterial coinfection associated with RSV bronchopulmonary infection in pediatric inpatients using washed sputum culture.

Materials and methods

Subjects were 188 pediatric inpatients aged 0 month to 5 years having RSV bronchopulmonary infection including bronchitis, bronchiolitis, and pneumonia in two hospitals in Chiba Prefecture between September 2005 and March 2007. On admission, after informed consent was obtained from the child's parents or guardians, nasopharyngeal aspirate and sputum were obtained. Nasopharyngeal aspirates were tested by BD RSV Examan (Becton-Dickinson, Fukushima, Japan) to detect RSV infection. Washed sputum bacterial culture was performed to detect bacterial infection.

Clinical diagnoses such as bronchitis, bronchiolitis, or pneumonia were made by the pediatricians in charge. Underlying conditions such as bronchial asthma or congenial heart disease were also evaluated by the pediatricians.

To obtain good-quality sputum samples from children, we typically use a tongue depressor with a light to depress the tongue and induce the cough reflex, then pick out sputum with a swab or aspirate sputum with a 1-ml disposable syringe. Within a few hours of sampling, the sample was alternatively washed three times in sterilized saline solution to remove contaminating bacteria from the saliva and upper respiratory tract. Small samples of washed sputum were cultured in sheep blood agar medium and horse blood chocolate agar medium.

Antimicrobial susceptibility tests were performed on isolated pathogenic bacteria using the micro-broth dilution method according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). Antimicrobial susceptibility of *Haemophilus influenzae* was determined by assessing minimum inhibitory concentration (MIC) to ampicillin (ABPC), and all *H. influenzae* strains were tested for β-lactamase production using nitrocefin-impregnated disks. Strains with ABPC-MIC values >2 μg/ml were considered to be ABPC resistant and those that did not produce β-lactamase and gave ABPC-MIC values >2 μg/ml were considered to be β-lactamase-nonproducing ABPC-resistant (BLNAR) strains. Strains with ABPC-MIC values of 2 μg/ml were considered to be ABPC intermediate sensitive (BLNAI) strains.

Antimicrobial susceptibility of *Streptococcus pneumoniae* was determined by MIC to penicillin G (PcG). Strains with PcG-MIC values of 4 μg/ml were considered to be penicillin intermediate resistant (PISP) strains and strains with PcG-MIC values >4 μg/ml were considered to be penicillin-resistant (PRSP) strains.

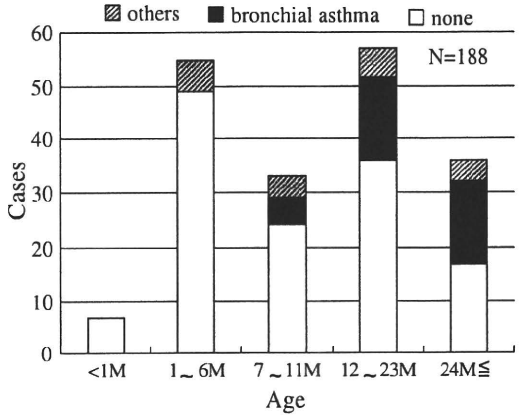

Fig. 1 Age distribution and underlying condition of pediatric inpatients with respiratory syncytial virus (RSV) bronchopulmonary infection. *M* months

Results

Figure 1 shows the age distribution and underlying condition of pediatric inpatients with RSV bronchopulmonary infection. Of the 188 inpatients with RSV bronchopulmonary infection, median age was 11 months (interquartile range, 4–21); 95 (50.5%) patients were aged less than 1 year, 57 (30.3%) were aged 1–2 years, and 36 (19.1%) were aged 2 years or more. Although all patients were admitted for respiratory disease, 29.3% (55/188) had underlying disease. Thirty-six patients (19.1%) exhibited bronchial asthma attacks. Overall, 28.7% (54/188) received oral antibiotics before admission to the hospital, most often amoxicillin and macrolide.

Pathogenic bacteria were isolated from 43.6% of the patients. The three most frequently isolated bacteria were *H. influenzae* (43.9%), *S. pneumoniae* (36.6%), and *Moraxella catarrhalis* (29.3%) (Table 1). Figure 2 shows the antimicrobial susceptibility of *H. influenzae* isolated from pediatric patients with RSV infection. We found that 47.2% of *H. influenzae* strains were β-lactamase-nonproducing ABPC-sensitive strains, whereas 38.9% were BLNAR strains. All *S. pneumoniae* strains were PcG sensitive, but 21.9% showed PcG-MIC values of 2 μg/ml.

