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Acute Kidney Injury in Critically Ill Patients Infected With 2009 Pandemic Influenza A(H1N1): Report From a Canadian Province

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Background: 2009 pandemic influenza A(H1N1) has led to a global increase in severe respiratory illness. Little is known about kidney outcomes and dialytic requirements in critically ill patients infected with pandemic H1N1.

Study Design: Prospective observational study.

Setting & Participants: 50 patients with pandemic H1N1 admitted to any of 7 intensive care units in Manitoba, Canada, were prospectively followed.

Outcome & Measurements: Outcomes were kidney injury and kidney failure defined using RIFLE (risk, injury, failure, loss, end-stage disease) criteria or need for dialysis therapy.

Results: The pandemic H1N1 group was composed of 50 critically ill patients with pandemic H1N1 with severe respiratory syndrome (47 confirmed cases, 3 probable). Kidney injury, kidney failure, and need for dialysis occurred in 66.7%, 66%, and 11% of patients, respectively. Mortality was 16%. Kidney failure was associated with increased death (OR, 11.29; 95% CI, 1.29-98.9), whereas the need for dialysis was associated with an increase in length of stay (RR, 2.38; 95% CI, 2.13-25.75).

Limitations: Small population studied from single Canadian province; thus, limited generalizability.

Conclusions: In critically ill patients with pandemic H1N1, kidney injury, kidney failure, and the need for dialysis are common and associated with an increase in mortality and length of intensive care unit stay.

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INDEX WORDS: Acute kidney injury; intensive care unit; influenza A(H1N1).

Recent reports from Canada, Mexico, the United States, and Australia have illustrated the burden of 2009 pandemic influenza A(H1N1) infection on intensive care unit (ICU) resources, with an emphasis on respiratory failure, mechanical ventilation, and extracorporeal membrane oxygenation.¹⁻⁷ Currently, little information exists about the impact of kidney injury and resource utilization in the form of dialytic support in critically ill patients with pandemic H1N1 infections.^{8,9} Patients admit-

ted to the ICU with acute kidney injury (AKI) are at increased risk of mortality, lengthened ICU and hospital stays, and the development of chronic kidney disease.¹⁰⁻¹⁸ It is unknown whether this observation can be extended to AKI in the setting of severe viral respiratory infections requiring ICU admission. During the severe adult respiratory syndrome coronavirus outbreak, kidney injury and the need for dialysis were uncommon; however, whether this holds true for pandemic H1N1 infection is unknown.^{17,18}

The objective of this study is to describe rates of kidney injury, kidney failure, and need for dialysis therapies in critically ill patients infected with pandemic H1N1.

METHODS

Study Population and Design

The study population consisted of all patients (aged >8 years) admitted to any of the 7 ICUs serving the Province of Manitoba, Canada (population, 1,200,000). Admissions for patients with 2009 pandemic influenza A(H1N1) infection-related critical illness from April 1, 2009, to August 27, 2009, were included. Local research ethics board approval was obtained.

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Data Collection

ICU data were collected prospectively for all patients with pandemic H1N1, as described elsewhere.⁶ Collected data include patient demographics, admitting and discharge diagnoses, laboratory values, physiologic variables, treatments, and in-hospital survival. Supplemental data and data validation for both cohorts were completed using independent retrospective chart review. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated at admission for all patients.¹⁹

Cohort Definitions

Infection with 2009 pandemic influenza A(H1N1) was classified according to the case definitions of the World Health Organization (WHO) and the Canadian National Microbiology Laboratory as follows. A confirmed case is defined as a person with an acute febrile respiratory illness with laboratory-confirmed influenza A(H1N1) virus (swine flu) infection (eg, at Cadham Provincial Laboratory/National Microbiology Laboratory) using 1 or more of the following tests: real-time reverse transcription–polymerase chain reaction (RT-PCR) or viral culture or pre/post antibody testing, and a probable case of infection is defined as a person with an acute febrile respiratory illness who is positive for influenza A, but negative for H1 and H3 using influenza RT-PCR or positive for influenza A using an influenza rapid test or an influenza immunofluorescence assay plus meets criteria for a suspected case.²⁰ Only confirmed or probable cases were included in our study. Critical illness and ICU admission were determined by the requirement for invasive or noninvasive mechanical ventilation, need for a fraction of inspired oxygen $\geq 60\%$, or need for intravenous inotropes or vasopressor medications requiring ICU admission.⁶ Chronic kidney injury was defined as baseline creatinine level $>140 \mu\text{mol/L}$. Dialysis dependence was defined as the need for dialysis therapy before admission to the ICU.

