

# Acute respiratory distress syndrome (ARDS) complicating influenza A/H1N1v infection – a clinical approach

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## Abstract

ARDS is defined as an acute inflammatory syndrome characterized with bilateral parenchymal lung infiltrates on chest radiograph and PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200 resulting from causes other than acute left ventricular dysfunction. Inflammatory lung lesions may be induced by different disorders, with sepsis being the leading cause of ARDS. Other causes include infectious pneumonia, aspiration of gastric contents, drugs, severe trauma, fat embolism, surface burn, massive blood transfusion. Influenza A/H1N1 infection seems to be responsible for the development of extremely severe type of ARDS with poor response to routine treatment. Despite great progress in the management of ARDS with novel agents and sophisticated techniques, including antimicrobial drugs, extracorporeal membrane oxygenation, prostaglandins, nitric oxide, prostacyclin, exogenous surfactant administration and activated protein C, supportive treatment based mostly on advanced mechanical ventilation in the intensive care units seems to be the most important for the prognosis.

## Key words

acute respiratory distress syndrome (ARDS), A/H1N1 influenza, mechanical ventilation

## INTRODUCTION

Human infection with the novel influenza A/H1N1 virus was first reported in April 2009. Since humans do not have immunity from the infection the incidence rates may be higher than those for seasonal influenza [1]. Novel influenza usually affects subjects below the age of 65, especially pregnant women, obese persons and patients with comorbidities, including asthma, chronic bronchitis, neoplasms and transplants. Young, previously healthy individuals can also be affected. Clinical presentation includes fever, cough, sore throat, hoarseness, malaise, muscular pain, diarrhea and vomiting, arthralgia, ostealgia, chills and headaches with ophthalmalgia, photophobia and touchable eyeballs [2]. Complications like bronchitis, pneumonia, myocarditis, pericarditis, encephalitis and shock affect people with immune system compromise. The course of influenza may be severe, especially in children and the elderly. According to a Dutch study, the mortality rate due to influenza is 0.71/10,000 in people aged 0–59, 58,19/100,000 in people aged 70–79 and 207,57/100,000 in people over 80 [2]. Influenza was the primary cause of death in 26% of patients, 34% died because of cardiovascular complications, and 17% due to

respiratory deterioration resulting from viral or bacterial pneumonias. Less commonly, influenza may evolve into ARDS [3]. The presented study describes a fatal case history of ARDS complicated by A/H1N1v infection.

## CASE REPORT

A 60-year-old patient with a history of hypertension and degenerative-discopathic lesions at L4-L5 previously treated in other departments was admitted to the Department of Internal Medicine because of dyspnea, dry cough and chest pain on deep breathing. In 2009 and 2010 the patient underwent operations because of lumbar discopathy and was perioperatively treated with analgetic drugs, including pethidine, paracetamol and ketoprofen. After the surgery the patient was hospitalized in the Department of Rehabilitation, where erythematous-edematous skin lesions with a haemorrhagic component and blisters, mostly on the internal surface of the upper limbs, developed. This was probably a side-effect of non-steroid anti-inflammatory drugs. The patient was transferred to the Department of Dermatology for further treatment based on intravenous dexamethasone and amoxicillin with clavulanic acid, which resulted in partial regression of skin lesions. After several days, symptoms of the lower respiratory tract infection occurred and the patient was transferred to the Department of Internal Medicine.

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On admission, the patient reported periodic dyspnea, cough productive of mucous sputum, sweating and weakness. Physical examination revealed fever of 38.5°C, arterial hypertension of 160/95 mmHg, tachycardia reaching 104/min, and a poorly tense pulse. Sibilant dry rales and dullness were found over the lung bases. ECG on admission showed regular sinus rhythm. The chest X-ray revealed increased bronchial markings in the right supradiaphragmatic region.