Discussion

RSV is the most important viral cause of lower respiratory infection in infants and young children throughout the world. Many advocate against the routine use of antibiotics in bronchiolitis because of the reported low incidence of

Table 1 Washed sputum culture result for 188 children with respiratory syncytial virus (RSV) bronchopulmonary infection

Dominantly isolated bacteria	Number of cases
Hi	28
Sp	24
Mc	18
Multiple bacteria	10
(Hi + Mc, Hi + Sp, Sp + MC)	(4, 4, 2)
Others	2
No pathogenic bacteria	106
Total	188

Hi, *Haemophilus influenzae*; Sp, *Streptococcus pneumoniae*; Mc, *Moraxella catarrhalis*

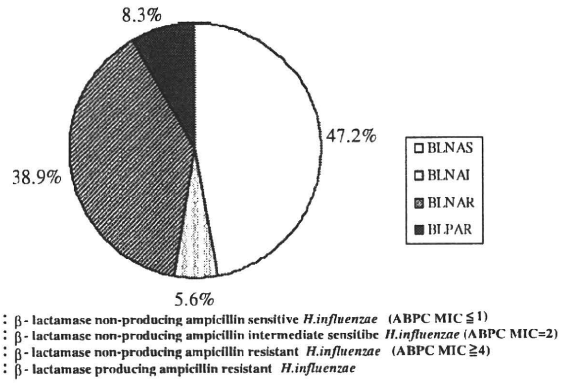

Fig. 2 Antimicrobial susceptibility of *Haemophilus influenzae* isolated from pediatric patients with RSV infection ($n = 36$)

concurrent or secondary bacterial infections in patients with RSV [12–17]. However, these studies focused on extrapulmonary bacterial coinfection, such as bacteremia and urinary tract infection. Some retrospective studies investigated the occurrence of bacterial coinfection in children with severe RSV infection requiring PICU admission and found the incidence of pulmonary bacterial coinfection to vary between 17.5 and 44% [4–6]. In these studies, the diagnostic yields of bacterial coinfection were obtained by bronchotracheal lavage. However, the incidence of bacterial coinfection with RSV bronchopulmonary infection in pediatric inpatients not requiring PICU admission and the prevalence of antimicrobial-resistant pathogenic bacteria isolated from these patients are unclear.

Physiologically, the lower airways are normally sterile. Nevertheless, the relationship between bacterial coinfection and viral respiratory disease has previously been recognized, having an escalating incidence with increasing severity of respiratory illness. The dilemma in young children with bronchopulmonary infection is that sensitive and specific laboratory methods for the detection of bacterial infections have not been established. Pathogenic bacteria can seldom be cultured from the blood, and invasive procedures such as lung puncture are not beneficial and are not used in clinical practice. Measurement of antibody responses to these bacteria offers a noninvasive approach. Several studies have shown that 30–70% of children with pneumonia develop IgG antibodies against these bacteria, and measurement of specific antibody responses has been used in research [18–21]. However, very few patients with viral upper respiratory tract infection develop serological responses to bacteria [22, 23], suggesting that respiratory viral infections do not provide nonspecific immune stimulation.

Conventionally, physicians and bacteriologists have accepted that microbiological examination of expectorated sputum should be performed to identify the bacterial pathogens in bronchopulmonary infections. Few studies have been carried out to evaluate the usefulness of sputum culture in the bacteriological diagnosis of pediatric patients with bronchopulmonary infection, as the collection of satisfactorily expectorated sputum samples in children is more difficult than in adults [8, 9, 11]. However, most pediatric inpatients with RSV bronchopulmonary infections had productive cough. Therefore, sputum can easily be obtained from children with RSV infection, irrespective of age. In this study, we clarified the etiology of bacterial coinfection associated with RSV bronchopulmonary infection in children using washed sputum culture, which is a useful means for improving sputum microbiological examinations. Pathogenic bacteria were isolated from 43.6% of the patients, which suggests that RSV bronchopulmonary infection in hospitalized children is often associated with bacterial infection in the lower airway. *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are the most common causes of bacterial respiratory tract infections in children. We found that 38.9% of *H. influenzae* strains were BLNAR. In Japan, the frequency of BLNAR strains causing respiratory infections has been increasing substantially, and this can diminish the antibiotic efficacy of both ampicillin and some cephems [24]. Our results indicate that suitable antibiotic selection is crucial for the treatment of bacterial coinfection with RSV bronchopulmonary infection.

The mechanisms by which RSV predisposes individuals to secondary bacterial infections are not completely understood. Some researchers recently reported that RSV infection increases the numbers of non-typeable *H. influenzae* and *S. pneumoniae* adhering to human respiratory epithelial cells in vitro and non-typeable *H. influenzae* and *S. pneumoniae* have been isolated more commonly and in larger numbers from patients with antecedent RSV infections than from patients without RSV infection, thus suggesting that viral infection increases bacterial colonization

[25–27]. RSV infection of respiratory epithelial cells promotes colonization by these bacteria. Secondary bacterial infection is an important risk factor for hospitalization with RSV infection. Strategies to prevent bacterial—RSV interaction in the lower respiratory tract may reduce the incidence of secondary bacterial complications of RSV infection.

We are aware of the limitations of our study. First, specific methods such as viral culture or real-time polymerase chain reaction (PCR) to detect viral RNA should be done instead of using conventional kits for detection of RSV to diagnose RSV infection. Second, not all the cases that yielded pathogenic bacteria did not require antibiotic treatment during RSV infection in this study (data not shown), so it is difficult to know which cases actually need antibiotics. We could say that the physician in charge should decide antibiotics use according to clinical findings, course, and washed sputum culture result. Further study will be needed to clarify the indication of antibiotic use during RSV infection.

