Life-threatening Respiratory Failure from H1N1 Influenza: Lessons from the Southern Cone Outbreak

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Introduction

A sharp increase in the hospitalization rate for pneumonia, particularly among adults between 20 and 40 years old, and an unusual series of deaths, coincident with an increase in laboratory-confirmed influenza cases, were reported in the spring of 2009 in Mexico. This outbreak appeared after the end of influenza season, and was associated with mortality in a younger age-group than the pattern observed in temperate areas in the northern hemisphere [1]. The concurrent finding of a novel, swine-origin influenza A virus (so called pandemic influenza [H1N1] 2009) from infected children in the United States [2] completed the picture.

This outbreak evolved rapidly and in a few weeks the number of cases with the same epidemiological and clinical characteristics increased globally; in 30 to 40 days the virus began to be clearly more virulent in the Southern Cone (a geographic region composed of the southernmost areas of South America, south of the tropic of Capricorn) and, consequently, by the first half of August, Argentina became the country with the highest rate of fatalities from pandemic influenza H1N1 2009 in relation to its population. During some weeks in June, the intensive care units (ICUs) in Buenos Aires experienced a sharp increase in cases of severe acute respiratory distress syndrome (ARDS) and these subjects typically became the predominant population of mechanically ventilated patients in these ICUs.

The aim of this chapter is to overview the characteristics of life-threatening respiratory failure from pandemic influenza H1N1 2009, trying to reflect on some practical issues that arose during this outbreak, and summarizing some of the rich experiences from Buenos Aires (**Table 1**) together with data retrieved from other recent international publications.

Why was Pandemic (H1N1) 2009 Flu So Prevalent in the Southern Cone?

Attack rates from influenza have been highly variable from outbreak to outbreak but are most commonly in the range of 5 to 10 % of the general population. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50 %, but an additional 25 % or more of individuals were probably subclinically infected with influenza A virus [3].

Perhaps the coincidence between the beginning of the winter season in the southern hemisphere and the high air-traffic between United States and Mexico and the countries from the Southern Cone, especially Argentina [4], produced an unusual

Table 1. Demographic and clinical data from 34 mechanically ventilated patients with severe influenza H1N1 2009 infection admitted during June, 2009 in the ICUs of two institutions in Buenos Aires [11, 36].

Characteristics	N = 34
Age	47.9 ± 16.9
Male sex, n (%)	15 (44.1 %)
APACHE II score*	20.6 ± 7.0
SOFA score*	7.3 ± 1.6
Associated Conditions	
Pregnancy	3
COPD or asthma	3
Organ transplant	2
AIDS	2
Colonic or lung Cancer	6
Chronic myeloid leukemia	1
Inmunosuppressive therapy	3
Body mass index > 30	6
Invasive mechanical ventilation, n (%)	34 (100 %)
ARDS, n (%)	31 (91.2 %)
PaO_2/FiO_2	114 (52 – 250)
Days on mechanical ventilation	13 (7 – 40)
Days on mechanical ventilation, survivors	27 (7 – 40)
Days on mechanical ventilation, non–survivors	13 (10 – 14)
Mortality	13 (38.2 %)

sharp increase in the number of cases and rapidly Argentina and Brazil became the countries with the highest numbers of deaths due to microbiologically confirmed pandemic influenza (H1N1) 2009. Consistent with this particular situation, the health system in the metropolitan area of Buenos Aires began to show evidences of collapse, use of ventilators increased critically, achieving an extremely unusual level; about a quarter of the available ICU beds were occupied by young and previously healthy patients with ARDS associated with severe bilateral pneumonia due to 'swine flu' who needed mechanical ventilation.

How Big was the Outbreak?

