Received: 2017.09.12
Accepted: 2017.11.06
Published: 2018.03.30

Fatal Acute Respiratory Distress Syndrome Due to Influenza A (H1N1) Infection in Patients After Kidney Transplantation: A Report of Five Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE 1 Paweł Zatorski
ABE 2 Agata Adamczyk
EF 3 Maciej Kosieradzki
EF 4 Teresa Baczkowska
CF 1 Dariusz Kosson
ADE 2 Janusz Trzebicki

1 Department of Teaching Anesthesiology and Intensive Therapy, Medical University of Warsaw, Warsaw, Poland
2 First Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Warsaw, Poland
3 Department of General and Transplantation Surgery, Medical University of Warsaw, Warsaw, Poland
4 Department of Transplantation Medicine, Nephrology, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Agata Adamczyk, e-mail: agata.adamczyk@wum.edu.pl
Source of support: Departmental sources

Background: In the general population, swine influenza is a self-limited infection. Patients after kidney transplantation, however, are at increased risk for complications and mortality from influenza A (H1N1). Acute respiratory distress syndrome (ARDS) complicates up to 55% of influenza-related pneumonia in hospitalized patients and carries a mortality of 40–46%. We describe our experience in intensive care of kidney transplant patients with ARDS complicating influenza A (H1N1) pneumonia during a flu outbreak.

Case Report: Five adult post kidney transplantation patients with progressive respiratory failure admitted to the ICU between February 2016 and April 2016 were included in this retrospectively analysis. All patients had influenza A (H1N1) viral pneumonia (confirmed with RT-PCR) complicated by ARDS and septic shock with multiple organ dysfunction syndrome. None of the patients received seasonal influenza vaccines. All patients had negative rapid influenza bedside tests, which resulted in delay of administration of antiviral therapy prior to admission to the ICU. All patients were managed with a lung protective ventilation strategy (average days of mechanical ventilation, 17.6 ± 15.3). Three patients required additional therapies for refractory hypoxemia, including high positive end-expiratory pressure and prone positioning. Extracorporeal membrane oxygenation was not implemented. Treatment with oseltamivir was added to a broad-spectrum antibiotic on the first to the fifth day of intensive care. Despite these measures, all patients eventually died.

Conclusions: Despite great progress in the management of ARDS, based mostly on advanced mechanical ventilation, early antiviral treatment of pneumonia caused by influenza A (H1N1) and annual vaccinations seem essential in prevention and management of influenza A (H1N1) infection among kidney transplant recipients.

MeSH Keywords: Influenza A Virus, H1N1 Subtype • Kidney Transplantation • Respiratory Distress Syndrome, Adult • Sepsis • Vaccination

Full-text PDF: <https://www.annalsoftransplantation.com/abstract/index/idArt/907083>

1912 1 — 16

Background

Influenza is an acute, usually self-limiting, febrile disease caused by infection with influenza A or B virus that occurs in seasonal outbreaks. Its clinical spectrum ranges from asymptomatic to life-threatening illness. Swine influenza A (H1N1) infection was the first pandemic of the 21st century which began in Mexico at the beginning of 2009 and has spread rapidly throughout the world [1]. Many patients with respiratory failure and severe pandemic influenza A (H1N1) pneumonia were young, obese, and diabetic, with preexisting lung disease as significant comorbidities. A number of pregnant women were also affected by this condition. The protective effect of older age has been attributed to preexisting cross reactive antibodies in older people from prior exposure to similar viral strains [2]. Risk factors for increased mortality included immunocompromised patients and recipients of solid-organ transplants (SOT), who were prone to severe pneumonia from influenza A (H1N1) viral infection [1]. However, data on the outcomes from the 2009 pandemic in recipients of SOT, including patients after kidney transplantation, are very limited. In general, 57% to 70% of SOT recipients with influenza were hospitalized, with 13–20% ICU admission rate [1,3]. In a multicenter cohort study of adult and pediatric transplant recipients with confirmation of influenza A infection, 10 out of 21 ventilated patients had passed away [1]. Similarly, in the retrospective analysis of pandemic influenza infection in a group of SOT recipients in Argentina, six out of nine ventilated patients in ICU had died. All deaths were directly attributed to flu infection [4].