In conclusion, nearly half of the pediatric inpatients with RSV bronchopulmonary infection showed secondary bacterial infection. The most common bacterial respiratory pathogens associated with RSV bronchopulmonary infection in children were BLNAR *H. influenzae* and *S. pneumoniae*. Therefore, we should pay attention to bacterial coinfection in the management of pediatric inpatients with RSV bronchopulmonary infection.

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ORIGINAL ARTICLE

Clinical characteristics and computed tomography findings in children with 2009 pandemic influenza A (H1N1) viral pneumonia

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Abstract

In this article we review the clinical characteristics and computed tomography (CT) findings in children with 2009 pandemic H1N1 influenza viral pneumonia. The medical charts of 88 children with pandemic H1N1 influenza virus infection, admitted to our hospital in Japan from 10 August to 28 December 2009, were reviewed; we compared the clinical features of these children with those of 61 children admitted with seasonal influenza A during the previous 3 seasons. Of 88 patients, 53 (60%) had radiographic findings consistent with pneumonia and 34 patients underwent a chest computed tomography (CT) scan. Pneumonia was a more frequent complication in children with pandemic H1N1 influenza compared with those with seasonal influenza (60% vs 11%; $p < 0.001$). The predominant CT findings were unilateral or bilateral multifocal consolidation (15/34; 44%) associated with ground-glass opacities in the peribronchovascular region. The second most common CT finding was unilateral diffuse consolidation or atelectasis in 1 or more lung zones (12/34; 35%). The chest CT findings of unilateral or bilateral multifocal consolidation often associated with ground-glass opacities were commonly seen in children with pandemic H1N1 influenza viral pneumonia. Atelectasis was seen in patients who required oxygen administration.

Introduction

2009 pandemic H1N1 influenza began in Mexico in April 2009 [1]. From Mexico its global spread was rapid. The clinical effects of pandemic H1N1 influenza vary from subclinical illness to severe respiratory failure and death, and resemble those observed in patients with seasonal influenza [2–6]. However, some clinical characteristics of pandemic H1N1 influenza differ from those of seasonal influenza, such as younger patient age, asthma as an underlying condition and more frequent pneumonia [2–4].

Recent studies on pandemic H1N1 influenza have shown that the main chest radiographic findings in adults with an advanced course of infection are bilateral consolidation and ground-glass opacities [7–9]. In children, prominent peribronchial markings with hyperinflation were determined to be the most common findings in mild cases, while bilateral symmetric multifocal areas of consolidation, often associated with ground-glass opacities, were found to be prominent in more severe cases, resembling the findings in adult patients [10]. However, to the best of our knowledge, there is little published information regarding the chest computed tomography (CT) findings of pandemic H1N1 influenza in children.

In this article, we present our experience with children admitted to hospital with 2009 pandemic H1N1 influenza. Our purpose was to evaluate the clinical characteristics and chest CT findings in children with this novel influenza viral pneumonia.

Methods

Approval for this study was obtained from the institutional clinical research ethics board with a waiver of informed consent because the study was

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retrospective. The study population included all paediatric patients (for the purpose of this study, any patient younger than 20 y was considered a paediatric patient) who were admitted to the Department of Paediatrics at NTT East Sapporo Hospital, Japan from 10 August to 28 December 2009 with flu-like symptoms. We excluded children admitted more than 3 days before the onset of flu-like symptoms, because the illness was deemed incidental to their admission.

Infection with type A influenza virus was confirmed in 88 children by rapid antigen detection from their nasal swabs. Seventeen of them were further examined for pandemic H1N1 influenza virus genome with a real-time reverse transcription polymerase chain reaction (RT-PCR), which proved to be positive in all. The others were presumed to have pandemic H1N1 influenza based on the fact that more than 99% of influenza viruses isolated in the community at that time were pandemic H1N1 influenza virus.

Of the 88 patients, 53 had radiographic findings consistent with pneumonia. Pneumonia was defined as inflammation of lung parenchyma characterized by consolidation of the involved area with the alveolar air spaces being filled with exudates, inflammatory cells and fibrin, confirmed by chest radiograph. Among these patients, 34 underwent a chest CT scan; this was performed in patients with relatively severe underlying respiratory distress, but was not done as a routine. Hypoxemia was defined as an oxygen saturation of less than 93% while the patient was breathing ambient air. Thirty-four patients were divided into 2 groups based on their clinical course: group 1 were children who required oxygen administration (n = 22) and group 2 were children who did not (n = 12). We compared the clinical features of these children with those of 61 children admitted with seasonal influenza A during the previous 3 seasons (2006/07 to 2008/09).

