Assessment of antiviral and antibiotic combination treatment in influenza-A H1N1 induced acute kidney injury among hospitalized patients

Azfar Athar Ishaqui[1,2]*, Amer Hayat Khan[1]*, Syed Azhar Syed Sulaiman[1], Mohammed Taher Alsultan[2], Irfanullah Khan[1] and Hamad Al Nami[2]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains, Malaysia
[2]King Abdulaziz Hospital, National Guard Health Authority, Alahsa, Saudi Arabia

Abstract: The aim of the study is to assess and compare the impact of antiviral drug alone and in combination with antibiotic for prevention of Influenza-A H1N1 induced acute kidney injury (AKI) in hospitalized patients. Hospitalized admitted patients with confirmed diagnosis of Influenza-A H1N1 infection were divided into two groups: group 1, which received antiviral (oseltamivir) drug alone and group 2, which received antiviral (oseltamivir) in combination with empirically prescribed antibiotic. Patients of both groups were assessed for incidences of AKI by two criteria i.e Acute Kidney Injury Network (AKIN) and RIFLE. A total of 329 patients (176 for group 1 and 153 for group 2) were enrolled. According to RIFLE criteria, 23(13%) of group 1 and 9(6%) patients of groups 2 were suffered from AKI with statistically significant difference ($P<0.05$). Also as per AKIN criteria, the incidence of AKI is statistically significantly difference ($P<0.05$) between both groups with 18(10%) patients and 6(4%) patients of group 1 and 2 respectively. Length of hospitalization was statistically less ($P<0.05$) in group 2 patients. The incidences of AKI in Influenza-A H1N1 treated with antiviral and antibiotic combination was statistically less as compared to patients who were given antiviral alone for treatment of influenza infection.

Keywords: Influenza A, H1N1 infection, acute kidney injury, AKIN, RIFLE.

INTRODUCTION

Acute kidney injury (AKI) commonly referred to as acute renal failure, is characterized by abrupt reduction in renal excretion function of kidneys (Bellomo, Ronco *et al*., 2004, Nissenson, 1998). The reduction in glomerular filtration rate (GFR) is used worldwide as an indicator of measuring kidney function. Measurement of GFR usually depends on the estimation of creatinine (Heemann, Abramowicz *et al*., 2011). AKI is also characterized by accumulation of different metabolic products such as nitrogen and urea. Decreases in urine output along with increased electrolytes are the clinical manifestations which are also associated/ kindred with AKI (Bellomo, Kellum *et al*., 2012).

In 2004, a consensus definition of AKI was proposed by Acute Dialysis Quality Initiative (ADQI) prominently known as RIFLE criteria. The RIFLE criteria defines AKI based on changes in prominent parameters of serum creatinine and urine output, which usually classified AKI into Risk, Injury, Failure, Loss and End stage Renal disease (Hoste, Clermont *et al*., 2006, Mehta, Kellum *et al*., 2007). AKIN introduces the criteria of increase in serum creatinine level of >0.3mg/dl to classify for AKI stage 1. Moreover, changes in serum creatinine value was no more to be referred to baseline value as defined in RIFLE criteria, instead changes in serum creatinine are need to be determined within a time span of 48 hours (Joannidis, Metnitz *et al*., 2009). The patients regardless of creatinine level and urine output classified to having stage 3 AKI, if they need to be put on renal replacement therapy (RRT) (Ostermann, Chang *et al*., 2005, Ricci, Cruz *et al*., 2011).

AKI was also found to be associated with severe hemodynamic instability in many severe infections. AKI has been reported to have been associated with Influenza-A H1N1 with studies stated up to 60% of severe infected patients (Abdulkader, Ho *et al*., 2010, Bagshaw, Sood *et al*., 2013, Martin-Loeches, Papiol *et al*., 2011). The two risk factors that are mainly found to be associated with AKI during Influenza-A H1N1 infection were obesity and diabetes (Keddis, 2015). Rhabdomyolysis has also been reported to be one of the cause of development of AKI in Influenza-A H1N1 infected patients (Unverdi, Akay *et al*., 2011). Development of chronic kidney disease along with increased mortality in influenza-A H1N1 associated AKI (Wald, Quinn *et al*., 2009).

Oseltamivir, an antiviral drug from class neuraminidase inhibitors has been found to be very effective in preventing and treating influenza infection (Low, 2008). Moreover, oseltamivir has been found effective in reducing various complications associated with influenza infection. Aside from antiviral drug, different antibiotic are also prescribed empirically in severe influenza infected patients for prevention of secondary bacterial

*Corresponding author: e-mail: dramer@usm.my

infections associated with influenza infection particularly Influenza-A H1N1 infection patients (Whitley, Hayden *et al*., 2001). The current study is focused on the impact of combination therapy of antiviral drug (oseltamivir) with antibiotics on AKI in influenza-A H1N1 infected hospitalized patients.

MATERIALS AND METHODS

Study settings

The current study was conducted in two campuses of a state-owned military hospital i.e., King Abdul Aziz Medical City, Riyadh and King Abdul Aziz Hospital, Alahsa. Both of them are tertiary care hospitals with combined bed facility of around 1800 beds. The hospital used to provide healthcare facilities mainly to the military personnel and employees of hospital. The study is approved by institutional review board of King Abdullah International Medical Research Center (KAIMRC), King Abdulaziz Hospital, Alahsa, Saudi Arabia.

