

Pneumonia and Pandemic Influenza A H1N1 Virus Infection: A Review of the Literature

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Abstract

Influenza viruses cause seasonal epidemics and occasional pandemics. On 18 March 2009, A novel swine origin influenza A (H1N1) virus was seen in Mexico, then a global outbreak of respiratory illness started. The new H1N1 virus usually attaches to tracheobronchial epithelial cells and the clinical picture ranges from transient lower respiratory tract infections to severe pneumonia leading to acute respiratory distress syndrome. The main complication is extension of viral infection to the alveoli that causes primary viral pneumonia. The most common radiologic findings are unilateral or bilateral ground-glass opacities and multifocal areas of consolidations. Bacterial coinfections, particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*, increase the severity of illness. Patients with underlying cardiopulmonary comorbid conditions, pregnancy and obesity appear to be at higher risk of severe pneumonia. The severe cases have required admission to intensive care units and needs to mechanical ventilation. H1N1 influenza virus is now in post-pandemic period; however, localized outbreaks of various magnitudes are being reported.

Keywords: H1N1; influenza; pandemic; pneumonia

Introduction

Swine flu or a novel swine-origin influenza A (H1N1) virus was first reported in Mexico in April 2009. The pandemic spread with the travellers throughout the world, by the start of human to human transmission (1,2). In June 2009, the World Health Organization (WHO), raised the pandemic alert level to phase-6. Further investigations revealed that the novel

swine origin influenza A (H1N1) virus represented a quadruple reassortment of one human, one avian and two swine strains and the antigenic shift of the virus occurred in pigs. The H1N1 pandemic moved into the post-pandemic period in August 2010 and nearly 18,500 confirmed deaths have been reported globally (2).

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Influenza A viruses is a member of Orthomyxovirus family, with 16 subunits of hemagglutinin and 9 subunits of neuraminidase proteins used for antigenic subtyping. The virus causes a very contagious respiratory tract infection. The H1N1 infections occurred mostly in children, females and young adults. Major complication of the infection is pneumonia that occurred by the extension of H1N1 virus to alveoli and sometimes bacterial coinfections, and once the virus causes respiratory failure, the mortality rate increases dramatically (2-4). Complications including pneumonia and acute respiratory distress syndrome occurred in some of the cases, especially those affected by comorbidities including obesity, pregnancy, diabetes mellitus, cardiopulmonary and neuropsychiatric diseases (3,5-7).

In this review, we briefly summarize the epidemiology, pathogenesis, clinical and radiological manifestations, risk factors, pulmonary involvements and management of the pneumonia related with pandemic influenza A (H1N1) virus infection based on the literature.

EPIDEMIOLOGY

Influenza A pandemics have occurred 3 times in the 20th century: Spanish flu (H1N1 in 1918) responsible for 50-100 million deaths, Asian flu (H2N2 in 1957) responsible for 1 million deaths, and Hong-Kong flu (H3N2 in 1968) responsible for 700,000 deaths worldwide. Influenza A (H1N1) reemerged in 1977 to periodically circulate concurrently with

H3N2 subtypes. Antigenic drift represents the minor changes in the structures of antigenic glycoproteins; hemagglutinin (H) and neuraminidase (N) of influenza virus and it is responsible for the seasonal epidemics each year. Influenza pandemics occur less frequently, as a result of major changes in antigenic structure (antigenic shift).

The epidemiologic investigations of pandemic Influenza (H1N1) 2009 virus infection indicated that children and young adults have had the highest attack rates and hospitalizations. (8,9). In contrast to seasonal influenza, and the most hospitalizations due to pandemic infection was observed in young and healthy adults or adolescents (8,9). The relative sparing of elderly patients is likely due to immunological memory of the individuals who exposed to a type of H1N1 virus similar to the 2009 pandemic strain previously (10-12). As an example, an analysis of 532 cases of 2009 pandemic H1N1 influenza A in the USA has revealed that 60% of the cases were seen in the patients younger than 18 years and that only a small amount (5%) occurred in the patients elder than 50 years (12). Complications leading to hospitalization and possibly death occurred particularly in some of the subjects with underlying chronic cardiopulmonary disease, immunosuppressive states, pregnancy and post-partum states, diabetes mellitus, obesity and children with neurological disabilities (1,5), (Table 1).

