Original Article

Characteristics of Hospitalized Patients with Severe and Non-Severe Pandemic Influenza A (H1N1) in Saurashtra Region, India (Two Waves Analysis)

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Abstract

Background: In India, the first case of 2009 pandemic influenza A (H1N1) virus infection was reported in May 2009 and the same in Saurashtra region in August 2009. We describe the epidemiology and factors associated with severe and non-severe cases of 2009 influenza A (H1N1) infection reported in the Saurashtra region. **Materials and Methods:** From September 2009 to January 2011, we reported 511 patients who were infected with 2009 influenza A (H1N1) virus and admitted in different hospitals of Rajkot city. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing was used to confirm infection. Factors associated with severe cases were determined by comparing with non-severe cases. **Results:** Out of 511 patients, 140 had severe disease (requiring intensive care or died) and 371 non-severe diseases (admitted in wards and survived). Median age of 30 years; median time of 5 days from onset of illness to diagnosis, and 4 days median time was reported for hospital stay among severe disease patients. More than half (60.7%) were females. Out of the patients with severe disease, 52.1% patients residing in urban area (OR = 1.68, CI = 1.13-2.49). Significant association was reported among severe disease patients for delayed referral from general practitioner/physician after initial treatment. All patients received antiviral drug, however, only 27.1% received within 2 days of illness. Presence of coexisting condition (pregnancy (OR = 0.19, CI = 0.08-0.48) was strongly associated with severe disease. **Conclusion:** Delayed referral from general practitioner/physician, duration of antiviral treatment, presence of coexisting condition (i.e., pregnancy) were responsible for intensive care or mortality among severe influenza A (H1N1) illness.

Keywords: Epidemiology, influenza A (H1N1), intensive care, pregnancy, reverse transcriptase-polymerase chain reaction, severe disease

Introduction

The novel influenza A (H1N1) virus was first detected in Mexico[1] during April 2009, and then in United States (US).[2] The scientists call this a 'quadruple reassortant' virus and hence this new (novel) virus is christened "Influenza A (H1N1) virus".[3,4] The World Health Organization (WHO) raised the pandemic level from 5 to 6, the highest level, after the documentation of human to human transmission of the virus in at least three countries in two of the six world regions defined by the WHO.[5]

India reported first confirmed case of influenza A (H1N1) during May, 2009.[6] Gujarat state reported first H1N1 positive confirmed case during June 2009.[7] Saurashtra region is the western part of Gujarat state, reported first case in August 2009.[8] Although many individuals presented with mild, self-limited illness, no signs of pulmonary involvement; some people required intensive care and received maximal life support measures.[9,10] The objective of present study was to identify characteristics associated with severity of disease in 511 confirmed cases of pandemic H1N1 influenza, hospitalized in various hospitals of Rajkot.

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Materials and Methods

Data sources

Total 511 patients found positive for pandemic Influenza A (H1N1) and admitted in different hospitals of Rajkot from September 1, 2009 to January 31, 2011 combining two waves, were included for analysis. Though no cases were reported

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after November 2010, the surveillance was continued till February 2011.

Categorization of influenza A (H1N1) case

Ministry of Health and Family Welfare (MOHFW), Government of India (GOI) had issued guidelines for categorization of influenza A (H1N1) cases during screening for home isolation, testing treatment, and hospitalization [Table 1].[11] Current report describes total 511 patients belonging to category C who were tested and confirmed, hospitalized, monitored, and included in the analysis. A confirmed or suspected case was defined as per the MOHFW guidelines.[12]

Criteria for intensive care unit admission

All patients were categorized as: (1) Cases as severe influenza A (H1N1) patients - those patients needed intensive care unit (ICU) or died. Patients with one or more of following feature were admitted in ICU: (a) SpO_2 < 60 mm Hg, (b) Not maintaining SpO_2 with oxygen mask, (c) tachypnea and dyspnea, (d) respiratory rate > 40/min, (e) with altered sensorium, (f) patchy consolidation on X ray chest. (2) Controls as non-severe influenza A (H1N1) patients – those admitted in wards survived and not needed intensive care. Patients not fulfilling any of above criteria were admitted in wards for clinical management.

For patients below 15 years of age following criteria were used to categorize as severe influenza A (H1N1) patients – PaO_2 < 60 mm of Hg, hypercapnoea (pCO_2 > 55 mm of Hg, severe metabolic acidosis (pH < 7.2), severe respiratory distress (respiratory rate > 70/min), severe lower chest wall indrawing, altered sensorium, grasping or apnea, and shock.

