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Acute Kidney Injury in Patients with Pandemic 2009 H1N1 Influenza A on Extracorporeal Membrane Oxygenation: Case Series and Review of the Literature

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Abstract

Purpose of review: To investigate the association, pathophysiology and clinical outcome of acute kidney injury (AKI) in critically ill patients with H1N1 Influenza.

Recent findings: Several observational studies have shown a high incidence of AKI requiring renal replacement therapy (RRT) in patients with confirmed H1N1 Influenza A. Patients with H1N1 Influenza who develop AKI were more likely to have the following risk factors: obesity, diabetes, greater severity of illness index scores and suffered from prolonged hospitalizations and increased in-hospital mortality compared to patients without AKI. We review the characteristics of five cases of confirmed H1N1 infection complicated by severe respiratory distress requiring extracorporal membrane oxygenation support (ECMO) who developed AKI and its impact on in-hospital morbidity and mortality.

Summary: Recent evidence has shown that patients with H1N1 have an increased risk of developing severe AKI requiring renal replacement therapy. The cause of AKI in these patients is multifactorial and is exacerbated by the use of ECMO. Acute kidney injury in H1N1 is associated with significantly increased in-patient morbidity and mortality and poor renal recovery.

Keywords

Acute kidney injury, 2009 H1N1 Influenza A, Renal replacement therapy, Critically ill patients, Extracorporeal membrane oxygenation

Introduction

The H1N1 influenza A (swine flu) was first recognized in 1918 during the influenza pandemic and was first isolated from humans in 1974 [1,2]. Several reports of H1N1 influenza A was reported between 1958 and 2005 with mortality rates up to 17% [1]. In 2009 worldwide outbreak of H1N1 influenza A led the world health organization to raise its pandemic alert to its highest level [3]. H1N1 influenza A was found to be associated with significantly higher mortality in all age groups compared to seasonal influenza where mortality was limited to patients with extremes of age and comorbid conditions [4-7]. Sixty one million cases were identified between 2009 and 2010 with more than 50% of affected individuals between the ages of 18 and 64 [4-7].

For most patients the clinical course of H1N1 influenza A infection typically resolves within a few days with no significant sequelae. However, there are several reports of patients who developed respiratory failure and acute respiratory distress syndrome (ARDS) necessitating mechanical ventilation and in severe cases extracorporal membrane oxygenation (ECMO) [8]. Acute kidney injury (AKI) has been reported to occur in two thirds of patients with complicated clinical course of H1N1 [9]. Obesity, diabetes and immunocompromised state have been identified as risk factors for development of AKI during H1N1 infection. The purpose of this review is to evaluate the association of AKI with H1N1 in patients with respiratory failure and highlight a series of five cases of patients with AKI and H1N1 on ECMO support and their outcome at a single center.

Epidemiology and Complications of H1N1 Influenza

The H1N1 influenza A evolved from the avian-origin when it was first observed in 1918 in Spain [10]. Since that time there were multiple outbreaks in 1968, 1998 and 2009 [10]. It was thought to enter both human and swine at the same time after evolving from avian origin. Swine acts as an intermediate host for transmission and genetic re-assortment as they are thought to be susceptible to human and avian viruses [5,11,12]. The mixing between different strains can cause emergence of new strains with an increased pandemic potential in different hosts [12]. Climate changes and rapid globalization also contribute to the H1N1 Influenza A outbreaks [10].

With the first outbreak in 2009 H1N1 influenza A was recognized to be associated with a more severe clinical course with increased hospitalization and flu related mortality compared to seasonal influenza. While seasonal influenza was associated with significant hospitalizations and mortality in patients older than 65 years of age, H1N1 influenza A was found to afflict younger patients between 18-64 years [4-7]. The susceptibility of this younger age group is thought to be due to lack of prior influenza vaccination thus making them more susceptible to H1N1 influenza A infection [7].

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Table 1: Summary of the 4 major studies evaluating the risk factors and outcomes of AKI development in patients with H1N1 Influenza A infection.