Two experienced radiologists reviewed all chest CT scans independently in random order and decided the final interpretation by consensus. The reviewers were aware of the diagnosis of pandemic H1N1 influenza, but they were blinded to all other clinical information and the original radiological report of chest radiographs. The chest CT scans were evaluated for the pattern of lung parenchyma abnormalities such as ground-glass opacities (GGO), consolidation and nodular and reticular opacities. The presence of atelectasis, pleural effusion, mediastinal emphysema and lymph node enlargement was also assessed. GGO were defined as increased attenuation without obscuring the underlying vessels. Consolidation was defined as homogeneous opacification of the parenchyma with obscuring of the underlying vessels. Nodular opacities were defined as focal round opacities; reticular opacities were defined as linear opacities forming a mesh-like pattern. Atelectasis was defined as decrease or loss of air in all or part of the lung, with resulting loss of lung volume itself.

The anatomical distribution was characterized as unilateral or bilateral, and each lung was divided into upper, middle and lower lung zones. The distribution of parenchyma abnormality was categorized as focal, multifocal or diffuse. Focal implied a single focus of abnormality, multifocal as more than 1 focus and diffuse as involving the volume of 1 lung.

The CT studies were performed using a 320-MDCT scanner (Aquilion ONE, Toshiba, Japan). The protocol used was as follows: end-inspiratory acquisition, 120 kV, 50–165 mAs, and 1-mm reformation. The images were viewed on both lung (window width 1000 HU; level −700 HU) and mediastinal (window width 330–400 HU; level 40–50 HU) settings. No patient received intravenous contrast medium.

Continuous variables were summarized as mean (± standard deviation) or median (with interquartile range (IQR)). For categorized variables the percentage of patients in each category was calculated. Clinical characteristics were compared between children with pandemic H1N1 influenza and those with seasonal influenza with the use of the Wilcoxon rank-sum test, Chi-square test, or Fisher's exact test, as appropriate. The extent of chest CT abnormality was analyzed using Fisher's exact test. Anaysis was performed using computer software StatMate, version IV (ATMS, Japan). A p-value of less than 0.05 was considered statistically significant.

Results

Difference between clinical characteristics of pandemic H1N1 influenza and seasonal influenza A

The characteristics of 88 in-patients with pandemic H1N1 influenza and 61 with seasonal influenza A are summarized in Table I. The children with pandemic H1N1 influenza were significantly older than those with seasonal influenza (median age 6 y vs 1 y; $p < 0.001$). There was no difference in sex distribution. Underlying medical conditions were observed in 59% of the subjects with pandemic H1N1 influenza and 26% of those with seasonal influenza ($p < 0.001$). Children with pandemic H1N1 influenza were more likely to have asthma than those with seasonal influenza (35% vs 7%; $p < 0.001$). Compared with seasonal influenza, pneumonia was a more frequent complication with pandemic H1N1 influenza (60% vs 11%; $p < 0.001$), while febrile seizures were less frequent (6% vs 23%; $p < 0.01$). There were no differences in the leukocyte counts and levels of C-reactive protein between the 2 groups.

Table I. Characteristics of children who were admitted to the hospital with seasonal influenza A and 2009 pandemic influenza A (H1N1) virus infection.

Characteristic	Seasonal influenza A (Dec 2006–June 2009) (n = 61)	Pandemic H1N1 influenza (Aug 2009–Dec 2009) (n = 88)	p-Value
Male sex, n (%)	32 (52%)	53 (60%)	$p = 0.35$
Age y, median (IQR)	1 (1–4)	6 (3–8)	$p < 0.001$
Medical condition			
Any, n (%)	16 (26%)	52 (59%)	$p < 0.001$
Asthma, n (%)	4 (7%)	30 (35%)	$p < 0.001$
Complication			
Pneumonia, n (%)	7 (11%)	53 (60%)	$p < 0.001$
Febrile seizure, n (%)	14 (23%)	5 (6%)	$p < 0.01$
Length of hospital stay days, median (IQR)	4 (3–5)	5 (4–6)	$p < 0.01$
Laboratory data, mean ± SD			
Leukocyte count, per mm^3 (n)	8816 ± 4604 (n = 57)	8876 ± 4646 (n = 84)	$p = 0.94$
C-reactive protein, mg/dl (n)	2.23 ± 2.63 (n = 58)	2.51 ± 2.62 (n = 84)	$p = 0.53$

IQR, interquartile range; SD, standard deviation.

Pandemic H1N1 influenza viral pneumonia—clinical information

Fifty-three children with pandemic H1N1 influenza suffered from pneumonia, which was confirmed by radiographic findings such as pulmonary consolidation; their characteristics are summarized in Table II. They consisted of 34 boys and 19 girls with a median age of 6 y (IQR 5–8 y). Four (8%) were under 2 y of age, 15 (28%) were between 2 y and 5 y old and 34 (64%) were over 5 y of age. One or more underlying medical conditions were observed in 34 patients (64%), and included asthma (n = 20), allergic predisposition without asthma (n = 10), neurological disease (n = 5), renal disease (n = 1) and heart disease (n = 1). The time between the onset of symptoms and admission to the hospital was a median of 1 day (IQR 1–3 days). Thirty-three patients (62%) were admitted to the hospital within 24 h of the onset of symptoms. The arterial blood oxygen saturation was generally low – median of 91% (IQR 88–95%); 33 (62%) required oxygen administration. The duration of oxygen administration ranged from 1 to 13 days (median 2 days, IQR 2–4 days).

