

Keys to managing cases of severe influenza A (H1N1)v in the emergency department

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An outbreak of new influenza A (H1N1)v was declared in April 2009, and on June 11 the World Health Organization declared a level 6 pandemic. The diagnostic criteria are the same as those for seasonal influenza: the sudden onset of a high fever, cough, sore throat, and muscle pain. Symptoms are usually mild and remit within 3 days, but a small percentage of patients have fever and progressive respiratory difficulty beyond that point. Paradoxically, in contrast with seasonal flu, patients over the age of 65 years who have chronic diseases make up less than 10% of the cases of the new influenza. A minority have primary viral pneumonia and respiratory distress. The patient profile is a 35-year-old male who, after 3 days with fever, develops progressive hypoxemia requiring intubation within 24 hours of admission. Adolescents and young adults make up the largest population group affected and illness is particularly severe during pregnancy, during the postpartum period, and in obese patients. In children, this influenza often presents with croup and bronchiolitis, although the respiratory syncytial virus is the main cause of those clinical pictures. Respiratory frequency should be monitored and a rate of more than 25 breaths/min considered a warning sign of severity. Continuous monitoring with a pulse oximeter is also advised and a fall in oxyhemoglobin saturation below 95% is another marker of severity. Steps should be taken to isolate patients to prevent transmission of the virus to health care staff or other patients. If complications or risk factors are present, oseltamivir should be started promptly, even if the patient has been ill for longer than 48 hours. [Emergencias 2009;21:370-375]

Key words: Influenza A. Pandemics. Fever.

Introduction

The world's worst flu pandemic started during the last months of World War I and claimed more victims than the war itself. In February 1918 the "three day fever" affected 8 million Spanish people, including King Alfonso XIII; in Madrid, it attacked a third of the population. The patients presented fever up to 40°C with cough and malaise which remitted after 3 days. The strain was fairly benign, attacking many but killing few. However, when the autumn came, it often led to pneumonia, with fatal results within 24 hours. Unlike seasonal flu where the most at risk were children aged less than 2 years and the elderly, "Spanish flu" appeared to affect people in the prime of life.

Ninety years later, in April 2009, an outbreak occurred in Mexico¹ caused by a new influenza

virus that presented characteristics of both American and Eurasian swine virus, avian influenza virus and human influenza virus. WHO follow-up of the global spread of this virus declared it a level 6 pandemic on 11 June 2009. In early August there were more than 220,000 reported cases including over 2,000 confirmed deaths worldwide.

In our country, data provided by the Sentinel Physician Network of the Influenza Surveillance System in Spain (<http://vgripe.isciii.com/flu/inicio.do>) showed the rate of influenza was 37.67 cases per 100,000 population in primary care centres at week 32 which ended on August 15 (Figure 1). At 15 August, there were 29 cases admitted to Spanish intensive care units (ICU) of a cumulative total of 77 patients, and 11 deaths were on record due to this new virus.

