RESEARCH PAPER

Clinical Profile and Outcome of Swine Flu in Indian Children

RASHMI RANJAN DAS, ABDUS SAMI, RAKESH LODHA, RICHA JAIN, S BROOR*, S KAUSHIK*, BB SINGH*, M AHMED*, RACHNA SETH AND SUSHIL K KABRA

*From the Departments of Pediatrics and *Microbiology, All India Institute of Medical Sciences, New Delhi 110029, India.*
Correspondence to: Dr SK Kabra, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India. skkabra@hotmail.com
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Objective: To describe the clinical characteristics and outcome of Indian children infected with 2009 H1N1 influenza virus.

Study design: Retrospective chart review.

Setting: Outpatient department and hospitalized patients in a tertiary care hospital.

Methods: Clinical details of 85 children (positive for the 2009 H1N1 virus infection tested by real-time reverse-transcriptase–polymerase-chain-reaction assay) were analyzed from medical charts.

Results: Of the 85 (55 boys) children positive for 2009 H1N1 virus infection, 64.7% were between 5 years to 16 years, and 35.3% were below 5 years age. The mean age of these children was 7.5±3.5 yr. Contact history was positive only in 22 (26%) cases. High grade fever was the most common symptom, followed by cough and rhinorrhea. Twenty-nine (34%) patients had an underlying co-morbid condition. Of the 34 patients who underwent chest radiography during evaluation, 18 children (52.9%) had findings consistent with lower respiratory tract infection. Antiviral therapy was initiated in 76 patients. Hospitalization was required in 30 (35.3%) children. Risk factors for hospitalization included underlying co-morbid condition, respiratory distress, vomiting, wheezing, diarrhea, hypotension and infiltrates/consolidation on chest radiograph. Mean length of hospitalization was 131±76 hours, irrespective of underlying disease. Three children developed Acute Respiratory Distress Syndrome and died.

Conclusions: Clinical features and routine laboratory investigations in children with swine origin influenza were non-specific. Children with co-morbid condition, respiratory distress, vomiting, wheezing, diarrhea, hypotension and infiltrates/consolidation on chest radiograph were at higher risk of hospitalization.

Key words: *Acute lung injury, ARDS, H1N1 influenza, Pandemic influenza, Swine origin influenza.*

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Swine origin influenza has become the first pandemic of the 21st century [1]. The currently circulating strain of swine origin influenza virus of the H1N1 strain has undergone triple reassortment and contains genes from the avian, swine and human viruses [2,3]. It is believed to be a legacy of the influenza pandemic of 1918-1919 the virus having adapted over the last 91 years and has now acquired the ability to not only infect but also spread within the human host [4]. The symptoms of 2009 H1N1 influenza are expected to be similar to the symptoms of regular human seasonal influenza and include fever, cough, sore throat and myalgia. A feature seen more frequently with 2009 H1N1 influenza is gastrointestinal upset with almost a quarter of patients presenting with vomiting and diarrhea [1,5].

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The epidemic of 2009 H1N1 influenza is spreading rapidly in the Indian subcontinent with more than 23727 cases and 782 deaths [6]. There have been sporadic reports about swine flu in pediatric population [7-9]. We hereby share our experience with 2009 H1N1 influenza in children seen between August and December 2009.

METHODS

We conducted a retrospective chart review of patients who were seen at our hospital from August to December 2009. Eligible patients were infants and children under the age of 16 years who were admitted to pediatric wards and intensive care unit (ICU) with a diagnosis of acute respiratory infection or fever; all such eligible children were tested for influenza viruses. In the out-patient department, children under the age of 16 years presenting with features of acute respiratory infection or fever were screened; children of the hospital employees underwent testing for influenza viruses in our center, while other children were referred to the government designated centers for the diagnostic test as per the government guidelines. The diagnosis of 2009 H1N1 influenza was confirmed by testing of combined nasal and throat swabs with the use of a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay. Children were treated with oseltamivir as per the available guidelines issued by the Ministry of Health, Government of India, which were periodically revised [10]. In children presenting with mild symptoms, the medication was administered if the RT-PCR assay confirmed the diagnosis. In children who were admitted with a suspicion of swine flu, medication was started after sending the sample for the RT-PCR test for 2009 H1N1 influenza; it was continued in those who tested positive.