Variables

Several types of data was collected from the patients: Date and time of admission to hospital/ICU, age, sex, residential status, co-existing conditions, date, and time of first symptoms. Also, as mentioned, data for other variables were collected [Table 2].

Data management

All patients' admission history and their medical records were assessed from swine flu ward for initial clinico-epidemiological details, and from medical record and statistics department after patient discharge/death from various hospitals of Rajkot city. Line list number was given to every patient to avoid duplication at any time during study period. Approval by institutional review board was not required because the present infectious disease was covered under epidemic act and the State Health Department[13] has implemented the Epidemic Disease Control Act, 1897.

Laboratory confirmation of infection

The influenza A (H1N1) virus was detected with the use of real time reverse transcriptase polymerase chain reaction (RT-PCR) assay by collecting two swabs from naso-pharynx and one from pharynx, in accordance with the protocol from the US centers for Disease Control and Prevention, as recommended by the WHO.[14]

Statistical analysis

All data was entered in MS Excel, and analyzed by using Epi Info software (version 3.5.1) from CDC.[15] Bivariate analysis was done using χ^2 test or Fisher`s exact test for analysis. Variables that showed $P < 0.20$ in bivariate analysis were selected for logistic regression to examine the relation between variables of interest and severity of disease. Results from logistic regression analyses expressed as odds ratio (OR), and 95% confidence intervals (CIs). The *P* values and CIs reported here reflect a two tailed α level of 0.05.

Results

Demographic and clinical characteristics of patients

Out of 511 cases of influenza A (H1N1), 140 patients (27.4%) reported with severe disease and 371 patients (72.6%) as non-severe disease [Table 2]. Among 140 severe disease patients, mortality was reported in majority (90.7%) patients, while only 9.3% patients needed intensive care and survived. Month-wise distribution of influenza A (H1N1) infected patients for two waves is shown in Figure 1.

The median age of 30 years was reported in both severe (range 4 months to 68 years) and non-severe disease patients (range 1 month to 70 years). More females (60.7%; OR = 0.53, CI = 0.36-0.79)

Table 1: Categorization of influenza A (H1N1) patients as per clinical features

Category and clinical features	Antiviral treatment	RT-PCR testing and hospitalization
Category A: Mild fever, cough/sore throat, bodyache, headache, diarrhea, vomiting. Patient should be monitored and reassessed after 24-48 h	Not needed	Not needed
Category B (1): Signs of category A, and/or high grade fever, severe sore throat. Home isolation is advisable	May be given	Not needed
Category B (2): Signs of category A, and/or any of the high risk conditions like, children with mild illness but with predisposing risk factors; pregnant women; persons aged 65 years or more; patients with lung, liver, hear, kidney diseases, blood disorders, diabetes, neurological disorders, cancer, HIV/AIDS; long term steroid therapy	Given	No testing required but hospitalization may be needed
Category C: In addition to signs and symptoms of category A and B, any of the following: Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails; children with red flag signs like somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing; worsening of underlying chronic conditions	Start immediately	Immediate testing and hospitalization

RT-PCR: Reverse transcriptase polymerase chain reaction; HIV/AIDS: Human Immunodeficiency Virus / Acquired Immuno Deficiency Syndrome

Table 2: Baseline characteristics of 2009 influenza A (H1N1) infected patients in Saurashtra region from September 2009 to January 2011

Characteristics	Severe influenza A (H1N1) (*N*=140)	Non-severe influenza A (H1N1) (*N*=371)
Age		
Median	30 years	30 years
Range	4 months-68 years	1 month-70 years
	N (%)	*N* (%)
Age group of patients (years)		
<15	34 (24.3)	80 (21.6)
15-24	14 (10.0)	68 (18.3)
25-44	54 (38.6)	127 (34.2)
45-64	36 (25.7)	86 (23.2)
≥65	2 (1.4)	10 (2.7)
Sex		
Female	85 (60.7)	168 (45.3)
Male	55 (39.3)	203 (54.7)
Residential status		
Urban	73 (52.1)	240 (64.7)
Rural	67 (47.9)	131 (35.3)
First treated at general practitioner/physician	82 (58.6)	165 (44.5)
Hospital stays (days)		
Median	4	7
≤2	50 (35.7)	20 (5.4)
3-5	42 (30.0)	100 (27.0)
6-10	21 (15.0)	171 (46.1)
≥11	27 (19.3)	80 (21.6)
Time interval from onset of illness to hospital admission and diagnosis (days)		
Median	5	5
≤1	12 (8.6)	20 (5.4)
2-4	45 (32.1)	160 (43.2)
5-10	76 (54.3)	168 (45.4)
>10	7 (5.0)	22 (5.9)
Antiviral treatment received	140 (100)	371 (100)
≤2 days after onset of symptoms	38 (27.1)	38 (10.2)
Patients kept on ventilators (days)	109 (77.9)	0
Median duration on ventilators	3	0
Hospital outcome		
Intensive care and survived	13 (9.3)	0
Intensive care and died	127 (90.7)	0