Laboratory tests performed on admission demonstrated an increased white cell count (15.1 K/uL) with high percentage of neutrophils (81.2%) and elevated C-reactive protein level (CRP 88.9 mg/l, upper normal value-5mg/l). Based on the physical, laboratory results and chest X-ray, diagnosis of the lower respiratory tract infection without lung involvement was established. Repeated electrocardiographic examinations and troponin T measurements excluded recent myocardial infarction as the cause of dyspnea. D-dimer evaluation denied pulmonary embolism. Empiric antibiotic treatment with ceftriaxone and azithromycin as well as oxygen supply were administered. After two days, the patient's condition deteriorated rapidly, complaining of severe dyspnea, and he was unable to speak in full sentences. On physical examination, cyanosis of the accessory muscles for ventilation was found. Auscultation revealed bilateral crackles suggestive of acute pulmonary oedema. No organic heart disease confirming a cardiac origin of pulmonary oedema was found on echocardiography. No significant arrhythmia or hypertension was found. The patient became confused and sleepy. Blood gases with  $pO_2$  of 39 mmHg and  $pCO_2$  of 29 mmHg suggested respiratory distress with urgent need for mechanical ventilation. Repeated X-ray revealed scattered parenchymal infiltrates affecting half of both lungs. Bilateral pleural effusion was found. Laboratory findings demonstrated CRP of 260 mg/l and worsening kidney function (creatinine 1.3 mg/dl). Blood and urine cultures were negative. Procalcitonin level was normal – 0.19 ng/ml (reference range <2). The primary diagnosis was ARDS due to viral pneumonia.

On admission to the Intensive Care Department the patient was responsive and alert (GCS 15), dyspneic with respiration rate 24/min; blood pressure 90/60 mmHg, regular pulse about 100/min, body temperature reached 38.5°C. The arterial blood gases were as follows:  $PaO_2$  – 42 mmHg,  $PaCO_2$  – 32 mmHg. Since the non-invasive ventilation with 50% oxygen supply had not been effective the patient was intubated. SIMV, the volume control mode, and 50% oxygen concentration were provided. A sedative infusion consisting of fentanyl and midazolam was initiated. Antibiotic therapy was continued with cefuroxime and ciprofloxacin; difluconazole was added. Dopamine and norepinephrine were administered because of hypotension and impaired peripheral perfusion. Chest X-ray repeated 8 hours later showed progression of bilateral scattered lung infiltrates (Fig. 1 and 2). Because of poor results of blood gases the inspiratory oxygen concentration was changed to 100% ( $FiO_2$  1.0). Insufficient response to mechanical ventilation and the need for pure oxygen supply confirmed the suspicion of ARDS.

On the 2<sup>nd</sup> day, acute renal failure developed with creatinine level at 3.1 mg/dL, and hemofiltration was started. Because the results of urine and blood cultures were negative, nasopharyngeal swab specimens were collected and sent to the Military Institute of Hygiene and Epidemiology, Biological Threat Identification and Countermeasures



**Figure 1.** Consecutive X-rays show rapid 48 hour progression of lung changes, from a normal radiogram (left image), through patchy parenchymal opacities localized symmetrically in both lungs to scattered, multifocal, wide-spread areas of parenchymal consolidation (right image).



**Figure 2.** Consecutive X-rays show partial regression of extensive lung consolidation areas (left image), through patchy parenchymal opacities, symmetrical in both lungs to the normal radiograph (right image) which took 10 days.

Centre Laboratory. The laboratory tests were positive for the presence of A/H1N1 virus. Oseltamivir was added at the initial dose of 75 mg twice a day. On the 4<sup>th</sup> day, the dose was doubled. Since there an increase in the procalcitonin level was observed, antibiotics were continued despite negative cultures. On the 3<sup>rd</sup> day, the patient's condition improved; chest X-rays showed regression of lung infiltrates and oxygen concentration was switched to 50%. On the 5<sup>th</sup> day, the patient again deteriorated. Due to the lack of improvement and low  $PaO_2$  despite the optimal treatment, the pressure-controlled ventilation (PCV) mode was started with reversed inspiratory/expiratory ratio (2 to 1) and  $FiO_2$  1.0. Neuromuscular relaxation with cis-atracurium infusion was required to improve oxygenation. On the 12<sup>th</sup> day, cardiac arrest occurred. The primary mechanism was pulseless ventricular tachycardia degenerating into asystole. After 20 minutes of resuscitation the patient died. Due to the fatal course of the disease, the Biological Threat Identification and Countermeasure Centre Laboratory decided to send the RT-PCR products to the BioVectis laboratory to confirm swine flu infection and to exclude co-infection using Multitemperature Single Strand Conformation Polymorphism (MSSCP method). For the purpose of the MSSCP analysis RT-PCR, the products obtained from a previously confirmed case of A/H1N1 infection collected in our hospital were added.

