Original Article

A CLINICAL ACCOUNT OF ICU CASES WITH SEVERE H1N1 (2009 PANDEMIC INFLUENZA A) INFECTION

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ABSTARCT

Objective: To determine clinical characteristics in adults with confirmed severe 2009 pandemic influenza A (H1N1) infection.

Study Design: A descriptive case series

Place and Duration of Study: The study was carried out at the department of Pulmonology and Critical Care, Military Hospital Rawalpindi, from 1st December 2009 to 30th May 2010.

Methodology: Fifteen in-hospital adults with severe H1N1 infection confirmed by reverse transciptase polymerase chain reaction (RT-PCR) were studied. A pre-designed patient data collection form was used to record clinical features, laboratory and radiological investigations and management data.

Results: Mean age for severe H1N1 cases was 41.56 ± 15.08 years and about 75% cases were from 20-40 yrs age group. Seventy five percent of our cases had at least one risk factor for complications with 2009 H1N1 infection; namely obesity – 33.3%, smokers – 26.7%, pregnancy, COAD and diabetes mellitus – 20% each. Fever (100%), cough (100%), and shortness of breath (93.3%) were the commonest symptoms. Radiographic abnormalities were bilateral patchy consolidations (60%), interstitial/reticular infiltrates (20%), and reticular shadows with areas of consolidation (20%). PaO_2/FiO_2 ratio was less than 200 in 60% cases on presentation. 73.3% cases had 1000-2000 (U/L) lactate dehydrogenase (LDH) levels while creatinine kinase (CK) levels were 400-1000 (U/L) in 66.7% cases. Six (40%) ICU cases with severe H1N1 infection died during hospital stay.

Conclusion: Severe H1N1 virus infection cases most commonly presented with fever, cough and shortness of breath. The severe H1N1 cases presenting with abnormal chest radiograph and hypoxemia require ICU care with high mortality.

Keywords: H1N1, 2009 pandemic Influenza A, PCR-RT.

INTRODUCTION:

As of 1st August, 2010; more than 214 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,449 deaths[1]. Though overwhelming majority of cases had mild self limiting disease, a minority have developed severe pneumonia leading to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction (MODS) associated with prolonged intensive care unit (ICU) stay and high mortality (17-54%)[2-4].

Our institute had first confirmed case of 2009 H1N1 on 6th Dec, 2009. Since this was a new and potentially serious infectious illness, all suspected cases of 2009 H1N1 were admitted and isolated from general population. This allowed us to monitor clinical features, identify risk factors, and recognize common laboratory abnormalities, radiological patterns and management strategies. This report summarizes the clinical characteristics of a series of first 15 cases with confirmed 2009 H1N1 infection requiring intensive care management.

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METHODOLOGY

This case series was conducted at the department of Pulmonology and Critical Care, Military Hospital Rawalpindi from 1st Dec 2009 to 30th May 2010. Ninty seven adults, 14-75 yrs of age of either gender were sequentially enrolled by convenient sampling and admitted to the hospital with suspected diagnosis of 2009 H1N1. A confirmed case was defined by a positive result of a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay performed at National Institute of Health – Islamabad Pakistan; performed on a nasopharyngeal swab taken by a medical officer

and sent in the viral transport medium at < 4^0C. A case was considered to have severe disease if two or more of the following were present: dyspnea (respiratory rate more than 24/min), cyanosis, h/o hemoptysis, altered mental status, hypotension, persistent high grade fever (more then 101^0F) beyond three days, oxygen saturation <92% in room air, pulmonary infiltrates on X-ray chest, more than thrice CK or LDH levels and presence of at least one of established risk factor associated with severe H1N1 infection like presence of COAD, Diabetes Mellitus, Pregnancy, etc. All patients with severe confirmed H1N1 infection cases were kept in intensive care unit. Barrier nursing care was provided to all cases and N95 respiratory mask was used by health care workers while attending 2009 H1N1 admitted cases.

All the data was recorded on preformed patient data collection form. Variables recorded included demographics, comorbidities, and time of onset, hospital admission, and time to first dose of antiviral therapy, microbiological findings and chest radiographic findings at ICU admission. Clinical features on presentation and relevant lab abnormalities including Creatinine phosphokinase (CK), Lactate dehydrogenase (LDH) and arterial blood gases were also recorded. Other investigations like ultrasonography, echocardiography, serum amylase, fiberoptic bronchoscopy, were done as per judgment of the managing team.