Study design

This retrospective study was conducted to assess the impact of combination therapy of antiviral drug and antibiotics medication on Influenza-A H1N1 infection associated AKI. In current study, all the hospitalized patients with confirm diagnosis of Influenza-A H1N1 infection during the study period of three year (2016-2018) were studied. The patients were divided into two groups based on the drug treatment. First group includes those patients who were treated with antiviral drug i.e oseltamivir alone in starting 96 hours after the confirmed diagnosis of Influenza A-H1N1. The second group includes those patients who were initiated on antiviral drug oseltamivir together in combination with empirically prescribed antibiotic for prevention of co-secondary bacterial pneumonia infection which is considered as one of the major complication associated with Influenza A-H1N1 patients especially in patients who were unvaccinated for pneumococcal and influenza vaccine. The decision of initiating antibiotic was taken by infectious disease consultant based on clinical experience of suspecting any secondary bacterial infection based on clinical and radiological examination of patient.

Incidence of AKI in both treatment groups is assessed by using two criteria i.e. RIFLE and AKIN based on the elevation in serum creatinine or GFR. According to RIFLE criteria, incidence and severity of AKI is divided into three classes i.e. Risk, Injury and Failure. "Class Risk" is defined as change in serum creatinine to 1.5 times of baseline or decrease in GFR greater than 25%. Patient considered to be suffered from "Class Injury", if patient's serum creatinine becomes 2 times greater of baseline or GFR decreased more than 50%. Patients considered having "Class Failure" incidence when serum creatinine becomes more than 3 times than baseline or decrease in GFR more than 75%. Patients considered to be suffered with Loss of Kidney function or End-stage kidney disease when patient has loss of kidney function for more than 4 weeks or more than 3 months respectively. For AKI incidence, the deterioration should be sudden (1-7 days) and should persist for more than 24 hours (Lopes and Jorge, 2013).

AKIN definitions were used for the determination of incidences of AKI associated with Influenza-A H1N1 infection according to the elevation of glomerular filtration rate or change in urine output (Martin-Loeches, Papiol *et al*., 2011). According to AKIN, stage I AKI is defined as abrupt increase in serum creatinine kinase level ≥0.3 mg/dl OR increase in serum creatinine level of 1.5-2 fold from baseline. A patient is considered to have stage II AKI when there was an increase of serum creatinine of > 2 to 3 fold from baseline. Incidence of Stage III AKI referred to increase in serum creatinine of more than 3-fold increase from baseline OR increase in serum creatinine to more than 300% from baseline. A patient was also considered to have Stage III incidence whenever there was an initiation of renal replacement therapy.

All the enrolled patients were further assessed for the time taken to recover from AKI i.e., return of serum creatinine to baseline value. Flow chart of methodology is summarized in fig. 1.

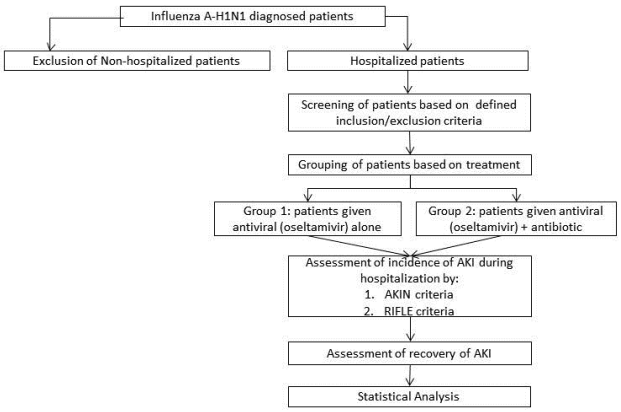

Fig. 1: Methodology Flow Chart

Inclusion criteria

- Hospitalized patient at a participating site with confirmed Influenza infection screening reverse transcriptase polymerase chain reaction (RT PCR) or conventional PCR assay on one respiratory specimen: nasopharyngeal aspirate (NPA), Nasopharyngeal swab, nasal wash, nasal swab and throat swab.
- Adults, including pregnant and breast feeding women.
- Patients who have been initiated on Oseltamivir therapy during hospitalization days within six hours after influenza infection detection.
- Severely ill influenza patients who need to be admit to intensive care unit within 48 hours of admission

Exclusion criteria

- Patients who tested negative for influenza infection on polymerase chain reaction assay testing (PCR testing) were excluded from the study.
- Patients with age less than 18 years.
- Presence of self-reported or medically documented significant medical condition of ongoing malignancy.
- Known allergy to treatments for influenza (including but not limited to oseltamivir).
- Volunteers who have received antiviral preparations immunoglobulins or blood transfusions or any other preparation in 4 weeks prior to inoculation of the tested preparation.
- Patients having incomplete demographics and incomplete laboratory findings.