All 53 patients diagnosed as having viral pneumonia were treated with antiviral drugs: 32 with zanamivir, 20 with oseltamivir and 1 with a combination of oseltamivir and zanamivir. Among them, 46 (87%) received antiviral drugs within 48 h of the onset of symptoms. In addition, all patients received 1 or more types of antibiotic, that is, cefotaxime in 48 patients, clindamycin in 10 and minocycline in 2. Fifty patients (94%) received corticosteroids intravenously. Methylprednisolone was used in 47 patients, hydrocortisone in 2 and dexamethasone in 1. Two patients received high-dose intravenous methylprednisolone (pulse) therapy. Of the 53 patients, 2 were admitted to the intensive care unit (ICU) because of respiratory distress, but did not require intubation or mechanical ventilation. All patients recovered and were discharged from hospital, and the duration of hospital stay ranged from 3 to 13 days (median 5 days, IQR 5–6 days).

CT imaging findings of pandemic H1N1 influenza viral pneumonia (Figures 1, 2)

Chest CT scans were performed in 34 patients with viral pneumonia between 0 and 7 days after the onset of symptoms (median 1 day, IQR 1–2 days); the findings are summarized in Table III. Regarding the pattern of abnormalities, GGO were seen in 20 (59%) of the patients: 15 were multifocal and 5 were diffuse. Consolidations were seen in 30 (88%) of the patients: 15 were multifocal, 12 were diffuse and 3 were focal. As to the region of consolidation, 21 had peribronchovascular (PBV) consolidation and in 6 it was subpleural. Pleural effusion and mediastinal emphysema were seen in 8 and 3 of group 1 patients (n = 22), respectively, compared with 1 and none of group 2 patients (n = 12). Lymph node swellings were seen in 12 (35%) patients (7 from group 1 and 5 from group 2).

The distribution of lung abnormalities were bilateral in 18 (53%) of the patients and unilateral in the remaining 16 (47%). None of patients had nodular opacities or reticulation. There was no difference in the pattern of abnormalities and distribution between the study groups except for atelectasis, which was seen in 41% (9/22) of group 1 vs none (0/12) of group 2 patients ($p < 0.05$).

The most common chest CT findings were unilateral or bilateral multifocal consolidation (15/34), often associated with diffuse or multifocal GGO in the PBV region (21/34), most commonly in the lower

Table II. Summary of clinical characteristics of 53 children with 2009 pandemic influenza A (H1N1) viral pneumonia.

Characteristic	*n* (%)
Male sex, *n* (%)	34 (64%)
Age	
Median y (range, IQR)	6 (1–16, IQR 5–8)
<2 y, *n* (%)	4 (8%)
2–5 y, *n* (%)	15 (28%)
>5 y, *n* (%)	34 (64%)
Medical condition, *n* (%)	
Any	34 (64%)
Asthma, persistent type	7 (13%)
Asthma, intermittent type	13 (25%)
Allergic predisposition other than asthma	10 (19%)
Days from illness to admission, median days (range, IQR)	1 (0–7, IQR 1–3)
Duration of hospital stay, median days (range, IQR)	5 (3–13, IQR 5–6)
Oxygen saturation on room air (%), median (range, IQR)	91 (85–99, IQR 88–95)
<91%, *n*/total *n* (%)	25/52 (48%)
≥91%, *n*/total *n* (%)	27/52 (52%)
Treatment	
Use of antibiotics, *n* (%)	53 (100%)
Use of antiviral drugs, *n* (%)	53 (100%)
Use of antiviral drugs within 48 h onset of illness, *n* (%)	46 (87%)
Oseltamivir	20 (38%)
Zanamivir	32 (60%)
Combination therapy with oseltamivir plus zanamivir	1 (2%)
Use of corticosteroids, *n* (%)	50 (94%)
Hydrocortisone	2 (4%)
Methylprednisolone	47 (89%)
Dexamethasone	1 (2%)
Pulse therapy	2 (4%)
Oxygen administration, *n* (%)	33 (62%)
Duration of oxygen administration, median days (IQR)	2 (2–4)
Laboratory data, mean ± SD	
Leukocyte count, per mm^3	9760 ± 5223
C-reactive protein, mg/dl	3.17 ± 2.92

IQR, interquartile range; SD, standard deviation.

(25/34) and the upper (20/34) lung zones. The second prominent chest CT finding was unilateral diffuse consolidation or atelectasis in 1 or 2 lung zones with or without GGO (12/34).

Discussion

The pandemic H1N1 influenza virus is a new strain of triple-reassortant influenza A (H1N1) virus containing genes from swine, avian and human influenza viruses [2]. It was first identified in Mexico in April 2009 [1] and underwent rapid global spread. The World Health Organization (WHO) declared a pandemic Phase 6 on 11 June 2009 [11]. By 7 May 2010, more than 214 countries had reported laboratory confirmed cases of this pandemic influenza, including at least 18 001 deaths [12]. In Japan, since the first confirmed case was reported in May, the cumulative number of influenza-like illnesses reached approximately 20 million nationwide by 26 February 2010 [13].