By the time of writing this chapter, during the end of the winter in the southern hemisphere, it is evident that pandemic H1N1 influenza is highly prevalent in South America. In September 2009, the World Health Organization (WHO) Director General, Margaret Chan, estimated that up to 30 % of people in densely populated countries risk being infected with H1N1 pandemic 2009 influenza, while Dr. Thomas Frieden, head of the US Centers for Disease Control and Prevention, predicted that about 800,000 people may potentially have been infected in New York City by the spring. These figures are difficult to extrapolate globally and to confirm, as epidemiological studies looking at the population at risk in different world areas are lacking, but the huge number of severely ill patients with ARDS due to primary influenza pneumonia (an extremely unusual complication) observed in the Southern Cone, suggest that these estimations could be realistic. Calculating the population-corrected mortality rate from estimations made in New Zealand [5], it can be inferred that by the end of winter in the southern hemisphere, up to about 40 % of the population in Argentina could be infected by this novel agent.

Common Complications of Influenza

Influenza complications during seasonal influenza occur most frequently in patients older than 64 years old, in those with chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnant women in the second or third trimester, particularly in the 1918 and 1957 pandemics, had a higher risk of complications, especially of primary influenza pneumonia, and higher hospitalization rates.

Pneumonia is the most significant complication of influenza. The presentation of pneumonia includes: 'Primary' influenza viral pneumonia secondary bacterial pneumonia and mixed viral and bacterial pneumonia. Primary influenza viral pneumonia may be the least common of the pneumonic complications but it is also the most severe. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest X-ray findings consistent with diffuse interstitial infiltrates and/or ARDS may be present (**Fig. 1**). Viral cultures of respiratory specimens, especially if

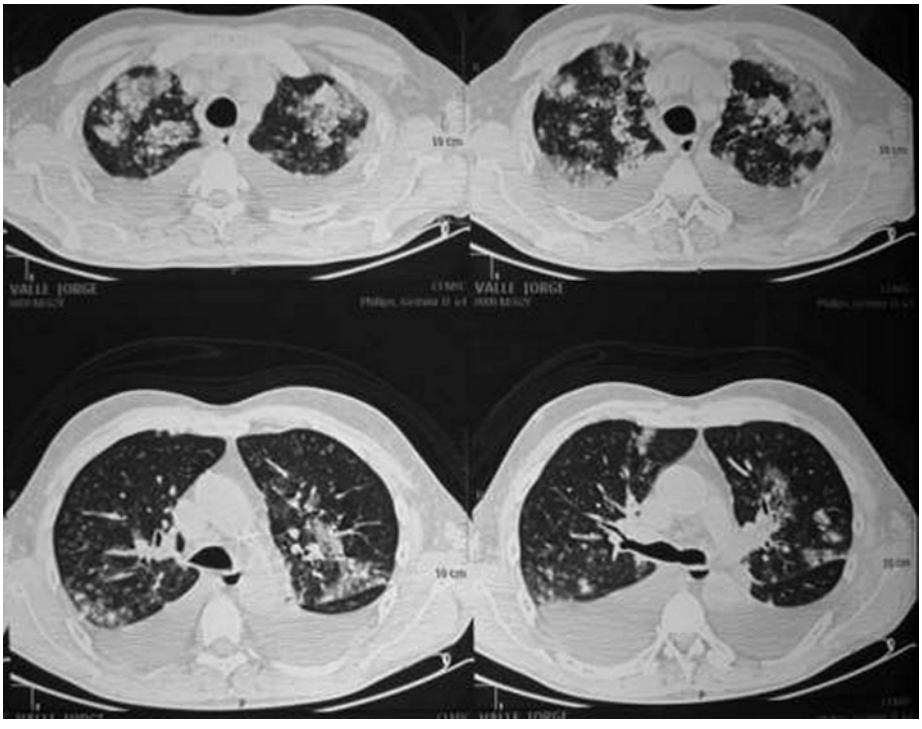

Fig. 1. Four slices of the lung computed tomography (CT) scan of a 62 year-old renal transplant patient with an influenza-like illness showing severe bilateral multilobar infiltrates and acute respiratory distress syndrome. Real time reverse-transcriptase polymerase chain reaction (RT-PCR) of a pharyngeal swab was positive for influenza A H1N1 2009. The CT scan shows patchy distributed air-spaced consolidation, more evident in the upper lobes and predominant in the periphery of the lungs. Moderate bilateral pleural effusion is also present.

