Severe Respiratory Sequelae Of H1N1 : Clinical Features, Management And Outcome – A Review

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Since the outbreak of the novel influenza H1N1 in April 2009 in Mexico, more then half a million cases have been recorded with more then 6000 deaths. In contrast to seasonal flu, this virus appears to have a predilection for the young, obese and pregnant. It's most important and almost fatal complication is Acute Respiratory Distress Syndrome (ARDS). Intensive care units (ICU) around the world have scrambled to upgrade various treatment modalities including high frequency oscillation ventilation, inotropes, antivirals and antibiotics in an effort to reduce the mortality arising out of this complication. More importantly, this complication appears reversible if adequate and early therapy is instituted. In particular, rescue therapies that allow the lung to rest appear to have brought success in some clinical settings. This article describes the experiences of seven centers that have used various modalities as rescue therapy in patients having Acute Respiratory Distress Syndrome (ARDS). The experiences in 13 patients at the University of Michigan, 58 in Mexico, 168 in Canada, 180 patients at Leicester UK, 194 in Australia and New Zealand and case reports from Hong Kong and Singapore are described.

IeJSME 2010: 4(2): 10-17

Key Words: H1N1, ARDS, ventilation, ECMO

Introduction

The novel influenza, H1N1 flu appears to be significantly different from seasonal influenza in that it kills a much younger age group than ordinary flu according to the World Health Organization.[1] The US CDC (Centres for Disease Control) announced in October, 2009 that thus far 86 US children had died of H1N1 with most being in the 5 to 17-year old age group and in severe cases, patients deteriorate in around three to five days following symptoms with deterioration being rapid, many progressing to respiratory failure within 24 hours.[2]

Unlike seasonal flu which generally is a disease of the upper respiratory tract, novel influenza H1N1 appears to have a greater predilection for the lower respiratory tract causing pneumonia. Although the exact role of obesity is poorly understood at present, obesity and especially morbid obesity have been present in a large portion of severe and fatal cases. Obesity has not been recognized as a risk factor in either past pandemics or seasonal influenza.[2]

This review describes clinical features, laboratory findings and reviews the clinical management and outcomes in 7 centers/regions that utilized various modalities as rescue therapy in patients who sustained serious respiratory sequelae especially ARDS as a complication of H1N1. The experiences in 13 patients at the University of Michigan, 7 in Canada, 168 patients at Leicester UK, 194 in Australia and New Zealand, 1 case report from Hong Kong and 2 from Singapore are described. The review further compares the results of 4 centers that managed patients with influenza like illnesses (ILI), the majority of whom were later confirmed to have H1N1 who subsequently developed serious respiratory complications especially acute respiratory distress syndrome (ARDS), the condition's most serious complication.

United States

At the initial outbreak of novel influenza A (H1N1) in April 2009, the CDC reported the first two cases in the US.[3] Between May and June 2009, the University of Michigan received 13 patients for evaluation, 10 of whom were confirmed to have novel influenza A (H1N1) virus infection by testing of respiratory specimens with real-time reverse transcription-polymerase chain reaction (rRT-PCR). Of the 10, nine were obese (body mass index [BMI] ≥30), including seven who were extremely obese (BMI ≥40); five had pulmonary emboli; and nine had multiorgan failure.

The median white blood cell count (WBC) was normal. All ten patients had elevated aspartate

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transaminase (AST) levels. Six had elevated creatine phosphokinase (CPK) levels. Chest radiograph findings in all 10 patients showed bilateral infiltrates consistent with severe multilobar pneumonia or ARDS. Computed tomography (CT) of the chest confirmed pulmonary emboli in four patients. All 10 patients were referred because of severe hypoxemia, ARDS and an inability to achieve adequate oxygenation with conventional ventilation modalities. The median age was 46 years (range: 21-53 years).There were three fatalities; the time from illness onset to death ranged from 17 to 30 days.

Nine patients were admitted for multiorgan failure and all nine manifested septic shock requiring inotropic support. All 10 patients required tracheostomy. All patients received antibiotic therapy with oseltamivir and amantadine being administered beyond the standard 5-day course, including higher-dose oseltamivir (up to 150 mg orally twice a day). All 10 patients required initial advanced mechanical ventilation. Two patients required ECMO (Extracorporeal Membrane Oxygenation). Six required continuous renal replacement therapy (CRRT) for acute renal failure. Of the 10 patients, one patient remained in ICU requiring ECMO, one remained on advanced mechanical ventilation, five were transferred back to the referring facility in stable condition, and three died.

