ORIGINAL ARTICLE

Profiling the Mortality due to Influenza A (H1N1) pdm09 at a Tertiary Care Hospital in Jaipur during the Current Season - January & February 2015

Raman Sharma[1], Sujata Agarwal[2], Sudhir Mehta[1], CL Nawal[1], Sudhir Bhandari[3], Monika Rathore[4], Abhishek Agarwal[5]

Abstract

Background: The onset of winter of 2014-2015 saw an alarming spurt in influenza A (H1N1) pdm 09 leading to a significant mortality. Rajasthan was one of the foremost affected state bearing the frontal attack in which majority of deaths occurred early and in the young.

Objective: To sketch out the mortality profile with respect to demographic and clinical progression with an aim to identify the groups, this virus conspicuously picked up with a perspective to control some of the avoidable factors.

Methods: We analyzed the epidemiological data in 76 RT-PCR confirmed deaths of H1N1 patients that occurred between 1st January 2015 and 28 February 2015 over a period of 59 days at SMS Medical College Hospital, Jaipur.

Results: A total of 412 patients got hospitalized during two months period from 1st January 2015 to 28th February 2015, out of which 76 fatal cases presenting with category C symptoms along with radiological evidence of bilateral pneumonia were analyzed. 48.6% deaths occurred in the 18-40 years of age group. The mean age being 44.01 ± 15.07 years. Females had a marginally increased mortality rate (F: M-1.23:1). The mean time of onset of symptoms to hospitalization was 6.79 ± 4.63 days. Fifty-one (67.1%0) patients were from urban areas, whereas 25(32.89%) belonged to rural areas. Only 7.83% patients presented within 24 - 48 hours whereas 46% presented within 5 days of onset of symptoms. 66.9% succumbed within 5 days of hospitalization, despite of starting Oseltamivir in a dose of 150 mg/bd on the day of admission. 64.5% had predisposing risk factors. Bilateral pneumonia was observed in all the 76 patients, septicemia in 21.12%, MODS in 30.26% and AKI in 9.21%.

Conclusions: The in-hospital mortality of 17.79% despite of starting Oseltamivir has raised concern about identifying the so called "Rapid Progressors" [66.9% succumbing within 5 days of hospitalization]. As a corollary of this analysis the authors are of the opinion that a rejig of the existing guidelines to identify and treat influenza like illness be made available at the national level. What factors promote rapid progression especially in a group without any predisposing risk condition should form the focus of future studies. As risk group individuals formed a major chunk of deaths, the need to vaccinate this group should form a scaffold on which future directions and interventions have to be built up to combat the morbidity and mortality.

Editorial Viewpoint

- Expediated article due to the current epidemic of H1N1 influenza across the country.
- Factors predisposing to the infection and the mortality still not very clear.
- This is an observational study carried out during ongoing epidemic adding to our current understanding of H1N1 infection.

[1]Sr. Professor & Member Task Force Committee to Combat Swine Flu; [2]Assistant Professor, [3]Sr. Professor, [5]Associate Professor, Department of Medicine, [4]Professor, Department of Preventive and Social Medicine, SMS Medical College, Jaipur, Rajasthan
Received: 14.03.2015; Accepted: 16.03.2015

Introduction

As an infection, Influenza has remained a fascinating model of research for epidemiologist, physicians, molecular biologist and virologist. The unique characteristic of antigenic shift and drift mimics a science fiction, producing novel "transformers" eventually affecting population at large.

The signature of Influenza epidemics is usually expressed in the form of excess rate of pneumonia, progression to acute respiratory failure with resultant mortality and influenza-associated hospitalization.

A total of 5528 laboratory confirmed cases of Influenza A (H1N1) pdm09 were recorded in the state of Rajasthan during the two months period from 1st January 2015 to 28th February 2015, out of which a total of 285 deaths occurred due to the current circulating strain.

The first pandemic of influenza occurred in 1918 ("Spanish influenza"). It was attributed to human H1N1 virus estimated to have affected approximately 500 million persons worldwide (almost 1/5th of the world population), killing 40-50 million worldwide and 10 to 20 million in India with a mortality rate of 10%.[1,2] The current circulating novel virus, a remnant of the 1918 virus, first detected in 2009, is the 4th descendant of the 1918 virus causing the pandemic of 2009-2010. WHO declared the H1N1 outbreak a public health emergency in April 2009 and announced a global pandemic in June 2009 as shown in the Figure 1A. The pandemic was declared as ended in August 2010, and is now predicted to continue circulation as a seasonal virus for years to come[3] (Figure 1B).

Materials and Methods

The present study was a hospital-based observational study done in SMS hospital, Jaipur over a period of 59 days between 1st January and 28th February 2015. Patients who were admitted with suspected influenza and tested positive for RT-PCR H1N1 at our advanced Microbiology Research Lab were included in the study.