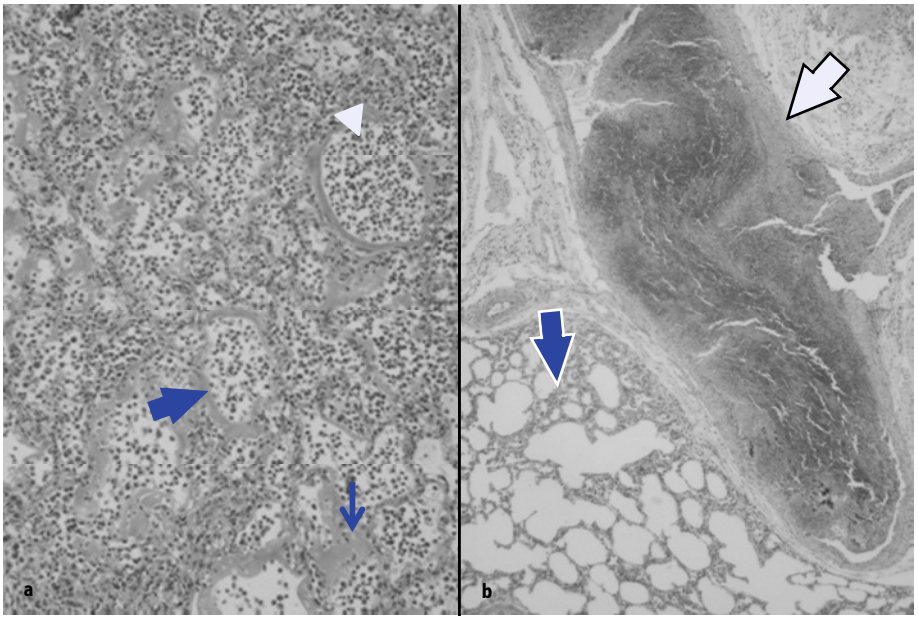

Fig. 2. A 29 year-old obese male with arterial hypertension secondary to Cushing's disease (hypophyseal adenoma) developed bilateral pneumonia and died from respiratory failure secondary to acute respiratory distress syndrome (ARDS) after 13 days on mechanical ventilation, with multiple organ failure, including renal and hemodynamic compromise requiring high doses of vasopressors. His disease began as an influenza-like illness 5 days before admission; influenza A H1N1 was confirmed with RT-PCR performed on pharyngeal swab. Post-mortem microscopic histopathologic findings in the lung included extensive alveolar edema (small arrow) replacing up to 90 % of the effective alveolar space, with hyaline membrane development (big arrow); alveolar cellular infiltrate and bacterial superinfection (arrowhead) were also observed (diffuse alveolar damage pattern) (panel a). There was also mild evidence of a fibroproliferative stage, microthrombi (gray arrow), small areas with well preserved pulmonary parenchyma (blue arrow), and hemorrhagic infarcts (panel b). Suprarrenal hyperplasia and acute tubular necrosis were found.

samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils (**Fig. 2**). Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Hyaline membranes can be found lining alveoli and alveolar ducts. Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but has also been reported in otherwise-healthy young adults as well as in older individuals with chronic pulmonary disorders.

Secondary bacterial pneumonia follows acute influenza; in these cases typically improvement in the patient's condition over 2 to 3 days is followed by a reappearance of fever along with clinical signs and symptoms of pneumonia, including cough, purulent sputum, and physical and X-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* – usual nasopharynx colonizers. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with

chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Risk Factors for the Acquisition of Severe H1N1 2009 Primary Influenza Pneumonia

The risk factors for acquiring severe H1N1 2009 primary influenza pneumonia include age (particularly young children) and comorbidities; some series have observed a particular prevalence of overweight individuals in this group of patients [1, 6, 7]. Obesity has not previously been mentioned among the risk factors for complications in patients with influenza. Being overweight is associated with a chronic increase in pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. In an experimental model of influenza A, Smith et al. described higher mortality rates in overweight patients than in lean controls related to minimally expressed interferon (IFN)-α and -β and a delay in expression of the pro-inflammatory cytokines, IL-6 and TNF-α, which may lead to increased morbidity and mortality from viral infections [8].

