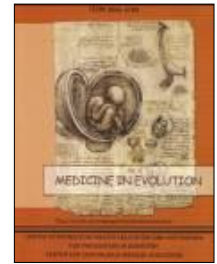# ACUTE RESPIRATORY DISTRESS SYNDROME SECONDARY TO INFECTION WITH INFLUENZA A (H1N1) VIRUS

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ABSTRACT

Acute respiratory distress is an extremely severe syndrome that affects the lungs widely caused by a variety of direct and indirect issues. Clinical disorders associated with acute respiratory distress are sepsis, infection with influenza A (H1N1) virus, aspiration, trauma, burns, massive blood transfusion, drugs, mechanical ventilation, acute pancreatitis.

A 52-year-old male was admitted to Infectious Diseases department with respiratory distress phenomena. The disease had an acute onset with high fever, productive cough, watery rhinorrhea, intense headache, vomiting. Clinical data, results of laboratory tests, chest X-rays and CT scans are presented in dynamics revealing a rapid progressive damage of pulmonary function. Suspicion of infection with influenza A (H1N1) virus was confirmed by RT-PCR. The patient was treated in intensive care unit and evolution was slowly favorable.

An etiological circumstance of acute respiratory distress in critically ill patient, besides those that are well known, is infection with influenza A (H1N1) virus. Multidisciplinary approach of this multifactorial pathologic process - ARDS, team activity (infectious disease doctor, lung disease specialist, intensive care specialist), in intensive care unit, promotes therapeutic success.

Key words: acute respiratory distress syndrome, influenza A (H1N1) virus, corticosteroids.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS), also known as respiratory distress syndrome is a life-threatening lung condition that prevents enough oxygen from getting into the blood, a serious reaction to various forms of injuries to the lung. It is characterized by inflammation of the lung parenchyma leading to impaired gas exchange with concomitant systemic release of inflammatory mediators causing inflammation, hypoxemia and frequently resulting in multiple organ failure [1].

Long time ago, it has been recognized that some patients with non-thoracic injuries, severe pancreatitis, massive transfusion, sepsis, and other conditions develop respiratory distress, diffuse lung infiltrates, and respiratory failure, sometimes after a delay of hours to days [2, 3].

A clear definition of the syndrome was developed in 1994 by the American-European Consensus Conference (AECC) on acute respiratory distress syndrome: an acute condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema. According to the AECC criteria, the severity of hypoxemia necessary to make the diagnosis of ARDS is defined by the ratio of the partial pressure of oxygen in the patient's arterial blood (PaO_2) to the fraction of oxygen in the inspired air (FIO_2). In ARDS, the PaO_2/FIO_2 ratio is less than 200. In addition, cardiogenic pulmonary edema must be excluded either by clinical criteria or by a pulmonary capillary wedge pressure lower than 18 mm Hg in patients with a Swan-Ganz catheter in place.[4]

ARDS is characterized by:

- Acute onset

- Bilateral infiltrates on chest radiograph sparing costophrenic angles
- Pulmonary artery wedge pressure < 18 mmHg or lack of clinical evidence of left ventricular failure suffices
- $PaO_2:FIO_2$ < 200 mmHg (26.7 kPa).

ARDS is associated with diffuse alveolar damage and lung capillary endothelial injury. The early phase is described as being exudative, whereas the later phase is fibroproliferative in character. Early ARDS is characterized by an increase in the permeability of the alveolar-capillary barrier, leading to an influx of protein-rich fluid into the alveoli. The main site of injury may be focused on either the vascular endothelium (eg, sepsis) or the alveolar epithelium (eg, aspiration of gastric contents) [5, 6].

Two types of alveolar epithelial cells exist. Type I cells, which make up 90% of the alveolar epithelium, are injured easily. Damage to type I cells allows both increased entry of fluid into the alveoli and decreased clearance of fluid from the alveolar space.

Type II alveolar epithelial cells have several important functions, including the production of surfactant, ion transport, and proliferation and differentiation into type l cells after cellular injury. Damage to type II cells results in decreased production of surfactant with resultant decreased compliance and alveolar collapse. Interference with the normal repair processes in the lung may lead to the development of fibrosis.