Observations and Results

A total of 76 deaths due to confirmed H1N1 influenza were studied. The mean age was 44.01 ±15.07 years. The case fatality rate was 17.9% (76 deaths out of 412 hospitalized patients). Most of the patients (91.8%) were in 18 to 65 years of age (Table 1). Male to female ratio was 1:1.2 (males 34 and females 42). Out of 42 females, 8 pregnant and 2 in postpartum period of within 2 weeks, succumbed to the disease.

Table 1: Age-wise distribution of cases

Age group	Number of patients	Percentage
18 – 25 years	15	19.7
26 – 40 years	22	28.9
41 – 65 years	32	42.1
66 yrs and above	7	9.2
Total	76	100

The urban to rural division of deaths was 51 (67.10%) to 25 (32.89%) respectively.

The mean time lag to hospitalization was 6.79±4.63 days, with a range of 1 day to 11 days. Majority of the patients (60.3%) presented between 72 hours and one week of symptoms onset (Table 2).

Mean time lag between hospitalization and death was 5.00±4.20 days, with a range from less than 1 day to 19 days. Almost 66.9% of the patients succumbed

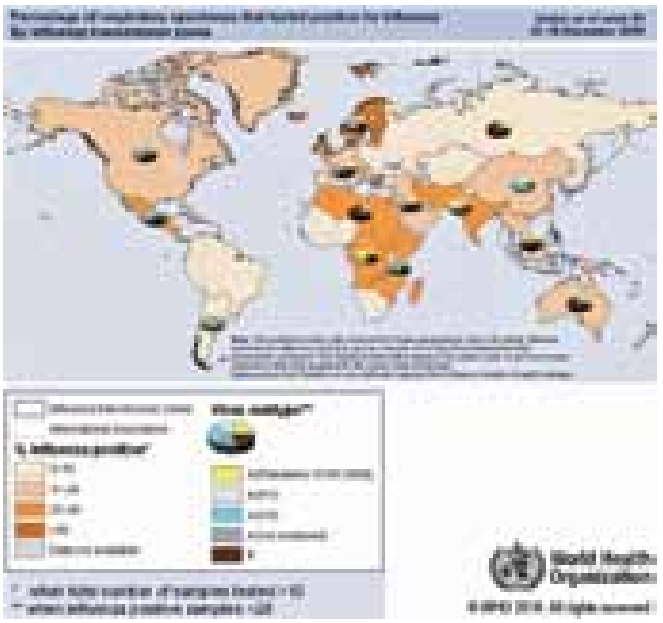

Fig. 1a: H1N1 global pandemic 2009

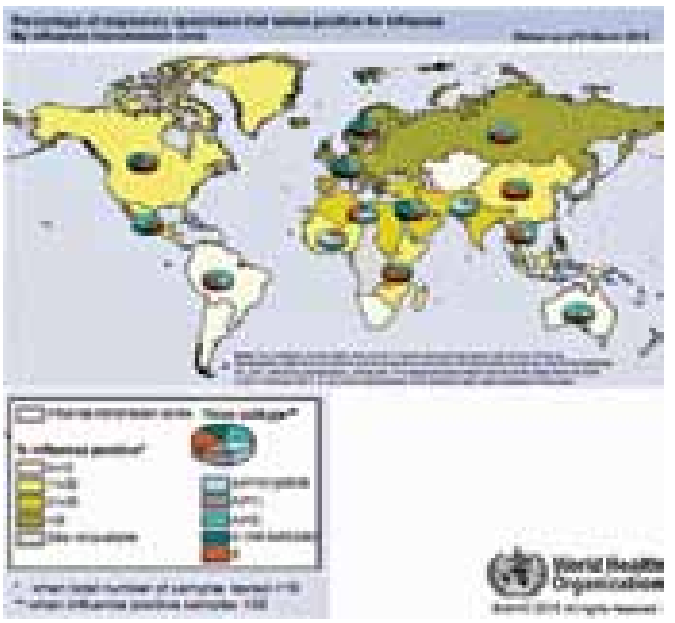

Fig. 1b: Status of H1N1 as of 6 March 2015

Table 2: Duration of illness*

Time lag	No. of pts. (n=76)	Percentage
Within 24 hours	2	2.63
24 - 48 hours	4	5.2
3 - 5 days	35	46.0
6 - 7 days	14	18.42
> 7 days	21	27.63

*Time lag between appearance of symptoms to hospitalization. Only 7.83% patients presented within 48 hours. 53.94% presented within 5 days of onset of illness. Mean time of presentation: 6.7 days.