ARDS can be diagnosed, provided cardiogenic pulmonary edema or alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates are excluded [5]. The Berlin definition of ARDS requires all of the following: respiratory symptoms beginning within one week from a clinical insult, bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or computed tomography, and respiratory failure could not be fully explained by cardiac failure or fluid overload [5,6]. Severity of hypoxemia defines the extent of ARDS by the ratio of arterial oxygen tension to a fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$). Severe ARDS means $\text{PaO}_2/\text{FiO}_2 \leq 100$ at positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O . Clinically, the acute phase of ARDS is characterized by cyanosis, hypoxemia, pulmonary edema, and marked respiratory failure over time, resulting in multiorgan failure and high mortality rates (up to 60%). In addition to influenza A virus, numerous disorders can cause ARDS: sepsis, pneumonia, trauma, and aspiration of gastric content [7].

Little is known about severe influenza A (H1N1) infection in immunocompromised patients, including transplant recipients. We report series of five cases with influenza A (H1N1) associated ARDS in patients after kidney transplantation.

Case Report

Five adult patients who were post-renal transplantation with progressive respiratory failure were admitted to the ICU between February 2016 and April 2016. Their age range was 59–65 years; two were women.

Three patients underwent cadaveric kidney transplantation more than 12 months prior to admission to the ICU (6, 12, and 17 years prior to admission); the remaining two patients were in an early post-transplantation period (20 days, 22 days). Median time from transplantation was 84 months.

Kidney transplantations had been performed for end stage renal disease (ESRD) resulting from: pyelonephritis, diabetic and hypertensive nephropathy, autosomal dominant polycystic kidney disease (ADPKD), and chronic glomerulonephritis. At the time of diagnosis, three patients were on triple drug immune suppression, and two patients received double therapy. All the patients had numerous medical conditions. Patient comorbidities are summarized in Table 1.

Most patients presented with fever, dry cough, dyspnea, and malaise. Symptom onset preceded hospitalization by five to 14 days. None of the patients had ever received an annual influenza vaccine. Prior to admission to the ICU, negative results of rapid influenza diagnostic tests were obtained (NADAL® Influenza A+B, Nal von Minden GmbH, Germany). On admission to the ICU, all patients were in septic shock requiring vasopressor support with APACHE II score ranging from 20 to 34 points, SOFA score ranging from 5 to 13, SAPS II score ranging from 49 to 70, and all GCS scores were 15. All patients initially received empiric broad-spectrum antimicrobial therapy for suspected bacterial infection, and bronchoscopy with bronchoalveolar lavage (BAL) was performed. Treatment with oseltamivir (75 mg twice a day) was initiated one to five days post ICU admission, before the results of RT-PCR were available. Oseltamivir resistance in influenza A (H1N1) virus was not tested. Immunosuppressive agents were stopped on the first day in the ICU, however all patients received systemic corticosteroids. Pneumonia was diagnosed based on respiratory symptoms and bilateral infiltrates seen on chest radiographs/CT scans. The diagnosis of influenza A (H1N1) viral infection was made based on a positive result of RT-PCR from specimens collected from the BAL. All patients had initial false-negative rapid antigen tests from nasopharyngeal swabs. Cytomegalovirus polymerase chain reaction (CMV PCR) was negative. All patients required tracheal intubation and mechanical ventilation for acute hypoxemic respiratory failure. Mechanical ventilation was managed according to the protective ventilation strategy, with low tidal volume ventilation (6 mL/kg IBW) and end-inspiratory airway pressure lower than or equal to 30 cm H_2O , very high PEEP, recruitment maneuvers,

Table 1. Characteristics of the patients.