TABLE 1: Risk factors for severe disease of pandemic (H1N1) 2009 virus infection

- Infants and young children <2 years
- Pregnant women
- Chronic pulmonary disease (e.g. asthma, COPD)
- Chronic cardiac disease
- Metabolic disorders, mainly diabetes mellitus
- Chronic renal and hepatic and neurological conditions

- Hemoglobinopathies, or immunosuppression (HIV infection, immunosuppressive medication or malignancy)
- Children receiving chronic aspirin therapy
- Persons aged 65 years and older
- Obesity (particularly morbidly obesity, BMI ≥ 40)

In pandemic influenza A (H1N1), obesity (body mass index ≥ 30 kg/m²) and morbid obesity (body mass index ≥ 40 kg/m²) were found to be independent risk factors for severe disease and mortality (5). This particular susceptibility to respiratory infection may be the result of disturbances in ventilatory mechanics and in the immune system, and an increased risk of thrombosis (5).

Another important risk factor for severe disease was pregnancy. Pregnant patients have 4-5 times more likely to develop severe respiratory illness. As a consequence, the hospitalization rate was significantly higher among pregnant women pregnant women represented 6.4% of hospitalized cases and 4.3% of death during the 2009 H1N1 pandemic (13). Maternal obesity and smoking during pregnancy were also associated with hospital admission and more severe disease. Most of the hospitalized patients are children (< 2 years of age), and those with chronic illness. Approximately 10-30% of all hospitalized patients have required admission to intensive care units (8). A case fatality rate of 0.45% has been reported for H1N1 infection (2). The mortality rates are high in the patients with respiratory failure changed between 17-28%, these are also older patients having several comorbid conditions (1,3).

SYMPTOMS AND SIGNS

Respiratory viruses account for 10% to 40% of community-acquired pneumonia (CAP) the most frequently encountered viruses in CAP are influenza A and B, adenovirus, and respiratory syncytial virus (14). The key feature of the

clinical presentation related to novel influenza A (H1N1) is a frequent association with pneumonia, compared with other viruses, and seasonal influenza. The incubation period of H1N1 is similar to that of seasonal flu. The spectrum of the disease is very large and it can be seen as a non-febrile, mild upper respiratory tract infection or a severe respiratory failure. Symptoms are high fever (typically $>38^{\circ}\text{C}$ and suddenly risen), cough, sore throat, malaise, arthralgia, myalgia, headache, gastrointestinal symptoms such as nausea, vomiting and diarrhoea (15). Complicated or severe influenza presents with shortness of breath, hypoxia and radiological signs of pneumonia. Hospitalized patients were evaluated by Riquelme et al. and they reported that nearly 40% of them associated with viral pneumonia and 10-30% of them needed to ventilatory support in ICU (8). Exacerbation of underlying chronic respiratory disease (asthma, COPD), central nervous system involvement, renal failure, multiorgan failure, and septic shock are the other systemic complications (15). Lymphocytes count relatively decrease and this is a nonspecific hematologic finding of influenza A (H1N1) pneumonia (16). Elevated number of leucocytes and neutrophils may show the bacterial coinfection and lymphopenia (< 800/mL) is generally associated with severe infection (16). High-dose corticosteroids treatment may increase the risk of invasive aspergillosis (17). The patients with H1N1 virus infection may come to emergency department, with a higher fever, lower systolic blood pressure, lower oxygen saturation level, and with a nonspecific laboratory findings such as leucopenia, relative lymphopenia,



thrombocytopenia, hypokalemia, elevated serum transaminases and elevated creatine phosphokinase (9,18,19).