During the early phase of this pandemic, it became apparent that the patient's age distribution differed from that of seasonal influenza. Sixty percent of patients with pandemic H1N1 influenza were 18 y old or less and only 5% were 51 y or older [2]. In our study, paediatric in-patients with pandemic H1N1 influenza were significantly older than those with seasonal influenza, that is, 55% were over 5 y of age and only 16% were under 2 y of age. These figures are similar to the initial reports from the USA [4], Chicago [14] and Toronto [15]. Interestingly, in Argentina [16], the majority of admitted children (75%) were younger than 2 y of age; 60% were infants under 1 y of age.

According to the USA report on a case series of hospitalized patients with pandemic H1N1 influenza from April to June 2009 [4], the virus caused severe illness, including pneumonia and acute respiratory distress syndrome (ARDS), and resulted in ICU admission in 25% of patients and death in 7%. In this series, antiviral drugs were administered to almost all patients; however, such therapy was generally started more than 48 h after the onset of illness. According to the WHO guidelines on the pharmacological management of influenza virus, patients who are at risk for pneumonia should be treated with oseltamivir or zanamivir as soon as symptoms develop, if possible [17]. Delayed initiation of antiviral therapy may have contributed to an increased severity of illness in the US series.

In our study, the time between symptom onset and admission was a median 1 day and 87% of patients received antiviral drugs within 48 h of the onset of symptoms. Of the total 53 patients with pneumonia, only 2 were admitted to the ICU, but did not require intubation or mechanical ventilation. All our patients recovered in a relatively short period of time. This may be due in part to early diagnosis with the rapid antigen test and early antiviral therapy.

Pandemic H1N1 influenza caused pneumonia more frequently than occurs with seasonal influenza [1–4]. Pathological evaluation of the lung showed alveolar damage, thick hyaline membranes and prominent fibroblast proliferation [1,18]. During the 1918 flu pandemic, a large number of deaths were associated with bacterial infection; however, in the patients with the present pandemic influenza, concurrent bacterial infection does not appear to be a major factor for deterioration in the illness. Lung damage was most likely due to the primary effect of influenza virus infection [1].

Our experience and previous reports [4,14–16] show that asthma is a more significant risk factor

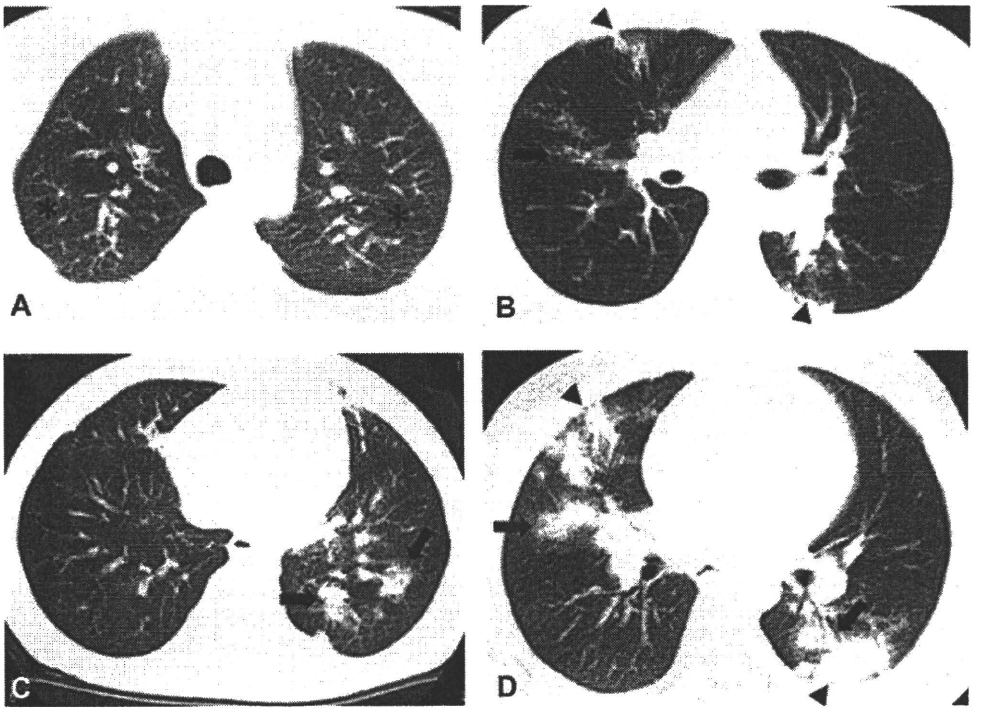

Figure 1. Representative axial chest CT findings in subjects with 2009 pandemic H1N1 influenza viral pneumonia. (A) 7-y-old boy admitted with a 1-day history of fever and headache, showing bilateral diffuse ground-glass opacities (asterisks). (B) 5-y-old girl admitted with a 1-day history of fever, cough and dyspnoea, showing multifocal consolidation associated with multifocal ground-glass opacities in peribronchovascular (arrows) and subpleural (arrowheads) distribution. (C) 8-y-old boy hospitalized with a 2-day history of fever, cough and dyspnoea, showing bilateral diffuse ground-glass opacities and unilateral multifocal consolidation in peribronchovascular distribution in the left lung (arrows). (D) 4-y-old girl admitted on the first day of illness because of fever and cough, showing bilateral consolidation in peribronchovascular (arrows) and subpleural (arrowheads) distribution.

