Abstract

Background: During spring of 2009, pandemic of Influenza A (H1N1) virus emerged and spread globally. We describe the clinical profile of patients who were found H1N1 Positive in Surat district from 27th June 2009 to March 2010.

Methods: Retrospective data of 824 patients from Surat district who were suspected with influenza like illness was collected. They were subjected to throat swab testing for H1N1. Out of them 154 were positive for 2009 H1N1 virus with use of real time reverse transcriptase polymerase chain reaction assay (Taqman real time PCR CDC protocol). Clinical parameters of these 154 patients were analyzed.

Results: Out of 824 suspected H1N1, 154 (18.68%) patients were confirmed (positive) for 2009 H1N1. Maximum (70.77%) patients are in age group 14-50 years. Male [86 (55.84%)] were affected more than females [68 (44.15%)]. 58 (37.66%) had underlying co-morbid condition. Fever (98.70%) and cough (94.15%) were the most common presenting symptom. Total 41 (26.62%) patients were put on mechanical ventilator, out of them 17 (41.46%) survived. Total 24 (58.53%) patients were initially put on noninvasive (Bipap) ventilator followed by invasive Mechanical ventilator, while 9 (21.95%) patients were put on only noninvasive (Bipap) ventilator and total 8 patients were put directly on invasive Mechanical ventilator. 154 H1N1 positive patients, who underwent chest X-ray on admission 112 (72%) had findings consistent with pneumonia/ARDS. Most common site is lower zone and simultaneous involvement of both lungs is more common than single lung involvement. Out of the 154 patients, those patients who received oseltamivir within 48 hour of onset of illness all were cured. Patients who expired had received oseltamivir after 48 hrs. Our data suggests that the use of oseltamivir was beneficial in hospitalized patients even up to 72 hrs of onset of symptoms. We observed no significant side effect of oseltamivir 150 mg twice day dose for 5-7 days. We observed two peaks of H1N1 during this period, second peak was less severe than first one.

Conclusions: During evaluation period, 2009 H1N1 influenza caused severe illness requiring hospitalization, including pneumonia and respiratory distress and co-morbid condition. Maximum patients were between age group of 14-50 year. Fever and cough were most common presenting symptoms. Nearly 36.36% patients had one or more underlying medical conditions. Mechanical ventilatory support had role in reduction in mortality. Patients seemed to be benefited from antiviral therapy if started within 72 hour of onset of symptom. There were no significant side effects of Oseltamivir observed in this study. Development of ARDS, requirement of mechanical ventilation and having co-morbid condition were poor prognostic factors. We observed two peaks of H1N1 during this period second peak was less severe than first one. It may be due to development of immunity, Disease awareness, early diagnosis and treatment and health education.

Introduction

In late March and early April 2009, an outbreak of H1N1 influenza a virus infection was detected in Mexico with subsequent cases observed in many other countries including India. On June 11, 2009, WHO raised its pandemic alert level to highest level phase 6 indicating widespread community transmissions in at least 2 continents. April 15, 2009, and April 17, 2009, the Centers for Disease Control and Prevention (CDC) confirmed the first two cases of human infection with a pandemic influenza A (H1N1) virus in the United States. The 2009 H1N1 virus contained a unique combination of gene Segments that had not previously been identified in humans or animals.

The U.S. centre for Disease control and Prevention released guidelines for the use of Antiviral in the treatment of H1N1 influenza and has emphasized that therapy should be started as soon as possible, since evidence of benefits is strongest for seasonal influenza when treatment is started within 48 hr. of illness onset. As of September 20, 2009, human infection with 2009 H1N1 virus had been identified in 191 countries and territories. As of 13 December 2009, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 10582 deaths. In this study we had analyzed the clinical profile, risk factor, effect of Oseltamivir, role of Mechanical ventilator in treatment of novel 2009-H1N1 Influenza infection.

Aims and Objectives

1. To study the clinical profile of H1N1 positive patients in Surat district.
2. To study effects of oseltamivir in H1N1 positive patients.
Table 1: Age and sex-wise distribution of H1N1 positive patient

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 year</td>
<td>15 (09.74%)</td>
<td>10 (06.49%)</td>
<td>25 (16.23%)</td>
</tr>
<tr>
<td>5-14 year</td>
<td>06 (03.89%)</td>
<td>00</td>
<td>06 (03.89%)</td>
</tr>
<tr>
<td>14-50 year</td>
<td>57 (37.09%)</td>
<td>52 (33.76%)</td>
<td>109 (70.77%)</td>
</tr>
<tr>
<td>50-65 year</td>
<td>05 (3.24%)</td>
<td>06 (03.89%)</td>
<td>11 (07.14%)</td>
</tr>
<tr>
<td>≥65 year</td>
<td>03 (1.94%)</td>
<td>00</td>
<td>03 (01.94%)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (44.15%)</td>
<td>68</td>
<td>154 (100%)</td>
</tr>
</tbody>
</table>

3. Role of mechanical ventilators in management of patients found positive for H1N1 infection.

4. To analyze of significant side effects of oseltamivir.

Materials and Methods

Inclusion criteria
1. All age group.
2. Both sex.
3. Laboratory confirmed case for novel influenza H1N1 by RT-PCR assay (TAQ MAN real time PCR CDC protocol).