PATHOGENESIS, PATHOLOGIC AND IMMUNOLOGIC FEATURES

Influenza virus attaches to ciliated columnar epithelial cells of respiratory tract via its surface hemagglutinin antigens after an inhalation of virus containing droplets. Respiratory defense mechanisms such as mucociliary clearance, secretion of specific secretory IgA antibodies help to remove some of the virus particles. However, the defense mechanism is impaired in smokers and elderly people (20-22). If the virus attaches to epithelial cells then invasion and viral replication occurs, subsequently newer viruses infect the other epithelial cells, shut off the synthesis of critical proteins, and ultimately lead to host cell death (23). In patients with uncomplicated influenza, bronchoscopic examination typically reveals diffuse inflammation and edema in the airways and biopsy shows the lymphocytic infiltration and desquamation of the ciliated columnar epithelium (24). In patients with primary viral pneumonia, pathologic examinations showed necrotizing tracheobronchitis, ulceration of the bronchial mucosa, intraalveolar hemorrhage, infiltration of alveolar spaces with fluid, fibrin, and cellular exudates, and lining of the alveoli with acellular hyaline membranes (25-27). Autopsies from the patients with primary influenza pneumonia confirmed similar results including bilateral severe interstitial inflammation, diffuse alveolar damage, hemorrhagic pneumonitis and virus particles observed particularly in the peripheric areas of the lungs (25,27). The lung damage in acute respiratory failure was most likely due to infection by the influenza virus.

Alveolar and respiratory epithelial invasion through the basement membrane, alveolar collapse by the loss of surfactant, secondary cytokine storm aiming to eradicate the virus

are the possible mechanism of tissue damage in H1N1 virus pneumonia (27). This is followed by exudation of macromolecules from the circulation and at the end of these reactions hyaline membranes occur. Neutrophilic infiltration in the pulmonary parenchyma may show the coexistence of bacterial infection (28). A number of inflammatory cells including macrophages and lymphocytes are present around bronchioles and small vessels. IL-4, IL-10 and iNOS expression is high in mononucleated cells (27). Immunological studies revealed that high plasma IL-6, IL-8 and MCP-1 levels are associated with intensive care admissions and pro-inflammatory cytokines IL-6, IL-8, and TNFR-1 are associated with pneumonia (27).

RADIOLOGIC FINDINGS

Bilateral, symmetric, and multifocal areas of consolidation often associated with ground-glass opacities are the predominant findings of influenza A H1N1 pneumonia and are often associated with a more severe clinical course (6,7,29,30), (Table 2, Figure 1,2 and 3). Other rarer radiologic manifestations are pneumothorax, pneumomediastinum, and atelectasis which are mostly seen in the state of acute respiratory distress syndrome (30). Additional findings include small pleural fluids, cavitation, necrosis, and thickening of bronchial wall (30). The most frequent findings on high resolution computerized tomography findings were the thickening of the peribronchovascular space, followed by intralobular septa thickening, subpleural septa thickening, bronchiectasis, mosaic image of perfusion, lymphadenopathies, pulmonary condensation zones, fibrotic bands, atelectatic bands and posterior basal thickening (31,32).

Figures: Computed tomography (CT) scans of the patients with confirmed primary influenza A H1N1 pneumonia from a late localized outbreak of influenza A H1N1 in eastern part of Black sea region, Rize, Turkey.



Figure 1: A 24 year-old male patient with 38,5 °C fever, cough and mild dyspnea, CT scan reveals bilateral multifocal, subpleural consolidations, he recovered after oceltamivir treatment.



Figure 2: A 38 year-old, female patient admitted to emergency department with 38 °C fever, cough, malaise, myalgia and dyspnea CT scan shows bilateral multifocal consolidations, and air-bronchograms in right lower lobe. She recovered completely after oceltamivir treatment.