Outcome Definitions

The primary outcomes were AKI and acute kidney failure according to the RIFLE (risk, injury, failure, loss, end-stage disease) criteria and use of renal replacement therapy.²¹ Secondary outcomes were length of ICU stay and 28-day mortality. The RIFLE criteria for kidney injury are a validated tool for determining kidney injury based on the presence of either an increase in serum creatinine level from baseline or a decrease in urine output.^{12,21-27} Severity is classified as risk of kidney injury and kidney failure. Dialytic therapies included the need for continuous replacement therapy and/or intermittent hemodialysis.

Data Analysis

Continuous variables of interest were summarized as mean or median with standard deviation or interquartile range, as appropriate. Between-groups comparisons in baseline admission characteristics, presence or absence of AKI, or need for dialytic therapies were made using independent-samples *t* test for continuous variables and χ^2 or Fischer exact test for dichotomous variables. Laboratory, clinical, and physiologic variables and outcomes were assessed dur-

ing ICU admission days 1, 3, 7, 14, and 28. Odds ratios for outcomes were determined using univariate logistic regression. The 95% confidence intervals (CIs) and *P* values were considered statistically significant for $P \leq 0.05$. Statistical analyses were performed using SPSS, version 16 (www.spss.com).

RESULTS

As of August 31, 2009, there were 221 hospitalized cases of pandemic H1N1 in the Province of Manitoba, Canada, with 11 confirmed deaths and 50 total admissions to the ICU for ventilator support.²⁸ Of 50 patients, 47 (96%) were confirmed and 3 (4%) were probable by WHO criteria.

The average age of patients admitted to the ICU with pandemic H1N1 was 35.5 ± 15.8 years, and most were female (72%). Racial information was available for 66 of 82 (80%) of the pandemic H1N1 cohort, corresponding to 48% aboriginal, 36% white, and 14% other. Admission characteristics for pandemic H1N1 patients

Table 1. Baseline Characteristics of Patients Admitted to the ICU With Pandemic H1N1 Infection

Admissions	50
Demographics	
Age (y)	35.5 ± 15.8
Women	36 (72)
Body mass index (kg/m ²)	34.8 ± 12.0
Comorbid conditions	
Arrhythmia	1 (2)
Asthma	12 (24)
Coronary artery disease	2 (4)
Cancer	1 (2)
Chemotherapy	1 (2)
Congestive heart failure	3 (6)
Chronic obstructive pulmonary disease	6 (12)
Diabetes	17 (34)
Hypertension	11 (22)
Immunosuppression	8 (16)
Peripheral vascular disease	3 (6)
Smoker	16 (32)
Steroids	11 (22)
Pregnancy	8 (16)
Pregnancy (wk)	25.8 ± 12.3
Chronic kidney disease	2 (4)

Note: Values expressed as mean \pm standard deviation, or number (percentage).

Abbreviation: ICU, intensive care unit.

are listed in Tables 1 and 2. Average body mass index was high ($34.8 \pm 12.0 \text{ kg/m}^2$), with the comorbid conditions of diabetes mellitus, cigarette smoking, asthma, and hypertension occurring in more than one-fifth of the cohort. Eight patients were pregnant at an average term of 25.8 ± 12.3 weeks. Mean APACHE II score and Glasgow Coma Scale were 19 ± 6 and 11.5 (interquartile range, 10-13), respectively. Most patients required vasopressor or inotropic blood pressure support medications (66%), and all required mechanical ventilation. Median creatine kinase value was increased at $325 \mu\text{mol/L}$ (interquartile range, 73-903).

Patient outcomes are listed in Table 3. AKI occurred in 66.7%; acute renal failure, in 66%; and the requirement for dialysis, in 22% of patients with pandemic H1N1. Of 11 patients requiring dialysis after admission to the ICU, 2 (22%) died and 1 (11%) required ongoing dialysis therapy upon discharge. Median length of stay was 16.0 days (interquartile range, 9-38), with mortality of 16%.