for hospitalization with pandemic H1N1 influenza than with seasonal influenza. Interestingly, not only symptomatic but also controlled-asthma were risk factors for increased severity of pandemic H1N1 influenza. Hyper-reactivity of the lower airway, which is thought to persist in controlled asthmatics, could act adversely. Further clinical and experimental studies are needed to elucidate the correlation.

In our series, most children with pneumonia developed respiratory distress within a relatively short time, as previously reported [1]. It has been reported that the time from hospitalization to the need for mechanical ventilation might be as short as 24 h or less [1]. Although the use of corticosteroids is the standard of care for children with viral or bacterial pneumonia, we used corticosteroids in the short term combined with antiviral drugs and antibiotics to prevent the onset or exacerbation of an asthma attack, because many children with pandemic H1N1 influenza had asthma as an underlying medical condition. Although the good outcome in our patients possibly reflects the early treatment with corticosteroids combined with antiviral drugs and antibiotics, the evidence supporting the benefits of corticosteroids in the treatment of the pandemic H1N1 influenza remains inconclusive. Further randomized controlled trials are needed to evaluate steroid efficacy.

The chest CT scan examinations were performed on median 1 day (IQR 1–2 days) after the onset of symptoms. Therefore almost all our CT findings represent the early stages of pandemic H1N1 influenza pneumonia. The most common CT findings were unilateral or bilateral multifocal consolidation, often associated with multifocal or diffuse GGO in PBV and/or subpleural distribution. These findings are consistent with those recently reported [7–9] in adult patients who had an advanced clinical course of pandemic H1N1 influenza requiring ICU admission and mechanical ventilation, although the clinical course of our patients was rather mild. The second most common CT findings were unilateral diffuse consolidation or atelectasis in 1 or 2 lung zones, with or without GGO. These findings are somewhat different from the typical pattern of pandemic H1N1 influenza pneumonia and resemble secondary bacterial lobar pneumonia, although its clinical course including its early onset and negative laboratory findings

