Influenza A non-H1N1 associated with acute respiratory failure and acute renal failure in a previously vaccinated cystic fibrosis patient

**ABSTRACT**

In the 2014 - 2015 season, most influenza infections were due to A (H3N2) viruses. More than two-thirds of circulating A (H3N2) viruses are antigenically and genetically different (drifted) from the A (H3N2) vaccine component of 2014 - 2015 northern and southern Hemisphere seasonal influenza vaccines. The purpose of this paper is to report a case of seasonal influenza A non-H1N1 infection that occurred in June 2015 in an adult cystic fibrosis patient with severe lung disease previously vaccinated with the anti-flu trivalent vaccine. The patient evolved to respiratory and renal failure (without rhabdomyolysis) and was placed under mechanical ventilation and hemodialysis. The clinical outcome was positive after 39 days of hospital stay. In addition, the patient was clinically stable after 18 months of follow-up. With the recent advances in critical care medicine and in cystic fibrosis treatment, survival with advanced pulmonary disease in cystic fibrosis presents new questions and potential problems, which are still being formulated.

**Keywords:** Cystic fibrosis; Influenza A virus; Respiratory insufficiency; Renal insufficiency; Case reports

**INTRODUCTION**

Influenza, commonly known as the flu, is an acute, contagious respiratory disease caused by influenza A or B viruses. It is estimated that 10% of the world population has at least one annual influenza episode. Patients with chronic disease, especially chronic lung disease, are more susceptible to serious complications caused by influenza. (1)

In December 2014, the Center for Disease Control and Prevention (CDC) reported that influenza activity in the northern hemisphere from November 2014 to early 2015 was mainly caused by the influenza A H3N2 virus. In addition, it was evidenced during this period that the effectiveness of the 2014 - 2015 vaccine for the northern hemisphere was very low, which was attributed to the fact that the circulating H3N2 virus was genetically different from the A H3N2 virus component of the vaccine, a fact attributed to a drift of the H3N2 virus after vaccine development. (2) A similar phenomenon occurred with the 2015 vaccine for the southern hemisphere, leading to the low effectiveness of vaccine protection. (3)

Recent evidence shows that, in cystic fibrosis (CF), respiratory viruses play an important role in this pathophysiological process, causing pulmonary exacerbations and leading to lung disease progression with increased bacterial...
adhesion. In particular, influenza virus is associated with more severe exacerbations, leading to prolonged hospitalizations, predisposing to bacterial infections and causing disease progression and marked loss in lung function.

This study aimed to report a case of seasonal influenza A non-H1N1 that occurred in June 2015 in a patient with CF who received the trivalent influenza vaccine in April 2015 and developed acute respiratory failure and acute renal failure without rhabdomyolysis after infection.

**CASE REPORT**

A male, 39-year-old Caucasian, diagnosed with CF since age 9 years old, homozygous for the F508del mutation, had exocrine pancreatic insufficiency, CF-related diabetes mellitus, obstructive azoospermia, chronic lung disease, bronchiectasis and chronic *Pseudomonas aeruginosa* infection. Prior spirometry, with severe airflow limitation and reduction of forced vital capacity, is presented in table 1.

| Table 1 - Spirometry and peripheral oxygen saturation before, immediately after and one year after the event |
| --- |
| August 2014 | August 2015 | August 2016 |
| VC (L) | 2.24 | 1.52 | 1.86 |
| VC (predicted %) | 54 | 37 | 45 |
| FVC (L) | 1.98 | 1.52 | 1.86 |
| FVC (predicted %) | 47 | 37 | 44 |
| FEV1 (L) | 1.17 | 0.75 | 1.01 |
| FEV1 (predicted %) | 33 | 21 | 28 |
| FEV1/FVC (%) | 61 | 55 | 55 |
| SpO2 in ambient air | 96 | 87 | 95 |

VC - vital capacity; FVC - forced vital capacity; FEV1 - forced expiratory volume in the first second; SpO2 - peripheral oxygen saturation. Post-bronchodilator results.

In June 2015, he was admitted to the emergency room of the Hospital de Clínicas de Porto Alegre, with continuous fever for 2 days (>38.5°C), severe cough, increased volume and purulence of expectoration, prostration, headache and progressive dyspnea. He denied myalgia. He reported that his wife, son and two other family members previously had respiratory symptoms, high fever and myalgias in the last week. He had regularly taken the flu vaccine and had received the trivalent vaccine in April 2015.

