RETROSPECTIVE STUDY OF H1N1 PANDEMIC-WHAT ANAESTHESIOLOGIST SHOULD KNOW ABOUT IT

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ABSTRACT: The aim of this article is to focus on the presenting features, prevention and management of H1N1 The clinical characteristics of a series of 10 patients with novel influenza A (H1N1) virus infection and ARDS necessitating ventilator support at Andhra Pradesh Government Chest and General Hospital a tertiary-care ICU in Hyderabad. Of the 10 patients 4 patients were obese (body mass index [BMI] ≥30), including 2 who were extremely obese (BMI≥40), none of them had progressed to multiorgan dysfunction syndrome (MODS).Of the 10 ICU admissions 8 patients died and 2 ICU patients survived the illness. Clinicians should be aware of the potential for severe complications of novel influenza A (H1N1) virus infection with fatal outcome particularly in those on ventilator support.

KEYWORDS: H1N1 Influenza Virus, Prevention, Management, Oseltamivir.

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INTRODUCTION: Some strains of H1N1 are endemic in humans and cause a small fraction of all influenza-like illness and a small fraction of all seasonal influenza. H1N1 strains caused a small percentage of all human flu infections in 2004–2005. Other strains of H1N1 are endemic in pigs (swine influenza) and in birds (avian influenza).

In June 2009, the World Health Organization (WHO) declared the new strain of swine-origin H1N1 as a pandemic. This strain is often called swine flu by the public media. This novel virus spread worldwide and had caused about 17,000 deaths by the start of 2010. On August 10, 2010, the World Health Organization declared the H1N1 influenza pandemic over, saying worldwide flu activity had returned to typical seasonal patterns. The Spanish flu, also known as la grippe, La Gripe Española, or La Pesadilla, was an unusually severe and deadly strain of avian influenza, a viral infectious disease, that killed some 50 to 100 million people worldwide over about a year in 1918 and 1919. It is thought to be one of the deadliest pandemics in human history.

The 1918 flu caused an unusual number of deaths, possibly due to it causing a cytokine storm in the body[1,2,3] (The current H5N1 bird flu, also an Influenza A virus, has a similar effect.)[1] The Spanish flu virus infected lung cells, leading to overstimulation of the immune system via release of cytokines into the lung tissue. This leads to extensive leukocyte migration towards the lungs, causing destruction of lung tissue and secretion of liquid into the organ. This makes it difficult for the patient to breathe. In contrast to other pandemics, which mostly kill the old and the very young, the 1918 pandemic killed unusual numbers of young adults,[4] which may have been due to their healthy immune systems mounting a too-strong and damaging response to the infection.[5]

While there are three types of influenza–Type A, B and C, Type A viruses are considered more lethal. Influenza A virus has two proteins on their surface, Haemagglutinin (HA) and Neuraminidase (NA). Many different combinations of HA and NA are possible giving rise to the different subtypes H1N1, H5N1 etc.

Antigenic variations have been described. Antigenic Drift is the gradual antigenic change over a period. Involves point mutations, responsible for frequent influenza epidemics.

Antigenic Shift is the sudden complete or major change. Leads to a novel subtype different from both the parents making it transmissible from person to person causing pandemics. Antigenic shift was responsible for Spanish, Asian, Hong Kong and current H1N1 pandemics.[6]

AIM AND OBJECTIVE: of the Article is to study the Role of anesthesiologist in the management of H1N1 Pandemic:

- ✓ As a team member in planning of isolation.
- ✓ Care of sterile surroundings and disinfection.
- ✓ HDU monitoring.
- ✓ ICU care of patients.

Pre requisites for a pandemic:

- Emergence of a novel virus to which all humans are susceptible.
- New virus is able to replicate and cause disease in humans.

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- Efficiently able to transmit from human to human.

All criteria are met for the novel influenza A H1N1.

The World Health Organization declared the first flu pandemic in 41 years. More than 300,000 cases with 3917 deaths reported by (WHO) as on Sept 20, 2009.H1N1 virus can be more virulent in developing countries. More than 191 countries have reported H1N1 cases.