Differences Comparing this Pandemic with the usual Seasonal Flu

In contrast to what happens with the usual annual seasonal influenza outbreak, in this outbreak of pandemic influenza H1N1 2009, young adults are dying and between one quarter and one half of the deaths around the world have happened in patients who were previously in good health and without any specific risk factors. In one of the earlier case report publications during the beginning of the pandemic in Mexico, the authors observed that 87 % of deaths and 71 % of cases of severe pneumonia involved patients between the ages of 5 and 59 years, compared with average rates of 17 % and 32 %, respectively, in that age group during the reference periods [1]. Features of this epidemic were similar to those of past influenza pandemics in that circulation of the new influenza virus was associated with an off-season wave of disease affecting a younger population [1].

Management

In the setting of a disease with very high mortality, with no available controlled human clinical data to guide clinicians, in which most patients present with severe disease, a number of combined strategies should be considered for therapy. These include pharmacological strategies (antiviral treatment) and non-pharmacological strategies (standardization of optimal ventilator and fluid management, especially for ARDS, and management of other complications) necessarily given empirically, as diagnostic confirmation using real time reverse-transcriptase polymerase chain reaction (RT-PCR), can take from several hours to days.

Non-pharmacologic Therapy

Ventilatory settings

Most of these patients have ARDS, and in these patients, ventilatory support should follow the concepts of protective ventilation, with a tidal volume (V_T) of 6 ml/kg of predicted body weight [9]. ARDS is usually severe, with PaO_2/FiO_2 < than 150 and positive end-expiratory pressure (PEEP) should be high and optimized according to a mechanical basis. In our experience, we initially select PEEP according to the methods used in the ExPress trial where PEEP was adjusted based on airway pressure and was kept as high as possible without increasing the maximal inspiratory plateau pressure above 28 to 30 cmH_2O [10]. In more severe respiratory failure, we also set PEEP according to the transpulmonary pressure, by using esophageal-pressure measurements. In secondary, but also in primary ARDS the lungs can suffer substantial effects of chest wall elastance and may be effectively compressed by high pleural pressures with their alveoli collapsed at the end of expiration, even though moderate or high PEEP levels are applied. Therefore, PEEP is set at a level necessary to obtain a positive end-expiratory transpulmonary-pressure to improve the oxygenation, an end-inspiratory transpulmonary-presure less than 20 cmH_2O to minimize stress-inducing ventilator lung injury, and a pulmonary driving pressure (end-inspiratory transpulmonary pressure less end-expiratory transpulmonary pressure) ≤ 10 cmH_2O to avoid strain-inducing ventilator lung injury (**Fig. 3**). Using these premises, the mean PEEP applied in patients with severe influenza H1N1 2009 and ARDS was 20 cmH_2O.

Interestingly, in contrast to other etiologies of ARDS, in primary influenza pneumonia, high PEEP levels were necessary for many days. In a group of 23 patients