STATISTICAL ANALYSIS

All the statistical analysis was done by using SPSS (version 17.0) and Graphpad Prism (version 5.0). Parameters of demographic data are presented as mean and Standard deviation (SD). Qualitative nominal data is represented as total number with percentage in parentheses. Chi-square test and unpaired t-test was used to evaluate univariate analysis.

RESULTS

A total of 466 hospitalized patients with confirmed diagnosis of Influenza-A H1N1 were studied altogether during the study period. All the studied patients were divided into two groups based on the treatment received for treatment of Influenza-A H1N1. Out of 446 patients, 241 patients were given oseltamivir alone (group 1) while 225 patients were given oseltamivir along with combination of empirically prescribed antibiotic (group 2). After carefully analyzing the patients according to above defined inclusion/exclusion criteria, a total of 176 and 153 who fulfilled the inclusion criteria for group 1 and group 2 respectively.

Male to female ratio of study participants was almost similar for both groups with an odd ratio of 1.3(0.68-2.3). Among female enrolled patients, pregnant women of different trimesters were also included which accounts for 2.5% and 3% for group 1 and group 2 respectively. The average age for patients for both groups is similar with no significant difference (P > 0.0.5). Elderly patients with age more than 60 years comprise 29% (51) and 34% (52) patients for group 1 and group 2 respectively. Among the distribution of comorbidities among study participants, hypertension was found to be most common. A total of 41 (12.5%) patients from both groups study participants found to be diagnosed with Influenza-A H1N1 despite receiving Influenza vaccine for the corresponding influenza season. Around 21% (69 patients) enrolled patients did not receive Influenza vaccine because of diagnosed during early days of influenza season. Summarized patients' characteristics are mentioned in table 1.

Table 1: Patient Characteristics of Study Participants

	Group 1 (oseltamivir alone)	Group 2 (oseltamivir + antibiotic)
Total patients		
No. of patients	176	153
Gender		
Male	81 (46%)	68 (44%)
Female	95 (54%)	85 (56%)
Age (years)		
Mean	55.01	55.79
SD	19.5	18.9
Range	(21-84)	(24-91)
Weight (kg)		
Mean	77.16	77.89
SD	19.2	17.6
Influenza Vaccination history		
Yes	24 (13.6%)	17 (11.1%)
No	152 (86.4%)	136 (88.9%)
Comorbidities		
Hypertension	58 (33%)	47 (31%)
Asthma	53 (30%)	41 (27%)
Diabetes	42 (24%)	35 (23%)
Heart failure	11 (7%)	6 (4%)
Others	9 (5%)	10 (7%)

Comparisons of different hematological laboratory parameters are shown in fig. 2. Mean red blood cell count showed no statistical difference between two treatment groups from first admission day till discharge day or fifth day of hospitalization. The comparisons are drawn for five days because usually the duration of empirical therapy of different antibiotics is for three days. Likewise, mean red blood cell count, no statistical difference was found during hospitalization days for mean lymphocyte count. Mean white blood cell count shows no statistical difference till day 2 of hospitalization for both treatment groups. But from third day of hospitalization, group 2 patients showed significant statistical difference ($P< 0.05$) as compared to group 1 patients. For group 2 patients, Day 4 and Day 5 showed more statistical improvement ($P< 0.001$) as compared to group 1 patients who treated with oseltamivir alone. Mean neutrophil count on day 4 also showed statistical improvement ($P< 0.05$) but showed no statistically difference on Day 5 which showed that combination treatment has some role in in improving mean neutrophil count. Fig. 3 shows comparisons of different biochemistry laboratory parameters for both treatment groups. No laboratory parameter showed statistically significant difference during any stage of treatment for both treatment groups.