At the physical examination, the patient had a blood pressure of 70/45mmHg, a heart rate of 105bpm, a respiratory rate of 30rpm, was cyanotic with accessory breathing muscle and prolonged expiratory time and had a peripheral oxygen saturation (SpO2) of 57% in ambient air. Cardiac auscultation revealed a regular two-beat rhythm; lung auscultation indicated vesicular murmur present in both lung fields, with diffuse fine and coarse rales; the patient’s abdomen was without changes, and his extremities were well perfused.

Initial laboratory tests showed a 34% hematocrit, 10.2g/dL hemoglobin, 22,660 leukocytes/mm³, 2% band-shaped, 86% segmented, 6% monocytes, 5% monocytes, 1% metamyelocytes, 95mg/dL urea, 2.37mg/dL creatinine (prior it was 0.79mg/dL), 6.6mEq/L potassium, 3.2mmol/L lactate, 145mg/dL CRP and 189U/L creatine phosphokinase (normal up to 190U/L). Common urine test results revealed citrine yellow urine, 26 leukocytes/μL, 13 red blood cells/μL and negative hemoglobin. An arterial blood gas test revealed 5 L/min oxygen per external nasal catheter, with a pH of 7.21, a partial carbon dioxide pressure (PaCO2) of 56.1mmHg, 24.4mEq/L bicarbonate, a partial oxygen pressure (PaO2) of 68.4mmHg and an oxygen saturation of 97%. The patient’s chest X-ray is shown in figure 1.

He received volume replacement with saline, correcting the systemic arterial pressure. Antibiotic coverage with piperacillin/tazobactam and intravenous tobramycin was initiated based on the sensitivity test of the last bacteriological examination of the sputum. Still within the first 24 hours of admission, noninvasive

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ventilation (NIV) and antiviral coverage with oseltamivir were initiated. After 48 hours of hospitalization, he evolved with respiratory failure and was transferred to the intensive care unit (ICU), requiring orotracheal intubation and mechanical ventilation. Initially, the patient was ventilated with controlled pressure, an inspired oxygen fraction (FiO\textsubscript{2}) of 0.40, a positive end-expiratory pressure (PEEP) of 8 cm\textsubscript{H}2O, a pressure over PEEP of 14 cm\textsubscript{H}2O, a respiratory rate of 18 breaths/minute, a tidal volume and a PaO\textsubscript{2}/FiO\textsubscript{2} of 198 mmHg, fulfilling the criteria for acute respiratory distress syndrome.(6)

There was also worsening renal function with an increase of creatinine to 5.87 mg/dL and oliguria. Dialysis treatment was initiated with continuous hemodialysis. The antibiotic scheme was modified to ciprofloxacin and vancomycin, maintaining piperacillin/tazobactam.

On the fifth day of hospitalization, a viral investigation was performed via polymerase chain reaction from a nasopharyngeal secretion sample, collected at the time of admission. The test was positive for influenza A non-H1N1 (an investigation of a universal gene of influenza A strains was positive, but the swine lines by gene amplification of H1 hemagglutinin and virus nucleoprotein were negative). The use of oseltamivir was maintained for 5 days.

There was favorable evolution and, 7 days after hospital admission, the patient could be extubated and was placed on NIV again. He was then on intermittent dialysis and was discharged from the ICU. In the ward, 1 week after discharge from the ICU, he experienced sudden worsening and was returned to the ICU but was managed with NIV, with a 2-day stay. Angiotomography of the thorax excluded the possibility of pulmonary embolism. The antibiotic scheme was modified to meropenem and polymyxin B (a new sputum culture evidenced multi-resistant \textit{P. aeruginosa}). He experienced progressive clinical improvement of his respiratory condition and resolution of acute renal failure. Hospital discharge occurred 39 days after admission.

On discharge, he received standard treatment for CF and continuous home oxygen therapy and was referred to a pulmonary rehabilitation program. Since the event, he has not required a new hospital stay. The patient’s last spirometry is presented in table 1. In December 2016 (18 months after the event), the patient was in pulmonary rehabilitation with oxygen therapy for exercise and at night, and he had been referred for lung transplantation (but not yet active on the list due to clinical stability).