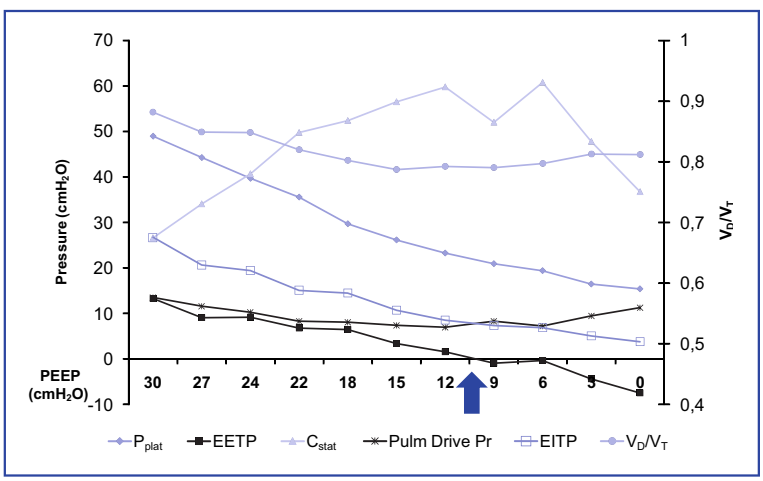

Fig. 3. Transpulmonary pressure and dead space ventilation during a decremental positive end-expiratory pressure (PEEP) maneuver in five patients with influenza H1N1 2009 pneumonia and severe ARDS. From these observations, we selected to use PEEP levels between 18 and 22 cmH_2O. At these PEEP levels, the end-inspiratory transpulmonary pressure (EITP) was less than 20 cmH_2O, the end-expiratory transpulmonary pressure (EETP) was positive, and the transpulmonary driving pressure (Pulm Driv Pr = EITP – EETP) was less than 10 cmH_2O. EETP became negative at PEEP less than 11 cmH_2O (arrow). Dead space ventilation (V_D/V_T) was high (range 0.79 – 0.88). V_D/V_T was lowest at a PEEP of about 15 cmH_2O. Pplat: plateau pressure; Cstat: static lung compliance.

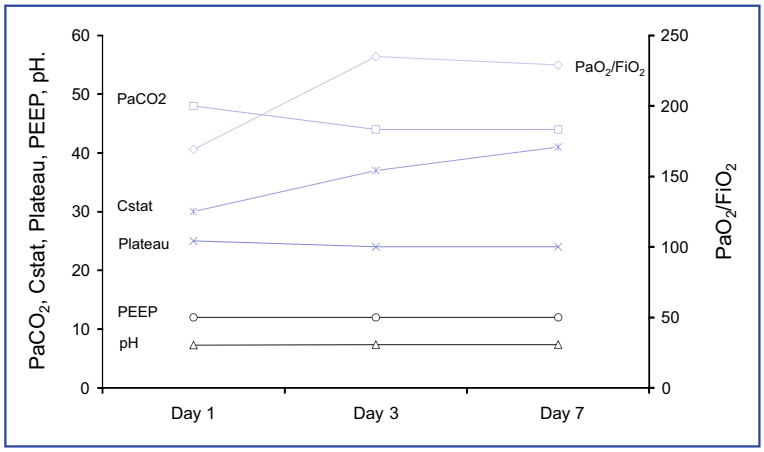

Fig. 4. Variation in gas exchange and respiratory system mechanics from the onset of mechanical ventilation in a group of mechanically ventilated ARDS patients with H1N1 pneumonia observed in one of our ICUs [11]. All variables improved from day 0 to day 3 of mechanical ventilation; however, in the majority of the patients the PaO_2/FiO_2 ratio remained low for many days, inducing us to maintain high levels of PEEP. Cstat: static lung compliance; PEEP: positive end-expiratory pressure

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managed by one of us (RV) in CEMIC Medical Center, the mean PEEP after 10 days on mechanical ventilation was 18 cmH_2O [11]. At the beginning of this outbreak, we decreased the PEEP level after a few days of mechanical ventilation, based on improvement in oxygenation levels; however, this produced a dramatic worsening of the PaO_2/FiO_2 ratio. Because of this observation, it was decided that, in patients with severe ARDS, high PEEP levels should be maintained for at least two weeks regardless of the oxygenation levels (**Fig. 4**).

Recruitment maneuvers

Most of the patients with severe influenza pneumonia responded to recruitment maneuvers. A recruitment maneuver in pressure controlled ventilation (PCV) with a PEEP of 25–30 cmH_2O and an inspiratory pressure of 25 cmH_2O (peak pressure 50–55 cmH_2O) was performed in patients with a $PaO_2/FiO_2 < 200$ mmHg. Many of these patients were young, healthy and had good cardiac performance and tolerance of high ventilatory pressures during the recruitment maneuver with adequate intravascular volume repletion.

Prone position ventilation

Several trials have demonstrated no survival benefit in ARDS patients managed in the prone position. However, these trials did not select the most severe patients. Many of our patients had severe ARDS with $PaO_2/FiO_2 < 100$ mmHg despite PEEP optimization and recruitment maneuvers. In this setting, prone ventilation was used and, if PaO_2/FiO_2 did not reach > 200 mmHg, a recruitment maneuver was applied in the prone position. Prone ventilation was used in 22 % of the patients with ARDS and in 50 % of patients with severe ARDS, and was associated with improved oxygenation and reduced distending pressures.