Indian data as on 16th September 2009:

- Total number of passengers screened: 68, 00,000.
- Total number of symptomatic patients tested: 30,839.
- Total number of confirmed cases: 6800.
- Total number of deaths reported: 208.

Spread of H1N1 and Factors Affecting Spread:

1. **Agent Factors:**

Source of Infection	Reservoirs of Infection
1. Case or Sub clinical case	1.HumanPrimary reservoirs
2. Communicability up to 8 days in adults and up to 2 weeks in children	2.Animals & birds-major reservoirs
3. Peak viral shedding-first 24hrs of symptoms	

Table 1

2. **Host Factors:** Affects all ages and both sexes equally. Although people in extremes of age and those with Co morbid diseases are affected more. Human immunity develops as Antibodies to H protein which neutralizes virus and Antibodies to N protein which modifies the infection. Immunity appears 1wk after the attack, reach maximum in 2 weeks and drops to pre infection level in 8-12months.
3. **Environmental Factor:** Seasonality affects the spread of the disease. In temperate zones epidemics occur in winter where as in tropics, epidemics occur in cold and damp weather. Sporadic cases can occur in any month. Overcrowding enhances transmission. Higher attack rates in closed population groups.

DISEASE TRANSMISSION: Air borne transmission occurs as droplet infection and droplet nuclei. The disease can also spread through direct contact and by transmission from objects.

Incubation Period Ranges From 18–24 Hours Communicability: 1day before the onset of symptoms to 7-10 days after becoming symptomatic.

Signs and Symptoms Requiring Hospitalization: Depending on the severity of the presentation the patients are divided into 3 categories.

Category A: Mild fever plus cough/sore throat with or without body ache, headache, diarrhea and vomiting. They do not require Oseltamivir and need symptomatic treatment at home. They should be reassessed after 24 to 48 hours. No testing of the patient for H1N1 is required.

Category B (**i**)**:** In addition to all the signs and symptoms of Category A, if the patient has high grade fever and severe sore throat.

Category B (ii): In addition to all the signs and symptoms of Category A, individuals having one or more of the following high risk conditions shall be treated with Oseltamivir. Children under five, pregnant women, those above 65 years, those with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS and Patients on long term cortisone therapy. No H1N1 tests are required for Category-B (i) and (ii) Patients may require home isolation and Oseltamivir.

Category C: In addition to the symptoms of Categories A and B, if the patient has one or more of the following, Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails; irritability among small children, refusal to accept feed; worsening of underlying chronic conditions. Such patients require testing, immediate hospitalisation and treatment.

Management of Hospitalized patients with suspected/ Proven H1N1:

Investigations: The base line hematological, renal and hepatic profile is done, to rule out Leukopaenia, Thrombocytopenia, Lymphopenia and increased levels of aminotransferase.

Chest x-ray: to rule out infiltrates/pneumonic consolidations/ARDS.

Specific Investigations:

1. Rapid assay kits: Requires nasal swab. Sensitivity is 70 to 75% and Specificity 80%. Positive results are obtained only if viral load is high. False negative is common.
2. RTPCR (Real Time Polymerase Chain Reaction): done for antigenic detection. More specific than rapid assay
3. Estimation of Antibody titers.
4. Viral culture–gold standard but may not be possible as a routine test.

SAMPLE COLLECTION: Samples can be: Throat swabs, Nasal swabs, Tracheal aspirates,Tracheo bronchial lavage which gives higher viral titers & yields. All the samples are transported in cold chain at 0-4^{0}C.

Secondary specimens: Plasma in EDTA for detection of viral RNA, Rectal swab in patients presenting with diarrhea, Spinal fluid if meningitis is suspected.

Stepwise Management of H1N1 Patient: Step wise management of H1N1 patient may be summarized as:

Step 1: Home isolation/OPD treatment.

Step 2: Hospitalization with Isolation of the affected and HDU care.

Step 3: ICU care with or without mechanical ventilation.