	Bagshaw et al. [18]	Martin-Loeches et al. [20]	Jung et al. [21]	Nin et al. [23]
Country	Canada	Spain	South Korea	Argentina, Uruguay and Chile
Study	Prospective multicenter	Prospective multicenter	Retrospective multicenter	Retrospective
Total # pts	562	661	221	84
%Pts with AKI	60.9%	17.7%	29%	51%
# of pts with AKI	342	118	50	43
Characteristics of AKI patients				
Age	49.1 (15.1)	44.9 (15.2)	66 (53-73)	46 (13)
Male (%)	165 (48.2)	77 (65.3)	26 (52)	30(72)
Body mass index(kg/m²)				33(2)
% BMI>30	-	-	22.6(4.3)	-
	118(34.5)	52 (44.4)	-	
Diabetes (%)	107(31.3)	19 (16.2)	16(32)	-
COPD (%)	56(16.4)	19 (16.2)	10(20)	-
CKD (%)	44(12.9)	Excluded	3(6)	-
APACHE II Score				
Mean(± SD)	23.0(9.6)	19.1 (8.4)	25.1 ± 7	20(7)
Median (IQR)				
SOFA Score				
Mean (± SD)	12.0(3.8)	8.7(4.2)	10.6 ± 3	-
ICU stay				
Mean (± SD)	-	19.4(16.5)	19.9 ± 11.4	-
Median (IQR)	12(7-24)	13 (7-30)	-	11(5-16)
Hospital stay				
Mean (± SD)	-	30.3(19.9)	26 ± 36.4	-
Median (IQR)	20(12-40)	26.5(13.7-44.2)	-	18(11-34)
Inotropic support (%)	222(64.9)	89(75.4)	42(84)	-
Renal replacement therapy (%)	85(24.9)	50(42.3)	19(38)	19(44)
AKI Criteria	RIFLE	AKIN	RIFLE	RIFLE
Mortality (%)	85(25.8)	52(44.1)	38(76)	31(72)
	(Hospital)	(ICU)	(Hospital)	(ICU)

*AKI: Acute Kidney Injury, COPD: Chronic Obstructive Pulmonary disease, CKD: Chronic Kidney Disease, APACHEII: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit, Categorical data are presented as n(%) and continuous data as mean(SD) or median(Q1-Q3)

The clinical presentation of H1N1 influenza A includes cough (98%), subjective fever (96%), fatigue (89%), headache and sore throat (82%) and diarrhea (48%) [13]. Thirty percent of patients infected with H1N1 develop severe pulmonary complications including hypoxia, ARDS and need for mechanical ventilation and intensive care (ICU) [8]. In addition, 67% of patients with H1N1 influenza A infection required ICU care and suffered from one of the following complications: influenza pneumonia with severe gas exchange abnormalities, superinfection with invasive bacteria and worsening organ dysfunction as a result of sepsis and impaired cardiopulmonary reserve [8,14-16].

The Association of AKI with H1N1 Influenza A Infection: Literature Review

Several studies evaluated the rate of AKI and associated mortality during the H1N1 influenza A pandemic. In this review, we searched the literature using OVID MEDLINE using the search terms Influenza A Virus, H1N1 and Acute Kidney Injury and narrowed down the search to those involving humans, studies available in full text and English language. Review articles and case reports were excluded from this review. Only four studies were identified worldwide that evaluated the rate and risk factors of AKI in patients with confirmed and/or probable cases of H1N1 influenza A and its impact on hospital related morbidity and mortality (Table 1).