Although the clinical criteria for uncomplicated

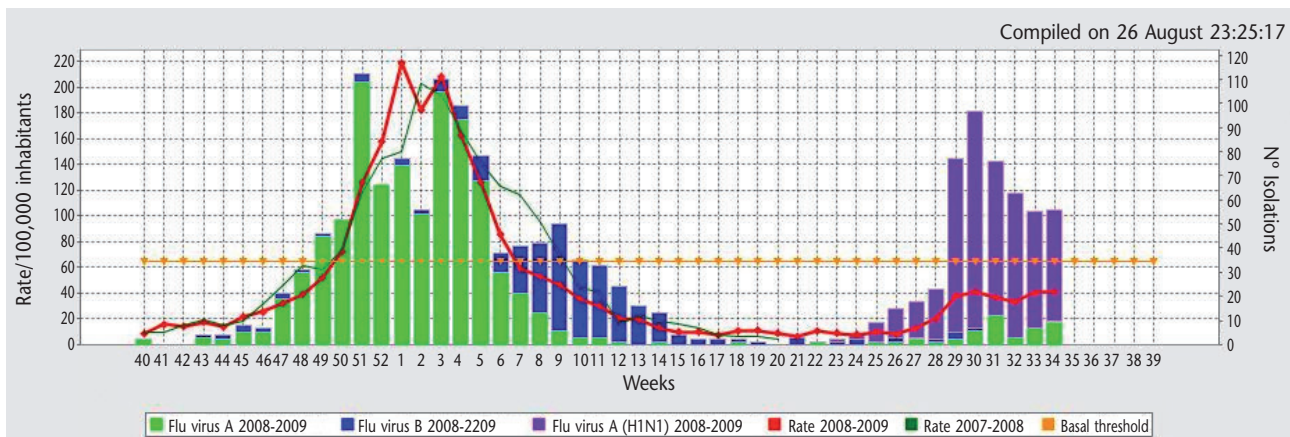


Figure 1. Viral detection rate and number of sentinel viral detections in Spain; 2008-2009.

influenza are indistinguishable from those of other viral infections, diagnostic criteria for the disease have been defined by the relevant national and international authorities based on acute onset (46% of cases) with the following symptoms¹:

- Fever $\geq 38^{\circ}\text{C}$ (96% of cases) and signs or symptoms of acute respiratory infection including cough (92%), sore throat (66%), headache, rhinorrhea, myalgias, respiratory distress (30%), which may or may not be accompanied by vomiting and diarrhea (25%).

- Bronchospasm, bronchitis and croup in children. One study has reported that, during outbreaks of influenza virus, the presence of fever and cough of 48 hours evolution has a positive predictive value of 79% for the diagnosis of influenza².

Epidemiologically, a "suspected case" is defined as any patient who meets the clinical criteria before microbiological confirmation, and a "confirmed case" as anyone with laboratory confirmation for the new virus A/H1N1v. A "serious case" is a person who presents a clinical picture compatible with influenza requiring hospital admission

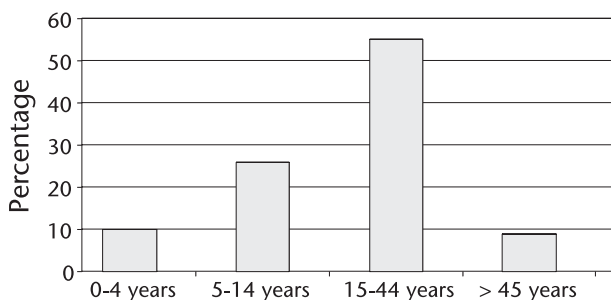


Figure 2. Rate of detection rate of influenza virus A/H1N1 by age group. Spain. Weeks 20-32, 2009.

due to the severity of the clinical picture (pneumonia, multi-organ failure) or who develops this picture during hospital admission for another reason. Also considered serious are those cases of pneumonia admitted to ICU in the absence of a known cause³.

The population groups most affected are adolescents and young adults, with 58% of incidence in the age group 15-24 years, followed by children under 5 years (Figure 2). These groups also present a high level of hospitalization. Although the largest number of deaths are found in these two population groups, patients over 65 years and with chronic disease proportionally present a high incidence of hospitalization and mortality⁴. Unlike seasonal flu, the low incidence (<10%) in the age groups > 65 years means we should not expect a substantial increase of diseases such as chronic obstructive pulmonary disease (COPD). The high-risk population is defined in Table 1 and admission criteria are defined in Table 2.

Table 1. High risk population according to modified criteria of the Ministry of Health

- Pregnant and postpartum women.
- Chronic Cardiovascular Disease (excluding hypertension).
- Chronic respiratory diseases (including bronchopulmonary dysplasia, cystic fibrosis and persistent moderate-severe asthma).
- Diabetes mellitus type I and type II with treatment.
- Moderate-severe renal failure.
- Hemoglobin disorder and moderate-severe anaemia.
- Asplenia.
- Advanced chronic liver disease.
- Severe neuromuscular diseases.
- Patients with immunosuppression (including that due to HIV or drug infection or organ transplantation).
- Morbid obesity (BMI ≥ 30).
- Children and adolescents under age 18 who receive prolonged AAS treatment because of the possibility of developing Reye syndrome.