Anti-retroviral therapy: Neuraminidase inhibitors[7] like Oseltamivir and Zanamivir block the spread of infected cells to healthy cells.

The Treatment Plan includes specific treatment with anti virals i.e Oseltamivir, Infection control, symptomatic & supportive treatment and Admission and discharge policy.

Oseltamivir: Early treatment improves survival when treatment is started early.

Dosage in Children (syrup form available): in children <15 kg the dose is 30mg bid, for 15-23kg 45mg bid, 23-40kg 60mg bid, >40 kg 75mg bid.

Dosage in Adults: is 75mg bid increasing to150mg bid in the event of severe symptoms, pneumonia or ARDS.

	Treatment dose	Prophylaxis dose
0 – 3 months	15 mg BD	Not indicated
3 – 6 months	20mg BD	20mg OD
6 – 11 months	25 mg BD	25 mg OD

Table 2: Dosage in children less than 1 year

Side Effects: Rash, itching, dizziness, drowsiness, hypersensitivity reactions, vomiting, diarrhea, stuffy nose, bronchitis, labored breathing.Safety precautions to be taken in patients with kidney diseases.

Zanamivir in H1N1 Management: Available as intranasal disk haler device. The main draw backs are that it cannot be given to children < 5yrs, uncooperative and aged patients and in seriously sick patients. Side effects include severe bronchospasm in patients with chronic lung disease. Dosage for Treatment: 10mg / BD / 5days.

Prophylactic Dose: Oseltamivir 75mg / day for 7-10 days after the last exposure. Ideal duration of prophylaxis for health worker is to continue prophylaxis as long as he is exposed to the patient. Zanamivir Prophylaxis: 10mg once till 7-10days after exposure

Prevention of H1N1: Prevention at individual level: Includes frequent hand washing, N95 mask and avoidance of frequent touching of face and mouth.

Prevention by the Health Personnel: PPE (Personal Protection Equipment): Includes change of Gloves between the patients, long sleeved gowns fitting snuggly at wrists, 3 layered surgical masks or N95 masks also known as particulate respirators. The device has submicron filter capable of excluding particles < 5 microns in diameter. Boots and Eye protection-face shields/ goggles also form part of PPE.

Disinfection and Disposal: Clean and disinfect patient's room every day including bed rails, tables, and equipment surfaces, BP cuff & stethoscope. House hold bleach Quaternary ammonia compounds, Chlorine compounds, Alcohol (Isopropyl 70%, Ethyl alcohol 60%), per oxygen compounds, Phenolic disinfectants may be used for disinfection.

Disposal: it is important to decontaminate the waste before disposal. Needles should be destroyed & deep burial done. Plastic ware should be mutilated at 160^0C for 20 min. followed by deep burial. Human tissues, cotton swabs, cultures should be incinerated. Reusable instruments should be chemically disinfected or autoclaved. Linen, gowns, foot ware should be boiled or disinfected with 5%bleach then produced for final washing.

Management of H1N1 Positive patients in Isolation ward or HDU / ICU:

Oxygen and Supportive Therapy: During oxygen therapy with mask, droplet infection cannot be prevented and may contribute to further spread of the disease. Continuous vigilance is mandatory as these patients may need ventilator support at any time. Supportive therapy includes treatment of hemodynamic compromise, Fluid and electrolyte balance, Nutritional support, Antiviral treatment: 150mg bid Oseltamivir and antibiotic coverage for secondary infections.

Indications for mechanical ventilation: Severe pneumonia and acute respiratory failure as evidenced by a Spo2 < 90% or a Pao2 < 60mmHg on oxygen, Type 1 or Type 2 respiratory failure or ARDS necessitate Mechanical Ventilation. Invasive ventilation with ETT and closed ventilation suction system is preferred as it is associated with less dissemination of the droplet infection. NIV is not recommended.

ICU Care of H1N1 Patient: Triage is a system to identify salvageable individuals, provide them critical or medical care to ensure saving as many lives as possible. Tools used for triage in ICU are CURB- 65 Scoring System and SOFA Score.