Adjunctive therapies to mechanical ventilation

We suggest the use of adjunctive therapies when plateau pressure is higher than 35 cmH_2O, despite a V_T of 6–8 ml/kg predicted weight, severe hypercapnic acidosis, and refractory hypoxemia (defined as a PaO_2/FiO_2 ratio < 100 mmHg after optimization of PEEP, recruitment maneuvers, prone position, and recruitment maneuvers in the prone ventilatory position). The adjunctive therapies developed to reduce the stress of mechanical ventilation on the already damaged lungs include: Nitric oxide (NO), extracorporeal membrane oxygenation (ECMO), arterial venous carbon dioxide removal, high-frequency oscillatory ventilation, and liquid ventilation. We prefer to use NO because of its availability and easy implementation and we have observed better improvement in oxygenation combining this therapy with prone ventilation, as previously described [12].

Non-invasive positive pressure ventilation (NPPV): NPPV has been used in respiratory failure due to viral pneumonia, even in cases of high transmission risk like in the epidemic of severe acute respiratory syndrome (SARS) in Hong Kong [13]. In one study, the efficacy in SARS pneumonia with mild acute lung injury (ALI) was high and no cases of healthworker infection were observed. However, application of NPPV to patients with H1N1 influenza has not been well evaluated and it is not indicated for impending respiratory failure. In mild cases or in patients with chronic obstructive pulmonary disease (COPD) or chronic respiratory restriction, NPPV could be useful to support the respiratory system, but it should be applied in healthcare facilities where staff have been adequately trained and with strict enforcement of personal protection measures; use of expiratory viral and bacterial filters are necessary to provide safer ventilation.

Pharmacologic Therapy

Antivirals

Most of the patients with influenza H1N1 2009 will recover without any antiviral therapy. Antivirals are indicated to prevent the rapid spread of the disease in a specific population, to prevent the pneumonia syndrome in susceptible patients, or to treat patients with influenza pneumonia. For critically ill influenza patients, antiviral treatment options are limited because no parenteral drug is available and no drug has been proved to be effective once life-threatening disease occurs. Currently, four antiviral drugs are available for the treatment of influenza: Amantadine, rimantadine (both cannot be used for the treatment of H1N1 influenza due to resistance), oseltamivir, available only for oral administration, and zanamivir, available as an inhalation agent; the two latter drugs are both sialic acid analogs that inhibit viral neuraminidases by competitively binding with the active enzyme site of influenza A and B viruses. The neuraminidase is critical for viral release from infected cells after replication. The earlier the administration of these agents, and the shorter the duration of fever, the greater the benefit of drug intervention [14, 15]. Oseltamivir has also been shown to reduce lower respiratory tract complications such as bronchitis and pneumonia [16]. In a prospective case control study, multivariate analysis suggested that treatment with oseltamivir decreased the likelihood of death (odds ratio 0.21 [confidence interval 0.06–0.80, p = 0.02]) [17]. Immunosuppressed patients (leukemia, organ transplantation, and hematopoietic stem cell transplantation) have a higher rate of viral pneumonia and higher attributable mortality [18]; viral shedding is also prolonged in these patients to an average of 11 days [19], which is associated with the development of resistance [20]. A standard dose and duration of

antivirals may not be adequate in this population; for these reasons, some authors have advocated a higher dose of oseltamivir (300 mg daily) in these patients [18].

During the pandemic, the therapeutic strategy proposed by the Argentinean Health Authority for mechanically ventilated patients with presumptive primary influenza pneumonia was to use oseltamivir at a dose of 300 mg daily during an extended period of time, typically until the patient was weaned from mechanical ventilation. The most frequent reported adverse effect seen with oseltamivir is nausea and vomiting, but this leads to medication interruption in only a small number of cases. Neuropsychiatric disorders (seizure, confusion or hyper-excitation of the nervous system) and severe skin reactions (e.g., toxic epidermal necrolysis) are more severe adverse events that have been observed in some cases during the pandemic. These unusual events have been related to a single nucleotide polymorphism in a gene located near the enzymatic active site of human cytosolic sialidase, a homolog of the virus neuraminidase that is the target of oseltamivir. This polymorphism has been found to occur in 9.3 % of the Asian population [21].

