

# Ventilatory support in the treatment of Influenza A H1N1 in an intensive care unit

○ suporte ventilatório no tratamento da Influenza A H1N1 em Unidade de Terapia Intensiva

El soporte ventilatorio en el tratamiento de la Influenza A H1N1 en Unidad de Terapia Intensiva

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## ABSTRACT

The pandemic caused by the virus Influenza A H1N1 has challenged health agents in intensive care units because of the early respiratory complications that jeopardize the patients' medical prognosis. Dealing with the influenza of this new century constitutes a major challenge nowadays. This study aims to perform a literature review on ventilatory support indicated for the treatment of influenza A H1N1 in intensive care units. Morbidity and mortality of any disease are associated with its severity. In the case of influenza A H1N1, they depend on aspects related to the emergence of new strains, the hosts, the delay in making the correct diagnosis and treating the disease adequately, and the mistaken identification of its possible complications. Common complications are: acute respiratory failure, acute respiratory distress syndrome and sepsis. As acute respiratory failure is observed, initial ventilatory support can be performed through non-invasive oxygen therapy with values <5L/min. If no clinical improvement is observed, the disease can evolve rapidly to acute respiratory distress syndrome and sepsis. In this case, continuity of any type of noninvasive mechanical ventilation is contraindicated, intubation and invasive mechanical ventilation must be started, and protective ventilation is the recommended procedure.

**Keywords:** Influenza A Virus; H1N1 Subtype; Respiration; Artificial; Intensive Care Units; Respiratory Insufficiency; Respiratory Distress Syndrome, Adult; Influenza, Human.

## INTRODUCTION

A widespread influenza A H1N1 pandemic began in 2009, and by April 2010, at least 17,483 deaths had been reported worldwide. The World Health Organization (WHO) classified the pandemic as alert level 6 to reflect the need to prevent this new variety of influenza<sup>1</sup>. This variety is considered new because there were other waves of epidemics during the 20<sup>th</sup> century. The H1N1 Spanish flu (1918-1919) affected 50% of the world's population and killed 20 to 50 million people; influenza A H2N2 (1957-1958) caused 70 deaths in the USA; and influenza A H3N2, which appeared in 1968, killed 1 to 4 million people<sup>2,3</sup>.

In Brazil, 46,100 cases had been reported by February 2010. In total, 2,051 of those patients died, and 75% of them developed chronic illnesses<sup>4</sup>.

According to the Brazilian Health Ministry, influenza A H1N1 is characterized by mild illness with low lethality. In 2010 the WHO classified countries as "without any occurrence of cases", "in transition", or "with sustained transmission". Brazil was included in the last category<sup>4</sup>.

The influenza A H1N1 virus may have undergone genetic recombination and could generate new waves of epidemics in the future with different virulence rates. If these changes have in fact occurred, the demand for outpatient and hospital assistance might increase in response to increases in both the severity of the disease and the number of deaths<sup>5</sup>. To deal with this possibility, health-care professionals must be aware of their role and the pertinent interventions at all levels of health-care assistance.

The current challenge is to determine the appropriate way to treat this new flu. Many studies have been devoted to influenza A H1N1 in high-complexity health care settings because the advances in intensive care have made it possible to reduce its mortality rates.

## OBJECTIVE

The objective of this study is to perform a literature review on the treatment of influenza A H1N1 with ventilatory support in Intensive Care Units (ICUs).

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## MATERIAL AND METHODS

This is a systematic review of literature that covers the appropriate ventilatory support for the treatment of influenza A H1N1 in ICUs through a survey of scientific articles from the following resources: Public Medline (PUBMED), the Latin-American and Caribbean Center of Information on Health Sciences (BIREME-Regional Library of Medicine/PAHO/WHO), Latin-American and Caribbean Literature on Health Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), Brazil's Ministry of Health, and corresponding books. The following search terms were used: influenza A H1N1, intensive care unit, acute respiratory failure, and acute respiratory distress syndrome.

## DISCUSSION

### MORBIDITY AND MORTALITY

Influenza is a disease that causes morbidity and mortality worldwide. Its pathogenesis is directly related to airway and lung infection after contact with infected respiratory secretions from coughing, sneezing, or other means<sup>5</sup>. The most common signs and symptoms are described in table 1.

**Table 1** – The most common indicators and symptoms/prognostic of patients diagnosed with influenza A H1N1 according to the frequency of clinical findings

Principais sinais e sintomas/ prognóstico	Perez-Padilha, 2009 %	Rello, 2009 %
Fever (> 38° C)	100	96
Cough	100	88
Dyspnea	100	Not reported
Blood-smearred expectoration	33	Not reported
Rhinorrhea	28	Not reported
Throat inflammation	Not reported	58
Asthenia	Not reported	30
Myalgia or arthralgia	44	69
Headache	22	59
Diarrhea	22	Not reported
Hypotension non responsive to volume expansion	50	Not reported
Sudden onset of symptoms	72	46
Need of invasive mechanical ventilation (IMV) at admission	56	68,8
Death	39	Not reported

Source: Perez-Padilha, 2009<sup>6</sup>; Rello, 2009<sup>7</sup>

The severity of influenza illness depends on several factors, such as the virulence of the agent, characteristics inherent to the host, delays in diagnosis and, consequently, in treatment, and misidentification of possible complications<sup>2</sup>.