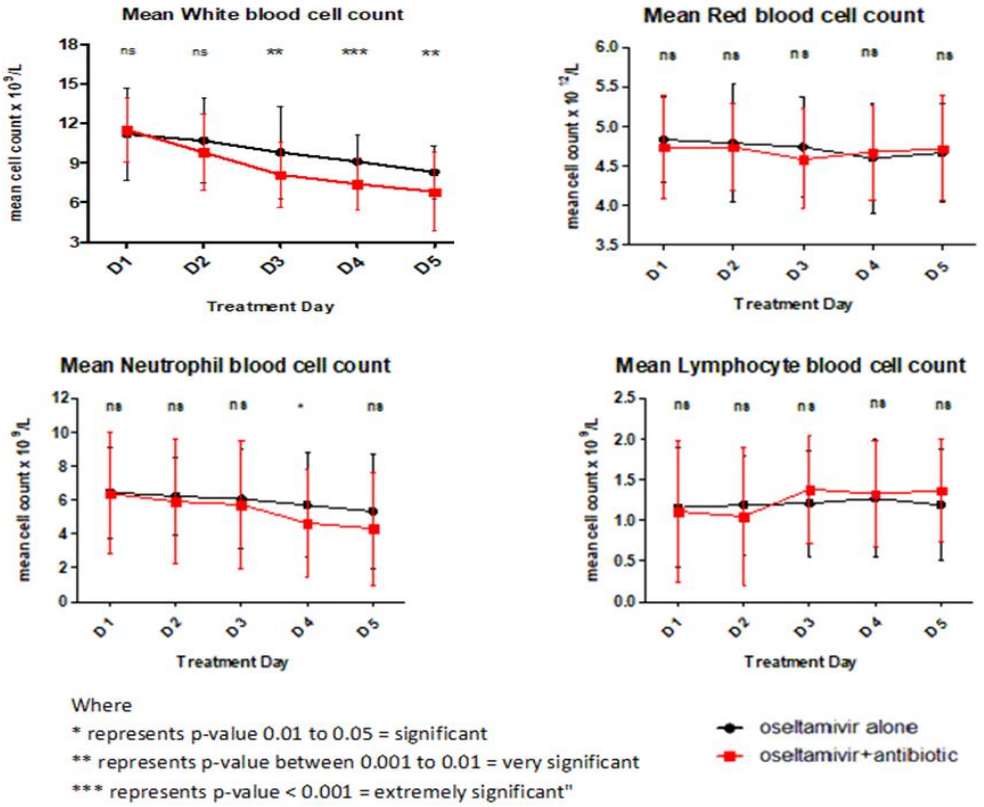

Fig. 2: Summary of hematology laboratory parameters for both treatment groups

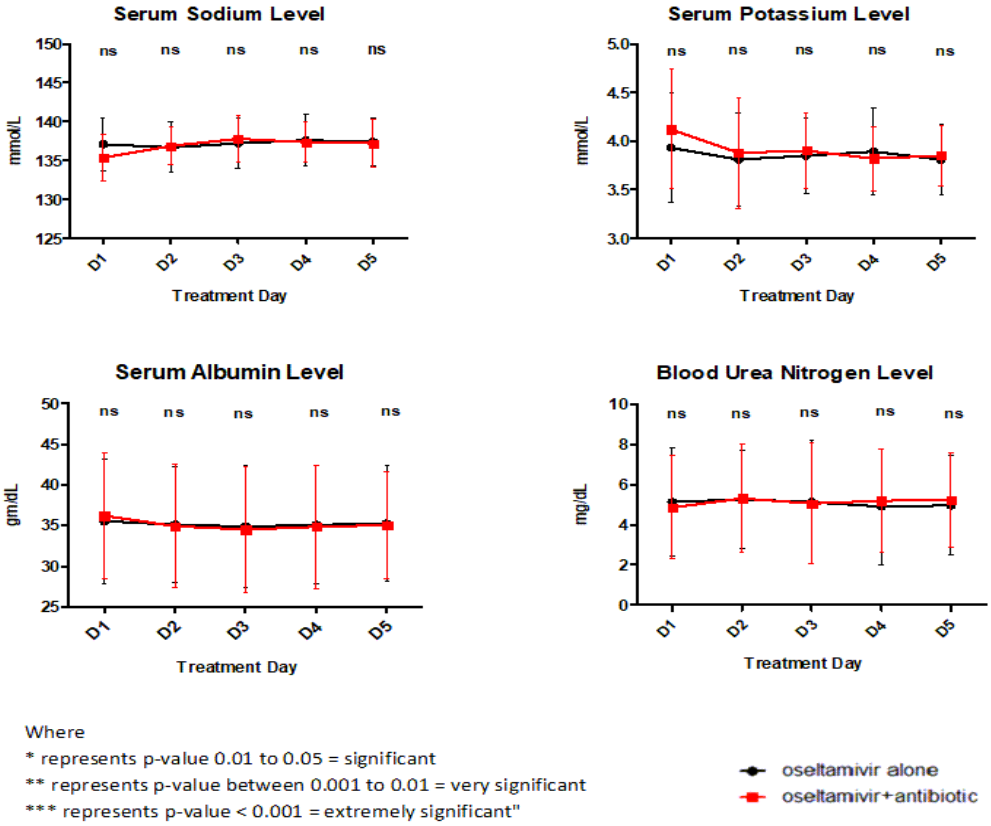

Fig. 3: Summary of biochemistry laboratory parameters for both treatment groups

Table 2: Acute kidney injury incidences according to RIFLE & AKIN criteria

	Group 1 (oseltamivir alone)	Group 2 (oseltamivir + antibiotic)	P-value
Serum Cretainine Baseline (umol/L)			
mean	92.6	90.2	0.91
SD	42.1	42.3	
minimum	321	267	
maximum	41	40	
Estimated GFR (ml/min)			
mean	126.4	120.6	0.62
SD	60.5	56.4	
minimum	17.1	23.1	
maximum	261	221	
Baseline criteria by hospital record			
no. of patients	54	69	
baseline criteria by hospital admission			
no. of patients	22	18	
AKI incidence by RIFLE CRITERIA			
no. of patients	176	153	
non-AKI	153	144	
AKI	23	9	<0.05
(a)Risk	19	7	<0.05
(b) Injury	4	2	0.68
(c) Failure	0	0	
AKI incidence by AKIN CRITERIA			
no. of patients	176	153	
non-AKI	158	147	
AKI	18	6	<0.05
(a)Stage 1	16	5	<0.05
(b) Stage 2	2	1	
(c)Stage 3	0	0	
Recovery of AKI			
during hospitalization	20	8	
within 30 days follow-up	3	1	
within 90 days follow-up	0	0	

Table 2 shows different parameters related to AKI for both treatment groups. No statistical difference was found between the serum creatinine and glomerular filtration rate for both treatment groups. The baseline serum creatinine for around 83% of total enrolled patients was taken by hospital record criteria i.e the serum creatinine value of patient's last visit of hospital within last 3-6 months before diagnosis of Influenza-A H1N1.