Exclusion Criteria
1. Laboratory confirmed negative for novel influenza H1N1 by RT-PCR assay (TAQ MAN real time PCR CDC protocol).
2. Those patients positive for influenza A.

We collected retrospective data of 824 patients from Surat district who were suspected with influenza like illness. All 824 patients were underwent for throat swab and nasal swab for H1N1 testing out of them 154 were positive for H1N1 virus with use of real time reverse transcriptase polymerase chain reaction assay (TAQ MAN real time PCR CDC protocol) and we had collected clinical data of all these positive patients.

Study design
From June 26, 2009, to March 2010, data of all suspected H1N1 (positive H1N1 confirmed by RT-PCR) patients were sequentially reviewed and medical-chart abstractions were performed which includes demographic data, underlying medical conditions, clinical signs and symptoms, selected laboratory tests, Radiographic findings and treatment course (time of starting oseltamivir after symptom onset.)

In India, revised guidelines on categorization of Influenza-A H1N1 cases during screening for home, isolation, testing, treatment and hospitalization was given by Ministry of Health and Family welfare. According to which all suspected cases were categorized into 3 category:

Category A
Patients with mild fever plus cough\ sore throat with or without body ache, headache, diarrhea, and vomiting.

Category B
1. In addition to above signs and symptoms patient has high grade fever and severe sore throat.
2. Patient has 1 or more of the following high risk conditions:
   - Children (<5 yr).
   - Pregnant women.
   - Persons aged more than 65 years or older.
   - Patients with lung disease, heart disease, liver disease, kidney disease, blood disorder, diabetes, neurological disorders, cancer and HIV/AIDS.

Category C
In addition to above signs and symptoms patient has:
- Breathlessness, chest pain, drowsiness, fall in B.P., sputum mixed with blood, bluish discoloration of nails.
- Worsening of underlying chronic conditions.
- Antiviral therapy is indicated in category B [1] and B [2] and C.

We had observed for any major side effect of Oeltamivir in dose 75 mg 2BID in cat-C patients We had also observed for role of mechanical ventilator Support requirement and mortality relation. We had received data for common site of pneumonia in positive patients. All the collected data we had put in master chart and made different statistical tables according to patient’s clinical profile. All tables were analyzed by using different statistical methods and results were obtained. From this result analysis various conclusions were made.

Results

1. Age and sex distribution (Table 1)
   - Total 824 patients with suspected H1N1 were screened and tested with RT-PCR for H1N1out of them 154 patients were found H1N1 positive.
   - Out Of these 20.12% (31) were of age <14 and 79.87% (123) pt were of age ≥14 year.
   - 2% (03) were above 65 years of age maximum 70.77% (109) patients are in age group 14-50 year.
   - Total 86 (55.84%) are male and 68 (44.15%) patients are female, Male have higher chance to get H1N1 infection than Female.

2. Month wise distribution (chart 1)
   - We observed two peak of Swine flu during study period one peak was in Sept-09 and second peak was in Jan -10 second peak less severe than first one.

3. Underlying co-morbid conditions in H1N1 Positive patients
   - 37.66% (58) patients had at least 1 underlined medical condition. These conditions included pregnancy 7(4.54%), hypertension 7 (4.54%), 25(16.23%) patients are <5 year and 3(1.94%) patients are of age >65 year which are high risk group.
   - Other co-morbid conditions were COPD, asthma, diabetes, IHD, HIV sero-positive, Tuberculosis of spine, Rheumatic Heart Disease, pulmonary Koch’s1(0.64%), Ewing’s Sarcomal(0.64%), G6PD Deficiency 1(0.64%), DCM1(0.64%), RHD1(0.64%).

4. Symptomatology in H1N1 positive patients (Table 2)
Table 2: Symptomatology in H1N1 positive patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>152</td>
<td>98.70</td>
</tr>
<tr>
<td>Cough dry/ with expectoration</td>
<td>145</td>
<td>94.15</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>134</td>
<td>87.01</td>
</tr>
<tr>
<td>Running nose</td>
<td>108</td>
<td>70.12</td>
</tr>
<tr>
<td>Throat pain</td>
<td>103</td>
<td>66.88</td>
</tr>
<tr>
<td>Headache/body ache</td>
<td>94</td>
<td>61.03</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>34</td>
<td>22.07</td>
</tr>
</tbody>
</table>

Our study shows fever present in 152 (98.70%) and cough is present in 145 (94.15%) other symptom are throat pain, breathlessness, running nose.