### DISCUSSION

With recent advances in CF treatment and intensive medicine, patients with advanced lung disease are living longer.(7) The present case report shows the evolution of an adult patient with previous severe lung disease, but stable, with acute respiratory failure, sepsis and acute renal failure, triggered by influenza, with a good clinical outcome after intensive support and documentation of clinical stability after 18 months of evolution.

Epidemiological data on influenza 2014 - 2015 show that the vaccine was effective in preventing 19% of influenza visits in all age groups; specifically, 18% for influenza A H3N2 and 45% for influenza B. Despite the low effectiveness of the influenza vaccine, influenza vaccination is recommended for all individuals aged ≥ 6 months.(2)

Antiviral medications, especially oseltamivir, are used as adjunctive measures to vaccination in the control of influenza.(10) The physician should consider that influenza activity is widespread; this diagnosis should always be considered in all cases of severe acute respiratory syndrome.(8-10) In the present case, the identification of the influenza A virus was made via molecular biology testing of the nasopharynx aspirate, emphasizing that our laboratory identified the presence of influenza A, excluding the presence of influenza virus H1N1. However, subtyping of the H3N2 virus was not performed. According to epidemiological data from the Department of Health of Rio Grande do Sul(14) and the Ministry of Health of Brazil,(12) the virus with the largest circulation in 2015 was influenza A H2N3. Thus, the viral identification of the reported case most likely corresponds to influenza A H3N2, which explains the disease despite adequate patient vaccination coverage.

Evidence for treating severe influenza is limited; therefore, recommendations on route of administration, dosage and time of use follow the general guidelines. The administration of oseltamivir via the nasogastric or nasoenteric route seems to guarantee adequate systemic absorption in the majority of cases of severe influenza. The standard oseltamivir regimen at a dose of 75 mg every 12 hours is recommended. However, although there is no definitive evidence, there are recommendations, in which, depending on clinical judgment, treatment time may be prolonged in severe cases and doses may also be doubled (150 mg every 12 hours). In the present case, the treatment was initiated early orally at admission and was subsequently maintained by nasoenteric route, but at usual doses and time.\(^{(8)}\)
Renal involvement in individuals infected with influenza A is uncommon. Acute renal failure has been most commonly reported in critically ill patients with H1N1. Reports of renal failure in cases of influenza A non-H1N1 are rare. The pathogenic mechanisms for the development of renal injury in influenza A virus infection are not fully understood. Potential causes are rhabdomyolysis, direct renal damage by virus, sepsis-related renal hypoperfusion and disseminated intravascular coagulation syndrome. Among them, rhabdomyolysis has been the most frequently reported cause. In the reported case, there was no evidence of rhabdomyolysis (absence of myalgias, urine was not dark, there was no hematuria on the reactant tape and creatine phosphokinase was normal). The most likely mechanism for renal injury was sepsis and renal hypoperfusion.

CONCLUSION

After 18 months of follow-up, the evolution of the presented case of cystic fibrosis with advanced lung disease, complicated by infection by influenza A non-H1N1 with respiratory sepsis, acute respiratory failure and acute renal failure was favorable.

RESUMO

No período sazonal compreendido entre 2014 e 2015, a maior parte das infecções por influenza decorreu do vírus influenza A H3N2. Mais de dois terços dos vírus influenza A H3N2 circulantes eram antígenica e geneticamente diferentes (drift) do componente A H3N2 da vacina da influenza sazonal 2014 - 2015 para os hemisférios norte e sul. O objetivo deste trabalho foi relatar um caso de infecção por influenza A sazonal não H1N1 ocorrido em junho de 2015 em um paciente adulto com fibrose cística com doença pulmonar grave, previamente vacinado com a vacina antigripal trivalente. O paciente evoluiu com insuficiências respiratória e renal (sem rhabdomiólise), sendo submetido à ventilação mecânica e à hemodiálise. A evolução clínica foi positiva após 39 dias de permanência hospitalar. Ainda, o paciente permaneceu clinicamente estável após seguimento de 18 meses. Com os avanços recentes na medicina intensiva e no tratamento, a sobrevivência com uma doença pulmonar avançada na fibrose cística apresenta novas questões e problemas potenciais, que ainda estão sendo formulados.