According to RIFLE criteria, around 32 (9.7%) patients suffered to have AKI of total enrolled patients. Out of total 32 patients, around 23 (72%) patients and 9 (28%) patients belonged to group 1 treatment protocol and group 2 treatment protocols respectively. The incidences of AKI during hospitalization for treatment of Influenza-A H1N1in group 2 patients who received combination treatment of oseltamivir and antibiotic was statistically significantly lowered ($P< 0.05$) as compared to patients who received oseltamivir alone. The severity of AKI according to RIFLE criteria into different classes/stages is mentioned in table 2.

Out of 32 patients who are defined to AKI for both groups, around 24 patients were also diagnosed to have AKI incidence according to AKIN criteria in which 18 patients belonged to group 1 treatment while 6 patients belonged to group 2 treatment protocol. The incidences of AKI as per AKIN criteria in group 2 patients who were given combination treatment was significantly lowered ($P<0.05$) as compared to the group 1 patients. The bifurcation of AKI severity into different stages according to AKIN criteria is mentioned in table 2 which shows that most of the patients suffered with stage 1 AKI. Recovery of patient's normal kidney function near to baseline serum creatinine was also monitored and most of the patients of both groups recovered before discharge from hospital while few left out patients recovered upon kidney function assessment on follow-up visit within 30 days of discharge from hospital.

Table 3 shows different clinical outcomes for both treatment group patients which shows that the patients who were initiated on combination therapy were statistically less associated with need of respiratory support and vasopressor use during incidence of AKI. Moreover, length of hospitalization days, statistical significant difference ($P<0.01$) was found between two treatment groups with group 2 patients have less mean

Table 3: Clinical outcomes of patients suffered from acute kidney injury

	group 1 (oseltamivir alone) n=23	group 2 (oseltamivir + antibiotic) n=9	P-value	Odds Ratio
Age of patient				
> 65 years, yes/no	14/9	2/7	0.049	5.44 (0.91-32.30)
Comorbidities				
Asthma	8/15	2/7	0.49	1.86 (0.3-11.2)
Diabetes	10/13	4/5	0.9	0.97 (0.2-4.5)
Cardiac	8/15	4/5	0.6	0.67(0.14-3.2)
Influenza vaccination				
unvaccinated, yes/no	21/2	9/0	0.36	0.45(0.02-10.4)
Need for ICU admission				
Yes/no	17/6	5/4	0.03	5.67(1.07-30.1)
Vasopressor use				
Yes/no	14/9	2/7	0.04	5.44 (0.9-32.32)
Mechanical Respiratory support				
Yes/no	18/5	4/5	0.02	7.2(1.3-39.57)
Oliguria				
Yes/no	9/14	2/7	0.36	2.25 (0.37-13.36)
APACHE II score				
Mean ± SD	19 ± 5.7	14 ± 4.9	0.03	
Need of dialysis during AKI				
Yes/no	8/15	2/7	0.18	4.27(0.45-40.46)
Hospital admission days				
Days, mean ± SD	6.67± 2.12	5.12± 1.56	0.01	
Incidences of co-secondary bacterial infections				
Yes/no	19/4	4/5	0.03	5.9(1.08-32.53)

days of hospitalization as compared to group 1 patients with treatment of oseltamivir alone.

The common antibiotics which are empirically used in combination with oseltamivir in group 2 patients include oral azithromycin, oral clarithromycin, ceftriaxone, oral cefuroxime and piperacillin/tazobactam which were given to 49 (32%), 18 (12%), 39 (25%), 11 (7%) and 29 (19%) respectively.

DISCUSSION

Influenza infection can affect renal function through a number of complications AKI, acute glomerulonephritis, minimal change disease, and acute tubulointerstitial nephritis (Dobson, Whitley *et al*., 2015). Observational studies suggest that the incidence of influenza-associated AKI ranges from 18% to 66% in patients cared for in an ICU setting (Martin-Loeches, Papiol *et al*., 2011, Nin, Lorente *et al*., 2011, Pettilä, Webb *et al*., 2011). The degree of renal failure can be quite severe, as 8%-22% of patients ultimately require renal replacement therapy during their hospitalization (Demirjian, Raina *et al*., 2011). A study conducted in China involving 426 H1N1-infected patients disclosed that the mean serum creatinine level (67±20 µmol/L) but did not stated AKI (Cao, Li *et al*., 2009). A report from Chile revealed that, 1562 patients were hospitalized with H1N1 infection, and 25% of those patients exhibited raised serum creatinine levels (Ugarte, Arancibia *et al*., 2010). Furthermore, another two studies investigating AKI in critically ill patients in Canada and Argentina revealed the prevalence of AKI to be 66.7% and 63.6%, respectively (Sood, Rigatto *et al*., 2010, Trimarchi, Greloni *et al*., 2010). All the stated studies did not correlated treatment given to the patient.