BMI: body mass index. AAS: anabolic-androgenic steroids.

Table 2. Hospital admission criteria for patients with influenza A (H1N1)

1. Chest x-ray with pulmonary infiltrates or other signs suggestive of pneumonia in a patient classified in a risk group
2. Severe breathing difficulty
 - Tachypnea or respiratory rate increase with:
 - Inability to complete relatively short sentences
 - Use of accessory muscles
 - Feeling of choking
 - tachypnea is considered significant:
 - Adults > 50 years > 30 breaths per minute
 - Young adults and adolescents > 25 breaths per minute
 - Children over 1 year: > 40 breaths per minute
 - Children under one year: > 50 breaths per minute
 - Oxygen saturation by pulse oximetry < 95% breathing room air. The absence of cyanosis is not considered a good criterion to discriminate severe disease
 - Respiratory exhaustion (apnea in children)
 - Abnormal breathing pattern with alternating fast and slow breaths or long pauses between breaths
3. Severe clinical evidence of dehydration or shock
 - Adults: systolic BP < 90 mm Hg or diastolic BP < 60 mm Hg
 - In children: BP values below two standard deviations for their age or slowed capillary refill time, decreased skin turgor, oliguria, and so on
4. Altered level of consciousness. Agitation or convulsions
5. Any serious immunocompromised patient (transplanted, HIV infected, prolonged treatment with corticosteroids, neutropenia etc.)
6. Other factors considered by healthcare professionals providing treatment, for example rapidly progressing or prolonged disease

BP: Blood pressure.

Characteristics of severe cases

Severe cases published in Mexico, Canada and USA⁵, and preliminary data from GTEI (working group of infectious diseases) of the Spanish Society of Intensive Care and Coronary Units (SEMICYUC)⁶, indicate that severe cases of influenza A (H1N1) have an average age under 40 years (although the range is wide) and comorbidities in half of cases (obesity in a third of them). Second and third trimester pregnancy and recent childbirth are also associated with primary viral pneumonia.

The average time between onset of symptoms and hospitalization is around 4 to 6 days and no patients had been treated with oseltamivir before admission. The average number of days between symptom onset and antiviral treatment was nearly 7 days in the Spanish group. The median between arrival at the emergency department (ED) and admission to ICU was one day.

Pneumonia with acute respiratory distress syndrome (ARDS)⁷ is the major cause of morbidity and mortality in the influenza pandemic. The pneumonia may be due to the virus (primary pneumonia) and usually appears in the first³⁻⁴ days of clinical illness, or due to the coexistence of a bacterial infection with viral infection occurring a

few days later (secondary pneumonia)⁸, although bacterial infection in cases of influenza A (H1N1) has been rare so far⁴. The coexistence of myocardial and kidney dysfunction is not uncommon. It must be differentiated from bronchiolitis, characterized by the presence of peribronchial interstitial opacity on chest X-ray, more common in children, with benign prognosis, and from heart failure.

The most severe form of presentation is that of a young adult with fever and respiratory distress in the first 4-6 days of illness, and opacities in two or more pulmonary lobes on chest X-ray, with progressive dyspnea and severe hypoxemia; most cases require intubation and mechanical ventilation. Expectoration is slight and may contain some blood cells. Chest X-ray may be indistinguishable from acute pulmonary edema with opacities in at least two lobes and perihilar congestion (Figure 3). There may be effusion. Severe primary pneumonia has a mortality rate exceeding 50% but is not common, except in times of pandemic when immunity to the circulating virus is minimal. Survivors present residual pulmonary fibrosis⁹ with decreased lung function.

Among the clinical features described on admission⁵, more than 80% of patients have high levels of LDH dehydrogenase (half the cases > 1,000 IU), creatine kinase (CK) > 1000 IU (for myositis or myocardial involvement), 61% lymphopenia in 61% of cases, increased liver enzyme in more than 50%, increased protein C reactive protein (CRP), elevated interleukin 6 and 25% present increased creatinine levels, as well as other laboratory abnormalities. All presented bilateral radiographic infiltrates with involvement of 3 quadrants in most patients.