The following groups and individuals with pre-existing health conditions are at a higher risk for influenza A H1N1 infection: indigenous people, pregnant women, children younger than 2 years old, elderly individuals over 60 years old, immunosuppressed individuals (due to organ transplant, leukemia, neoplasia, chemotherapy, or AIDS), and patients with chronic diseases (chronic kidney failure, diabetes, cardiovascular diseases, obesity, or liver disease)<sup>2,5</sup>.

### PRIMARY COMPLICATIONS

The disease severity and mortality are directly related to the complications associated with influenza A H1N1 infection. The primary complications are directly associated with the body's response to infection with the influenza virus and can range from mild to systemic and severe, including sepsis. Respiratory complications, such as acute respiratory failure (ARF), might appear at the onset of the disease and quickly progress to acute respiratory distress syndrome (ARDS). Therefore, admission to the ICU is indicated for any acute organ dysfunction related to the flu in combination with respiratory distress<sup>2</sup>.

### ACUTE RESPIRATORY FAILURE

The influenza virus can damage the parenchyma of the lungs, leading to hypoxemic forms of ARF with tachycardia, dyspnea, tachypnea, and sometimes cyanosis, which can lead to stupor<sup>8,9</sup>. The initial symptoms typically cause patients to seek assistance in outpatient facilities, which then refer them to hospitals where more accurate tests can be performed.

ARF can be diagnosed based on clinical symptoms and gasometrical tests that indicate a  $P_{O_2} < 60$  mmHg or a  $P_{CO_2} > 50$  mmHg<sup>9,10</sup>. Once ARF is diagnosed, a multidisciplinary health-care team should monitor the clinical signs and administer increasingly higher oxygen concentrations until the patient's oxygen saturation level is higher than 90%<sup>2</sup>.

Non-invasive mechanical ventilation (NIMV) is a therapeutic approach for ventilatory support that can be employed to improve gas exchange and decrease the probability of secondary complications associated with invasive techniques<sup>11</sup>. In patients with ARF of unknown etiology, NIMV can be used to correct hypoxemia by means of CPAP (continuous positive airway pressure), PEEP (positive end-expiratory pressure), and alveolar recruitment maneuvers<sup>12</sup>.

If the patient with H1N1 does not improve after oxygen therapy (oxygen supplementation greater than 5 L/min to maintain an oxygen saturation level greater than 90%), NIMV is contraindicated; misguided use might worsen the prognosis because this disease is known to progress quickly from ARF to ARDS, which is a serious condition requiring intensive care. In addition to respiratory complications, attention must be paid to cardiovascular complications such as arterial hypotension, which, together with other symptoms, might lead to shock. At this point, the importance of monitoring the patient is clear because if the patient does not improve, intubation and invasive

mechanical ventilation must begin immediately. Therefore, it should be stressed that NIMV is contraindicated for patients that are diagnosed with or are suspected to have H1N1<sup>2</sup>.

#### ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is a serious disease that initially presents as an acute lung lesion and is characterized by diffuse alveolar damage due to non-cardiogenic pulmonary edema arising from an increase in the permeability of the alveolar-capillary membrane of the lung. Diffuse pulmonary infection is a factor that directly predisposes patients to ARDS, whereas sepsis indirectly predisposes patients to ARDS<sup>9,12,13,14</sup>.

Despite intense research on ARDS, the mortality rates remain high, reaching approximately 30% to 40% and, in some instances, 60% to 80%<sup>11</sup>.

To diagnose ARDS associated with influenza A H1N1, the following criteria must be fulfilled: acute onset of lung affection (1 to 3 days), bilateral lung radiological infiltrate consistent with non-cardiogenic pulmonary edema<sup>14</sup>,  $PAO_2/FiO_2$  of less than 200, capillary pressure of less than 18 mmHg, lack of left ventricle dysfunction on either clinical or echocardiographic examination<sup>2,9,11,13</sup>. It is worth stressing that interstitial and alveolar edema and alveolar collapse cause alterations in pulmonary compliance, and high inspiratory pressure is then required to open the collapsed alveoli<sup>9,11</sup>.