The acute phase of ARDS usually resolves completely. Sometimes residual pulmonary fibrosis occurs, in which the alveolar spaces are filled with mesenchymal cells and new blood vessels. Progression to fibrosis may be pre-

dicted by the finding of increased levels of procollagen peptide III (PCP-III) in the fluid obtained by bronchoalveolar lavage (BAL).

ARDS can appear within 24 to 48 hours of an direct injury (trauma, burns, aspiration, drowning, massive blood transfusion, drug/alcohol abuse, pulmonary embolism, inhalation injury) or an acute illness (infectious pneumonia, sepsis, acute pancreatitis) [7, 8].

ARDS is a multifactorial disease process that occurs due to an environmental trigger on the background of a genetic predisposition. There is an association between genetic variations in the FAS gene and ARDS susceptibility. FAS gene encodes a protein that is a member of the TNF-receptor superfamily that plays a central role in the physiological regulation of programmed cell death, and has been implycated in the pathogenesis of various malignancies and diseases of the immune system.

Acute respiratory distress syndrome is usually treated in the intensive care unit. Ventilation is sometimes necessary through oro-tracheal intubation, or tracheostomy whenever prolonged ventilation (≥2 weeks) is deemed inevitable.

Treatment of the underlying cause is imperative, although sometimes it is difficult to identify it.

Appropriate antibiotic therapy must be administered as soon as microbiological culture results are available. More than 60% ARDS patients' experience pulmonary infection either before or after the onset of lung injury [9].

Fluid restriction is important as several studies have shown that pulmonary function and outcome are better in patients that lost weight. Significant improvement in ARDS can be obtained by using modest doses of corticosteroids by inhibiting arachidonic acid metabolism and reducing eosinophil activity. The initial regimen consists of methylprednisolone 2 mg/kg daily.

The dose of methylprednisolone can be tapered to 0.5-1.0 mg daily in 1–2 weeks [10, 11].

Repositioning into the prone position (face down) might improve oxygenation by relieving atelectasis and improving perfusion as distribution of lung infiltrates in acute respiratory distress syndrome is non-uniform. However, although the hypoxemia is overcome there seems to be no effect on overall survival [13].

CASE REPORT

A 51-year-old male with arterial hypertension and cholelithiasis was hospitalized during 02.02.2011–01.03.2011 to Infectious Diseases Department from Clinical Hospital of Infectious Diseases and Pneumophtisiology V.Babes Timisoara. The diseases had a sudden onset on 28.01 with high fever, productive cough, watery rhinorrhea, intense headache and vomiting. He was treated at home with ceclodyne (28–31.01) and augmentin afterwards (31.01–01.02). Symptoms persisted and he was admi-

tted to hospital in Lugoj 01.02–02.02 and treated with ampicillin 4 g/day and gentamicin 240 mg/day. The patient became critically ill with rapid acute distress, marked dyspnea, blood oxygen saturation varying between 66% and 80% with oxygen administered on mask and he was transferred with suspicion of infection with influenza A (H1N1) virus.

The physical exam revealed an anxious, restless patient, with pale, perspirated skin, severe dyspnea and or-

thopnea, bilateral basilar rales and decreased breath sounds throughout both lung fields. Temperature was 37,1°C, blood pressure 130/70 mm Hg, the pulse 96 beats per minute.

Ceftriaxone 2x2 g/day, ciprofloxacin 2x400 mg/day, dexamethasone 4x8 mg/day, tamiflu 2x75 mg/day, expectorants, antipyretics, gastric protectants were administered and oxygen therapy delivered via face mask.

Laboratory results are presented in table I. Leucopenia (L 3180/mm³) was associated with nonspecific inflammatory syndrome (ESR 30/55 mm, positive C reactive protein) and elevated enzymes (ALAT 48 u/l, ASAT 104 u/l, alkaline phosphatase 296 u/l, gamma-glutamyltransferase 140 u/l). Sputum culture revealed 40% Candida, 30% Neisseria, 20% Streptococcus viridians, 10% Gram negative bacilli. Diagnosis of infection with influenza A (H1N1) virus was confirmed by RT-PCR of pharyngeal and nasal exudates on 04.02.2011.