Diagnosis

ED strategy should focus on rapid triage based on the above-mentioned symptoms to identify patients, usually young, with respiratory frequency > 25 breaths/min and decreased oxygen saturation. Hypotension is rare and diarrhea (more common in children) may be a sign of high viral load. Definitive diagnosis requires laboratory culture of nasal exudate, sputum, nasotracheal aspirate or bronchoalveolar samples, although the results may take a few days. Currently, RT-PCR test is recommended for diagnosis¹⁰ with a sensitivity above 85%. In cases of high suspicion, treatment should be initiated, and if the nasopharyngeal RT-PCR test is negative a second sample must be analyzed

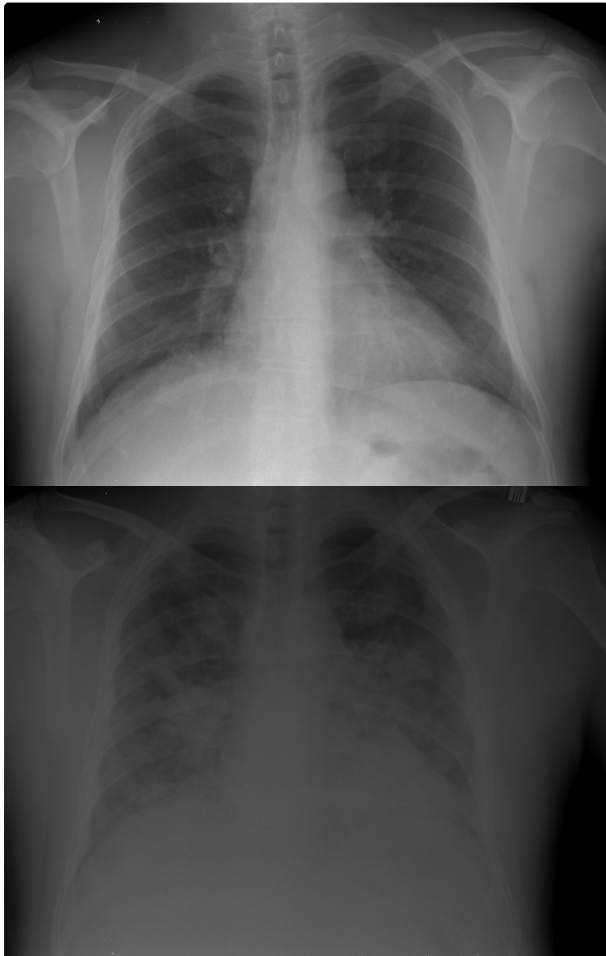


Figure 3. Patient aged 31 years with high fever, cough and scanty expectoration of 4 days evolution. Admission chest radiograph (top) and at 48 hours (below) prior to intubation. Diagnosis: viral pneumonia by A/H1N1v.

(preferably from respiratory secretions) before suspending treatment in high-risk groups.

Treatment in the Emergency Department

The recommended treatment is with neuraminidase inhibitors¹¹, mainly oseltamivir, at a dose of 75 mg/12 hours orally during 5 days, although some severe cases have received double doses for 2 weeks or until the RT-PCR was negative. The use of antivirals has been shown to reduce mortality in hospitalized patients even when treatment started after 48 hours of symptom onset¹². Although most cultures for bacteria are usually negative, many patients receive broad-spectrum antibiotics for their clinical situation, including macrolides for their immune-modulating effects.

Patients with severe respiratory difficulties (requiring > 50% oxygen) should be admitted to an ICU, for ventilation, with lung protection strategies being needed in > 80% of critically ill patients, as well as inotropic support and extrarenal filtering techniques. In situations where ventilator resources are limited, a triage protocol must be applied based on validated scales such as Sequential Organ Failure Assessment (SOFA)^{13,14}, since the severity indices usually used to predict 30-day mortality in severe community-acquired pneumonia (PSI, CURB-65) greatly underestimate the need for mechanical ventilation and/or vasoactive therapy in these patients¹⁵.