## DISCUSSION

ARDS is defined as an acute inflammatory syndrome characterized by bilateral parenchymal lung infiltrates on the chest radiogram with  $PaO_2/FiO_2$  ratio < 200 resulting from causes other than acute left ventricular dysfunction. Diffuse alveolar damage with increase in vascular permeability and surfactant damage are responsible for severe hypoxaemia. The mortality rate ranges from 40% – 80%. Inflammatory

lung lesions may be induced by different disorders, including infectious pneumonia, aspiration of gastric contents, drugs, severe trauma, fat embolism, surface burn, massive blood transfusion and sepsis being the leading cause [4, 5]. In the presented case, ARDS occurred in the course of influenza *A/H1N1v* infection, which has been found to be responsible for the development of this extremely severe type of ARDS with poor response to the treatment (e.g.  $\text{PaO}_2 < 60$  mmHg on  $\text{FiO}_2 > 60\%$  and  $\text{PEEP} > 15$  cmH<sub>2</sub>O). Approved predictors of the severe course of influenza *A/H1N1* in humans, including radiographic changes, increase in C-reactive protein level, peripheral oxygen saturation below 94% on breathing air, hypotension and previous immunosuppression were present in the presented case [3].

Chest radiography is the first-line imaging technique for diagnosing lung disorders resulting in acute respiratory distress. Henzler et al described alveolar consolidations, ground-glass opacities, reticular opacities and pleural effusion as the most common findings in 10 patients with *A/H1N1* infection [6]. Busi Rizzi et al report that the major radiological abnormalities were interstitial changes (60.0%), with (22.0%) or without patchy ground-glass appearance, and located in the lower lung zones (7.5%). Such changes are observed in the most non-complicated cases of swine-virus infection [7].

We have also observed multifocal, bilateral consolidations, ground-glass opacities and reticular opacities which spread all over the lungs within several hours, indicating the fulminant course of the disease and fatal outcome.

Skin lesions during influenza virus infection are rare and usually have a macular or maculopapular aspect. There is one case report of the pandemic 2009 *A/H1N1* virus infection associated with purpuric skin lesions on the limbs [8]. In the patient in the presented case, the skin lesions were not specific for influenza infection, being presumably the side-effect of non-steroid anti-inflammatory drugs.

Treatment of reversible causes, together with mechanical ventilation, are crucial for the management and prevention of MODS (multiple organ dysfunction syndrome). Since infection with influenza *A/H1N1* virus was confirmed in the presented case, antiviral drug oseltamivir was applied. Other drugs – zanamivir, a combination of oseltamivir and amantadine or rimantadine – were tried in humans with swine flu [3]. Although non-invasive positive pressure ventilation may be applied in selected patients, most require invasive mechanical ventilation. Low tidal volume ventilation (5–7 ml/kg) with end-inspiratory airway pressure less or equal to 30 cmH<sub>2</sub>O, decreases mortality in ARDS. Patients with a severe course of ARDS may require high PEEP with values up to 25 cmH<sub>2</sub>O and very low volumes of 200 ml, as well as the need for deep sedation and muscle relaxation to keep the patient's synchrony with the ventilator. PEEP adjustment is important to keep the lungs open without increase in inspiratory pressure. Ventilatory strategies include pressure-controlled ventilation, inverse ratio ventilation (IRV), airway pressure release ventilation (APRV), high-frequency ventilation (HFV). Liquid mechanical ventilation can be beneficial in some cases, but its effect on ARDS treatment is not well defined. In the patient in the presented case, typical volume-controlled positive pressure ventilation with sedation and muscle relaxation was applied.

Since there was no improvement, pressure-controlled inverse ratio ventilation was started. There are some reports that PCV does not improve oxygenation and has impact on the peak pressure rather than on the plateau pressure [9]. All these methods need evaluation in clinical trials.

Extracorporeal membrane oxygenation (ECMO) is considered the rescue therapy in patients with swine flu infection. Despite promising results of ECMO treatment, randomized clinical trials are needed for approval of this method. The same is reported on the proning effect [10]. Supportive care includes fluids, antibiotics, corticosteroids, prostaglandins, nitric oxide, prostacyclin, exogenous surfactant administration, lisofylline, ketoconazole and N-acetylcysteine. According to other reports, ceftriaxone, azithromycin, vancomycin and levofloxacin were preferred for treating co-infection and superinfections with *Escherichia coli*, *Streptococcus pneumoniae* and *Staphylococcus aureus* in patients with swine flu. To keep the patient as dry as possible, fluids should be applied cautiously except cases of sepsis. In most patients, pressors must be added to maintain peripheral perfusion. To date, activated protein C has not been proven to be effective [3, 4].

The patient in the presented case received cefuroxime and ciprofloxacin as well as difluconazole. Dopamine and norepinephrine were also administered because of hypotension. Intravenous methylprednisolone was maintained. No significant improvement was achieved. It seems possible that optimization of general supportive care is crucial for better outcome in such cases.

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