CURB–65 Scoring system takes into account Confusion, Urea >7mol/L or 40mg%, Respiratory rate >30/m, Blood pressure (S<90) (D<70), and an age of 65 yrs or more. Each factor is given a score of 1.The score is analyzed as:

Points	Risk profile	Recommendation
0 – 1	Low risk	OPD treatment
2	Increased risk	Admission or supervised OPD treatment
3 -5	High risk	Admit in ward/ ICU

CURB Score	Risk of death
0	0.7%
1	3.2%
2	13.0%
3	17.0%
4	41.5%
5	57.0%

Table 3: Risk of death increases as the score increases

Variable	0	1	2	3	4
PaO2	>400	</-400	</-300	</- 200	</- 100
Platelet Count	>1.5	</- 150	</- 100	</- 50	</- 20
Bilirubin	<1.2	1.2-1.9	2-5.9	6-11.9	>12
Hypotension	None	MBP<70	Dop </-5	Dop>5 Epi</-0.1	Dop>5Epi>0.1
GCS	15	13-14	10-12	6-9	<6
S.creatinine	<1.2	1.2-1.9	2-3.4	3.5-4.9	>5

Table 4: SOFA (Sequential Organ Failure Assessment) Scoring

Triage Code	Criteria	Action
Blue	Sofa >11	• Medical management • Palliative care
Red	Sofa<7	Highest priority
Yellow	Sofa 8-11	Intermediate priority
Green	No organ failure	• Discharge • Reassess

Table 5

Chief Concerns:

- Full course of Oseltamivir even if tested negative.
- Prevention of secondary complications.
- Personal protection.

"Personal protection of the medical care providers is as important as the care of the patient"

Discharge Criteria:

- Asymptomatic adult patients if afebrile with normal chest x- ray may be discharged after 7 days. Children < 12 yrs need isolation up to 2wks after becoming asymptomatic.
- If the patient remains symptomatic even after 5 days of antiviral therapy, continue treatment for 5 more days. If still symptomatic, antiviral resistance or secondary bacterial infection should be ruled out.

Special situations: People at greatest risk for 2009 H1N1 infection include Children, Pregnant women and People with chronic health conditions like asthma, diabetes or heart and lung disease.

H1N1 in Pregnancy: is associated with rapid disease progression manifesting as early primary pneumonia and subsequent ARDS requiring mechanical ventilation. Nasopharyngeal swabs for PCR are ideal as the rapid kit test may have high rates of false negative results. No recommendations are made for additional routine testing of amniotic fluid or placenta. In symptomatic patients Oseltamivir is the treatment of choice. For exposure prophylaxis Zanamivir is first line drug followed by Oseltamivir.

H1N1 in lactation: Newborns are at high risk of infection and should be considered infective if delivered 2 days before and 7days after illness. Mothers should avoid close contact with the infant until she has one of the three: Received the antiviral for 48 hours, Fever has resolved and Cough and secretions subsided. Mother should wear mask for 7days after the onset of symptoms and till she is symptom-free for 24 hours.

MATERIAL METHODS:

Our statistics in AP Govt. Chest and General Hospital as on October 30, 2009:

Total number of patients detected positive for H1N1–228.
Number of Patients treated in OPD-70.

Patients admitted in hospital in Isolation ward with HDU monitoring-158.

Patients admitted in ICU requiring Mechanical Ventilation – 10.

Patients successfully weaned off ventilator support & discharged from ICU-2.

Mortality in ICU-8.

Admission of the 10 patients in the ICU occurred during Aug 15th to Oct 20th 2009.The median age was 32.33+/- 2.3 years (range: 21--53 years); 6 patients were females including 1 pregnant patient. She was referred after the initial resuscitation to an obstetric centre where she succumbed to the disease. 4 of the patients were obese (BMI>30), including 2 who were extremely obese (BMI > 40).In the 8 fatal cases, the time from onset of illness to death ranged from 4 to 20 days.

Three patients received steroids during their illness before transfer to the ICU; all the patients received intravenous corticosteroids during their ICU hospitalization for continuation of therapy for the pulmonary disease.