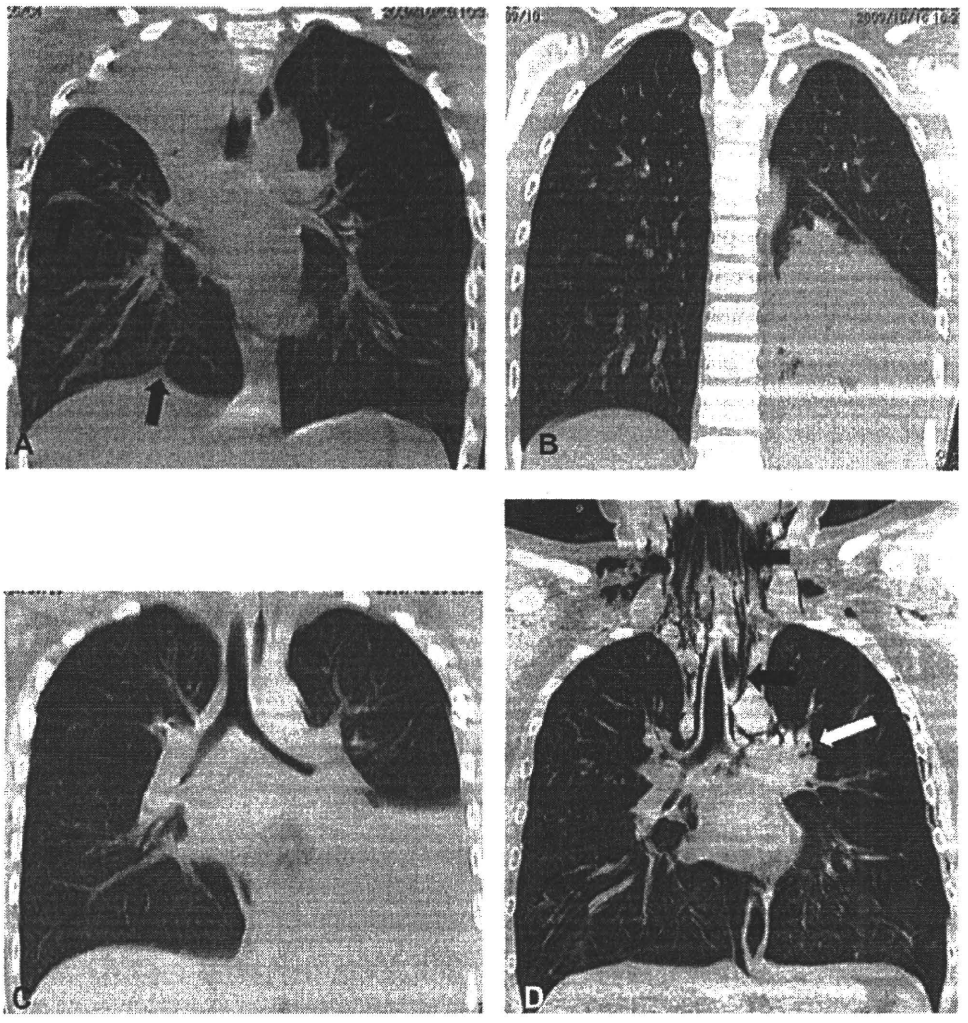

Figure 2. Representative coronal reformatted chest CT findings in subjects with 2009 pandemic H1N1 influenza viral pneumonia. (A) 8-y-old boy with pandemic H1N1 influenza admitted to the ICU because of respiratory distress, showing bilateral diffuse ground-glass opacity, atelectasis in right upper lobe and pleural effusion (arrows) in the right lung. (B) 7-y-old boy admitted with a 1-day history of fever, cough and dyspnoea, requiring oxygen administration, showing atelectasis of the left lower lobe. (C) 5-y-old boy admitted with a 1-day history of fever, cough and dyspnoea, showing atelectasis of left lower lobe and pleural effusion in the left lung. (D) 9-y-old boy admitted with a 1-day history of fever and dyspnoea, showing mediastinal and subcutaneous emphysema (arrows) and unilateral multifocal consolidation (open arrow) in left lower lobe.

for bacteria favour a primary viral pneumonia. All the patients with atelectasis who required oxygen administration had a relatively severe clinical course.

In general, the CT examination is more sensitive than chest radiography in detecting imaging abnormalities such as GGO and is also more accurate in identifying the distribution of lung pathology. These chest CT findings in the early stages of pandemic H1N1 influenza pneumonia could facilitate its early diagnosis and treatment and help to prevent its progression.

Our study has some limitations. First, it is retrospective in nature. Second, we do not have laboratory evidence of pandemic H1N1 influenza in a subset of patients who were confirmed to have only influenza A virus antigen. Third, all diagnostic testing and CT scans were obtained in a non-standardized fashion. Fourth, none of the patients underwent lung biopsy or autopsy that would have allowed CT findings with histopathological correlation.

In conclusion, early diagnosis of influenza A by rapid antigen test and early treatment with antiviral drugs combined with corticosteroids and antibiotics might effectively reduce the severity of pandemic H1N1 influenza. The chest CT findings of unilateral or bilateral multifocal consolidation often associated

Table III. Summary of chest CT findings in children with 2009 pandemic influenza A (H1N1) viral pneumonia.

CT findings	All (n = 34)	Group 1 (n = 22)	Group 2 (n = 12)	p-Value
Pattern of abnormality				
GGO	20 (59%)	11 (50%)	9 (75%)	$p = 0.27$
Multifocal	15 (44%)	9 (41%)	6 (50%)	$p = 1$
Diffuse	5 (11%)	2 (9%)	3 (25%)	$p = 0.32$
Consolidation	30 (88%)	21 (95%)	9 (75%)	$p = 0.12$
Multifocal	15 (44%)	11 (50%)	4 (33%)	$p = 0.48$
Focal	3 (9%)	2 (9%)	1(8%)	$p = 1$
Diffuse	12 (35%)	9 (41%)	3 (25%)	$p = 0.47$
Subpleural	6 (18%)	2 (9%)	4 (33%)	$p = 0.15$
PBV	21 (62%)	14 (64%)	7 (58%)	$p = 1$
GGO + consolidation	16 (47%)	10 (45%)	6 (50%)	$p = 1$
GGO only	4 (12%)	1 (5%)	3 (25%)	$p = 0.12$
Consolidation only	14 (41%)	11 (50%)	3 (25%)	$p = 0.27$
Atelectasis	9 (26%)	9 (41%)	0 (0%)	$p < 0.05$
Pleural effusion	9 (26%)	8 (36%)	1 (8%)	$p = 0.11$
Mediastinal emphysema	3 (9%)	3 (14%)	0 (0%)	$p = 0.54$
LN swelling	12 (35%)	7 (32%)	5 (42%)	$p = 1$
Distribution				
Bilateral	18 (53%)	11 (50%)	7 (58%)	$p = 1$
Upper	20 (59%)	13 (59%)	7 (58%)	$p = 1$
Middle	11 (32%)	7 (32%)	4 (33%)	$p = 1$
Lower	25 (74%)	18 (82%)	7 (58%)	$p = 0.22$
Single zone	16 (47%)	8 (36%)	8 (67%)	$p = 0.15$
Multiple zone	18 (53%)	14 (64%)	4 (33%)	$p = 0.15$

GGO, ground-glass opacities; PBV, peribronchovascular.

with GGO in PBV and/or subpleural distribution are common findings not only in adult patients with an advanced course of pandemic H1N1 influenza, but also in children with relatively mild clinical features. Unilateral diffuse consolidation or atelectasis in the early stages of the illness may identify those children who require more intensive therapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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