5. X-ray finding (Table 3)

72.72% (112) patients had abnormal X-ray suggestive of pneumonia/ARDS and 27.27% (42) pt had normal X-ray. Most common site of pneumonia bilateral, mid zone and lower zones. Simultaneous involvement of both lungs was found to be more common than single lung involvement. Upper lobe involvement is very uncommon.

6. Ventilator requirement and outcome (Table 4)

- 26.62% (41) patients required Mechanical ventilator. Out of this 41.46% (17 out of 41) patients were cured.
- Total 24 (58.53%) out of 41 patients were expired.
- 18 patient out of 24 developed ARDS.
- 41 (58.53%) patients were put on Mechanical ventilator. Out of these, 9 (21.95%) patients were put only on non-invasive ventilator, all were survived. 8 (19.51%) patients were put directly on invasive Mechanical ventilator, all were expired, 24 (58.53%) patients were initially put on non-invasive ventilator followed by invasive ventilator, and 16 pts. were expired.

7. Profile of H1N1 positive patients expired (Table 5)

In 24 expired patients 11 (45.83%) were male and 13 (54.16%) are female. So female mortality is more than male. Statistically no age specific survival seen (p=.33) we have observe co-morbid condition in 70.83% (17) present in expired patients it suggest that patients with H1N1 with co-morbid condition has poor prognosis. Of 24 expired patients 70.83% (17) patients had co-morbid medical condition and 29.16% (7) patients had no co-morbid condition, so co-morbid medical condition were associated with poor prognosis in H1N1 infection.

8. Effect of Oseltamivir (Table 6)

- Out of 154 patient 51 (33.11%) patients received oseltamivir within 72 hours of onset of illness. Out of them 3 (5.88%) were expired and 94.11% (48) patients cured from H1N1.
- Out of 154 patients 103 (66.89%) received oseltamivir more than 72 hour of onset of illness. Out of them 21 (20.38%) pts. were expired.
- So, antiviral therapy is more effective when started early (within 72 hrs of symptom onset), statistically we applied chi square test to this findings. It was suggestive that oseltamivir therapy is also as effective as within 48 hour (p= 0.007) Our study also had showed that Oseltamivir has role in reducing in mortality in swine flu if it is given within 72 hours of onset of illness.

Discussion

The H1N1 has caused pandemic alert all over the World since March 2009. The United States Centre for Disease Control and Prevention and WHO has given guidelines for the use of antiviral in the treatment of H1N1 influenza, according to which antiviral are indicated in the following situations:

1. All hospitalized individuals with suspected influenza virus infection or who were confirmed with throat swab, positive for 2009 H1N1 virus with use of real time reverse transcriptase polymerase chain reaction assay (TAQ MAN real time PCR CDC protocol).
2. Individuals with confirmed or suspected influenza virus infection who are severely ill, such as those
3. With lower respiratory tract infection, dyspnoea, tachypnoea, unexplained desaturation, and
4. Those are showing signs of rapid clinical deterioration.
5. Individuals with suspected or confirmed influenza infection who are at increased risk for complications like;
   - Children less than 5 yrs of age.
   - Age more than 65 yrs.
   - Pregnant women and women up to 2 weeks postpartum.
   - Less than 19 yrs of age and receiving long term aspirin therapy and who are at risk for Reyes syndrome.
   - Individuals of any age with chronic medical conditions like chronic pulmonary disease including asthma, heart...
disease, active malignancy, chronic renal insufficiency, chronic liver disease, immunosuppression including diabetes mellitus, haemoglobinopathies, sickle cell disease, certain rheumatological diseases, SLE, scleroderma.

- The choice of antiviral is neuraminidase inhibitor Oseltamivir and Zanamivir, which act by inhibiting aggregation and release of virus particles from infected cells. Oseltamivir is given in dose of 75 mg twice daily for 5 days. Zanamivir is given as inhalation, 5 mg, 2 puffs, and twice a day for 5 days.

The only i.v. preparation is Peramivir 600 mg i.v. OD. Apart from mild G.I. upset and rarely neuropsychiatric manifestations like insomnia, agitation and confusion, Oseltamivir is well tolerated.

Zanamivir is contraindicated in COPD and asthma as it can exacerbate bronchospasm.

The review of literature suggests that -Cytokine storm that is an aggravated response with high levels of circulating cytokines during the later stages of infection, is responsible for the pneumonia,

ARDS and deaths in H1N1 influenza. The newer therapies in the treatment of H1N1 influenza targets towards the inhibition of the cytokine storm. They include ACE inhibitors, angiotensin receptor antagonists, Statins, Gemiﬁbrogl, Nicotine, Corticosteroids, and Tumor Necrosis Factor-alpha blockers.