Table 3: Clinical features and coexisting conditions among influenza A (H1N1) infected patients

Characteristics	Severe influenza A (H1N1) (*N*=140)	Non-severe influenza A (H1N1) (*N*=371)
	N (%)	*N* (%)
Clinical features		
Cough	137 (97.9)	364 (98.1)
Fever (≥37.5°C)	132 (94.3)	353 (95.4)
Sore throat	74 (52.9)	232 (62.5)
Shortness/difficulty in breathing	99 (70.7)	263 (70.9)
Nasal catarrh	48 (34.3)	136 (36.7)
Headache	42 (30.0)	66 (17.8)
Vomiting	17 (12.1)	30 (8.1)
Coexisting conditions		
Any one condition	47 (33.6)	113 (30.5)
Hypertension	9 (6.4)	44 (11.9)
Diabetes mellitus	10 (7.1)	38 (10.2)
Chronic pulmonary diseases	3 (2.1)	19 (5.1)
Pregnancy*	14 (10.0)	8 (2.2)
Seizure disorder	3 (2.1)	11 (3.0)
Chronic heart diseases	4 (2.9)	5 (1.3)
Thalassemia	3 (2.1)	2 (0.5)
Chronic renal failure	1 (0.7)	2 (0.5)

*$P<0.05$

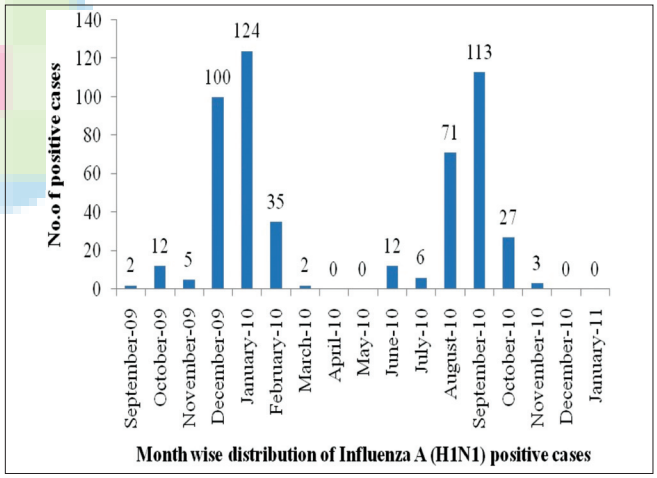

Figure 1: Month wise distribution of infected influenza A (H1N1) cases from September 2009 to January 2011 in Saurashtra region

needed intensive care than males. Total 47 (31.3%) cases had an underlying medical condition [Table 3], reported more among severe disease patients (33.6%). Diabetes mellitus (DM) (10.2%) and/or hypertension (11.9%) was mainly reported underlying condition among non-severe disease. However, pregnancy (10.0%; $P < 0.05$) was reported mainly among patients with severe disease [Table 3]. Among reported female patients, 14 were pregnant with a range of 4 to 9 months of amenorrhea, A significant risk of severe disease was reported with pregnancy (OR = 0.19, CI = 0.08-0.48) . Various laboratory and radiological findings were reported [Table 4]. Pneumonia was reported more among patients with severe disease (86.7%; OR = 0.30, CI = 0.16-0.53) [Table 5].

Treatment outcome

More than half of the patients with severe disease, that is, 58.6% and 44.5% non-severe disease patients were first treated by general practitioner/physician and then referred to a higher centre (OR = 0.56, CI = 0.38-0.83). Among 140 severe disease patients who needed intensive care, 90.7% reported mortality and 9.3% survived.