In a study of 562 patients with H1N1 influenza A infection, 61% developed AKI as defined by RIFLE criteria [17,18]. On univariate analysis, compared to no-AKI patients, patients with AKI were more likely to be obese (34.5% vs. 14.6%, P<0.0001), have underlying chronic kidney disease (CKD) (12.9% vs. 1.8%, p<0.0001), diabetes (31.3% vs. 17.7%, P=0.0004) and significantly higher APACHE II and SOFA scores (23 ± 9.6 vs. 18.1 ± 7.6, P<0.0001) and (12 ± 3.8 vs. 9.7 ± 3.2, P<0.0001) respectively. On multivariate analysis, obesity, CKD and increasing APACHE II scores were significantly and independently correlated with AKI in this cohort. Among patients who developed AKI, clinical outcomes were significantly worse (more prolonged ICU stay with median length of stay of 12(7-24) vs. 10 (6-16) (P=0.002) in the no-AKI group. Interestingly in-hospital mortality increased with increased AKI severity and was significantly higher in the AKI group (25.8% vs. 13%, P=0.0003). However, on multivariate analysis of predictors of in-hospital mortality, only age and APACHE II scores were independent predictors of mortality in this study and both of these variables were significantly associated with AKI, therefore AKI by itself was not an independent predictor of hospital mortality.

The largest study that evaluated patients with confirmed H1N1 influenza and AKI showed an AKI incidence of 17.7% using the AKIN criteria [19,20]. Compared to patients with no-AKI, patients with AKI were more likely to be male (77(65.3%) vs.288 (53%), P=0.01) and have diabetes (19(16.2%) vs.52 (9.6%), P=0.04). There was a trend towards higher BMI in the AKI group (52(44.4%) vs.196 (36%), P=0.09]. Similar to the Canadian study, patients with AKI had significantly higher APACHE II and SOFA scores (19.1 ± 8.4 vs. 12.6 ± 5.9, P<0.001) and (8.7 ± 4.2 vs. 4.8 ± 2.9, P<0.001) respectively. Similarly patients with AKI had more prolonged hospitalizations: median ICU days (13(7-30) vs. 8(4-17), P<0.001) and hospital length of stay (26.5 (13.75-44.25) vs. 15 (9-27), P<0.001). In-hospital mortality was significantly higher in the AKI group compared to the no-AKI group (52(44.1%) vs.72 (13.3%), P<0.001) [20]. It should be noted that on multivariate analysis, only AKI stage III was independently associated with increased in-hospital mortality (OR 4.81 (2.17-10.62, P<0.001).

Table 2: Summary of the 5 cases of patients with H1N1 Influenza A infection and AKI on ECMO support

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	59	64	42	56	38
Sex	Female	Male	Male	Female	Male
Hypertension	No	Yes	No	Yes	No
Diabetes	Yes	Yes	No	No	No
Dyslipidemia	No	Yes	No	No	No
Coronary artery disease	No	Yes	No	No	No
Heart failure	No	No	No	No	Yes
Immunocompromised	No	No	Yes	No	No
Weight (kg)	90	124.6	92.1	87.9	78
Body mass index (kg/m^2)	33.4	38.5	29.1	33.1	25.5
H1N1 PCR confirmed	Yes	Yes	Yes	Yes	Yes
Days in Hospital	25	34	55	25	42
Days in ICU	25	34	55	25	25
Days on ECMO	19	34	21	20	9
Days on CRRT	20	15	14	9	9
Days on Ventilator	23	34	55	23	9
SOFA Score	14	8	17	16	12
APACHI II Score	37	33	29	38	29
Day of Hospital admission	1/29/2014	1/17/2014	1/15/2014	1/29/2014	2/1/2014
Type of ECMO	VV	VV	VV	VV	VA
Onset of AKI after initiation of ECMO	Before	19 days after	20 days after	Before	Before
CPK (u/L)	18	26	21	404	1775
Schistocytes on blood smear	No	No	No	No	No
Discharge	SNF	Death	Death	Death	SNF

*ICU: Intensive Care Unit, ECMO: Extracorporeal Membrane Oxygenation, CRRT: Continuous Renal Replacement Therapy, SOFA: Sequential Organ Failure Assessment, APACHEII: Acute Physiology and Chronic Health Evaluation II, AKI: Acute Kidney Injury, CPK: Creatine Phosphokinase