But there is no doubt as to the efficacy of antiviral in the treatment of H1N1 influenza esp. if Started within 48 hours of onset of illness, which halts the progress of the disease by preventing the cytokine storm. In our study, a significant proportion of hospitalized patients had ﬁndings on chest radiography suggestive of pneumonia, and the majority had bilateral inﬁltrates. Although it is difﬁcult to precisely determine the cause of pneumonia from radiograph. During the 1957–1958 inﬂuenza Pandemic, Louria et al.,7 reported ﬁndings of diffuse bilateral inﬁltrates in patients with primary inﬂuenza viral pneumonia, whereas lobar inﬁltrates were seen in patients with secondary bacterial Infections. Better studies are needed to correlate radiographic ﬁndings with the cause of pneumonia during inﬂuenza outbreaks. In the absence of accurate diagnostic methods, patients who are hospitalized with suspected inﬂuenza and lung inﬁltrates on chest radiography should be considered for treatment with both antibiotics and antiviral drugs.8 The majority of 2009–H1N1 viruses that have been tested at the CDC to date have been susceptible to two neuraminidase inhibitors, oseltamivir and zanamivir, and resistant to two adamantanes, amantadine and rimantadine.8,9 Recent guidelines from The Infectious Diseases Society of America recommended the use of antiviral drugs in adults and children who are hospitalized with seasonal inﬂuenza, regardless of the underlying illness or inﬂuenza- vaccination status.6 Current interim CDC guidelines for pandemic and seasonal inﬂuenza recommend the use of either oseltamivir or zanamivir for hospitalized patients with suspected or confirmed inﬂuenza and for outpatients who are at high risk for complications.10 Although the evidence of a beneﬁt of antiviral therapy is strongest when treatment is initiated within 48 hours after the onset of illness. A prospective cohort study of oseltamivir therapy in hospitalized patients with inﬂuenza observed a reduction in mortality, even when such therapy was initiated more than 48 hours after illness onset.11 Recent data from Thailand also showed that oseltamivir therapy was associated with survival in Hospitalized patients with influenza pneumonia.12 Under an Emergency Use Authorization, the FDA recently approved oseltamivir therapy for 2009 H1N1 infection even if it is initiated more than 48 hours after the onset of illness and also approved its use in children under the age of 1 year.13 Data from our study suggest that the use of antiviral drugs is beneﬁcial, especially when initiated early (within 72 hours of onset of illness), since patients who were admitted to an ICU were less likely to have received such therapy within 48 hours after the onset of symptoms.

**Conclusion**

- Male were more affected than female.
- Most common age group of affection was 14-50 years.
- 37.66% (58) patients had at least 1 underlined medical co-morbid condition. These conditions included pregnancy 4.54% (7), hypertension 4.54% (7), COPD, asthma, diabetes, IHD, HIV seropositivity, tuberculosis spine.
- Fever and cough were most common presenting symptoms.
- Most common site of pneumonia was bilateral mid zone and lower zone. Simultaneous Involvement of both lungs was more common than single lung involvement. Upper lobe involvement was very uncommon.
- Mechanical ventilator had role in reducing the mortality.
- Development of ARDS, requirement of mechanical ventilation and having co-morbid condition were poor prognostic factors.
- Female having higher mortality than male. Statistically there was no age or sex specific mortality seen. (p=0.33).
- 33.11% (51) patients had received oseltamivir within 72 hrs and out of these 3 (5.88%) patients expired. 66.88% (103) patients had received it more than 72 hrs and out of these 20.38% (21) patients expired. (p=0.007) This finding are suggestive that oseltamivir therapy is also as effective when started within 48 hour our study also had showed that it is as effective if taken within 72 hrs of onset of symptoms.

Clinicians should consider inﬂuenza, including 2009 H1N1 infection, in the differential diagnosis for patients presenting with fever and respiratory illness or pneumonia. Empirical antiviral treatment for patients with suspected inﬂuenza or pneumonia. The present study deﬁnitely proves that there is a better outcome in patients of H1N1 inﬂuenza when treated with Oseltamivir within 48 hours of onset of symptoms. It is also effective even up to 72 hrs of illness. Ventilator has role in reducing mortality from H1N1 so poor prognostic factors are co-morbid medical condition, development of ARDS, delay in starting antiviral therapy (more than 72 hrs).

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district nodal officer, Surat), epidemic medical officer Surat District, for helping in data collection.

References

5. Ministry of Health and Family Welfare-Govt.of India Pandemic Influenza A (H1N1)-Guidelines on Categorization of Influenza A H1N1 cases during screening for home isolation, testing treatment, and Hospitalization (Revised on 05.10.09) (http://mohfw-h1n1.nic.in).