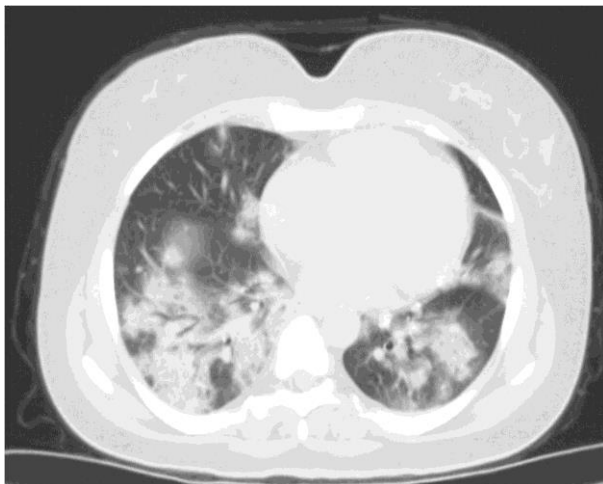


Figure 3: A 29 year-old female patient with obesity (BMI: 36,15 kg/m²), 39 °C fever, severe dyspnea, she admitted to emergency department after 7 days from onset of symptoms and CT scan revealed bilateral multifocal ground glass appearance. She had a

rapidly progressive pneumonia and respiratory failure leading to acute respiratory distress syndrome, needed intensive care having hypoxemia (PaO₂/FiO₂ <300 mm Hg), invasive mechanical ventilation was performed but she died during the second day of ICU treatments.



TABLE 2

Chest Computed Tomography Findings in Influenza A (H1N1) Pneumonia

Parenchymal findings

- Consolidation: Unilateral, bilateral, focal, multifocal, multifocal bilateral, subpleural, peribronchovascular, diffuse
- Ground-glass opacity: Unilateral, bilateral, focal, multifocal, multifocal bilateral, subpleural, peribronchovascular, diffuse
- Air-bronchograms, reticular pattern, nodular pattern, tree-in-bud appearance
- Atelectasis
- Cavitations and necrosis
- Thickening of bronchial walls

Pleural findings

- Pleural effusion, pneumothorax

Mediastinal findings

- Pneumomediastinum, lymphadenopathy

COINFECTIONS AND COMPLICATIONS

A lower respiratory tract involvement was seen from 19% to 50% of the H1N1 virus infection (10,11,14). The impact of viral and bacterial coinfection was reported in several studies (14,33-35). As an example Marcos studied 181 patients with confirmed influenza A (H1N1), and 12% of them had coinfection with at least one or more respiratory viruses (33). It is found that the most common concomitant viruses were rhinovirus, enterovirus, coronavirus and parainfluenza virus. The existence of coinfections with the other viruses may cause a severe clinical illness and consequently a longer period of hospitalization. (4,33,35). Bacterial coinfection has been reported with rates between 15-28% (11, 36-38). The commonest agent for a bacterial coinfection was *S. pneumoniae*, and followed by *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, and *Streptococcus agalactiae* (4,11,33,39). Geriatric patients and the presence of underlying comorbidities particularly have an increased risk for bacterial coinfections (4). Influenza virus usually causes transient lower respiratory tract infections, corresponding with virus attachment to tracheobronchial epithelial cells and patients recovers without any medical care. The main complication is extension of viral infection to the alveoli that causes primary viral pneumonia (6,7). Bacterial coinfection was determined in lung tissue specimens from 29%

of the patients with fatal cases of confirmed H1N1 infection, caused mainly by *Streptococcus pneumoniae* and *Staphylococcus aureus* (4). In spite of performing an optimal ventilatory support, there may be a refractory hypoxemia and hypercapnia. In these patients, extracorporeal membrane oxygenation (ECMO) can be an alternative management (3). However, the high mortality rates in the reported ECMO series led to the loss of hopes that raised by this technique. Hypotension requiring vasopressor treatment and acute renal failure are the main complications in H1N1 patients in ICU (40,41). Patients with severe illness die from secondary multiorgan insufficiencies caused by severe hypoxemia and hypotension. Recent investigations reported that the current severity scores of community acquired pneumonia (CURB-65 and pneumonia severity index) could not estimate the mortality in many hospitalized patients (42,43).