Patient	A	B	C	D	E
Age (years)	63	60	65	59	61
Sex	Female	Male	Male	Male	Female
BMI (kg/m ²)	25.3	23.1	24.7	25.9	27.6
Time since KTx	6 years	12 years	22 days	17 years	20 days
Other comorbidities	COPD, HTN, DM, recurrent UTI, nephrolithiasis, S/P left nephrectomy, secondary anemia, cholelithiasis, H/O monoclonal gammopathy, smoking	DM, CAD, HTN, S/P MI, hyperuricemia, hyperlipidemia, bilateral blindness due to diabetic retinopathy	HTN, S/P MI, CAD, COPD, polycystic liver, hiatal hernia, BPH, carotid arteries' stenosis, H/O colon polyps, GERD	CAD, S/P MI, HTN, H/O pericarditis with pericardial effusion, H/O pancreatitis, S/P bilateral nephrectomy, hyperlipidemia, smoking	HTN
Initial influenza symptoms	Dry cough, fever, dyspnoea	Progressive respiratory failure	Clinical symptoms of pneumonia	Fever, cough, malaise, oliguria, tachypnoe	Fever, dry cough few days before admission
Length of hospital stay before ICU admission (days)	15	22	22	3	3
Immunosuppression before flu symptoms	Methylprednisolone, everolimus, mycophenolate mofetil	Mycophenolate mofetil, cyclosporin A	Methylprednisolone, cyclosporin A	Methylprednisolone, mycophenolate mofetil, tacrolimus	Prednisone, tacrolimus, everolimus, thymoglobulin
In the ICU:					
PaO ₂ /FIO ₂	116	150	74	114	98
SOFA score on admission/maximal/mean	13/17/15.2	8/15/11.5	8/17/14.4	5/15/11.3	12/19/11.8
APACHE II	31	28	28	20	34
SAPS II on admission	64	70	65	49	56
Length of ICU stay/mechanical ventilation/muscle paralysis (days)	10/10/0	12/12/1	10/10/4	11/11/0	47/45/0
Need for vasopressors (days)	10	12	7	9	45
CRRT (days)	9	12	7	5	45
Use of prone position	Yes	No	Yes	Yes	No
Day of oseltamivir initiation (dose: 75 mg bid)	1	1	5	3	1
CRP initial/final (mg/L)	84/333.6	119.6/83.8	248.3/122.1	135.6/401	96.9/141.5
PCT initial/final (ng/mL)	0.3/1.5	2.6/14.0	4.3/10.6	0.4/2.9	0.2/1.2

Table 1 continued. Characteristics of the patients.

Patient	A	B	C	D	E
Radiological changes	ARDS-type lesions on CXR	Ground-glass opacity	Interstitial middle and lower lobe consolidations on CXR, left sided pleural effusion	Interstitial middle and lower lobe consolidations on CXR	Diffuse interstitial consolidations, ground-glass opacity in CT
Antibiotics used	Vancomycin, TMP/SMX	Meropenem, Vancomycin	TMP/SMX, Imipenem, Levofloxacin	Imipenem, Clarithromycin, Vancomycin	Colistin, Meropenem, TMP/SMX, Fluconazole, Clarithromycin, Vancomycin, Levofloxacin, Ceftriaxone
Coinfection	<i>E. faecium</i> in urine cultures	None	None	<i>S. epidermidis</i> in blood cultures	<i>P. aeruginosa</i> in BAL and urine cultures

APACHE II – Acute Physiology and Chronic Health Evaluation II; ARDS – acute respiratory distress syndrome; BAL – bronchoalveolar lavage; BMI – body mass index; BPH – benign prostatic hyperplasia; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; CRP – C reactive protein; CRRT – continuous renal replacement therapy; CT – computed tomography; CXR – chest X-ray; DM – diabetes mellitus; GERD – gastroesophageal reflux disease; HTN – hypertension; KTx – kidney transplantation; MI – myocardial infarction; PaO₂/FiO₂ – ratio of arterial oxygen tension to a fraction of inspired oxygen; PCT – procalcitonin; SAPS II – Simplified Acute Physiology Score II; SOFA – Sequential Organ Failure Assessment; TMP/SMX – trimethoprim-sulfamethoxazole.

neuromuscular blocking agents (in two cases), and prone positioning (in three cases). Mean PaO₂/FiO₂ on the day of ICU admission was 110.4±27.7. Two patients had severe ARDS and three patients had moderate ARDS on the first day in the ICU. All patients were consulted with the reference center for extracorporeal membrane oxygenation (ECMO), but because of immunosuppression and critical condition needs, they were disqualified from this form of rescue therapy. Of all five ARDS cases, bacterial cultures within the first 24 hours following ICU admission was positive in three patients. Of these, gram-positive pathogens prevailed in one patient (in blood cultures), and gram-negative pathogens in the remaining two patients (in BAL and in urine cultures). From the first to the second day all five patients received continuous renal replacement therapy (CRRT) – continuous veno-venous hemodialysis – due to kidney graft dysfunction with creatinine level at average of 2.6±2.3 mg/dL. ICU stays ranged from 10 to 47 days. ARDS progressed and the patients developed multiple organ dysfunction syndrome. All of the patients died after an average of 18.0±16.2 days of treatment in the ICU.