We examined the association between kidney disease and length of stay and mortality in patients with pandemic H1N1 (Table 4). Because

Table 2. Selected Physiologic and Laboratory Characteristics of Patients on Admission to the ICU With Pandemic H1N1

Mean APACHE II score	19.2 \pm 6.5
Mean arterial pressure (mm Hg)	74.1 (62.3-83.1)
Glasgow Coma Scale	11.5 (10.0-13.0)
Inotropes or vasopressor medications	33 (66)
Mechanical ventilation	50 (100)
Central venous pressure (mm Hg)	11.0 (7.5-16.0)
Positive end-expiratory pressure (mm Hg)	10.0 (8.0-14.5)
White blood cell count ($\times 10^9/\text{L}$)	6.9 (3.7-12.4)
Platelets ($\times 10^9/\text{L}$)	172 (123-228)
Creatine kinase (U/L)	325 (73-903)
Troponin T ($\mu\text{g/L}$)	0.03 (0.01-0.22)
Alanine transaminase (U/L)	35.5 (21.0-70.5)
Aspartate aminotransferase (U/L)	67.0 (33.5-127.3)
Creatinine ($\mu\text{mol/L}$)	72 (48.0-111)

Note: Values expressed as number, mean \pm standard deviation, number (interquartile range), or number (percentage). Conversion factor for creatinine in $\mu\text{mol/L}$ to mg/dL , $\times 0.0113$; no conversion necessary for troponin T in $\mu\text{g/L}$ and ng/mL or white blood cell count and platelets in $10^9/\text{L}$ and $10^3/\mu\text{L}$.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

Table 3. Outcomes of Patients With Pandemic H1N1 Influenza A Admitted to the ICU

Kidney injury	32/48 (66.7)
By urine output criteria	29/48 (60.4)
By creatinine criteria	12/48 (25)
On day 1	23/48 (48)
Kidney failure	33/50 (66)
By urine output criteria ^a	20/50 (40)
By creatinine criteria	13/50 (26)
On day 1	14/50 (28)
Length of ICU stay (d)	16.0 (9.0-38.0)
Dialysis at discharge	1 (2)
Dialysis	11 (22)
Death	8 (16)

Note: Values expressed as number (percentage) or number (interquartile range). By RIFLE criteria, kidney injury is defined as doubling of serum creatinine level or urine output $< 0.5 \text{ mL/kg/h}$ for 12 hours. Kidney failure is defined as tripling of serum creatinine level or serum creatinine level $\geq 353.6 \mu\text{mol/L}$ with an acute increase $> 44 \mu\text{mol/L}$ or urine output $< 0.3 \text{ mL/kg/h}$ for 24 hours or anuria for 12 hours.²¹ For the kidney injury cohort, patients with chronic kidney disease ($n = 2$) were excluded.

Abbreviations: ICU, intensive care unit; RIFLE, risk, injury, failure, loss, end-stage disease.

of our small sample size, only univariate associations were explored. As expected, the odds of death was substantially higher in those who experienced kidney failure (odds ratio, 11.29; 95% CI, 1.29-98.8) and length of stay was increased in all patients who required dialysis (relative risk, 2.38; 95% CI, 2.13-25.75; data not shown).

Key characteristics of patients who experienced a kidney outcome are listed in Table 5. AKI was more frequent in older patients (38.4 vs 28.7 years; $P = 0.02$), whereas kidney injury and failure were more common in patients with higher

Table 4. Univariate Impact of Kidney Injury, Kidney Failure, and Need for Dialytic Therapies on Mortality in the ICU

	OR for Mortality	95% CI
Dialysis (all)	1.21	0.23-5.00
Acute kidney injury	5.67	0.65-49.62
Acute kidney failure	11.29	1.29-98.8

Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Table 5. Characteristics of Pandemic H1N1 Patients With and Without Kidney Injury, Kidney Failure, and Requirement for Dialysis