The study was conducted as a retrospective analysis of de-identified data. We obtained demographic, clinical, laboratory, epidemiologic, and radiologic data from a chart review. Hypoxemia was defined as an oxygen saturation of less than 93% while the patient was breathing ambient air.

Statistical analysis: The data were managed on Microsoft Excel and analyzed on Stata 9.0 (Stata Inc, College Station, TX). The chi-square test or Fisher's exact test was used to assess the statistical significance of differences in categorical variables, and the Wilcoxon ranksum test was used to compare continuous variables. A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Of the 260 children tested, a total of 85 (55 boys) children were found to have 2009 H1N1 infection during study period (August to December 2009) (***Table* I**). Twenty-nine (34%) patients had significant pre-existing disorders including asthma (9), chronic respiratory illness (6), neurological problems (4), malignancy (2), immunodeficiency (1), disseminated tuberculosis (1), chronic liver disease (1), chronic kidney disease (1), and restrictive cardiomyopathy (1).

After fever, cough and coryza were the most common symptoms. Other symptoms included sore-throat, vomiting, headache, diarrhea, respiratory distress, myalgia, lethargy, decreased oral accep-tance, hypotension, wheezing, croup, flushed face. Mean (± SD) duration of symptoms was 3.9 (± 2) days and median duration was 5 days (range, 1-15).

Antiviral therapy (oseltamivir) was initiated in 76 (89%) patients at a mean of 5.3 ± 1.8 days after the onset of illness. Fifty two patients (68%) started showing response to oseltamivir (in form of being afebrile and improved subjective wellbeing) within 24 hours. Out of 85 children, 9 recovered without administration of oseltamivir or antibiotic. In 44 (51.8%) children, antibiotics were started either due to severe upper respiratory or chest symptoms or possible infection/sepsis. Twenty six children received oseltamivir alone for recovery.

Thirty (35.3%) children required hospitalization for various reasons. Among 20 children having respiratory distress, 17 children were hypoxic at admission and required oxygen therapy. Of these 17 children, 6 children required mechanical ventilation

TABLE I DEMOGRAPHIC PROFILE OF CHILDREN WITH 2009 H1N1 INFLUENZA (*N*=85)

Characteristics	Number (%)
Males	55 (64.7)
Age (mean)	7.5 ± 3.5 years
≤ 2 years	06
2-5 years	25
5- 9 years	25
9-16 years	29
History of contact	22 (26)
History of foreign travel	2 (3)

as well as vasoactive medication support for shock. Mean length of hospitalization was 131±76 hours.

Three children developed ARDS and succumbed to the illness, all other children recovered. Of the 3 children who died, one (12 years old) had underlying steroid resistant nephrotic syndrome with chronic kidney disease and he was admitted with diagnosis of severe pneumonia and tested positive for H1N1 influenza infection; the child died within 24 hours of admission. Another (age 9 years) had diagnosis of refractory epilepsy with developmental delay and he was admitted with severe pneumonia. The third child (2.5 years) who died had diagnosis of tuberous sclerosis with Lennoux-Gastaut syndrome and presented with ARDS with refractory shock and died of refractory hypoxemia.