According to this study, there were statistically significant features between survivors and nonsurvivors regarding the success of noninvasive ventilation (NIV) in the view of time to confirmation of the H1N1 virus infection after hospital admission, and PaO₂/FiO₂ ratio. Failure of NIV, late diagnosis, and a late onset to antiviral therapy would contribute to mortality (43). Children receiving chemotherapy and with immunosuppressive condition have a higher mortality rates (44). In Table 3, the main predictors of mortality are reported.

TABLE 3

Predictors of mortality

- Late diagnosis after the symptoms (7.2 ± 3.8 d)
- Late onset to oseltamivir therapy (> 48 h)
- Altered mental state
- Respiratory failure (dyspnea, cyanosis, a respiratory rate ≥ 30)
- Morbid obesity (body mass index > 40kg/m²)



- Strong ion gap, acid-base disturbance
- Immunosuppression and chemotherapy (malignancy)
- Increased extent of pulmonary infiltrate on follow-up chest x-ray > 50%
- High APACHE II Score at admission(> 21)
- Noninvasive ventilation failure ($\text{PaO}_2/\text{FiO}_2 < 140$, arterial pH <7.31, SOFA > 5.1)

The mortality rates were reported between 2.7-11% in various studies and they were found higher in the patients who required mechanical ventilation and aged 50 or older (28,45,46). During the postpandemic period, particularly elderly patients and the ones with chronic comorbidities mostly affected by influenza A (H1N1) virus (47). Severe complications of the disease are worsening of underlying chronic disease (e.g. asthma, chronic obstructive pulmonary disease and heart failure), progressive pulmonary infection, acute respiratory distress syndrome with refractory hypoxemia, severe bacterial coinfection, septic shock, acute kidney failure, multiple organ failure, myocarditis and encephalitis.

DIAGNOSIS

Clinical diagnosis in the context of local influenza activity should inform treatment initiation. Monto et al. suggested a simple diagnostic hypothesis with a 79% positive predictive value, during an influenza epidemics the patients presenting with both cough and fever ($>38^\circ\text{C}$) within the first 48 hours of symptom onset are very likely to have actual influenza (50). Nasopharyngeal aspirates or swabs should be taken to identify the virus and to confirm definite diagnosis after the onset of symptoms. Endotracheal or bronchoscopic aspirates have higher diagnostic yields in patients with lower respiratory tract illness.

The gold standard diagnostic test is the virus culture but the results can be obtained after several days (23). The real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) swine flu panel is a fast and reliable diagnostic test and used for detection of pandemic influenza A H1N1 strain (35,48). The

direct fluorescent antigen influenza test is another diagnostic assay with a sensitivity of 93%, requires experienced technical persons and fluorescent microscope (49). A negative result of any rapid diagnostic test cannot exclude the diagnosis of influenza infection in a clinical or epidemiological suspicion, during a pandemic and if initial tests are negative for influenza A H1N1 virus, diagnostic tests should be repeated within 2-3 days.

MANAGEMENT

Clinical triage algorithms for H1N1 pneumonia according to the WHO recommendation is shown in Table 4 (2). Most of the patients with influenza A H1N1 infection recover without any severe complication. Supportive treatments such as non-steroidal anti-inflammatory drugs (e.g. paracetamol) for the relief of fever and pain, fluid rehydration can be provided. Aspirin may cause Reye's syndrome in children with influenza infection and should be avoided.

Influenza A (H1N1) virus is resistant to the M2 inhibitor antiviral drugs (amantadine and rimantadine) but it is susceptible to neuraminidase inhibitors (oseltamivir and zanamivir) in most of the cases. Sporadic oseltamivir resistance has been reported (28). Early oseltamivir therapy can shorten the duration of symptoms; for high-risk patients or progressive clinical illness, oseltamivir or zanamivir should be initiated within 48 h of the onset of disease (28,51). The recommended standard dose of oseltamivir is 75 mg twice daily for 5 days for adults and 3 mg/kg twice daily for 5 days for children 6 to 12 months of age. In severe cases oseltamivir treatment is recommended in higher doses as twice 150 mg



daily at least 10 days (51). The recommended dose of Zanamivir for adults and children (>5 years) is twice 5 mg inhalations daily for 5 days, for influenza treatment.