Special mention of non-invasive mechanical ventilation (NIMV) is necessary: it is not indicated in ARDS, given the high failure rate, since high ventilation pressures and high PEEP are required. Unpublished data suggest increased mortality in patients with influenza A (H1N1) v who were intubated after receiving NIMV (Canada teleconference with WHO official Rob Fowler 28 July who said that of 45 patients with NIMV, 41 had to be intubated). If NIMV is used, it must be considered a high-risk technique for producing aerosols, so it must be administered under conditions of strict isolation, preferably negative pressure rooms and double-circuit respirators. It is crucial not to delay intubation of these patients.

Evolution of severely ill patients

In the Mexican series of severely ill patients⁴, mortality was 7/18, with an average stay in ICU of 14 days. Those who died presented significant differences in terms of hypotension refractory to fluid administration, need for intubation and mechanical ventilation within 24 hours of admission, acute renal failure, pH, PaO₂/FiO₂, APACHE II and SOFA.

Of the first 23 ICU cases reported by GTEI of SEMICYUC⁶, most of whom with primary viral pneumonia, 78% had some type of organ dysfunction in addition to respiratory distress (21.7% renal failure) and 26.1% received prone ventilation. Mortality in the intubated patients exceeded 33% and often required more than 10 days of mechanical ventilation. Details about the first serious cases admitted to ICUs in Spain up to July 31 will be published shortly¹⁶.

One factor contributing to mortality is delayed admission and late administration of antiviral medication. In contrast, concurrent bacterial infection seems not to be a decisive factor in poor

outcome. Although some of the American study patients developed nosocomial pneumonia, lung damage was basically due to primary involvement of the influenza virus, although the role of the immune reaction on the lung is controversial. Autopsies of primary influenza pneumonia revealed bilateral hemorrhagic pneumonitis with interstitial inflammation, diffuse alveolar damage and high viral loads in the periphery of the lungs¹⁷, similar to that seen in varicella-zoster pneumonia¹⁸.

A special case: the pregnant patient

The pregnant patient presents increased risk of complications following infection with A (H1N1) v and is four times more likely to require hospitalization¹⁹; 17% of hospitalized patients in California were pregnant women²⁰, as were a third of the 39 who died in Rio de Janeiro (WHO telecommunication 19 August). The effect of pregnancy is greater if the patient also has other risk factors, with larger increases in the possibility of hospital admission. Clinical manifestations are similar to the rest of the population, but more often show shortness of breath. Of the 34 patients in the study by Jamison et al, 32% reported contact with a sick relative. Five of the 34 pregnant women died but none of the 5 infants of these patients had evidence of infection by A virus (H1N1) v and all evolved normally. Vertical transmission is exceptional. Patients with pulmonary involvement must be placed under continuous monitoring by pulse oximetry due to the rapid evolution of hypoxemia.

Although no data exist on the safety of oseltamivir in pregnant women regarding the adverse effects on the foetus, the high risk of complications means the women should be treated early with this drug at standard doses. Notably, of the first 13 patients who died in our country, three were young pregnant women.

Isolation measures in the Emergency Department for severely ill patients

It is difficult to know how many patients may visit the ED with these symptoms, but as an example, Figure 4 shows recent emergency room visits in New York City. If infection by A (H1N1) v is suspected, immediate isolation measures are adopted to control droplets and contact, with surgical masks for patients and a distance of at least one metre away from other people. Staff must also use surgical masks and gloves, and hand washing before and after contact with patients²¹.

The most severe cases require the use of techniques with a high risk of generating aerosols, such as respiratory samples, orotracheal intubation and mechanical ventilation. During the performance of these techniques, individual protective gear must be used, including gowns, gloves, FFP3 masks and glasses. Virologic filters must be used both in the manual resuscitator bag (Ambu®) and in the expiratory limb of respiratory support machines, with particular attention given to transfers within the hospital, since most of the known contacts with healthcare professionals occur in examinations or manoeuvres that generate aerosols. Documented