All cases with features of severe H1N1 disease requiring ICU admission were given Cap Oseltamivir (Tamiflu) 150mg twice daily for ten days while those with radiological features of pneumonia and hypoxemia were also started on combination of intravenous Inj Levofloxacin 500-750mg once daily and Inj Meropenem 500-1000 mg thrice daily depending on body weight of the patient. Inj Heparin – 5000 units twice daily were administered subcutaneously to all ICU cases except those with coagulopathy / thrombocytopenia. Patients were discharged once they were afebrile for at least more then 48hrs and had no respiratory symptoms. Repeat RT-PCR was not done.

Data was processed on statistical package for social sciences (SPSS) version 18. Continuous variables like age, duration of illness before presenting to institution, duration of hospital stay, etc were derived as means while categorical variables like gender, presence of different risk factors were described in percentages / frequencies.

RESULTS

Our institute had 36 confirmed cases of 2009 H1N1 out of which data of 15 (42%) ICU cases is presented. Mean age for severe H1N1 cases was 41.56 ± 15.08 years and 11 (73%) cases were from 20-40yrs age group. Both genders were affected equally while 5 (33%) were obese (BMI of more than 30 Kg/meter square) and 26.7% of our cases were smokers. History of COAD and Diabetes Mellitus was noted in 20% while another 3 were pregnant. One case had the history of concomitant use of oral steroids (Tab prednisolone – 20mg/day) while none had vaccination for seasonal influenza / flu, contact with confirmed case of H1N1 infection, history of chronic liver disease, malignancy or rheumatological illnesses. Clinical features are as given in table 1; while lab and radiographic findings are given in table 2.

About 66.7% of our cases had less than 92% oxygen saturation on room air at the time of hospital admission while PaO_2 / FiO_2 ratio was less then 200 in 9 (60%) cases and was 200-300 in 4 (26.7%) cases. Raised alanine aminotransferase (> 42 U/L) was noted in 33.3% (5) cases while 2 (13.3%) cases had minimally deranged renal functions.

Cap Oseltamivir was started within five days of start of illness in 13.3% cases while in 73.3% and 13.3 % cases it was started in 5-10 days and after 10 days of start of illness respectively. All ICU cases were given double dose (150mg twice daily) of Cap Oseltamivir for 10 days. Ten (66.7%) of our ICU cases required mechanical ventilation; five for less than five days and one case remained on mechanical ventilation for 25 days. Bedside percutaneous dilatational tracheostomies were done in three (20%) cases. All cases were started on intravenous Inj Levofloxacin 500-750mg once daily and Inj Meropenem 500-1000 mg thrice

Table 1: Clinical Features of Severe H1N1 infection in 15 cases.

Symptoms	No. of Cases / Total no (%)
Temperature (>100F)	15/15 (100%)
Cough	15/15 (100%)
Shortness of breath	14/15 (93.3%)
Flu / rhinorrhea	10/15 (66.7%)
Myalgias	10/15 (66.7%)
Headache	10/15 (66.7%)
Chest pain	5/15 (33.3%)
Confusion	5/15 (33.3%)
Nausea and vomiting	5/15 (33.3%)
Signs	
Tachypnea (> 24/min)	15/15 (100%)
Crepts on chest auscultation	13/15 (86.7%)
Throat Congestion	8/15 (53.3%)
Wheezing	5/15 (33.3%)

daily depending on body weight of the patient. Antibiotics were changed according to available culture sensitivity reports. Inj Heparin – 5000 unit twice daily subcutaneously was given to all cases. Mean duration of ICU stay was 11.28 ± 8.99. Six (40%) of our ICU cases (all requiring mechanical ventilation) died during hospital stay.

DISCUSSION

We report a small case series of fifteen hospitalized cases with confirmed severe pandemic 2009 H1N1 infection. About 2/3 of our cases were from 20-40yrs age group while same age group was afflicted in 50% cases of severe H1N1 in Spain[4]. In other studies 60-70% cases were in 15-50yrs age group[3,5]. Seventy five percent (12) of our cases had at least one risk factor for complications with 2009 H1N1 infection while six of them had two risk factors each. Rello[4] and Zarychnaski[6] have reported presence of one risk factor in 75-76% of their cohorts of severe H1N1 cases while co-morbid conditions were found in 67% cases with 2009

Table 2: Laboratory and Radiographic Findings in H1N1 cases.