Table 3: Duration of hospitalization

Duration of hospitalization (in Days)	No. of patients	Percentage
< 1	7	9.20
1 - 5	44	57.89
6 - 10	25	32.89

67% of the patients succumbed within 5 days of hospitalization.

Table 4: Predisposing risk factors /co-morbid conditions

Risk-group	No. of patients	Percentage
Diabetes mellitus	13	17.1
COPD /asthma/ pulmonary tuberculosis	11	14.4
Pregnancy/ postpartum	10	13.1
Old age >65 yrs	8	10.5
Renal diseases	6	7.9
Cardiac disorders	3	3.9
Liver diseases	2	2.6
Cerebrovascular accident	2	2.6
Obesity BMI >35	1	1.3
Pancytopenia	1	1.3
No risk factor	27	35.5

within 5 days of hospitalization and most received Oseltamivir in a dose of 150 mg twice a day.[4,5] Seven cases (9.2%) died within a few hours after presenting to hospital (Table 3). All case fatalities were in category C of severity at the time of admission. Fourteen patients (18.4%) were hemodynamically unstable at presentation.

Presence of co-morbidity was an important contributing factor. Forty-nine patients (64.5%) had 1 or more co-morbid condition and 27 patients (35.5%) had no risk factors or comorbid illness. Diabetes was the most common risk factor found in 13 patients (17.1%), followed by chronic pulmonary diseases namely, COPD/bronchial asthma/pulmonary tuberculosis in 11 patients (14.4%). Ten patients (13.1%) were pregnant or in post-partum period (Table 4).

All 76 patients had bilateral pneumonia on presentation, which progressed to acute respiratory distress syndrome (ARDS) and eventually had to be put on invasive mechanical ventilation. 21.12% had septicemia and MODS was observed in 30.2%. The common isolates from tracheal culture comprised *Enterobacter, Acinetobacter, Pseudomonas* and coagulase-negative *Staphylococcus* (Table 5).

Discussion

Human seasonal influenza affects primarily the very young, elderly, and those with co-morbidities. But the epidemiologic hallmark of pandemic influenza is its "pandemic signature meaning most early mortalities are among young healthy adults.[6]

The current epidemic was analyzed for case fatality characteristics of deaths which occurred from 1st January 2015 to 28th February 2015. The noteworthy features were rapid progression of disease and high early mortality.

The demographic profile of 76 fatal cases revealed a mean age of 44.01 years. 47.43% deaths were recorded in the age group of 18 to 40 years. Regan et al[7] in their study also recorded a mean age of 45 years.

The mean interval between symptom onset to hospitalization was 6.7 days with a range of less than 1 day to 11 days. Majority of the patients (60.3%) presented between 72 hours and 1 week of symptom-onset. In the study done by Regan et al,[7] the mean interval to hospitalization was 3 days, whereas Fajardo-Dolci et al from Mexico in 2009 reported a mean interval of 6.3 days.[8]

At presentation all the 76 patients had bilateral pneumonia on chest X-ray.

Only 7.89% presented within 48 hours of onset of symptoms, 46% presented within 5 days of onset of illness while the majority, 72.1% presented within a week of symptom onset. This probably indicates an overwhelming virulence. The fact that all 76 patients were having category C symptoms severity, with radiological signs of bilateral pneumonia and early onset of respiratory failure with initiation of Oseltamivir on the day of admission or prior to admission (4 were started Oseltamivir before admission) implies that Oseltamivir may not be effective if pneumonia has already set in or sets in rapidly. The "critical phase" in influenza starts much earlier (57.4% presented with a short history of 5 days or less). The need to identify the factors of these rapid progressors shall remain a daunting task. Out of 76 patients 14 were hemodynamically unstable at admission requiring vasopressor support.

In our series, mean duration of hospitalization was 5 days with a range from less than 1 day to 19 days, but the majority (66.9%) succumbed within 5 days of hospital admission. In the series of Regan et al, a mean interval of 12 days of hospitalization has been reported.[7]

Among the major predisposing risk factors diabetes was seen in 17.1%, chronic lung conditions in 14.4%, pregnancy/post-partum state in 13.1%. 64.5% of the patients who died had one or more risk factors.

All of them required invasive mechanical ventilation with a mean time of starting mechanical ventilation being 3.43 days (range 3.43 ± 2.53). Use of lung protective strategy of low tidal volume and adequate pressure was the standard protocol followed.[9,10]

Culture samples were obtained

Table 5: Complications in 76 deaths

Complication	Deaths (%)
Bilateral pneumonia with ARDS	76 (100)
Multiple organ dysfunction (MODS)	23 (30.2)
Septicemia	15 (19.7)
AKI (acute kidney injury)	7 (9.2)

from tracheal aspirates leading to identification of sepsis in 21.12% with isolates comprising *Enterobacter*, *Acinetobacter*, *Pseudomonas* and coagulase-negative Staphylococci. Specific antimicrobial coverage was instituted in tandem with the institutional microbial sensitivity pattern.