The third study was a retrospective analysis of 221 patients in South Korea with confirmed H1N1 influenza A infection [21]. Sixty four patients (29%) developed AKI using the RIFLE criteria and 78.1% of those developed AKI within 72 hours of ICU admission. Similar to previous studies, there was a higher predilection for patients with AKI to have underlying diabetes compared to those who did not develop AKI (16 (32%) vs.27 (15.8%), P=0.015). Baseline CKD was identified as a significant risk factor for AKI in patients with H1N1 influenza A infection (3(6%) vs. 2(1.2%), P=0.043). Moreover, patients with an immunosuppressed state were at higher risk for developing AKI (24(48%) vs.46 (26.9%), P=0.006) with the majority of the cases having underlying hematologic malignancies (10(20%) vs.9 (5.3%), P=0.01). Again noted is a significantly higher severity of illness index scores in the AKI group compared to the no-AKI group (APACHE II (25.1 ± 7 vs. 16.4 ± 7.4, P<0.001) and SOFA (10.6 ± 3 vs. 6.5 ± 3.3, P<0.001)). Patients with AKI were more likely to require ECMO support compared to patients with no-AKI (6(12%) vs. 6(3.5%), P=0.02). Unlike previous studies, there was no statistically significant difference in the ICU or hospital length of stay between the AKI and no-AKI groups. However, consistent with previous studies hospital mortality was significantly increased in the AKI group (38(76%) vs. 49 (28.7%), P<0.001) [22].

The fourth study was a retrospective observational study of 84 patients admitted to the ICU with confirmed H1N1 Influenza A. Acute kidney injury (using RIFLE criteria) developed in forty three (51%) patients and 24% required renal replacement therapy [17]. Compared to patients without AKI, those with AKI had significantly higher APACHE I II scores (20 ± 7 vs. 17 ± 7, P<0.05) and increased ICU mortality (31(72%) vs. 16(39%), P<0.05) [23].

Pathophysiology of AKI in H1N1 Influenza A

Acute kidney injury in critically ill patients with pandemic H1N1 Influenza A is common. Several pathophysiologic mechanisms have been proposed to explain the heightened risk for AKI. The most commonly implicated is renal hypoperfusion and renal vasoconstriction with resultant acute tubular necrosis [24-26] due to hemodynamic compromise and vasodilatory shock state. Thrombotic microangiopathy, rhabdomyolysis, postinfectious glomerulonephritis, acute tubulointerstitial nephritis and anti-GBM disease were reported in the context of H1N1 influenza A infection but their occurrence is rare [27]. An autopsy study of five patients whose death was attributed to H1N1 influenza A infection were examined with immunohistochemical detection of influenza A/H1N1 viral antigen [9]. Numerous viral antigens were localized in the cytoplasm of glomerular macrophages. There were no glomerular lesions but all patients had some degree of acute tubular necrosis. It is not clear based on the current evidence if there is any direct effect of H1N1 influenza A on renal tubular cells.

AKI is frequently observed in the clinical use of ECMO due to ischemic acute tubular necrosis or hemolysis. The initiation of ECMO can cause hemodynamic instability thus impairing the effective renal blood flow causing ischemic reperfusion renal injury [28]. Other predisposing factors that exacerbate the renal injury include systemic inflammation from exposure of the blood to the artificial surfaces [29,30] and hypercoagulable state [28,31,32]. Hemolysis with subsequent hemoglobinuria causing tubular injury is another common cause of AKI during ECMO support. Hemolysis can be exacerbated by fluid/air interface and the excessive negative pressure generated [33,34]. These factors must be taken into account when considering AKI occurrence in patients with H1N1 influenza A infection on ECMO support.