All the10 patients transferred to the ICU required mechanical ventilation with high mean airway pressures (32--45 cm H20).Upon transfer to the ICU, 4 patients had elevated white blood cell counts (17–19,700 cells/ mm3) and one had a decreased white blood cell count (3,200 cells/mm3). The mean white blood cell count (WBC) was 9,500 cells/mm3 (range: 3,200--19,700 cells/mm3). All 10 patients had elevated aspartate transaminase (AST) levels. The mean AST level was 92.5 IU/L.

Chest radiograph findings in all the 10 patients were abnormal, with bilateral infiltrates consistent with severe multilobar pneumonia[8] or ARDS. All patients received prophylactic systemic heparin anticoagulation. None of the 10 patients had clinical evidence of concomitant disseminated intravascular coagulation.

The ABGs of these patients revealed extreme hypoxemia (lowest 34.6 on FiO2 1), increased PAO2-PaO2 gradient, hypercapnia (highest 85 mmHg), combined respiratory and metabolic acidosis as evidenced by decreased pH.

OBSERVARTION AND RESULTS: None of the 10 patients had evidence of bacterial infection after admission to the ICU or in subsequent blood, endo tracheal, or urine cultures. All patients received broad spectrum antibiotics upon transfer to the ICU.

The timing of antiviral treatment initiation, the estimated median number of days from illness onset to initiation of antiviral treatment was 8 days (range: 5-12 days). During their care at the ICU, all 10 patients were administered oseltamivir beyond the standard 5-day course, including higher-dose oseltamivir (up to 150 mg orally twice a day), with dose adjustment for decreased renal function.

We could successfully wean 2 patients with severe ARDS. Rest eight of the patients succumbed to the disease. The most prominent factor in ARDS of H1N1 origin was severe and refractory hypoxemia not responding to the routine ARDS protocols. As literature says ECMO may increase the survival in these patients.[9]

DISCUSSION: All influenza viruses change constantly. Swine Flu is no exception. Pigs can be infected by avian and human influenza as well as swine influenza viruses. When influenza viruses from different species infect pigs, the viruses can reassort (i.e. swap genes) and new viruses that are a mix of swine, human and/or avian influenza viruses can emerge. The pandemic of H1N1 is due to a new strain so emerged and it is no longer a Swine Flu. Human to human transmission of H1N1 virus has occurred making it a pandemic disease.

To develop any vaccination it will take 6 months period after the breakdown of a pandemic. A seasonal vaccine will not protect against 2009 H1N1. There are efforts to bring a live attenuated inhalational vaccine into the market. A new vaccine is expected in March 2010. Indian companies licensed to manufacture the vaccine are Serum institute of India, Bharat Biotech & Pennacia Biotech. At present there is no vaccine to protect against H1N1 virus.

Management and general guidelines for H1N1 induced bacterial pneumonia with streptococcus pneumoniae[9,10] and ARDS is no different from the general management of ARDS. But the rapid progression of the disease and the extensive pulmonary involvement leads to refractory hypoxia posing a difficult situation for maintaining oxygenation**.** Improving Oxygenation through Alveolar recruitment maneuvers, ensuring adequate ventilation and preventing hypercarbia as far as possible (role of prone position ventilation not proved), adequate fluid management, appropriate antibiotic coverage, early enteral nutrition all play an important role in the positive course of the disease. Full course of Oseltamivir 150mg, bid should be continued even if throat swab is tested negative. ICU care of the patient should aim at the Prevention of secondary complications.

CONCLUSION: Clinicians should be aware of the potential for severe complications of novel influenza A (H1N1) virus infection with fatal outcome particularly in those on ventilator support. The most prominent factor in ARDS of H1N1 origin was severe and refractory hypoxemia not responding to the routine ARDS protocols.

Anaesthesiologist has an important role to play right from the preventive measures to be taken to cut the spread the infection to fulfilling his responsibility in ICU management of severe pulmonary infection which is the fatal outcome of H1N1 infection.

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