The current manuscript is the first, to our knowledge, to have evaluated the incidence of acute renal injury in patients with influenza who were treated by oseltamivir alone and oseltamivir-in-combination with antibiotics for prevention and/or treatment of secondary bacterial infection. Our result demonstrated that incidence of acute renal injury is significantly low in patients treated with oseltamivir-in-combination with antibiotics as compare to alone oseltamivir treated patients. The RIFLE criteria, which was employed to define AKI in the study represent a highly sensitive diagnostic tool (Bellomo, Ronco *et al*., 2004). Conversely, AKIN is aimed to assist international, interdisciplinary, and inter-societal relationships to ensure improvement in the area of AKI and achieve the useful results for patients with or at risk for AKI (Mehta, Kellum *et al*., 2007). Renal impairment as a manifestation of

severe H1N1 infection have been demonstrated in reports presenting that significantly high median creatinine levels in non-survivors compared to survivors (Domínguez-Cherit, Lapinsky *et al*., 2009, Kumar, Zarychanski *et al*., 2009) and a need for renal replacement therapy has also been observed in severe H1N1 infected patients (Miller III, Markewitz *et al*., 2010, Nicolay, Callaghan *et al*., 2010, Rello, Rodríguez *et al*., 2009). Conversely, renal consequences following influenza A viral infection are quite infrequent, only in critically ill patients (Vasilijevic, 2016). It is important to mention here that influenza A infections rarely cause AKI and as such AKI seems mostly secondary to rhabdomyolysis (Bellomo, Pettilä *et al*., 2010). Furthermore, influenza A infection is not associated with increased risk for AKI. Obesity, elevated CK levels, and pre-existing comorbidities are associated with AKI; and the latter is an independent risk factor for all-cause hospital mortality (Demirjian, Raina *et al*., 2011).

Secondary bacterial pneumonia is one of the most common complications during influenza virus epidemics and pandemics which subsequently increases mortality in infected patients (van Krüchten, Wilden *et al*., 2018). A study conducted in Canada reported clinical confirmation of secondary bacterial pneumonia in 41 cases (24.4% of all study patients) following ICU admission and out of which 18 cases were because of Staphylococcus aureus and 5 cases were due to Streptococcus pneumonia (Kumar, Zarychanski *et al*., 2009). The renal dysfunctions including AKI, rhabdomyolysis, hemolytic uremic syndrome etc. which might happen after secondary bacterial kidney infection can deteriorate overall medical condition (Vasilijevic, 2016). The results of current study showed that group of patients treated with oseltamivir combination therapy with antibiotics had low incidence of AKI because of the antibacterial coverage provided from antibiotics thus preventing incidence AKI resulting from bacterial load. For Group 1, around 19 (82.6%) patients were also diagnosed with co-secondary bacterial infections from 23 patients diagnosed with AKI. In contrast, only 4 (44.4%) patients diagnosed with co-secondary bacterial infections out of 9 patients with AKI for patients given combination therapy.

Influenza viruses are global pathogens that infect up to 20% of the world population each year and cause significant morbidity and mortality (Fischer II, Chason *et al*., 2014). Although antibiotics can help reduce the impact of co/secondary bacterial infection, we still need to better understand the interactions between viruses, bacteria and their host, and to fully understand all mechanisms of disease taking in consideration the incidence of acute kidney injury (Morris, Cleary *et al*., 2017). Early recognition of the extra-pulmonary manifestations of influenza infection is critical to the initiation of therapeutic interventions and organ-specific supportive care.

Licensed seasonal trivalent influenza vaccine and live attenuated influenza vaccine display a mean efficacy of 60% in healthy adults and 83% in children, respectively (Ohmit, Petrie *et al*., 2013, Osterholm, Kelley *et al*., 2012). Vaccination can reduce illness and lessen severity of infection, particularly in groups at risk for complications of influenza, including young children and the elderly (Houser and Subbarao, 2015). The best way to prevent influenza-associated disease burden is vaccination (Radin, Hawksworth *et al*., 2016). Since most of our study subjects were unvaccinated, elderly with chronic comorbidities, therefore, such study population considered to be high risk for severe Influenza A-H1N1 infection. Antiviral-antibiotic combination therapy proved to be effective for elderly patients with 2 (22.2%) out of 9 incidents of AKI for group 2 patients which is significantly low ($P< 0.05$) as compare to 14 (60.2%) out of 23 patients with AKI who were aged 65 years or more.

Bacterial secondary infections or co- infections associated with cases of influenza are a leading cause of severe morbidity and mortality, especially among high-risk groups such as the elderly and young children (Joseph, Togawa *et al*., 2013). Some studies have reported on comorbidities of patients with coinfection and found that older age (Ahn, Kim *et al*., 2011, Martín-Loeches, Sanchez-Corral *et al*., 2011), a higher APACHE II score (Martín-Loeches, Sanchez-Corral *et al*., 2011, Yan, Xu *et al*., 2011), diabetes (Choi, Hong *et al*., 2012), and sepsis were risk factors for co-secondary infection as well as AKI (Choi, Hong *et al*., 2012).