Antibacterial antimicrobials

Because of the high frequency of bacterial co-infection, antibiotic administration is recommended for all patients with pandemic H1N1 2009 influenza infection who require admission to a critical care unit. In immunocompetent patients, without recent antibiotic exposure, combination therapy with a beta-lactam plus a macrolide or a respiratory fluorquinolone, is recommended [22].

Corticosteroid therapy

Corticosteroids may be used to treat airflow obstruction due to asthma or COPD, to maintain immunosuppression in transplant patients, and when adrenal dysfunction is suspected because of refractory vasodilatory shock. Corticosteroids are not indicated for ALI; prolonged or high-dose corticosteroid therapy can result in serious adverse events, including opportunistic infections. In patients with H5N1 pulmonary infection, corticosteroids were not effective and in one series mortality was 59 % in 29 recipients of corticosteroids, compared with 24 % in 38 patients who did not receive corticosteroids [23]. One exception to this is cryptogenic organizing pneumonia (COP) described below under ‘complications’.

Complications

Bacterial Infection

In addition to primary viral pneumonia, viral and bacterial co-infection and secondary bacterial pneumonia are frequent. Co-infection with *S. pneumoniae, S. aureus*, and *Mycoplasma pnemoniae* has been detected in some of the reported series from Argentina; this co-infection occurs after several days of influenza infection and occurs more frequently in the elderly and in patients with chronic pulmonary diseases [24]. It has been observed in one series that 9 % of hospitalized patients with community-acquired pneumonia had dual infection with a respiratory virus and a bacterial pathogen, influenza being the most common viral agent [25]. Proposed theories for the high incidence of superimposed bacterial infections in influenza pneumonia emphasize the synergistic effects of viral and bacterial pathogens in producing lung injury. Studies suggested that influenza virus can directly damage the respiratory epithelium, allowing free access to invading bacteria. It has also been demonstrated that some

Staphylococcus and *Streptococcus* strains may increase viral replication and pathogenicity, contributing to influenza viral pneumonia [26].

Pulmonary Embolism

Pulmonary embolism has not been recognized as a common complication of severe influenza with ARDS. However, in a series of 10 patients with pandemic influenza H1N1 2009 infection and ARDS at a tertiary-care ICU in Michigan, five had pulmonary emboli [6]. Influenza infections have been associated with procoagulant changes [27]. Pathologic fibrin deposition also occurs in the vasculature in ARDS and pulmonary artery thrombi are found, implying an anatomic mechanism for the occurrence of increased pulmonary vascular resistance in ARDS [28]. It remains unknown whether these cases were secondary to some of the several risk factors that these bed-ridden severely ill patients had, or whether it was a direct consequence of a particular risk in influenza patients. Meanwhile, clinicians should periodically search for thrombosis and if necessary use chest multislice spiral computed tomography (CT) to confirm pulmonary embolism.

Extrapulmonary Manifestations

Influenza virus does not replicate in the alveoli or tissues beyond the respiratory tract. Histopathological analyses revealed that no virus was detected in the liver, spleen, kidney, or brain of animals inoculated with influenza H1N1 2009 virus at 3 or 7 days after inoculation [29]. However, myocarditis and pericarditis have been described in association with influenza infection and it has been suggested that influenza-associated myocarditis can take two forms: Immediate, associated with fulminating disease, and delayed, occurring during late convalescence [30].