There was a predominance of males, a high prevalence of obesity (especially extreme obesity), clinically significant pulmonary emboli and multiorgan failure. Only three of the patients in this series had underlying conditions. The high prevalence of obesity in this case series is striking. Obesity has not been identified previously as a risk factor for severe complications of seasonal influenza.

Patients were monitored for rapid clinical deterioration, especially oxygenation and potential complications (e.g., respiratory failure, ARDS, multiorgan failure, septic shock, and pulmonary emboli). Empiric antiviral treatment is recommended for all hospitalized patients at admission with suspected novel influenza A (H1N1) virus infection, Empiric antibiotic agents were used as appropriate. Depending on the antiviral susceptibilities of circulating influenza A virus strains, either zanamivir monotherapy or combination therapy with oseltamivir were administered until final virus identification was available. In communities in which novel influenza A (H1N1) virus is the predominant circulating influenza virus, oseltamivir or zanamivir is recommended as early as possible even before diagnostic testing results are available. Negative results of rapid influenza diagnostic tests, immunofluorescence, or viral culture do not exclude the possibility of novel influenza A (H1N1) virus infection.

Mexico

Guillermo and colleagues conducted an observational study of critically ill patients at six hospitals in Mexico that treated the majority of such patients with confirmed, probable, or suspected 2009 influenza A (H1N1) between March 24 and June 1, 2009.[4] They reported that H1N1 was associated with severe acute respiratory distress syndrome and shock, and had a fatality rate of about 40 percent. Between March 18 and June 1, 2009 - 5,029 cases and 97 documented deaths occurred in Mexico.

They were among 899 patients with confirmed or suspected cases who were admitted to the hospitals during that time; many of them faced delays in admission to the ICU, and four died in emergency departments. Of these patients 58 became critically ill. The critically ill patients had a median age of 44 years. Most were treated with antibiotics, and 45 patients were treated with oseltamivir and zanamivir. Fifty-four patients required mechanical ventilation.

Critically ill patients affected a young patient group. Fever and respiratory symptoms were harbingers of disease in almost all cases. There was a relatively long period of illness prior to presentation to the hospital, followed by a short period of acute and severe respiratory deterioration. Obesity was the most common "comorbid"

condition, found in 21 of the 58 patients, followed by smoking, hypertension, and diabetes.

By 60 days, 24 of the critically ill patients (41.4 percent) died. Patients who died had greater initial severity of illness, worse hypoxemia, higher creatinine kinase levels, higher creatinine levels, and ongoing organ dysfunction. All but two patients received mechanical ventilation for acute respiratory distress syndrome (ARDS). Those who survived were in the ICU for a median of 13.5 days and on a ventilator for a median of 15 days (many received ventilation outside the ICU). The common factor appears to be that these patients are extremely difficult to ventilate. The authors propose that it is the same problem as for pregnant women – encroachment of the thoracic space which gives rise to severe pneumonias in a restricted lung.[5]

Canada

Anand Kumar et al gathered data in 168 critically ill patients with 2009 influenza A (H1N1) infection in 38 adult and pediatric intensive care units (ICUs) in Canada between April 16 and August 12, 2009. They identified 162 confirmed cases and 6 probable ones.[6]

Among the 168 patients the mean age was 32.3 years; 113 were female (67.3%) and 50 were children (29.8%). Overall mortality among critically ill patients at 28 days was 14.3%. A third of the patients were obese, and 67% were female. Fifty-one patients had major underlying conditions, with chronic lung disease, obesity, hypertension, and smoking the most common. Evidence of bacterial pneumonia was seen in 24%.

Creatine kinase was moderately elevated over the first week. The mean leukocyte count was normal at admission. Secondary bacterial pneumonia was found in 41 cases (24.4%) mainly by *Staphylococcus aureus* and *Streptococcus pneumoniae*. Neuraminidase inhibitors were administered to 152 patients (90.5%). All patients were severely hypoxemic at ICU admission. Mechanical ventilation was received by 136 patients (81.0%). The median duration of ventilation was 12 days and ICU stay was 12 days.

Barotrauma occurred in 14 patients (8.3%). Therapies for oxygenation failure included neuromuscular blockade (47 patients; 28.0%), inhaled nitric oxide (23 patients; 13.7%), high-frequency oscillatory ventilation (20 patients; 11.9%), extracorporeal membrane oxygenation (7 patients; 4.2%), and prone positioning ventilation (5 patients; 3.0%). The primary reported causes of death included severe acute respiratory distress syndrome and hypoxemia; secondary infection and sepsis; multiorgan dysfunction syndrome, malignancy, chronic obstructive pulmonary disease, primary cardiac arrest, tension pneumothorax, cerebral edema; and undetermined etiologies.