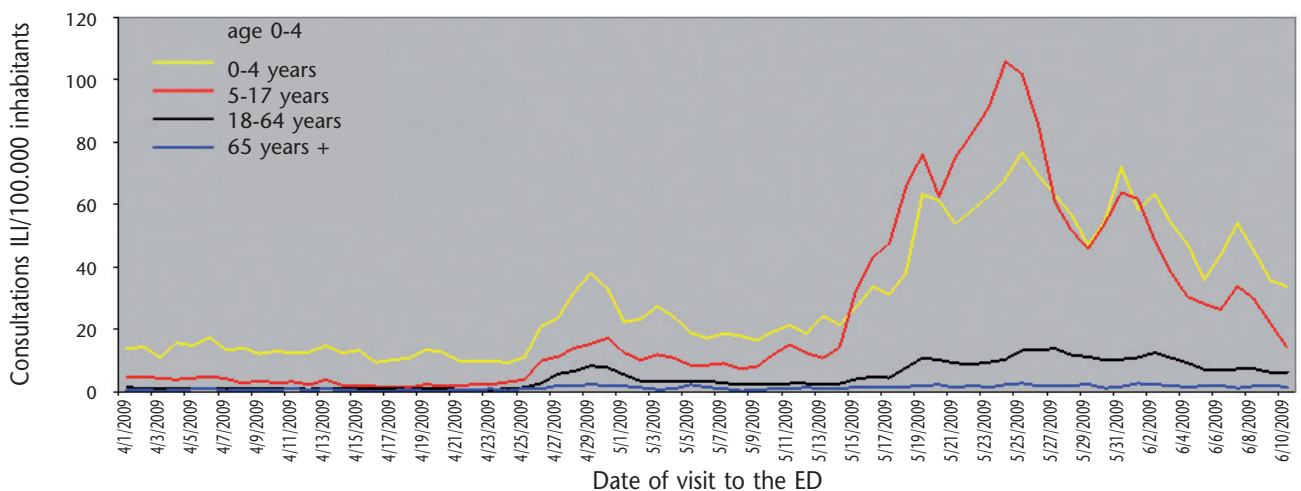


Figure 4. The graph represents the number of visits for influenza-like illness (ILI) at 50 hospital emergency departments (EDs) in the City of New York in four age categories. The data do not represent confirmed cases of infection by influenza A (H1N1). (<http://www.nyc.gov/html/doh/html/pr2009/pr042sp-09.shtml>).

infection with influenza A (H1N1) v in healthcare professionals must be declared as a professional disease²². The protocols of action elaborated in a multidisciplinary manner, available from the website of the Ministry of Health and Public Health, are an excellent tool for professional activity.

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Puntos clave para la orientación y manejo terapéutico de los casos graves de gripe A(H1N1)v en urgencias

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En abril de 2009 se declaró un brote de gripe por un nuevo virus A(H1N1)v y el 11 de junio la OMS declaraba en nivel 6 de pandemia. Los criterios diagnósticos son idénticos a gripe estacional: la aparición brusca de fiebre alta, tos, dolor de garganta y mialgias. El cuadro suele ser banal y remitir en 3 días. Un bajo porcentaje de pacientes presentan fiebre y dificultad respiratoria progresiva que va más allá de los 3 días. La paradoja con la gripe estacional es que los mayores de 65 años con enfermedades crónicas representan menos del 10%. Una minoría de los casos presentan una neumonía viral primaria y distrés respiratorio. El perfil del paciente grave es de un adulto joven que después de tres días de fiebre presenta hipoxemia progresiva que requiere intubación en 24 horas. La población más afectada es la de adolescentes y adultos jóvenes, con especial gravedad en algunas mujeres embarazadas, en el postparto y en obesos. En niños, el *crup*, y la bronquiolitis son formas de presentación frecuente. Hay que medir la frecuencia respiratoria (alerta si es mayor de 25x') y hacer la pulsioximetría (alerta si es menor del 95%) para identificar casos graves. Las medidas de aislamiento en el manejo de estos pacientes son esenciales para evitar la propagación entre personal sanitario y a otros pacientes. En grupos de riesgo y casos con complicaciones no hay que demorar el empleo de oseltamivir, aunque lleven más de 48 h de evolución. [Emergencias 2009;21:370-375]

Palabras clave: Gripe A. Pandemia. Fiebre.