Case Series

We identified five cases of PCR-confirmed H1N1 influenza A complicated by ARDS necessitating mechanical ventilation and ECMO support in 2014 at a single medical center. All five cases were admitted to the hospital in a two week span (middle of January to beginning of February). Mean age was 51 ± 13 years, all were Caucasian and three were male. All five patients developed severe oliguric AKIAKIN stage 3 requiring continuous renal replacement therapy (CRRT) in the form of continuous veno-venous hemodiafiltration.

Baseline characteristics are shown in table 2. None of the five patients had prior history of CKD based on history and/or creatinine measurements prior to hospitalization; mean creatinine on admission to ICU was 2.44 ± 1.46mg/dl. None had a prior history of any pulmonary disease. The first four cases required veno-venous ECMO and case five required veno-arterial ECMO. The mean days on ECMO were 21.5 ± 12.5 days and on CRRT 14.5 ± 5.5 days. Total days in the ICU and hospital were the same 40 ± 15 days. APACHE II and SOFA scores were 33 ± 4.5 and 12 ± 4 respectively which were significantly

Table 3: Definitions and criteria

Acute Kidney Injury Definitions [17,19]:

RIFLE (Risk/Injury/Failure/Loss/End stage)	AKIN (Acute Kidney Injury Network)
An increase in serum creatinine of ≥ 50% developing over <7 days OR A urine output of <0.5ml/kg/hr for >6 hours	An increase in serum creatinine of ≥ 0.3mg/dL or ≥ 50% developing over < 48 hours OR A urine outpuat of <0.5ml/kg/hr for >6 hours

RIFLE and AKIN staging Definitions [17,19]:

Staging	Increase in serum creatinine		
RIFLE	Risk: >1.5-fold from baseline or GFR decrease >25%	Injury: > 2-fold increase or GFR decrease >50%	Failure: >3-fold increase or GFR decrease 75% or creatinine ≥ 4.0mg/dL
AKIN	Stage 1: ≥ 0.3mg/dL or ≥ 1.5-2-fold from baseline	Stage 2: >2 to 3-fold	Stage 3: > 3-fold OR creatinine ≥ 4.0mg/dL or on renal replacement therapy

APACHE II Scoring System criteria [37]:

Rectal temperature	Creatinine
Mean arterial pressure	Hematocrit
Heart rate	White blood cell count
Respiratory rate	Glasgow coma score
A-a gradient	Age
pH or bicarbonate level	Chronic disease
Sodium	Potassium

SOFA Scoring criteria [38]:

Ratio of arterial oxygen tension to fraction of inspired oxygen
Amount of vasopressor support
Bilirubin level
Platelet level
Glasgow coma score
Serum creatinine or urine output

higher than in previously reported cases of AKI with H1N1 influenza A infection. Three of the five patients had a bacterial co-infection. Case 2 suffered from E-Coli 0157:H7 gastroenteritis. Case 4 had methicillin resistant staphylococcal pneumonia and bacteremia and case 5 had methicillin sensitive staphylococcal pneumonia. All patients suffered from septic shock requiring vasopressor support. In three cases the onset of AKI was prior to the initiation of ECMO. In the other two cases oliguric AKI occurred 19 and 20 days after ECMO cannulation. None of the five patients had laboratory evidence of rhabdomyolysis or hemolysis. All patients had vasodilatory shock secondary to H1N1 infection and required pressor support at the onset of oliguric AKI prompting initiation of CRRT. None of the patients had exposure to venous or arterial contrast or nephrotoxic medications except antibiotics which were renally dose adjusted by the ICU pharmacist. Three of the five patients died during their hospitalization. Case one was dismissed to skilled nursing facility on maintenance hemodialysis. Case three recovered renal function back to baseline and was also dismissed to skilled nursing facility (Table 3).