The chest radiograph on 01.02 showed no pleuro-pulmonary involvement (fig.1) but one day later infiltrative opacities of costal, subcostal intensity bilaterally predominantly in the lower lung zones appeared (fig.2).

Chest CT scan on 08.02 revealed ground glass attenuation bilaterally, peripherally and predominantly subpleurally and in the lower lung zones, with a diffuse or patchy distribution;

peri and intralobular interstitial marking was pronounced subpleurally bilaterally, especially in the lower lung zones (fig.3).

Despite treatment the general condition of patient continued to impair (extremely agitated, without fever, marked orthopnea, perioral cyanosis, bilateral crackles in both lower lings zones, SaO2 75-85% with oxygen delivered by mask) and he was transferred to intensive care unit during 05.02-14.02. The primary treatment was completed with fluconazol 150 mg/day, aerosol with acetylcysteine, hydrocortisone hemisuccinate, ventolin, saline solution. Periodically the patient was placed in prone position. Evolution was slowly favorable, dyspnea rendered, crackles were replaced by bronchial rales, spontaneous SaO2 was 95%.

Dynamics of biological tests is shown in table I and improvement of radiologic image in figure 4. Diffusion capacity pulmonary function test on 11.05.2011 showed only a mild reduction of transfer factor through pulmonary alveolar-capillary membrane.

From 25.02 dexamethasone was replaced by prednisone 50 mg daily and tapered gradually afterwards. Evolution was favorable, without symptoms, lab tests on 22.03 presented in table II, chest X ray on 22.03 without active pleuro-pulmonary lesions (fig.5) and CT scan on 23.03 – aspect of interstitial pneumopathy.

Table 1 Results of laboratory tests

| DATE	02.02	04.02	23.02
Leucocyte /mm³	3180	9110	4600
Neutrophilic leukocyte %	80	86	75
ESR mm/1-2 hour	30/55	25/55	5/10
ALAT u/l	48	111	75
ASAT u/l	104	178	24
Alkaline phosphatase u/l	296	364	200
γGT u/l	140	372	259
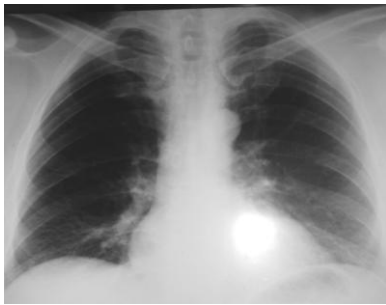
Fig. 1. Chest X ray (01.02.2011): without active pleuro-pulmonary lesions.
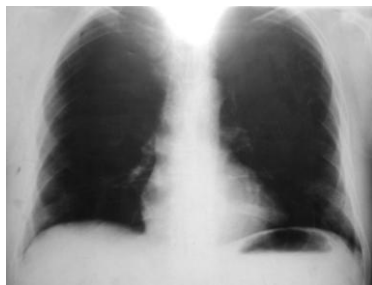

Fig. 2. Chest X ray (02.02.2011): infiltrative opacities of costal, subcostal intensity bilaterally predominantly in the lower lung zones.
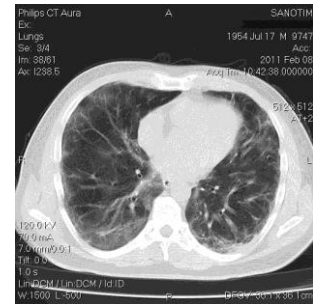
Fig. 3. Chest CT scan 08.02.2011: ground glass attenuation bilaterally, peripherally and predominantly subpleurally and in the lower lung zones.
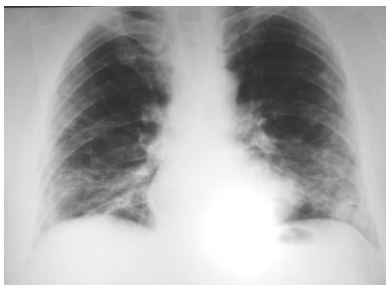
Fig. 4. Chest X ray (15.02.2011): resolution of radiologic changes.

Fig. 5. Chest X ray (22.03.2011): no active pleuro-pulmonary changes.

Fig. 6. Chest CT scan (23.03.2011): interstitial pneumopathy.