In previous influenza pandemics, an increased predilection for infection among children and young adults has been documented.[7] These data suggest that severe disease and mortality in the current outbreak is concentrated in relatively healthy adolescents and adults between the ages of 10 and 60 years, a pattern reminiscent of the 1918 H1N1 Spanish pandemic.[8,9]

The tendency of females to develop severe infection is striking. A general female susceptibility has not been observed in other influenza case series.[10,11] In most infectious diseases and related conditions such as sepsis and septic shock, males represent a larger proportion of cases and have a higher mortality. The explanation for increased risk of severe disease and death among females in this report is unclear but the role of pregnancy as a risk factor has been noted in previous influenza pandemics.[12,13]

Among critically ill patients, obesity has been shown to be a risk factor for increased morbidity, but not consistently with mortality.[14-16] The association of obesity with severe 2009 influenza A (H1N1) infection has been reported by others and may be a novel finding of this pandemic.[5]

The relative absence of serious comorbidities emphasizes that young, relatively healthy adults were the primary population affected. Apart from the usual symptoms seen in seasonal influenza, these cases stand out for the presence of gastrointestinal tract symptoms,

dyspnea, purulent sputum production, and occasional frothy lung fluid on cough or endotracheal aspiration.

The authors concluded that severe illness arises in a young, previously healthy population with a high probability of survival given the availability of appropriate resources. If, as expected, the prevalence of 2009 influenza A (H1N1) infection increases with the upcoming flu season, there will be an acute increase in demand for ICU care, including the need for rescue therapies that are not currently widely available.[16,17] Clinicians and policy makers will need to examine feasible methods to optimally expand and deploy ICU resources to meet this need.

United Kingdom

Giles Peek and associates at Leicester aimed to delineate the safety, clinical efficacy, and cost-effectiveness of a treatment modality called extracorporeal membrane oxygenation (ECMO) and compared it with conventional ventilation support in severe acute respiratory failure in adults who have a high mortality despite improvements in ventilation techniques and other treatments (eg. steroids, prone positioning, bronchoscopy, and inhaled nitric oxide).[18] The majority of these patients had developed ARDS as a result of influenza-like illnesses including H1N1 and were referred to Glenfield Hospital, Leicester where the study was based.

They randomly assigned 180 adults to conventional management or referral to consideration for treatment by ECMO. Eligible patients were aged 18-65 years and had severe but potentially reversible respiratory failure. 180 were enrolled and randomly allocated to consideration for treatment by ECMO (n=90 patients) or to receive conventional management (n=90). 68 (75%) patients actually received ECMO; 63% (57/90) of patients allocated for treatment by ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management.

They recommend transferring of adult patients with severe but potentially reversible respiratory failure on optimum conventional management to a centre with an ECMO-based management protocol to significantly improve survival without severe disability.

Australia And New Zealand

In Australia, Davies et al reported that most patients who underwent extracorporeal membrane oxygenation (ECMO) for respiratory failure survived their struggle with pandemic H1N1 flu. Of the 68 patients treated with ECMO during the winter, 54 survived. They suggest that their results should aid healthcare planning and clinical management for these complex patients during the ongoing pandemic.[19]

They examined data from all 68 patients treated with ECMO in Australia and New Zealand at the 15 ICUs providing the service. The study found that 68 patients with severe influenza-associated ARDS were treated with ECMO. An additional 133 patients with influenza A received mechanical ventilation, but not ECMO, in the same ICUs. The authors estimated the incidence of ECMO use for confirmed and suspected H1N1 to be 2.6 per one million people. Assuming a similar incidence of ECMO use for the current flu season in the Northern Hemisphere, the U.S. and Europe might expect to provide treatment for 800 and 1,300 patients, respectively. The median age of the patients in their study was 34.4, and half were male.

Again, the most common comorbidities were obesity in 50%, asthma in 28%, and diabetes in 15%. Nearly one in 10 was pregnant. More than a quarter (28%) were coinfected with a bacterium, most commonly *Streptococcus pneumoniae* and *Staphylococcus aureus*. Almost all of the patients (94%) received oseltamivir (Tamiflu) for a median duration of eight days. The median duration of ECMO was 10 days. Most patients (81%) received rescue therapies for acute respiratory distress syndrome, including recruitment maneuvers (67%), inhaled nitric oxide (32%), epoprostenol (22%), prone positioning (20%), and high-frequency oscillatory ventilation (5%).