Mean (SD) total leukocyte count was 7915 (3908)/mm^3 and mild leucopenia (<5000/mm^3) was observed in 35% children (includes 2 children with febrile neutropenia). Mean (SD) hemoglobin level (*n* = 41) was 10.9 (1.3) g/dL with low level (<10 g/dL) observed in 8 children. Mean (SD) platelet count (*n*=41) was 2.01 (1.09) lakh/mm^3 with thrombocytopenia (platelets <150000/mm^3) being observed in 37.5% children (15/41). Four children (out of 30) had elevated total serum bilirubin (>1mg/dL) and among these 2 had underlying chronic liver disease. Fourteen children (out of 30) had elevated ALT and AST, with 10 children having elevation of both ALT and AST >2 times upper normal limit (0- 40 IU/L). Abnormalities in chest radiography were detected in 18 (out of 34) children on presentation/admission or during hospitalization. The most common features were infiltrates either unilateral or bilateral (41.2%) followed by consolidation patch involving one or both lung fields (11.8%).

Few bacterial co-infections were detected as bacterial diagnostic tests were not performed in all patients; blood samples for cultures were taken only in hospitalized children. Only one of the hospitalized children had blood culture positive sepsis (*Klebsiella pneumoniae*).

The risk factors for hospitalization are shown in ***Table* II**. The mean age of children who required hospitalization was lower than those who received ambulatory care. The risk factors for hospitalization were: children with underlying co-morbid condition, and children with symptoms like-respiratory distress, vomiting, wheezing, or diarrhea. Children having infiltrates/consolidation patch on chest radio-

TABLE II RISK FACTORS FOR HOSPITALIZATION IN THE STUDY POPULATION

Characteristics	Group A *n* = 55	Group B *n* = 30	*P* value
Age (y) (mean ± SD)	8.2 ± 3.3	6.4 ± 3.8	0.018
Sex; male (%)	31 (56.4)	24 (80)	0.029
Underlying co-morbid condition (%)	8 (14.5)	21 (70)	<0.001
Symptoms (%)			
Respiratory distress	0	20 (66.7)	<0.001
Vomiting	9	8 (26.7)	<0.001
Wheezing	1	7 (23.3)	0.002
Diarrhea	0	3 (10)	0.04
Duration of symptoms at presentation (d) (mean ± SD)	3.5 ± 1.3	4.7 ± 2.6	0.03
Interval between onset of symptoms and initiation of oseltamivir (d) (mean ± SD)	4.8 ± 1.3	6.1 ± 2.1	0.007
Infiltrates/consolidation on chest radiograph (%)	1/13 (7.7)	17/21 (80.9)	<0.001
Antibiotic treatment (%)	24 (43.6)	20 (66.7)	0.042

SD = standard deviation; Group A received ambulatory treatment; Group B received hospitalization. Number in parentheses are percentages.

WHAT IS ALREADY KNOWN?

- The clinical features of the ongoing Swine origin influenza pandemic are non-specific and are similar to other viral infections.

WHAT THIS STUDY ADDS?

- Clinical features and routine laboratory investigations in children with swine origin influenza were non-specific.
- Risk factors for hospitalization include: underlying co-morbid condition, respiratory distress, vomiting, wheezing, diarrhea, or hypotension, infiltrates/consolidation on chest radiograph.
- Majority of the children with swine origin influenza had a benign course and a good outcome.

graph were also more prone for hospitalization. Children who were hospitalized had a longer duration of symptoms and also a longer interval between onset of symptoms and initiation of oseltamivir.

DISCUSSION

As of 10 January 2010, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza (H1N1) 2009, including at least 13554 deaths [11]. But in the Indian subcontinent, there are more than 23727 laboratory confirmed cases with more than 782 (3.3%) deaths [6]. Our experience of the pediatric 2009 H1N1 influenza infection in New Delhi, India, shows that presentations can be atypical, severity is associated with underlying disease, and rates of secondary bacterial infection are low.