In current study, group 2 patients which were given combination therapy were associated with statistically significant less incidences of AKI and low APACHE II score along with low rate of ICU admission, need of respiratory support and vasopressor use which clearly indicates that less severity and slower disease progression of Influenza A-H1N1 infection in patients who were initiated on antibiotic along with oseltamivir soon after the diagnosis of influenza infection specially in high risk patients.

CONCLUSION

AKI is recognized as one the common complication associated with severe Influenza A-H1N1 infection especially in patients with suspected co-secondary bacterial infection which is one the leading cause of mortality in influenza infection patients. Early initiation of empirical prescribed antibiotic in combination with antiviral medication in patients with suspected co-secondary bacterial infection in severe influenza A-H1N1 infection patients proven to be an effective combination therapy resulted in statistically significant less incidences of AKI as compare to patients which were given antiviral drug alone. The combination therapy was also found to be

associated with fewer incidences of need of ICU admission, vasopressor use, and need of mechanical ventilation along with statistically less hospitalization days.

REFERENCES

Abdulkader RC, Ho YL, de Sousa Santos S, Caires R, Arantes MF and Andrade L (2010). Characteristics of acute kidney injury in patients infected with the 2009 influenza A (H1N1) virus. *Clin. J. Am. Soc. Nephrol.* CJN., 00840110.

Ahn S, Kim WY, Kim SH, Hong S, Lim CM, Koh Y, Lim KS and Kim W (2011). Role of procalcitonin and C reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia. *Influenza Other Respir Viruses* **5**(6): 398-403.

Bagshaw SM, Sood MM, Long J, Fowler RA and Adhikari NK (2013). Acute kidney injury among critically ill patients with pandemic H1N1 influenza A in Canada: cohort study. *BMC Nephrol.*, **14**(1): 123.

Bellomo R, Kellum JA. Ronco C (2012). Acute kidney injury. *The Lancet.*, **380**(9843): 756-766.

Bellomo R, Pettilä V, Webb SA, Bailey M, Howe B and Seppelt IM (2010). Acute kidney injury and 2009 H1N1 influenza-related critical illness. *Cardiorenal Syndromes in Critical Care*, Karger Publishers. pp.310-314.

Bellomo R, Ronco C, Kellum JA, Mehta RL. Palevsky P (2004). Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* **8**(4): R204.

Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, Liang Z-A, Liang L, Zhang SJ and Zhang B (2009). Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N. Engl. J. Med.* **361**(26): 2507-2517.

Choi SH, Hong SB, Ko GB, Lee Y, Park HJ, Park SY, Moon SM, Cho OH, Park KH and Chong YP (2012). Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am. J. Respir. Crit. Care Med.* **186**(4): 325-332.

Demirjian SG, Raina R, Bhimraj A, Navaneethan SD, Gordon SM, Schreiber Jr MJ and Guzman JA (2011). 2009 influenza A infection and acute kidney injury: incidence, risk factors, and complications. *Am. J. Nephrol.* **34**(1): 1-8.

Dobson J, Whitley RJ, Pocock S and Monto AS (2015). Oseltamivir treatment for influenza in adults: A meta-analysis of randomised controlled trials. *The Lancet* **385**(9979): 1729-1737.

Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, Poblano-Morales M, Baltazar-Torres JA, Bautista E and Martinez A (2009). Critically ill patients with 2009 influenza A (H1N1) in Mexico. *Jama.*, **302**(17): 1880-1887.

Fischer II WA, Chason KD, Brighton M and Jaspers I (2014). Live attenuated influenza vaccine strains elicit a greater innate immune response than antigenically-matched seasonal influenza viruses during infection of human nasal epithelial cell cultures. *Vaccine,* **32**(15): 1761-1767.

Heemann U, Abramowicz D, Spasovski G, Vanholder R. transplantation ERBPWGok (2011). Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement, Oxford University Press.

Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D and Kellum JA (2006). RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care,* **10**(3): R73.

Houser K and Subbarao K (2015). Influenza vaccines: challenges and solutions. *Cell Host Microbe,* **17**(3): 295-300.

Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W and Metnitz PG (2009). Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.*, **35**(10): 1692-1702.

Joseph C, Togawa Y and Shindo N (2013). Bacterial and viral infections associated with influenza. *Influenza Other Respir Viruses*, **7**: 105-113.

Keddis IAQaMT (2015). Acute Kidney Injury in Patients with Pandemic 2009 H1N1 Influenza A on Extracorporeal Membrane Oxygenation: Case Series and Review of the Literature. *J. Clin. Nephrol. Ren. Care*, 1(1).

Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K and Lamontagne F (2009). Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *Jama.*, **302**(17): 1872-1879.

Lopes JA and Jorge S (2013). The RIFLE and AKIN classifications for acute kidney injury: A critical and comprehensive review. *Clin Kidney J.*, **6**(1): 8-14.

Low D (2008). Reducing antibiotic use in influenza: challenges and rewards. *Clin Microbiol Infect,* **14**(4): 298-306.

Martin-Loeches I, Papiol E, Rodriguez A, Diaz E, Zaragoza R, Granada RM, Socias L, Bonastre J, Valverdú M and Pozo JC (2011). Acute kidney injury in critical ill patients affected by influenza A (H1N1) virus infection. *Crit Care,* **15**(1): R66.