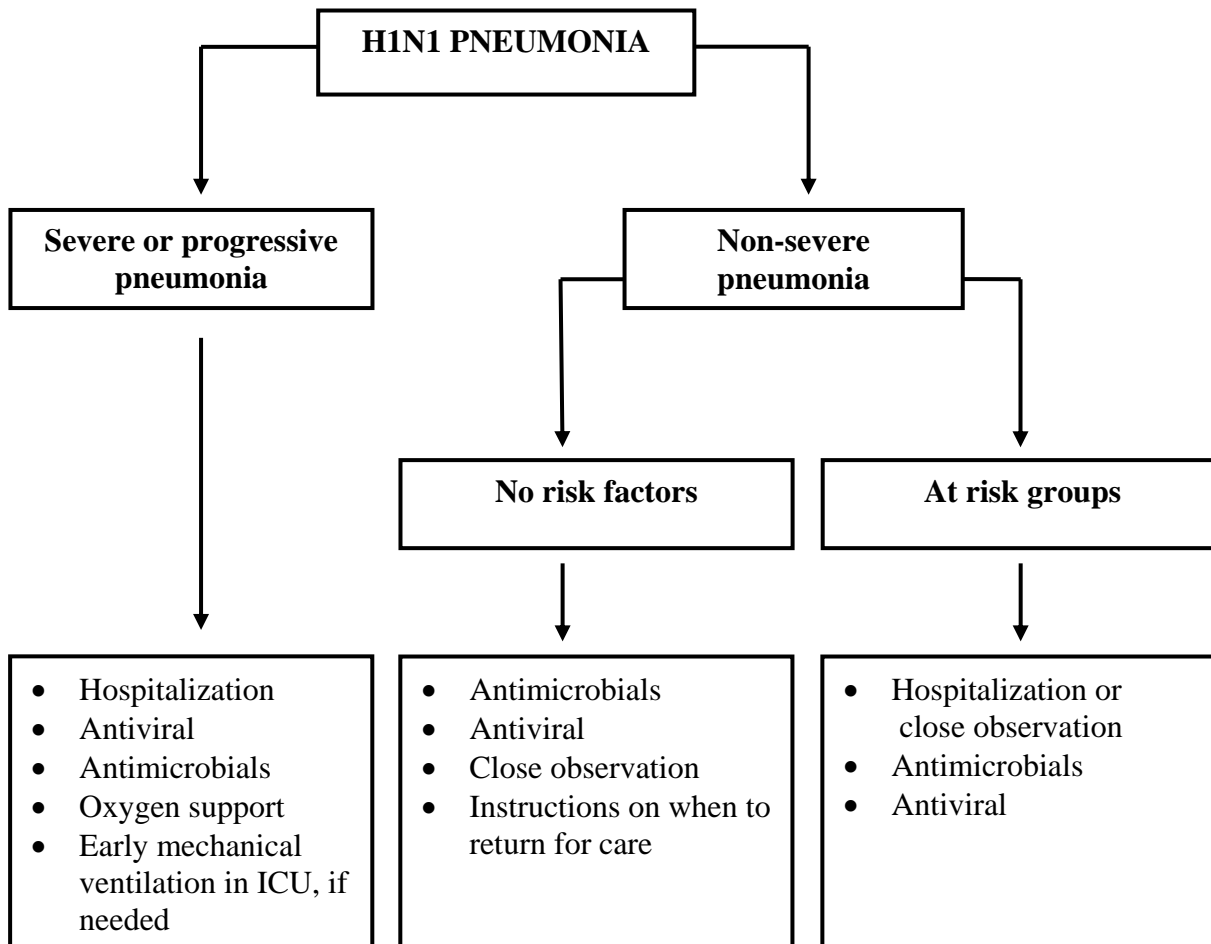
Antimicrobial treatment should follow the recommendations of IDSA/ATS CAP guidelines if any pathogen(s) are present: use a beta-lactam plus either macrolide or a respiratory fluoroquinolone (48). The use of vancomycin and linezolid against methicillin-resistant *S. aureus* should be limited to patients with a compatible clinical presentation such as shock and necrotizing pneumonia in intensive care units or microbiologically confirmed infection (38,39). Corticosteroid treatment is controversial in influenza infections. Long term and high dose use of systemic corticosteroids may cause some complications such as fungal infections (e.g. invasive aspergillosis). On the other hand, low doses of systemic corticosteroids and vasopressor agents may be considered in septic shock. Arterial blood oxygen saturation levels (SaO₂) should be kept over 90% (92-95% for the pregnant), with additional oxygen via nasal cannula or mask (52). Infants are in risk group to have a severe illness and arterial oxygenations may be impaired quietly so the physicians should be careful. Blood pressure and pulse rate levels should be closely monitored in acute lung injury and acute respiratory distress syndrome. Intravascular fluid and electrolyte balance may be impaired during systemic inflammation, the