Discussion

Fulminant progression of viral pneumonia culminating in ARDS proves that the immunosuppression represents an enormous risk factor for serious pulmonary complications of infection with the influenza A (H1N1) virus. In the general population,

ARDS complicates up to 55% of influenza pneumonia in hospitalized patients and carries a mortality of 40–46% [8]. In the population of SOT recipients with 2009 viral influenza A (H1N1) pandemic pneumonia, mortality in ICUs was reported to be 47% to 66% [1,4]. Over a three-month period in 2016, our ICU managed five patients after renal transplantation with severe influenza A (H1N1) infection complicated by ARDS, with five fatal outcomes. Several factors could have contributed to such high mortality in the case series presented.

Initial critical conditions described by mean SOFA scores (8.6±3.2), APACHE II scores (26.2±5.2), and SAPS II scores (60.8±8.2) probably added to the high mortality seen in these patients. Moreover, all patients were in septic shock with graft dysfunction requiring CRRT. Previous studies showed that in a mechanically ventilated general population of patients with influenza A (H1N1) infection, that high APACHE II scores, low PaO₂/FiO₂, use of inotropes, requirement of renal replacement therapy, and need for prone positioning were independent predictors of hospital mortality [9]. Additionally, acute kidney injury was a common complication of severe 2009 influenza A (H1N1) infection in patients admitted to ICUs. Influenza A (H1N1) infection was reported in up to one third of patients, and was associated with increased mortality [10]. Similarly, Smud et al. found a significant association with allograft dysfunction in severe cases admitted to the ICU compared to those with the mildest course of infection [4]. Other significant predictors of unfavorable outcomes in SOT recipients with influenza

A (H1N1) infection were septic shock at presentation, pneumonia and secondary/concomitant pulmonary infection, and diabetes mellitus [3]. In our case series, two of five patients suffered from diabetes, but all had many others concomitant conditions (see Table 1). Additionally, one patient suffered from bacterial pneumonia (*P. aeruginosa* as identified from collected BAL). It has also been reported that influenza appears to be most dangerous in the early post-transplant period (<three months) [3]. In our case series, two patients were admitted to the ICU at 20 and 22 days after renal transplantation. Both had severe ARDS with $\text{PaO}_2/\text{FiO}_2 < 100$ and APACHE II scores of 34 and 28, respectively. Although there is no clear evidence, some authors suggest that the influenza A (H1N1) viral infection in renal transplant recipients might have a more severe presentation than in the general population [11].

Another factor explaining high mortality in our case series was a delay in antiviral therapy. Previous studies have shown that starting antiviral treatment within 48 hours of symptom onset was associated with a decrease in admission to the hospital and ICU, reduced need for mechanical ventilation, and lower death rate [1]. Indeed, prior to ICU admission, our patients were hospitalized three to 22 days in other units, where diagnostics were initiated. All patients had negative rapid influenza bedside test results, which was a reason for the delay in administering antiviral therapy. Lai et al. (2010) has reported suboptimal sensitivity of rapid antigen testing for influenza [12]. Hence, clinicians should be aware of the possibility of false-negative results of rapid influenza diagnostic tests (particularly enzyme immunoassay). Early antiviral therapy is associated with better outcomes, and is the only modifiable prognostic factor [3]. Although sporadic, resistance of the virus to oseltamivir could also be a cause of fatal outcomes. First isolated cases of oseltamivir resistance were reported in a renal transplant recipient with a rapid-onset severe primary viral influenza A (H1N1) pneumonia [13]. Similarly, rapid selection of resistance during oseltamivir therapy (9–14 days) were described in immunocompromised patients during the 2009 influenza A (H1N1) virus pandemic [14]. We did not test for virus susceptibility in our patients.