Renal Failure

Renal failure has been described in a number of influenza patients [7, 31]. It is usually the consequence of shock and multiorgan dysfunction. We recommend adequate fluid replacement and, in patients with severe ARDS, fluid infusion should not be restrictive and diuretic use should be avoided to prevent the progression of renal dysfunction [11]. Using this strategy in our patients, the positive fluid balance at the 7^{th} day was 10,000 ml and hemodialysis was necessary in only 18 % of patients [11]. Occasionally, rhabdomyolysis may facilitate the development of renal failure; in fact, high levels of serum creatine phosphokinase have been described in reports of H1N1 infection [31].

Cryptogenic Organizing Pneumonia

This condition, occasionally associated with influenza, is characterized by progressive respiratory failure after 1 week of influenza symptoms with chest computerized axial tomography demonstrating multiple, bilateral, patchy alveolar opacities [11]. If identified, this complication must be treated with high doses of corticosteroids [32].

Prognostic Factors for Fatal Influenza Pneumonia

Ho et al. performed a study to define the prognostic factors for fatal adult influenza pneumonia [33]. Univariate analysis demonstrated that, compared with survivors of septic shock, a respiratory rate ≥ 25 breaths per min, an arterial pH < 7.35, a PaO_2/FiO_2 ratio < 150 mmHg, a creatinine value ≥ 2 mg/dl, a pneumonia severity index (PSI) of IV or V, and an APACHE II score ≥ 20 were all associated with decreased survival. Adjustments were made for septic shock, respiratory rate, arterial pH, creatinine and PSI in the Cox proportional hazard model. The multivariate analysis demonstrate that only the PaO_2/FiO_2 ratio < 150 mmHg ($p = 0.024$) and an APACHE II score ≥ 20 ($p = 0.017$) remained associated with death. In another study, the development of ARDS and a history of immunosuppression were independent risk factors for hospital mortality in critically ill patients with confirmed influenza virus infection [34].

Preventive Measures

The emergence of an antigenically novel influenza virus to which little or no antibody was present in a community, resulted in an extensive outbreak; the absence of antibody is worldwide, and for that reason there has been a pandemic. Independent of this antigenically new virus, questions regarding the potential effectiveness of vaccination for seasonal influenza arises. In one interim analysis of the pandemic in Australia, the authors found that there was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group [35]. A new vaccine has been developed, but there have been concerns based on the experience during the 1976–77 flu season, during which a swine flu outbreak at Fort Dix, New Jersey led the federal government to expedite vaccine production. Some 40 million people had been vaccinated by the time Guillain-Barré syndrome was identified as a side effect. However, with the pandemic as a reality, it is considered that the benefit of the vaccine far outweighs the risks.

Conclusion

Pandemics provide the most dramatic evidence of the impact of influenza. The morbidity and mortality caused by this first influenza pandemic in the 21st century, characterized by an unusual increase in the number of cases of primary viral severe community-acquired pneumonia requiring mechanical ventilation, has been substantial. Interestingly this higher incidence of severe cases appeared in a younger age group than that usually involved in the annual seasonal flu outbreak. The percentage of the population that acquired influenza during this pandemic has not yet been estimated but certainly it was much higher than during seasonal influenza; this higher incidence may explain the high number of cases of severe primary pneumonia observed in the Southern Cone. The apparently less aggressive nature of the infection and the younger population affected may explain an estimated mortality rate of 0.05–0.1 %, lower than that observed in seasonal influenza, as complications and mortality in seasonal flu are more frequent among patients ≥ 65 years old and in those with chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression, also usually associated with older age.

Improved and standardized optimal ICU care for patients with influenza H1N1 2009, including young and immunocompetent patients, with or without comorbidities, should lead to lower mortality than that previously observed for influenza pneumonia when mechanical support is required.

The pandemic H1N1 2009 influenza has resulted in tremendous pressures on the critical care system. The unexpected and rapid influx of such a large number of patients to emergency room and critical care services has highlighted not only a shortage of critical care capacity but also an inadequate supply of critical care resources. The extreme severity of ARDS in these patients has necessitated a change in the usual approach to the management of these patients to improve success rates.

The health system must be prepared to reallocate resources in response to demand. Therefore, early recognition of probable viral pneumonia is crucial in order to implement early infection-control strategies and to reduce transmission to health-care workers who are at high risk for exposure to these pathogens.

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