Hemorrhagic complications were common, occurring in 54% of ECMO patients. The most common sources were ECMO cannulation sites (22%), the gastrointestinal

tract (10%), and the respiratory tract (10%). Clinicians in Australia were "forewarned" of what to expect before swine flu arrived in Australia, by the experiences of doctors in Mexico and the U.S. When the outbreak of swine flu was announced in Mexico, many young people were presenting with severe pneumonia. They suggest that ECMO should be considered when an adult with respiratory failure has a 50% chance of dying and is indicated if there is an 80% chance of dying using conventional algorithms that take into account blood gases, ventilator pressure, the extent of shock, and other factors.

Hong Kong

Hong Kong had more than 10,000 cases of the virus confirmed by 27th August 2009. Forty-four were in serious condition and four had died, 17 had recovered and discharged. The total number of patients who required ventilation is unknown but Liong et al reported one case of ECMO done on a 37-year-old Filipino woman who developed ARDS.[20] As in the western world, the clinical features were similar but in this particular case, the ASRDS features were atypical on Chest X-ray.

The Filipino woman had presented with fever and failed to respond to treatment by her general practitioner. She complained of influenza-like symptoms and was subsequently hospitalized 10 days after the onset of symptoms where she was found to have severe pneumonia associated with severe hypoxemia. Her initial chest X-ray (CXR) showed bilateral lung air-space consolidation. A nasopharyngeal aspirate (NPA) was negative for influenza A and B rapid antigen, as was the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for novel influenza A (H1N1) on her throat and nasal swab. She was commenced on imipenem/cilastatin and azithromycin but her condition deteriorated rapidly and required intubation and mechanical ventilatory support the day after admission.

Influenza A (H1N1) infection was confirmed when her initial aspirates tested positive after a second round of testing. Oseltamivir 75 mg twice daily was started on day 3 of admission. The dose of oseltamivir was increased to 150 mg twice daily and Zanamivir was also given as the patient was critically ill and did not respond well to oseltamivir as there was concern about oseltamivir resistance.

She was given nebulised zanamivir 15 mg diluted in 2 ml normal saline for 4 doses over 3 days. It was discontinued following severe desaturation. Despite aggressive treatment, she had refractory hypoxaemia. ECMO was instituted on day 7 of her admission. On commencement of ECMO, the patient had no other vital organ failure and her oxygenation improved initially. However she could not be weaned to a lower level of ventilatory support to prevent barotrauma. The patient had clinical evidence of ventilator-associated pneumonia on day 12. She developed septic shock requiring inotropic support and acute renal failure requiring intermittent renal replacement therapy. She subsequently developed haemolysis, which precluded the use of ECMO which was stopped. She succumbed eventually the same day. A lung autopsy specimen revealed ARDS.

Singapore

The Singapore General Hospital reported two cases that underwent ECMO as a result of patients coming down with H1N1 induced ARDS. Thus far Singapore has recorded a total of 1217 cases with 19 deaths. **[27]** This city-state's acute care hospitals are well equipped to deal with respiratory complications of the novel influenza but no large scale studies have been reported except for two case reports. The first was a 36 year old security guard who presented with fever and influenza-like symptoms to his GP. Despite treatment, his fever failed to subside after a week. He developed severe breathlessness within 24 hours requiring ventilation and failed to respond to conventional mechanical ventilation therapy. He was subsequently placed on ECMO for a week. He was later weaned off ECMO to ventilation therapy before recovering. He was eventually discharged 17 days after admission but with residual decrease in

effort tolerance. The second patient was a 20 year old lady who was treated at the National University Hospital. Clinicians have noted that like elsewhere, H1N1 is peculiar in that it is young people who appear to progress rapidly to respiratory distress.[21]

Discussion

There are many conservative measures in treating H1N1 patients with serious respiratory sequelae and ARDS. These include prone positioning, aggressive diuresis/ultrafiltration, HFOV, shunt reduction maneuvers (high mean airway pressures, inhaled nitric oxide and use of prostacyclin) and ECMO if all of these maneuvers fail in the face of worsening barotrauma especially in young patients with a potentially reversible disease such as the novel H1N1. The Australian and Cesar studies suggest that ECMO is a modality that can indeed save lives as a rescue therapy when conventional methods fail.[18,19]

Data observed from 4 of these centers, 3 of whom had access to advanced ventilation therapies including ECMO appear to suggest that mortalities may be reduced if such sophisticated technologies are available. **[Table 1]** The four studies further emphasize the point that novel influenza H1N1 affects the fairly young. The mortality rate of 23% from the UMHS (University of Michigan Health System) is relatively high, but this could be attributed to the small number of patients (13) and also this study was one of the first reports to emerge during the pandemic.[3]