Martín-Loeches I, Sanchez Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, Albaya A, Cerdá E, Catalán RM and Luque P (2011). Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A (H1N1) virus. *Chest* **139**(3): 555-562.

Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG and Levin A (2007). Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care,* **11**(2): R31.

Miller III RR, Markewitz BA, Rolfs RT, Brown SM, Dascomb KK, Grissom CK, Friedrichs MD, Mayer J, Hirshberg EL and Conklin J (2010). Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza A (H1N1) infection. *Chest,* **137**(4): 752-758.

Morris DE, Cleary DW and Clarke SC (2017). Secondary bacterial infections associated with influenza pandemics. *Front Microbiol.,* **8**: 1041.

Nicolay N, Callaghan MA, Domegan LM, Oza AN, Marsh BJ, Flanagan PC, Igoe DM, O'Donnell JM, O'Flanagan DM and O'Hora AP (2010). Epidemiology, clinical characteristics and resource implications of pandemic (H1N1) 2009 in intensive care units in Ireland. *Crit Care Resusc.,* **12**(4): 255.

Nin N, Lorente J, Soto L, Ríos F, Hurtado J, Arancibia F, Ugarte S, Echevarría E, Cardinal P and Saldarini F (2011). Acute kidney injury in critically ill patients with 2009 influenza A (H1N1) viral pneumonia: An observational study. *Intensive Care Med.,* **37**(5): 768-774.

Nissenson AR (1998). Acute renal failure: definition and pathogenesis. *Kidney Int. Suppl.,* **66**: S7-10.

Ohmit SE, Petrie JG, Malosh RE, Cowling BJ, Thompson MG, Shay DK and Monto AS (2013). Influenza vaccine effectiveness in the community and the household. *Clin Infect Dis.,* **56**(10): 1363-1369.

Osterholm MT, Kelley NS, Sommer A and Belongia EA (2012). Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* **12**(1): 36-44.

Ostermann M, Chang R and Group RIPU (2005). Prognosis of acute renal failure: An evaluation of proposed consensus criteria. *Intensive Care Med.*, **31**(2): 250-256.

Pettilä V, Webb SA, Bailey M, Howe B, Seppelt IM and Bellomo R (2011). Acute kidney injury in patients with influenza A (H1N1) 2009. *Intensive Care Med.,* **37**(5): 763-767.

Radin JM, Hawksworth AW, Myers CA, Ricketts MN, Hansen EA and Brice GT (2016). Influenza vaccine effectiveness: Maintained protection throughout the duration of influenza seasons 2010-2011 through 2013-2014. *Vaccine,* **34**(33): 3907-3912.

Rello J, Rodríguez A, Ibañez P, Socias L, Cebrian J, Marques A, Guerrero J, Ruiz-Santana S, Marquez E and Del Nogal-Saez F (2009). Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1) v in Spain. *Crit Care,* **13**(5): R148.

Ricci Z, Cruz DN and Ronco C (2011). Classification and staging of acute kidney injury: Beyond the RIFLE and AKIN criteria. *Nat. Rev. Nephrol.,* **7**(4): 201.

Sood MM, Rigatto C, Zarychanski R, Komenda P, Sood AR, Bueti J, Reslerova M, Roberts D, Mojica J and Kumar A (2010). Acute kidney injury in critically ill patients infected with 2009 pandemic influenza A (H1N1): Report from a Canadian province. *Am J Kidney Dis.,* **55**(5): 848-855.

Trimarchi H, Greloni G, Campolo-Girard V, Giannasi S, Pomeranz V, San-Roman E, Lombi F, Barcan L, Forrester M and Algranati S (2010). H1N1 infection and the kidney in critically ill patients. *J. Nephrol.,* 23(6): 725-731.

Ugarte S, Arancibia F and Soto R (2010). Influenza A pandemics: clinical and organizational aspects: the experience in Chile. *Crit Care Med.,* **38**: e133-e137.

Unverdi S, Akay H, Ceri M, Inal S, Altay M, Demiroz AP and Duranay M (2011). Acute kidney injury due to rhabdomyolysis in H1N1 influenza infection. *Ren Fail* **33**(4): 450-451.

van Krüchten A, Wilden JJ, Niemann S, Peters G, Loffler B, Ludwig S and Ehrhardt C (2018). Staphylococcus aureus triggers a shift from influenza virus induced apoptosis to necrotic cell death. *FASEB J.*, **32**(5): 2779-2793.

Vasilijevic J (2016). Characterization of pathogenicity factors of a lethal influenza a (h1n1) 09 (Doctoral dissertation, Universidad Autonoma de Madrid).

Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JG and Group UoTAKIR (2009). Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *Jama.,* **302**(11): 1179-1185.

Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, Mills RG and Ward P (2001). Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis. J.,* **20**(2): 127-133.

Yan X, Xu H, Liu Y, Qu F, Yu H, Wang Y, Li Y and Liu D (2011). influenza A (h1n1) Virus Complicated With Bacteria Infection: 903. *Respirology,* **16**: 60.