Variable	Value
Hemoglobin (g/dl)	
Mean ± SD	11.91 ± 1.86
< 10 g/dl	2/15 (13.3 %)
Total Leukocyte count – per micro liter	
Mean ± SD	12.51 ± 6.75 x 10^9 / L
Less than 4000	2/ (13.3 %)
4000 – 10000	5 (33.3%)
More then 10000	8 (53.3 %)
Lymphocyte percentage	
Less than 20	10 (66.7%)
Platelet count – per micro liter	
Mean ± SD	225.25 ± 100.22 x 10^9/L
Less than 150	3/15 (20 %)
Creatinine Kinase (U/L)	
Mean ± SD	1239.68 ± 1120.67
400-1000	10 (66.7 %)
>1000	5 (33.3%)
Lactate Dehydrogenase (U/L)	
Mean ± SD	1862.18 ± 1381.38
1000-2000	11/15 (73.3%)
>2000	4/15 (26.7%)
Quantitative C-reactive Protein (mg)	
Mean ± SD	39.18±29.08
12-24	12 (80 %)
>24	3 (20%)
Abnormal chest radiograph on admission (no/total no (%)	15/15 (100%)
Reticular / interstial infiltrates only	3/15 (20%)
Bilateral Consolidations	9/15 (60 %)
Reticular shadows with consolidation	3/15 (20%)

H1N1 infection in another study[7]. However, no co-existing medical conditions were reported in 25-50% of hospitalized or died H1N1 cases[8,9]. Thirty three point three percent of our cases were obese which is comparable to reported incidence of about 30% in other studies[4,7,8]. Patients of severe or fatal H1N1 infection are estimated to be 5-15 times more likely to be obese[8]. Twenty six point seven percent of our cases had history of smoking which is similar to reported incidence of 28% in a study from Canada[6]. Smoking is also a recognized risk factor for developing more severe disease[9]. Twenty percent of our cases had COAD which is comparable to reported incidence of 28%[6] and 29%[10] in other cohorts of ICU cases with severe H1N1. Pregnant patients have accounted for up to 9-13% of severe H1N1 hospitalized or died cases[8,9] which is comparable to our study.

Most common symptoms in our case series were fever (100%), cough (100%) and shortness of breath (93.3%). Fever has been noted in 93%, 100%, and 100%; cough in 96%, 100% and 89%; and dyspnea in 87%, 100%, and 66% in studies of severe H1N1 cases from Canada[6], Mexico[3] and Utah[10] respectively. Rhinnorhea was noted in more then 66.7% of our cases which is quite high as compared to reported incidence of 28% in another study[3]. It may be due to concomitant harsh winters; as more than 90% of cases reported in Dec, 2009 and Jan, 2010; leading to probable overlap of seasonal flu symptoms and thus higher incidence of rhinorrhea. Abdominal symptoms like nausea, vomiting and pain abdomen were seen in 33.3% cases in our study. Zarychanski and colleagues[6] reported abdominal symptoms in 51% of their cases with severe H1N1 cases while same were 22% in a study from Mexico[3]. These differences in clinical features probably indicate the differential racial pathophysiological / immunological responses to H1N1 infection or may be due to different subtypes of the H1N1 in various regions of the world.

Presence of dyspnea, cyanosis, hemoptysis, chest pain, altered mental status, persistent high grade fever beyond three days and hypotension mark a more severe disease[11]. More so, delay in presentation to hospital is also identified as a risk factor to develop more severe disease[3,7]. The main clinical syndrome in 49-72% cases requiring intensive care has been diffuse viral pneumonitis associated with hypoxemia, ARDS, and sometimes shock and renal failure[8,9]. Other important clinical syndromes include severe, prolonged exacerbation of COAD or asthma (14-15%), bacterial co-infections, and decompensations of serious co-existing illnesses[8,11].

Laboratory findings in severe cases include leukopenia, lymphopenia, elevated creatinine kinase, lactate dehydrogenase, alanine aminotransferase and creatinine[12,14,18]. Leucopenia (13.3%) in our cases was rather lower then the reported incidence of 20%[7] and 21.4%[5] in other studies while thrombocytopenia (20%) was comparable to the study from United States[7] (18%). Sixty six point seven percent of our cases had elevated CK levels to more than twice the upper limit of normal which is comparable to noted incidence of 62%[3] and 81%[4]. Hundred percent of our cases had raised LDH levels like studies from Mexico[3] and Spain[4]; while 73.3% of those had 1000-2000 (U/L) LDH levels which are higher than noted incidence of 53%[3]. In hospitalized H1N1 cases, raised LDH and CK levels with thrombocytopenia and metabolic acidosis have been associated with poor prognosis[3,12].