Discussion

H1N1 influenza A has been recognized to cause significant morbidity and mortality in all age groups and especially in young adults. The 2009 pandemic affected over sixty million patients with over a third of patients developing respiratory failure and up to 70% requiring ICU care. Several studies worldwide evaluated the association of H1N1 influenza A infection with AKI between 2009 and 2010. The rate of AKI varied widely among the studies and ranged from 18 to 61%. Several risk factors for AKI were identified. In two studies, patients with H1N1 infection who developed AKI were more likely to have diabetes and be obese. The association of diabetes as well as obesity with increased risk for AKI in different settings has been previously reported [18,20,21,23]. One study suggested that an immunosuppressed state due to hematological causes increased the risk for AKI in the context of H1N1 infection. In contrast, in a brief report of 22 patients with H1N1 influenza A infection, patients with non-hematological causes of immunosuppression were noted to be more likely to develop AKI [22]. However, data on how hematological immunosuppression was defined was lacking in that report and a comparison cohort was not analyzed. Therefore there is insufficient data to inform how the type of immunosuppression may impact the risk of AKI in patients with H1N1 influenza A infection.

The association of baseline CKD with increased risk for AKI has been previously reported [18,21,23] and was found to be a significant risk factor in two studies. Of note, all four studies showed markedly increased APACHEII and SOFA scores in patients with AKI compared to those who did not develop AKI suggesting that the severity of illness was likely a greater contributor to the development of AKI than any direct effect that H1N1 infection might have had on the kidney.

The use of ECMO in patients with ARDS secondary to H1N1 influenza A has been increasing with evidence suggestive that it contributes to improved survival [36]. However the use of ECMO has been shown to be associated with increased risk for AKI and volume overload. Acute kidney injury has been shown to occur in 70-85% of patients on ECMO [34,35]. Acute kidney injury in critically ill patients is associated with 78% mortality compared to 20% in patients with no-AKI [35]. Therefore the development of AKI on ECMO support may negate any survival benefit in patients with ARDS. In our series, all patients received ECMO and three of the five patients died during the hospitalization. It should be noted however that the APACHE II score in our cohort was 33.5 ± 4.5 which is significantly higher than that reported in other studies of H1N1 and AKI. Moreover it is important to note that AKI developed in the majority of patients prior to addition of ECMO support which suggests that the primary pathophysiology of AKI in our case series was driven by the overall severity of illness in these patients as all suffered from vasodilatory shock requiring pressor support. It is conceivable that the addition of ECMO support precipitated further renal injury however this cannot be determined from this case series. It is interesting to note however that the two patients who required ECMO support after the onset of AKI both died during their hospitalization. Davis et al conducted an observational study of 61 patients with confirmed H1N1 influenza A and respiratory failure that required ECMO support for a median duration of 10 (7-15) days [35]. In that cohort, there was evidence of survival benefit in the ECMO group compared to conventional ventilation group. However the incidence of AKI and need for renal replacement therapy were not reported [35,36]. Our case series highlights a unique cohort of patients with AKI requiring renal replacement therapy and longer duration of ECMO support (21.5

± 12.5 days). Larger studies evaluating similar patients on ECMO support are needed in order to better assess the benefits and risks of ECMO support in that cohort of patients and its effect on renal and patient survival.

The development of AKI in patients with H1N1 was shown to be associated with increased in-hospital morbidity and mortality and these findings were consistent across all studies. Several studies showed increased length of stay in patients with AKI. Alarmingly all studies showed that the development of AKI during H1N1 infection was associated with increased mortality. This is consistent with previous literature showing the association of AKI with mortality [18,20,21,23]. In our case series, all the cases of AKI were attributed primarily to septic shock and only one patient recovered renal function. Therefore patients with H1N1 influenza A infection who require ECMO support appear to have severe AKI with poor renal recovery.

Conclusion

H1N1 influenza A infection continues to carry significant health burden to this day. There is an increased risk for development of AKI in patients with H1N1. The use of ECMO in this patient cohort may increase the risk of AKI. The development of AKI during the clinical course of H1N1 is associated with significant in-hospital morbidity and mortality. Further studies are needed to evaluate the impact of early recognition and management of AKI on the clinical course of H1N1 influenza A infection and the risks and benefits of ECMO support in this patient cohort.

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