After the diagnosis worsens from ARF to ARDS, invasive mechanical ventilation (IMV) must be started immediately. The literature indicates that the ventilator parameters in these patients must correspond to a protective ventilation pattern (low tidal volume of approximately 6 mL/Kg) that restricts airway pressure to less than 35 cmH<sub>2</sub>O. PEEP can be adjusted to approximately 10 cmH<sub>2</sub>O or by titration of 2 cmH<sub>2</sub>O from the inflection point of the respiratory system pressure-volume curve. Combined with other modalities of intensive care, a protective ventilation strategy reduces the mortality rate by approximately 30% to 40%<sup>12</sup>.

#### SEPSIS

Another complication of influenza A H1N1 is sepsis, which is one of the most severe manifestations. The clinical and immunopathogenic features of sepsis amplify the initial damage. Thus, early diagnosis and treatment are crucial to achieve a satisfactory outcome<sup>5</sup>. The intensity of the inflammatory response and the severity of organ dysfunction define the clinical manifestations of sepsis. Several organs/systems might be affected by sepsis, including the central nervous system (e.g., septic encephalopathy), the lungs (e.g. ARDS), the kidneys (e.g., acute renal failure), the gastrointestinal system (e.g. organ ischemia), the cardiovascular system (arterial hypotension), and others<sup>12</sup>.

As a rule, patients with sepsis generally exhibit multiple organ failure. In a study by Rello<sup>7</sup>, 75% of influenza A H1N1 patients developed sepsis. Nevertheless, it is worth noting that progression to this level is often because of

comorbidities or other factors (obesity, diabetes, or pregnancy).

Antimicrobial drugs must be started immediately to treat sepsis, and well-established guidelines must be followed to limit damage to microcirculation. This approach, together with protective ventilation, minimizes further damage to the functional units of the lungs. Therefore, ventilatory support should be started as it would be for ARDS because the two conditions are usually associated<sup>12</sup>.

#### EVIDENCE ON VENTILATORY SUPPORT

According to the *Consenso Brasileiro de Ventilação Mecânica* (Brazilian Consensus on Mechanical Ventilation), ventilatory support aims to maintain a sufficient degree of gas exchange and avoid lung damage associated with ventilation<sup>13</sup>.

Several authors have published case reports that establish how to clinically manage and initiate ventilatory support for influenza A H1N1 patients. Yokoyama<sup>15</sup> reported the case of a 44-year-old obese female patient who was diagnosed with influenza A H1N1 and manifested signs of ARF. The patient was initially started on oxygen therapy. Due to her clinical progression, she was transferred to the ICU, where she was subjected to non-invasive ventilatory support (BIPAP and CPAP). According to Yokoyama, the progressive improvement in this patient was due to drug therapy (oseltamivir), but no data was reported regarding the patient's response to NIMV. However, this may be an isolated case because other literature reports discourage the use of NIMV in these patients to avoid respiratory complications and progression to ARDS<sup>2</sup>. Patients subjected to NIVM improved only temporarily and have a reduced respiratory effort; however, all of these patients required intubation and IMV because NIVM does not hinder progression to ARDS<sup>16</sup>.

Rello demonstrated that 68.8% of patients with influenza A H1N1 infection need invasive ventilatory support, which supports the findings of Perez-Padilha, who reported a rate of 55.5%. In the Rello study, 41.17% of the patients exhibited complications such as ARDS. Additionally, the  $PaO_2/FiO_2$  ratio average was 164 and 53 after IMV in the surviving and non-surviving groups, respectively. None of the previous studies discuss the ventilator modes and modalities used<sup>6,7</sup>. However, the *Consenso Brasileiro de Ventilação Mecânica* recommends ventilation modes with limited pressure and a decreasing flow wave because it provides better distribution of air in the lungs, generates lower airway pressure levels, and reduces respiratory effort. Special attention must be paid to tidal volume because it is not ensured by this ventilator mode<sup>13</sup>.

Respiratory failure is quite common in rapidly progressing influenza A H1N1, and 10% to 30% of patients require intensive care<sup>3</sup>. IMV is complex in these patients and requires specialized knowledge and equipment. Kaufman reported six case studies on this disease and found that low tidal volume (6 mL/Kg ideal body weight) and a high PEEP (15-20 cmH<sub>2</sub>O) and pressure-limited ventilator mode must be applied, which supports the *Consenso Brasileiro de Ventilação Mecânica*<sup>13</sup>.

Protective mechanical ventilation (volume controlled; TV 6 mL/Kg;  $P_{\text{plateau}} \leq 30$  cmH<sub>2</sub>O; BR: 6-35 ipm/min; I:E = 1:1 - 1:3) improves survival rates, has fewer complications, requires a shorter duration of MV, and reduces the mortality by approximately 34% to 58% in ARDS patients compared to conventional ventilation (volume controlled; TV 12 mL/Kg;  $P_{\text{plateau}} \leq 50$  cmH<sub>2</sub>O; BR: 6 - 35 ipm/min)<sup>3,17,18</sup>.