Common chest radiographic patterns in pandemic H1N1 ranges from multifocal infiltrates to localized consolidations and nodular alveolar opacities like ARDS[13] while mediastinal lymphadenopathy[14] and small pleural effusions[15] are also noted in other studies. All of our cases had abnormal chest radiographs which are similar to other cohorts of severe H1N1 cases from Spain[4] and Mexico[4]. Bilateral patchy consolidations were noted in 60% cases which is comparable to reported incidence of 61.6%[3], 71.8%[4] and 73%[7] in other studies. Reticular infiltrates and mixed lesions were noted in 20% of our cases while a study from Melbourne reported multifocal reticular changes in 27% cases[13]. Chest computed tomography in H1N1 cases has shown areas of

ground glass opacities, air bronchograms, and alveolar consolidation, particularly in lower lobes[15].

Two third of our cases had hypoxemia (SpO_2 <92% on room air), signifying severe nature of the illness. All of them had PaO_2 / FiO2 ratio consistent with ARDS (< 200, 9 (60%) cases) or ALI (200-300, 4 (26.7%) cases). A comparable incidence was noted by Miller and colleagues who have reported ARDS and ALI in 64% and 35% of their H1N1 cases admitted to ICU respectively. Sixty six point seven percent of our ICU cases required mechanical ventilation and 20% of them ultimately required bed side percutaneous dilatational tracheostomies. Lung protective ventilation strategy was used for all mechanically ventilated cases as per ARDS Net trial recommendations; however no 'rescue therapies' like extracoprporeal membrane oxygenation, high-frequency oscillation ventilation, prone positioning, inhaled nitiric oxide, etc were offered.

All of our ICU cases were given double dose (150mg twice daily) of Cap Oseltamivir for 10 days. Cap Oseltamivir was started within five days of start of illness in 13.3% cases while in 73.3% and 13.3 % cases it was started in 5-10 days and after 10 days of start of illness respectively. In varied studies the median time for start of antiviral treatment in severe H1N1 cases had been eight days[3] and four days[4]. Early therapy with oseltamivir in patients with 2009 H1N1 may reduce the duration of hospitalization[16] and the risk of progression to severe disease requiring ICU admission or resulting in death[17]; but viral loads peak at around 1-2 days post symptoms in H1N1 cases that leaves a narrow window of opportunity for effective antiviral therapy to commence[18]. Double dose of oseltamivir (150mg twice daily) for prolonged duration (upto 10 days) have been used in patients with evidence of pneumonia or disease progression[15].

All of our cases received antibiotics which is comparable to overall use of antibiotics in 94% of ICU H1N1 cases in another study[10]. As bacterial co-infections in H1N1 cases has been found in 36-48% of fatal cases[19,25], empirical use of antibiotics is recommended. Fourty percent of our ICU cases (all requiring mechanical ventilation) died during hospital stay. Padilla and colleagues[3] reported a mortality of 38.8% in their cohort of severe H1N1 cases presenting with respiratory failure while Miller and colleagues[10] noted a mortality if 17% in H1N1 cases requiring ICU care. The higher death rate in our case series is probably due to delayed presentation to the hospital (thus delayed institution of antiviral therapy), majority of cases with hypoxemia, raised CK and LDH levels and radiological abnormalities; all of which are risk factors to develop more severe disease and thus death. Overall case fatality ratio for H1N1 is estimated to be less then 0.5%[21]; but 14-46% of ICU H1N1 cases have been reported to die[7,8,11,12,17]. In fatal H1N1 cases, most consistent histopathological findings are varying degrees of diffuse alveolar damage with hyaline membranes and septal edema, tracheitis, and necrotizing bronchiolotis[13,14]. Other autopsy findings include hemophagocytosis, pulmonary thromboembolism, pulmonary hemorrhage, and myocarditis[22].

CONCLUSION

Most of the severe 2009 pandemic H1N1 virus infection cases had an underlying risk factor / co-morbidity while fever, cough and shortness of breath are the most common clinical features. At the same time, severe H1N1 cases presenting with abnormal chest radiograph and hypoxemia required ICU care with high mortality.

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