Descritores: Fibrose cística; Virus da influenza A; Insuficiência respiratória; Insuficiência renal; Relatos de casos

REFERENCES

1. World Health Organization. Influenza virus infections in humans (February 2014). Note [Internet]. 2014;February. Available from: http://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/influenza_virus_infections_humans_feb14.pdf?ua=1
2. Flannery B, Clippard J, Zimmerman RK, Nowalk MP, Jackson ML, Jackson LA, Monto AS, Petrie JG, McLean HQ, Belongia EA, Gaglani M, Berman L, Font J, Sessions W, Tkaker SN, Spencer S, Fry AM; Centers for Disease Control and Prevention. Early estimates of seasonal influenza vaccine effectiveness - United States, January 2015. MMWR Morb Mortal Wkly Rep. 2015;64(1):10-5.
3. São Paulo (Estado). Secretaria de Estado da Saúde. Coordenadoria de Controle de Doenças. Centro de Vigilância Epidemiológica “Prof. Alexandre Vranjac”. Divisão de Imunização. Informe Técnico. 17a Campanha Nacional de Vacinação CONTRA a influenza A H3N2. 2015:1-16 [Internet]. (cited 2018 Feb 4). Available from: http://ftp.cve.saude.sp.gov.br/doc_tec/clin/IMUNI2015_INFORME_CAMPAHIA.pdf
4. Wat D, Gelder C, Hibbitts S, Cafferty F, Bowler I, Pierrepont M, et al. The role of respiratory viruses in cystic fibrosis. J Cyst Fibros. 2008;7(4):320-8.
5. Orna JSR, Neaul KM, Victor JC, Wold A, Attken ML, Goss CH. Influenza-associated cystic fibrosis pulmonary exacerbations. Chest. 2010;137(4):852-60.
6. Weinberger SE, Crockhl BA, Mandel J. Acute respiratory distress syndrome. In: Weinberger SE, Crockhl BA, Mandel J. Principles of Pulmonary Medicine. 6th ed. Philadelphia: Saunders; 2014. p. 351-63.
7. Hodson ME, Simmonds NJ, Warwick JW, Tullis E, Castellani C, Assael B, Dodge JA, Corey M. International Study of Aging in Cystic Fibrosis. An international/multicentre report on patients with cystic fibrosis (CF) over the age of 40 years. J Cyst Fibros. 2008;7(6):537-42.
8. Fiore AE, Fry A, Shay D, Gubareva L, Breev JS, Ysikyl TM; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza-recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(1):1-24.
9. Nardocci P, Guille C, Lobo SM. Severe virus influenza A H1N1 related pneumonia and community-acquired pneumonia: differences in the evolution. Rev Bras Ter Intensiva. 2013;25(2):123-9.
10. Duarte PA, Venazzi A, Youssif NC, Oliveira RC, Tannus LA, Duarte CB, et al. Outcome of influenza A (H1N1) patients admitted to intensive care units in the Paraná state, Brazil. Rev Bras Ter Intensiva. 2009;21(3):231-6.
11. Governo do Estado. Rio Grande do Sul. Boletim semanal de Vigilância da Influenza/RS - 2015. Casos de SRAG notificados segundo encerramento. SRAG - Classificação final SRAG por Influenza por outros vírus respiratórios SRAG por outros agentes etiológicos SRAG não especificada SRAG em ines [Internet]. Porto Alegre; 2015. (cited 2018 Feb 4). Disponível em: http://www.saude.rs.gov.br/upload/arquivos/201702/15134502-1474054884-boletim-semanal-vigilancia-da-influenza-se52-2015.pdf
12. Secretaria de Vigilância em Saúde. Influenza: Monitoramento até a Semana Epidemiológica 52 de 2015. Bol Epidemiológico [Internet]. 2016;47:1-10. (cited 2018 Feb 4). Disponível em: http://portalsaude.saude.gov.br/images/pdf/2016/marco/04/Boletim-Epidemiolo--gico-Influenza-SE52-2015-completo.pdf
13. Seivignani G, Sgares MF, Marques GL, Freitas AK, Gentili A, Chula DC, et al. Acute kidney injury in patients infected by H1N1: clinical histological correlation in a series of cases. J Bras Nefrol. 2013;35(3):185-90.
14. Watanabe T, Yoshikawa H, Abe Y, Yamazaki S, Uehara Y, Abe T. Renal involvement in children with influenza A virus infection. Pediatr Nephrol. 2003;18(6):541-4.