All patients received the antiviral drug, oseltamivir [Table 2]. Out of 140 severe disease patients, 27.1% received antiviral

Table 4: Laboratory and radiological findings of influenza A (H1N1) infected patients[a]

Characteristics	Severe influenza A (H1N1) N/N (%)	Non-severe influenza A (H1N1) N/N (%)
Leukocyte count		
Mean count	9499±9321	7799±4659
Leukopenia (<4,000/mm^3)	25/112 (22.3)	69/341 (20.2)
Leukocytosis (> 10,000/mm^3)	36/112 (32.1)	81/341 (23.8)
Hemoglobin gm/dL	11.36±2.49	11.64±2.51
Anemia		
Mild (10.0-11.0 gm/dL)	19/113 (16.8)	34/343 (9.9)
Moderate (8-10 gm/dL)	21/113 (18.6)	51/343 (14.9)
Severe (<8 gm/dL)	8/113 (7.1)	31/343 (9.0)
Lymphocyte count		
<1500/mm^3 in adults	55/81 (67.9)	117/261 (44.8)
<3000/mm^3 in children	6/26 (23.1)	12/76 (15.8)
Platelet count		
Mean count	216,904±136,777	244,144±126,626
Thrombocytopenia (<150,000/mm^3)	30/105 (28.6)	63/312 (20.2)
Thrombocytosis (>350,000/mm^3)	30/105 (28.6)	114/312 (36.5)
Elevated alanine aminotransferase (>40 U/L)		
Any deviation	41/48 (85.4)	99/145 (68.3)
≥2×the upper limit of normal range	36/48 (75.0)	72/145 (49.7)
Elevated aspartate aminotransferase (>40 U/L)		
Any deviation	16/37 (43.2)	54/113 (47.8)
≥2×the upper limit of normal range	3/37 (8.1)	36/111 (32.40)
Elevated total bilirubin (>1.2 mg/dL)	12/52 (23.1)	45/148 (30.4)
Erythrocyte sedimentation rate		
>15 mm/h in male patients	13/35 (37.1)	44/122 (36.1)
>20 mm/h in female patients	10/35 (28.6)	40/122 (32.8)
Chest X-ray findings		
Done	111/140 (79.3)	288/371 (77.6)
Pneumonia found*	104/111 (93.7)	221/288 (76.7)
Antibiotic treatment received	123/140 (87.9)	341/371 (91.9)
Corticosteroid treatment received	66/140 (47.1)	101/371 (27.2)

[a]Plus-minus values are mean±SD, *P<0.05

drug within 2 days of onset of illness. Median time of 3 days for ventilator support, more than 5 days hospitalization ($P < 0.05$), and antiviral drug administration ($P < 0.05$) has been reported among severe disease patients.

Discussion

Present study mentions severe influenza A (H1N1) virus infection in residents of Saurashtra region. A total of 511 patients reported confirmed and were hospitalized during the study period, and categorized as patients having severe ($N = 140$) and non-severe disease ($N = 371$).

Patients with severe diseases reported median age of 30 years which is higher than that of Portugal (23)[16] and South Korea (11),[17] but lower than that was observed in a study from Canada (37).[18] Two-third patients with severe disease were above the age group of 25 years in which 60.7% were females. It indicates that adults and females[19] (OR = 0.53, CI = 0.36-0.79) appear to be at higher risk of death due to pandemic influenza A (H1N1) virus infection compared to children or teenagers. More cases of severe influenza were reported from the urban area (OR = 1.68, CI = 1.13-2.49) than rural area.[19] This may be because of dense population in urban area favors spread of virus infection.

Among all the patients, a median time of 5 days was reported from onset of illness to diagnosis of influenza A (H1N1). More than half (58.6%) of the patients with severe disease were treated first at general practitioner/physician (OR = 0.56, CI = 0.38-0.83) and then referred to a higher center. The time duration between onset of illness and hospital admission and diagnosis was more than other countries.[19,20] The possible justification is that patients seek treatment at local level from general practitioners and physicians, but with no or little improvement after initial treatment, they were referred to a higher center for further investigation and management. Present study reported median time of 4 days for hospital stay among severe disease patients (OR = 0.24, CI = 0.16-0.37) with 65.7% patients having less than 5 days of hospital stay; compared to 7 days median time and 32.4% non-severe disease patients. It also indirectly reflects that patients with more severe disease with delayed referral, reaches to higher center at critical stage.