Alveolar recruitment maneuvers were reported to be crucial for improving ventilation in ARDS patients. Previous studies have indicated that procedures employing progressive PEEP and 15 cmH<sub>2</sub>O inspiratory pressure delta might be required to maintain proper function of the alveolar units. Time since disease onset also influences treatment success; the earlier treatment is started, the higher the odds of success<sup>13,18</sup>.

The efficiency of conventional IMV is not sufficient for ARDS patients because acceptable clinical standards are

difficult to maintain even in combination with other strategies such as ventilation in the prone position, high-frequency ventilation (HFV), or supplementation with nitric oxide. Extracorporeal membrane oxygenation was shown to be more appropriate for treatment of ARDS because it improves survival by up to 71%. However, this finding should not discourage the use of other therapeutic approaches in clinical practice<sup>19,20</sup>.

## CONCLUSION

We conclude that patients with influenza A H1N1 exhibit frequent respiratory complications. These respiratory complications require ventilatory support and oxygen therapy during acute respiratory failure, whereas invasive mechanical ventilation and protective ventilation are indicated for the treatment of acute respiratory distress syndrome and sepsis.



## O suporte ventilatório no tratamento da Influenza A H1N1 em Unidade de Terapia Intensiva

### RESUMO

A pandemia por influenza A H1N1 vem desafiando as equipes de saúde das unidades de terapia intensiva, por se apresentar com complicações inicialmente respiratórias que comprometem o prognóstico do paciente. O desafio da atualidade é saber lidar com a gripe do novo século de forma adequada. O objetivo deste estudo é realizar uma revisão da literatura sobre o suporte ventilatório indicado no tratamento da influenza A H1N1 na unidade de terapia intensiva. A morbi-mortalidade de qualquer doença está relacionada à sua gravidade, e no caso da influenza A H1N1 depende de aspectos ligados a novas cepas, ao hospedeiro, ao retardo no diagnóstico correto e, conseqüentemente, do tratamento correto e da identificação inapropriada das possíveis complicações. Complicações comuns são: insuficiência respiratória aguda, síndrome da doença respiratória aguda e sepse. Ao sinal da insuficiência respiratória aguda, o suporte ventilatório inicial pode ser não invasivo, por oxigenioterapia com valores < 5L/min; não havendo melhora do quadro clínico, a doença pode evoluir rapidamente para síndrome da doença respiratória aguda e sepse, sendo então contraindicada a continuidade da ventilação mecânica não invasiva, qualquer que seja sua modalidade, não se devendo protelar a intubação e suporte ventilatório mecânico invasivo, sendo neste mais indicada a ventilação protetora.

**Palavras-chave:** Vírus da Influenza A Subtipo H1N1; Respiração Artificial; Unidades de Terapia Intensiva; Insuficiência Respiratória; Síndrome do Desconforto Respiratório do Adulto; Influenza Humana.

## El soporte ventilatorio en el tratamiento de la Influenza A H1N1 en Unidad de Terapia Intensiva

### RESUMEN

La pandemia por influenza A H1N1 viene desafiando los equipos de salud de las unidades de terapia intensiva (UTI), por presentarse con complicaciones inicialmente respiratorias que comprometen el pronóstico del paciente. El desafío de la actualidad es saber lidiar con la gripe del nuevo siglo de forma adecuada. El objetivo de este estudio es de realizar una revisión de la literatura sobre el soporte ventilatorio indicado en el tratamiento de la influenza A H1N1 en la unidad de terapia intensiva. La morbimortalidad de cualquier enfermedad está relacionada a su gravedad, y en el caso de la influenza A H1N1 depende de aspectos ligados a nuevas cepas, al huésped, al retraso en el diagnóstico correcto y, consecuentemente, del tratamiento correcto y a la no identificación adecuada de las posibles complicaciones. Complicaciones comunes son: insuficiencia respiratoria aguda, síndrome de la enfermedad respiratoria aguda y sepsis. Habiendo señal de insuficiencia respiratoria aguda, el soporte ventilatorio inicial puede ser no invasivo, por oxigenoterapia con valores < 5L/min.; no presentando mejora del cuadro clínico, la enfermedad puede evolucionar rápidamente para síndrome de enfermedad respiratoria aguda y sepsis, siendo entonces contraindicada la continuidad de la ventilación mecánica no invasiva, cualquiera sea su modalidad, no debiendo postergar la intubación y el soporte ventilatorio mecánico invasivo, siendo más indicada en este caso la ventilación protectora.

**Palabras clave:** Virus de la Influenza A Subtipo H1N1; Respiración Artificial; Unidades de Terapia Intensiva; Insuficiencia Respiratoria; Síndrome de Distrés Respiratorio del Adulto; Influenza Humana.



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