The lower mortality rates reported by Davies and Kumar is a possible reflection of what White and Angus emphasized in their editorials that critical care specialists and even primary care physicians may have to recognize the fact that respiratory sequelae associated with H1N1 could be better managed if these serious complications are recognized early, triaged and managed in units that can apply sophisticated rescue therapies rapidly as the complications are potentially reversible.[6,19,25] The mortality rates of 13.4% and 17.4% by Davies and Kumar respectively reflect this scenario where ICUs in their studies had access to advanced therapeutic maneuvers.[16,19]

In direct contrast, the high mortality rate of 41.4% of Guillermo et al from Mexico is indeed of great concern. One must recall that the pandemic began in an unprepared Mexico and its fatal respiratory complications could possibly have overwhelmed its critical care infrastructure. Guillermo attributes the high mortality, especially in the young to the fact that Mexico is a developing nation and it is possible that by contrast with developed nations, Mexico has a higher young population. He further points out that the 2009 influenza A (H1N1) could be unique to Mexico and may be related to a variety of factors, including climate, air quality, the higher altitude in Mexico City; delay between illness onset and presentation to the hospital with severe disease, decreased potential access or presentation of the population to acute care compared with other settings.[4]

Liong et al although conceding that ECMO is an effective way to support patients with refractory hypoxaemia who fail to respond to conventional ventilatory strategies as reported by Gattinoni, the CESAR trial and Nehra, indicate however they faced serious diagnostic problems in the beginning with their patient as all tests regarding the novel influenza returned as negative. They suggest clinicians maintain a high level of suspicion for ARDS and treat patients empirically without waiting as the respiratory complications of the swine flu tend to be rapid.[22-24]

They conclude that ECMO is not a risk-free procedure as it can cause severe haemolysis, hemorrhage, and haemodynamic instability. It is also labor-intensive and technically demanding and is unrealistic and too costly to provide this procedure to every critically ill patient with influenza A (H1N1) in the midst of a pandemic when the demand for critical care services have already been stretched to the limit.

The Cesar and Australian trials however, have indicated that ECMO should be considered for most patients who cannot receive lung-protective ventilation

and should be implemented early, possibly before 7 days. With the winter almost here in the Northern Hemisphere, there could be resurgence in respiratory failure secondary to viral necrotizing pneumonia related to H1N1 influenza that will increase demand for critical care services.

The Canadian, Leicester and Australian studies in particular are important lessons in the local context as anesthetists and critical care specialists could perhaps ensure that ICU facilities and especially rescue therapies such as high-frequency oscillatory ventilation, nitric oxide and even perhaps ECMO be made available to treat patients with the novel influenza H1N1.[6,18,19]

Conclusion

H1N1 can produce a rapidly progressive respiratory failure that is refractory to conventional mechanical ventilation, often in young, healthy patients – a group who are not currently a priority group for H1N1 vaccination.[25,26] The rapid onset of refractory hypoxemia, together with multisystem organ failure and hypotension, suggests that clinical outcomes will depend on clinicians' ability to apply sophisticated mechanical ventilatory support and adjunct therapies. The most serious of its complications, rapid ARDS, appears potentially reversible if patients are triaged, categorized and treated early. Unlike the 1918 Spanish Flu, this pandemic's mortality appears to have been curtailed by the availability of antivirals, antibiotics, vasopressors, ventilators and better ICU care.[8,9] Although there is a very high fatality rate per case of infection, it is essential that health planners anticipate and prepare critical care facilities to further reduce the mortality as the virus has a tendency to cause potentially reversible ARDS.

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TABLE 1: Shows the different centers with critically ill patients that developed ARDS as a complication of ILI and the subsequent mortality rates. The patients who were defined as critically were the ones that required mechanical ventilation, an FiO2 of more 60% or inotropes. mortality rates.

Author	Country	Advanced ICU Modalities Present HFOV/ ECMO	Median Age (yrs)	No. of patients with ARDS	No. of patients ventilated	No. of patients on ECMO	Total number of deaths	Deaths in Percentage
UMHS	USA	Yes	46	13	10	2	3	23%
Davies et al	Australia / New Zealand	Yes	34.4	194	133	61	26	13.4%
Kumar et l	Canada	Yes	32.3	168	160	8	29	17.3%
Guillermo et al	Mexico	No	44	58	56	0	24	41.4%

UMHS : University of Michigan Health System
ILI : Influenza like illnesses