Current interim CDC guidelines for pandemic and seasonal influenza recommended the use of either oseltamivir or zanamivir for hospitalized patients.[21] Indian government authorities have recommended and supplied oseltamivir to the state governments for distribution in tertiary care centers and district. In the present study area, all the influenza A (H1N1) infected fatal cases received oseltamivir after hospital admission. However, only 27.1% severe disease patients received it within 2 days of onset of illness which when compared was higher in China (12.8%),[22] but lower than in United States (38-50%).[23] Initial primary treatment at general practitioners or local physician level and delayed referral to higher center and investigation, may be a possible explanation for delayed start of oseltamivir in suspected or confirmed influenza A (H1N1) patients. When started early, antiviral drug has beneficial effect. Study reported that patients admitted to ICU or died were less likely to receive such therapy within 48 hours after onset of symptoms.[20] After complete course of oseltamivir therapy (OR = 0.38, CI = 0.22-0.67), the present study

Table 5: Correlates of disease severity among severe (*N*=140) and non-severe (*N*=371) influenza A (H1N1) patients

Characteristics	Severe influenza A (H1N1) (*N* (%))	Non-severe influenza A (H1N1) (*N* (%))	*P* value	Odds ratio	95% Confidence interval
Sex: Female vs. male	85 (60.7)	168 (45.3)	0.00	0.53	0.36-0.79
Residential status: Urban vs rural	73 (52.1)	240 (64.7)	0.00	1.68	1.13-2.49
First treated at general practitioner/physician	82 (58.6)	165 (44.5)	0.00	0.56	0.38-0.83
Hospital stay: ≤5 vs>5 days	48 (34.3)	251 (67.7)	0.00	0.24	0.16-0.37
Time from onset of illness to diagnosis: ≤5 vs>5 days	86 (61.4)	251 (67.8)	0.17	1.32	0.88-1.98
Interval from symptom onset to antiviral treatment: ≤2 vs. >2 days	38 (27.1)	38 (10.2)	0.00	0.30	0.18-0.50
Time from antiviral drug started to outcome: <5 vs. ≥5 days	99 (70.7)	161 (86.1)	0.00	0.38	0.22-0.67
Pneumonia	104 (86.7)	221 (66.2)	0.00	0.30	0.16-0.53
Pregnant females (females aged 18-45 years)	14 (10.0)	8 (2.2)	0.00	0.19	0.08-0.48

shows 90.7% mortality in severe disease patients which when compared is higher than that reported in Turkey (50.8%).[24] This is possibly because of delayed referral and initiation of antiviral drug.

Month wise distribution shows two different waves. During the first wave, number of cases increases rapidly from December 2009 onwards. Highest positive cases (124) were reported during January, followed by decline upto March 2010. It signifies the relationship between influenza virus and cold season, as maximum number of cases occurs during these months of winter season.[10,20] Second wave starts from August, 2010 to November 2010. No cases were reported thereafter. The second wave had started in monsoon season, suggesting that high humidity may favor the spread of influenza A (H1N1).

Present study reported that majority of the patients in both categories had cough, fever, shortness of breathing, and sore throat, likewise patients of US[20] and Canada.[19] Current study reported that 42.5% severe influenza A (H1N1) patients have any one coexisting condition (OR = 0.53. CI = 0.31-0.90), which was 53% in France,[25] and 57.7% in China.[26] Pregnancy was a well documented risk factor for severe infection and death in seasonal influenza and in previous pandemics.[26,27] In this study, pregnancy was reported as a risk factor (OR = 0.22, CI = 0.06-0.76) in 11.5% severe influenza A (H1N1) cases than among non-severe influenza A (H1N1) cases.[26-28] Out of ten severe disease pregnant cases, two were in second trimester and eight were in third trimester.

Pneumonia was reported more among patients with severe disease (86.7%; OR = 0.30, CI = 0.16-0.53), higher than that reported in Korea (70.7%)[29] and Brazil.[30] In absence of accurate diagnostic methods, patients who were hospitalized with suspected influenza and lung infiltrates on chest radiography should be considered for treatment with both antibiotics and antiviral drugs.[31]

Limitations

Our study also has some limitations. The data was taken only from hospitalized patients. Therefore, patients who were infected in the community and did not go to the hospital were not included in our study. All diagnostic testing was clinically driven, and other investigations were not obtained in a standardized fashion. Despite the use of a standardized data collection form, not all information was collected for all patients.

Considering association between coexisting condition and severity of disease, it is possible that the presence of a coexisting condition that makes ICU admission more likely might also have made ascertainment of virologic infection, thus producing an inflated estimate of any potential association. With regards to the present study, the relative impact of the direction of this type of selection bias, known as Berksonian bias, is uncertain.

Conclusion

The severity of illness among influenza A (H1N1) infected patients was associated with delayed referral from general practitioner/physician, duration of antiviral treatment, and presence of coexisting condition, especially pregnancy. These findings may be different during the future waves, owing to the timely deployment of an effective vaccine, to viral mutation, and resistance to antiviral drugs.

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