The proportion of children who had an underlying condition in our study (38%) was similar to that reported in children with seasonal influenza (31-43%) [12-14]. As in patients with seasonal influenza, asthma was the most common underlying conditions in our patients [12]. Antiviral drugs were administered to most patients (89.4%), but such therapy was started more than 48 hours after the onset of illness in a majority of the patients. The interval between the onset of symptoms and the initiation of oseltamivir was longer in children who were hospitalized than those who received ambulatory care. This is similar to that reported in other series [15,16]. Due to non-specific symptomatology children who had not received oseltamivir timely had high probability of hospitalization, thus adding to the impression of delayed administration of oseltamivir in hospitalized children. Secondly, being a tertiary care hospital, children referred from outside with severe illness (without obvious cause) were tested only after getting admitted to our hospital; there was a time gap for administration of oseltamivir after onset of illness.

While the risk factors/groups are not well defined for the 2009 H1N1 influenza, they are likely to be similar to those for seasonal influenza. Patients susceptible to severe disease are – those younger than five years and over sixty five years of age, pregnant women, those with systemic illnesses, adolescents on aspirin, residents of nursing homes and immune suppressed. Among these, children younger than 4 years have the highest complication and death rates [16]. Pediatric data for severe disease include: chronic respiratory illness including asthma, neuromuscular disorders, cerebral palsy, developmental delay, immunodeficiency, heart disease, and prematurity [7,9,16].

Majority of children with underlying disease fully recovered, which may be explained by seeking medical attention before serious complications as many were children of parents who are employed in our hospital, this group also includes children in follow up clinics for major illnesses. Hospitalized children were more likely to receive antibiotics in view of possible sepsis/infection or complications. Patients who expired came to hospital in an advanced stage of illness. Out of three deaths, two occurred in children who presented with serious complication of acute lung injury and one had

profound shock at presentation. All expired within 24 hours of hospitalization.

We found history of contact in only 26% children; this suggests that H1N1 flu was widespread in the community. Travel history was also not significant now as only two children had history of foreign travel. Clinical features and routine laboratory investigations were non-specific and also could not be distinguished from other viral infections, as described previously. The clinical features of patients who were hospitalized with 2009 H1N1 influenza were generally similar to those reported during peak periods of seasonal influenza and past pandemics with an acute onset of respiratory illness [17-20]. Whereas diarrhea or vomiting have occasionally been reported in children during peak periods of seasonal influenza [18], these symptoms were reported in 10-27% of patients in our study. Incidence of diarrhea was reported to be between 8-20% and vomiting in 10-40% in children infected with swine origin H1N1 infection [9,16]. In one report incidence of diarrhea or vomiting was reported to be in 42% of children [15]. As found in other studies, occasional case may present without respiratory symptoms. Recovery was very fast in all the patients irrespective of underlying illness, which is in contrast to other studies. Some patients recovered without complications even without antiviral therapy, so antiviral therapy may not be required in all cases. Few complications in the patients including those with underlying high risk illness tells that majority of children will have a benign course.

Our study has several limitations. In this retrospective chart review, majority of the patients we evaluated were children of hospital employees, who may seek early evaluation and treatment. The number of children evaluated was also small (though it is the largest data on pediatric H1N1 flu from a single centre). We evaluated only patients with confirmed 2009 H1N1 influenza virus infection, so the group may not be representative of patients who may not have been tested. Finally, despite the use of a standardized data-collection form, not all information could be collected for all patients.

Clinicians should consider H1N1 influenza in the differential diagnosis of children with pre-existing disorders who present acutely to health services even if there are no classic flu like symptoms or an alternative diagnosis is suspected, especially if there are severe symptoms or underlying disease. It is imperative that further data are collected prospectively on the clinical presentations and predictors of severity in H1N1 influenza.

To conclude, H1N1 infection should be considered in the differential diagnosis for patients presenting with fever and respiratory illness or pneumonia. Majority will have a benign course. As the 2009 H1N1 pandemic evolves, continued investigation is needed to better define the clinical spectrum of disease and risk factors for an increased severity of illness, which will allow for improvements in treatment guidance.

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