	Kidney Injury		P	Kidney Failure		P	Dialysis		P
	No (n = 18)	Yes (n = 30)		No (n = 25)	Yes (n = 25)		No (n = 39)	Yes (n = 11)	
Age (y)	28.7 ± 12.3	38.4 ± 16.5	0.02	34.1 ± 15.8	36.9 ± 16.1	0.5	35.4 ± 16.9	36.0 ± 11.8	0.9
Female	5/18 (28)	9/30 (30)	0.6	19/25 (76)	8/25 (32)	0.8	29/39 (74)	7/11 (64)	0.5
Aboriginal	6/18 (33)	17/30 (57)	0.1	10/25 (40)	14/25 (56)	0.4	20/39 (51)	4/11 (36)	0.5
Body mass index (kg/m ²)	29.0 ± 2.4	38.5 ± 2.4	0.02	31.3 ± 2.3	39.1 ± 2.8	0.04	34.1 ± 2.2	37.2 ± 3.5	0.5
Diabetes mellitus	3/18 (17)	13/30 (43)	0.07	8/25 (32)	9/25 (36)	0.5	13/39 (33)	4/11 (36)	0.9
Hypertension	2/18 (11)	9/30 (30)	0.3	4/25 (16)	7/25 (28)	0.2	7/39 (18)	4/11 (36)	0.2
Pregnancy	4/18 (22)	4/30 (13)	0.5	5/25 (20)	3/25 (12)	0.4	6/39 (15)	2/11 (18)	0.9
Asthma	1/18 (6)	11/30 (37)	0.02	1/24 (4)	11/25 (44)	<0.001	9/39 (23)	3/11 (27)	0.9
Glasgow Coma Scale	10.3 ± 1.3	10.6 ± 1.0	0.9	9.7 ± 1.2	10.7 ± 1.0	0.5	10.8 ± 0.8	7.9 ± 1.8	0.2
APACHE II score	16.3 ± 1.8	20.9 ± 1.1	0.04	17.5 ± 6.6	21.1 ± 6.0	0.06	18.9 ± 6.6	20.3 ± 6.4	0.5
BP support agents	9/18 (50)	23/30 (77)	0.1	13/25 (52)	20/25 (80)	0.07	24/39 (62)	9/11 (82)	0.3
MAP (mm Hg)	67.7 ± 15.1	78.5 ± 17.9	0.05	69.5 ± 15.5	78.7 ± 18.4	0.07	72.0 ± 15.9	80.1 ± 21.2	0.1
WBC (×10 ⁹ /L)	8.6 ± 2.0	9.0 ± 1.4	0.9	9.4 ± 1.5	11.7 ± 3.8	0.6	12.1 ± 2.5	5.3 ± 1.8	0.04
Creatine kinase (μmol/L)	667.5 ± 203.8	646.1 ± 186.3	0.9	680.9 ± 166.9	592.4 ± 219.3	0.8	567.3 ± 122.8	860.0 ± 428.4	0.4
ICU length of stay (d)	17.8 ± 3.7	25.5 ± 3.5	0.2	20.2 ± 3.2	24.7 ± 4.0	0.4	19.3 ± 2.6	33.3 ± 6.4	0.02
Dialysis	0/15 (0)	11/18 (61)	0.008	0/25 (0)	11/25 (44)	<0.001	NA	NA	NA
Death	1/18 (6)	7/30 (23)	0.2	1/25 (4)	8/25 (32)	0.02	7/39 (18)	2/11 (18)	0.9

Note: Values expressed as mean ± standard deviation or number of patients (percentage). No conversion necessary for WBC count in 10⁹/L and 10³/μL.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BP, blood pressure; MAP, mean arterial pressure; NA, not applicable; WBC, white blood cell count.

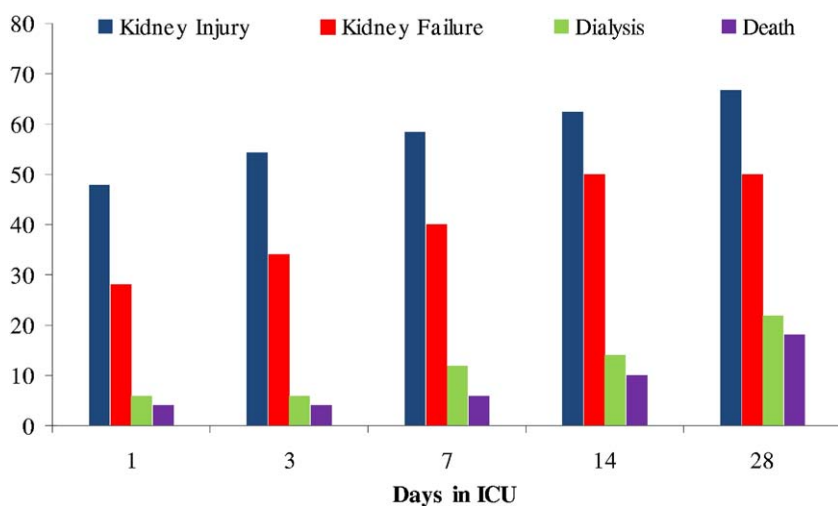


Figure 1. Cumulative proportion of kidney injury, kidney failure, dialysis requirements, and death over time in 50 critically ill patients with pandemic H1N1. Cross-sectional data were obtained on days 1, 3, 7, 14, and 28 of intensive care unit (ICU) admission. Data presented as percentages when kidney injury and kidney failure were determined according to RIFLE (risk, injury, failure, loss, end-stage disease) criteria.

body mass index and a history of asthma. Again, the requirement for dialysis therapy was associated with an increase in length of ICU stay ($P = 0.02$).