Table 2 Dynamics of laboratory results

DATE	22.03
Leucocyte /mm^3	17.930
Neutrophilic leukocyte %	75
ESR mm/1-2 hour	20/45
ALAT u/l	53
ASAT u/l	25
Alkaline phosphatase u/l	154
γGT u/l	59

RESULTS

Acute respiratory distress syndrome is a condition and not a disease, lung injury is a manifestation of a systemic pathology, complicated with multiple organic disfunctions (respiretory, hepatic, cerebral, kidney), till multiorgan failure, with high mortality. Although ARDS results from a variety of different causes (sepsis, trauma, aspiration, inhalation, drugs, etc.) the pathogenesis is the same with two phases. The results of direct effect on the alveolar epithelial cells appear in early phase, whereas indirect effects resulting

from systemic inflammatory process mediated by cytokines are observed in later phase.

In presented patient infectious causes that had generated ARDS were obvious, other causes were quickly eliminated after anamnesis, physical exam and laboratory tests. The character of infectious agent (virus, bacteria, rickettsia, mycoplasma, fungus, etc.) was more difficult to establish.

Clinical and radiological signs were non specific, but computed tomography of the chest demonstrated the heterogeneous nature of alveolar damage. The risks of transferring an oxygen dependent patient to the CT scanner have to be considered carefully.

Rapid acute distress, fever over 38^0C, nonspecific inflammatory syndrome (neutrophil leukocytosis, elevated ESR, positive C reactive protein) suggested a bacterial cause, but the epidemiologic context, clinical data and evolution of disease incriminated influenza A (H1N1) virus and treatment with tamiflu was started immediately. Subsequently the lab tests arrived and confirmed diagnosis.

Expression of multiple organ failure, different enzyme levels were elevated (ASAT, ALAT, alkaline phosphatase, gamma glutamyl transferase) and were corrected by therapy (values in table I).

High flow oxygen therapy (FiO_2) delivered via a tight-fitting face mask was enough, mechanical ventilation with positive end-expiratory pressure was not necessary, although atelectatic and partially flooded alveoli can be "recruited" to participate in gas exchange under certain ventilator regimes.

Fluid intake was restricted to diuresis plus 500-700 ml of liquids. It was demonstrated that a conservative fluid management strategy reduces ICU stay and pulmonary function and outcome are better in patients that had pulmonary wedge pressure lowered by diuretics or fluid restriction.

Distribution of lung infiltrates in acute respiratory distress syndrome is non-uniform. Repositioning into the prone position (face down) improved oxygenation by relieving atelectasis and improving perfusion. However, although the hypoxemia is overcome there seems to be no effect on overall survival. Prone position increases compliance and recruitment of atelectatic basal regions in addition to improving clearance of respiratory secretions.

Corticosteroids, primary in high-dose, and tapered slowly afterwards must be administered for long periods of time to prevent emergence of pulmonary fibrosis that involves such cases.

Nevertheless respiratory failure phenomena ceded slowly and the patient could be transferred in infectious diseases department only on the XIIIth day of treatment.

This critically ill patient with ARDS presented some peculiar aspects that differed from other subjects with influenza:
- the patient was afebrile during his illness, except the beginning;
- mialgia, ocular pain, that are characteristic for infection with influenza virus were completely absent;
- the patient had no risk factors associated with severe influenza infection, as obesity, his body mass index being 22,5 kg/m^2;
- leucopenia encountered in viral infections coexisted with neutrophil leukocytosis, elevated ESR, positive C reactive protein.

Although evolution was slow but favorable without installation of pulmonary fibrosis, with normal spirometry and diffusion capacity at three months after onset of illness.

CONCLUSIONS

- An etiological circumstance of acute respiratory distress in critically ill patient, besides those that are well known, is infection with influenza A (H1N1) virus.
- Multidisciplinary approach of this multifactorial pathologic process - ARDS, team activity (infectious disease doctor, lung disease specialist, inten-sive care specialist), in inten-sive care unit, promotes therapeutic success.
- Basic management includes good supportive care and treatment of the underlying cause.
- In this case, immediately, incisive treatment with high doses of corti-coids, high flow oxygenotherapy, together with other drugs impro-ved prognosis of this patient.

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