Conclusion

To treat the patients who present with early bilateral pneumonia remains a formidable task. As delineated in our study, the majority of patients presented within 5 days of the onset of illness and received Oseltamivir in adequate doses, yet these patients succumbed to this viral illness. The authors are of the opinion that categorization of severity of illness has been useful, yet there is a significant proportion of cases who progress rapidly. What factors contribute to rapid progression whether virulence, drug resistance, host factors or structural reformation of the virus, should form the epicenter of focus especially in people without any risk factors.

Identifying influenza-like illness (ILI) symptoms of fever, myalgias, cough, rhinorrhea alongwith an important sign of pharyngeal congestion and treating them early with Oseltamivir along with preferential and relevant vaccination / annual revaccination of risk groups, specifically pregnant females / diabetics and patients with chronic lung conditions like fibrosed lungs due to pulmonary tuberculosis in our country, besides, bronchial asthma or COPD, should help to curb down the morbidity and mortality rates.

With the advent of vaccination, the concept of "ring prophylaxis"[11] meaning that use of Oseltamivir chemoprophylaxis more widely than just among the close contacts should take the back stage.

The importance of participation of physicians and healthcare workers to identify ILI patients and recommending them home isolation[12] cannot be undermined to stall the "herald waves" of imminent influenza. However, a sort of non-confrontational antagonism does exist between principles of internal medicine and principles of alternative medicine. The practice of herbal / Ayurvedic preparations like *KADA* (an Ayurvedic concoction) has been much publicized without any scientific foundation or head-on trials. The possibility thus remains that people with influenza-like illnesses may avoid seeking proper medical care and resort to alternatives with the hope of a cure, protection or both.

Acknowledgement

The sudden rise in swine flu cases in the first few weeks of January 2015 led to formation by the State Government of Rajasthan of a very proactive task force to intimidate the demon of H1N1. The chairman of this task force was none other than the eminent physician and neurologist Padmashree Dr. Ashok Panagariya (Professor Emeritus), along with Mr. J.C. Mohanty, Principal Secretary, Department of Medical Education, Mr. Mukesh Sharma, Principal Secretary, Department of Health, Dr. S.P. Singh, Joint Secretary, Department of Medical Education, Government of Rajasthan. Dr. U.S. Agarwal, Principal and Controller, SMS Medical College, Jaipur, Dr. B.R. Meena, Director Medical Health Services, State of Rajasthan and various experts. The authors thankfully acknowledge their guidance, encouragement and support for this work.

References

1. Fineberg HV. Pandemic Preparedness and Responses - Lessons from the H1N1 influenza of 2009. *N Engl J Med* 2014; 370:1335.
2. Chandra S, Noor EK. The evolution of pandemic influenza evidence from India. *BMC Infectious Diseases* 2014; 14:510.
3. Fred F. Ferri's Clinical Advisor 2015: Influenza; Basic Information. Pg.655.
4. WHO Guidelines for Pharmacological Management of Pandemic Influenza A (H1N1) 2009 and other influenza viruses. Revised February 2010 Part I Recommendations Rec 03 Pg. 12.
5. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. *N Engl J Med* 2010; 362:1716.
6. Cunha BA. Swine Influenza (H1N1) Pneumonia: Clinical Considerations. *Infect Dis Clin North Am* 2010; 24:204.
7. Regan J. Epidemiology of influenza A (H1N1) pdm09-associated deaths in the United States, September–October 2009. www.influenzajournal.com, Published Online 16 July 2012, Pg. e174.
8. Fajardo-Dolci G. Comparing Deaths from Influenza H1N1 and Seasonal Influenza A: Main Sociodemographic and Clinical Differences between the Most Prevalent 2009 Viruses. Influenza Research and Treatment. Volume (2012), Article ID 501784.
9. Ramsey CD, Kumar A. Influenza and Endemic Viral Pneumonia. *Critical Care Clinics* 2013; 29:1076-1077.
10. Hui DS, Lee N, Chan PKS. Recent advances in Chest Medicine: Clinical Management of Pandemic 2009 Influenza A (H1N1) Infection. *Chest* 2010; 137:916–925.
11. Timothy M. Uyeki. 2009 H1N1 Virus Transmission and Outbreaks. *N Engl J Med* 2010; 362:23.
12. Temte JL. Basic Rule of Influenza: How to Combat the H1N1 Influenza (Swine Flu) Virus. American Fam Physician 2009; 79:938-9.