essential volume supplementations should be maintained.

MECHANICAL VENTILATION

Mechanical ventilation is needed as a general treatment modality in most of the patients with influenza A H1N1 pneumonia. An ideal protective mechanical ventilation strategy with a tidal volume lower than 6 mL/kg and with a lower plateau pressure than 30 cmH₂O can increase survivals (53). Additionally, Boots et al. successfully used some alternative ventilation modes such as high frequency oscillatory and airway pressure release ventilation in severe hypoxemic patients during the 2009 H1N1 influenza pandemic in Australia and New Zealand (52). When an outbreak of H1N1 respiratory illness started, several investigations stated that mechanical ventilation failed to recover the disease (13,31,53-57). However, recent studies have reported the effectiveness of NIV in some of the cases with severe respiratory failure related to H1N1 pneumonia and early mechanical ventilation was strongly recommended (13,56,57). In some of the cases with H1N1 pneumonia and severe respiratory failure, an optimal arterial blood oxygen saturation level (> 90%) cannot be maintained by noninvasive or even by invasive mechanical ventilation. The method of extracorporeal membrane oxygenation (ECMO) is an alternative but the survival results are controversial (57-60).



Table 4: Clinical triage algorithms for H1N1 pneumonia (risk factors was shown in Table 1)

INFECTION CONTROL

Vaccination is the best protection method during a viral pandemic. During a pandemic period, health care providers should be obligated to follow the WHO guidance of standard and droplet infection control methods and patients with respiratory symptoms should be strongly encouraged for using protective masks, washing hands with soap and disposing of any infected wastes (61). Whenever performing bronchoscopy or any high risk aerosol-generating procedures involving aspiration of the respiratory tract, a particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, and gloves should be used, and the procedures should be carried out in an adequately ventilated room. Special attention is recommended for health care providers of

immunosuppressive patients who may shed virus for a longer time period (>7 days) and are also at increased risk for development of antiviral-resistant virus.

CONCLUSIONS

Influenza A (H1N1) virus causes a higher incidence of severe pneumonia compared with other viruses and seasonal influenza. Several preexisting conditions such as obesity, pregnancy, chronic cardiopulmonary disease, diabetes mellitus, neurological disabilities predispose to disease severity. Early oseltamivir therapy can shorten the duration of symptoms; for high-risk patients or progressive clinical illness, oseltamivir or zanamivir should be initiated within 48 h of the onset of disease. In cases with severe H1N1 pneumonia accompanying with bacterial coinfection; an

appropriate antimicrobial treatment, early onset of oxygenation and mechanical ventilatory support can decrease the mortality rate. Delays in diagnosis and medical care may increase the mortality.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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