References:

1. Kumar D, Michaels MG, Morris MI et al: Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: A multicentre cohort study. *Lancet Infect Dis*, 2010; 10: 521–26
2. Jaber S, Conseil M, Coisel Y et al: ARDS and influenza A (H1N1): Patients' characteristics and management in intensive care unit. A literature review. *Ann Fr Anesth Reanim*, 2010; 29: 117–25
3. López-Medrano F, Cordero E, Gavalda J et al: Executive summary. Management of influenza infection in solid-organ transplant recipients: Consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin*, 2013; 31: 528–34
4. Smud A, Nagel CB, Madsen E et al: Pandemic influenza A/H1N1 virus infection in solid organ transplant recipients: A multicenter study. *Transplantation*, 2010; 90: 1458–62
5. Ferguson ND, Fan E, Camporota L et al: The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med*, 2012; 38: 1573–82
6. Ranieri V, Rubenfeld GD, Thompson B et al: Acute respiratory distress syndrome: The Berlin Definition. *JAMA*, 2012; 307: 2526–33
7. Short KR, Kroeze EJ, Fouchier RA, Kuiken T: Pathogenesis of influenza-induced acute respiratory distress syndrome. *Lancet Infect Dis*, 2014; 14: 57–69

Importantly, none of the patients had received influenza vaccines. Neither those patients who had been transplant candidates for a short time, nor those who were many years post renal transplantation, had received influenza vaccinations. Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients from 2009 recommended that all potential candidates for solid organ transplantation and SOT recipients should receive inactivated influenza vaccine annually [15]. Given the high rate of complications of influenza infection, especially in the early post-transplant period, administration of the influenza vaccine may be considered after the first month of the transplantation [3,15]. In a multicenter study carried out in SOT recipients with confirmed influenza infection, 53% had received one dose of the 2010–2011 trivalent seasonal influenza vaccine. Although influenza vaccination did not preclude symptomatic influenza, it reduced the risk of pneumonia by 70% [16]. Our experience strongly supports systematic vaccination of wait-listed renal transplant candidates and renal transplant recipients.

The present study had some limitations. We described a relatively small sample size in one tertiary care hospital and in one seasonal flu outbreaks. Thus, our findings may have limited generalizability and require replication in multicenter prospective studies.

Conclusions

It is essential to consider influenza in the differential diagnosis of pneumonia during the influenza season in renal transplant recipients. Prevention of infection by immunization, combined with early identification (using RT-PCR) and prompt antiviral treatment might be critical in determining mortality rates.

Conflict of interest

None.

8. Van Ierssel SH, Leven M, Jorens PG: Severe influenza A(H1N1)2009 infection: A single centre experience and review of the literature. *Acta Clin Belg*, 2011; 67: 1–6
9. Estenssoro E, Ríos FG, Apezteguía C et al: Pandemic 2009 influenza A in Argentina: A study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med*, 2010; 182: 41–48
10. Martin-Loeches I, Papiol E, Rodríguez A et al: Acute kidney injury in critical ill patients affected by influenza A (H1N1) virus infection. *Crit Care*, 2011; 15: R66
11. Joob B, Wiwanitkit V: Novel H1N1 influenza infection among post-renal transplantation subjects: A mini review. *Saudi J Kidney Dis Transpl*, 2015; 26: 1006–8
12. Lai AR, Keet K, Yong CM, Diaz JV: Severe H1N1-Associated acute respiratory distress syndrome: A Case Series. *Am J Med*, 2010; 123: 282–85
13. Shetty AK, Ross GA, Pranikoff T et al: Oseltamivir-resistant 2009 H1N1 influenza pneumonia during therapy in a renal transplant recipient. *Pediatr Transplant*, 2012; 16: 153–57
14. Memoli MJ, Hrabal RJ, Hassantoufighi A et al: Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. *Clin Infect Dis*, 2010; 50: 1252–55
15. Danzinger-Isakov L, Kumar D: Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant*, 2009; 9(Suppl. 4): S258–62
16. Perez-Romero P, Aydillo TA, Perez-Ordoñez A et al: Reduced incidence of pneumonia in influenza-vaccinated solid organ transplant recipients with influenza disease. *Clin Microbiol Infect*, 2012; 18: E533–40