Time courses of AKI and kidney failure, need for dialysis, and death during the first 28 days of admission to the ICU are shown in Fig 1. AKI, kidney failure, and initiation of dialysis therapy occurred within 24 hours of ICU admission in 47.9%, 28%, and 6%, respectively. Most kidney injury and kidney failure occurred within the first 14 days (30 of 32 and 33 of 33 patients, respectively), whereas dialysis requirements peaked at day 28.

DISCUSSION

Our present investigation of the impact of pandemic H1N1 on kidney injury includes a large cohort of critically ill patients and use of a standardized validated definition for kidney injury, with serial measurements performed prospectively during the patients' ICU stays. This allowed identification of the high number of patients affected by kidney injury and its subsequent impact on mortality and ICU resources. The major finding of our study is that kidney injury was common, occurred early in a high proportion of infected patients, and was associated with higher odds of death and longer length of stay.

On June 11, 2009, the WHO raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission

on at least 2 continents.²⁹ The second wave of the pandemic has strained health care resources in both hemispheres, with a large proportion of ICU occupancy dedicated solely to patients infected with pandemic H1N1.^{1-4,30,31} Most admissions to the ICU are for respiratory failure and mechanical ventilation. Acute kidney failure is an important complication in critically ill patients and is associated with increased mortality, length of stay, and cost.^{10,14,15,32} However, little is known about AKI⁵⁻⁷ in critically ill patients with pandemic H1N1. To our knowledge, ours is the first study to describe the impact of pandemic H1N1 on the time course of kidney injury, kidney failure, and anticipated need for dialysis therapy in critically ill patients.

AKI occurred frequently, with 66.7% of the pandemic H1N1 cohort affected during their ICU admission. Most experienced kidney injury (30 of 32 patients) within the first 24 hours of admission. Twenty-two percent of patients required dialysis; fortunately, most who survived (89%) did not require ongoing dialysis. We believe these findings are of importance for both prognostic and resource planning purposes in this important emerging pandemic.

Early reports of patients with pandemic H1N1 did not identify kidney failure or injury as a factor associated with death.^{1,3} However, these reports were limited by the method used to identify kidney injury, which was nonstandardized and largely limited to identification of kidney disease as a pre-existing comorbid con-

dition,^{30,31} an average of serum creatinine measurements,^{5,6} dialysis requirements only,^{4,7} or not mentioned.² In our study, we showed that kidney failure, defined according to validated and reproducible criteria, was associated with an odds ratio for death of 11.29 (95% CI, 1.29-98.9). Our cohort experienced an ICU mortality rate of 13%, which is consistent with other reports.^{1,5,6} In addition, patients requiring dialysis therapies had a longer ICU stay.¹⁶ Both these observations are consistent with the literature about the impact of AKI on patient outcomes in the ICU.^{10,12,13,16,23,32-36}

Most patients who experienced kidney failure with the need for dialysis recovered (10 of 11 patients; 89%), which is not surprising considering their young age and few comorbid conditions. Multiple large observational studies have shown an increased risk of chronic kidney failure, end-stage renal disease, and mortality in patients who experience AKI requiring temporary dialysis.^{10,11,13-15,33,37} It is unclear whether patients who experienced AKI with the need for dialysis therapy will be at a greater chance of progression to chronic kidney disease in the future, and periodic routine monitoring of kidney function in survivors would be advisable.

The pathophysiologic mechanism of the kidney injury likely is multifactorial acute tubular necrosis. Hypoperfusion, renal vasoconstriction, and rhabdomyolysis in the setting of a severe systemic inflammatory response with cytokine cascade likely are occurring concurrently and to varying degrees.^{38,39} Although speculative, it is possible that pandemic H1N1 leads to a heightened inflammatory response in infected young patients, thereby leading to a greater degree of injury and subsequent mortality. Whether successive seroconversion to the pandemic H1N1 virus ameliorates or modifies the course of kidney injury is unknown.

Of note, large proportions of the infected population were female (72%) and aboriginal (48%), suggesting a possible genetic, hormonal, or environmental predisposition to infection or a disproportionate immune response. Numerous other studies have reported the increase in infection in female individuals and pregnant women.^{1,5,6,40} In our study, 8 of 36 females were pregnant, with no detectable increase in adverse kidney outcomes.

Several limitations of the present study merit emphasis. Although our study included a large cohort (N = 50) of critically ill patients with pandemic H1N1, the sample size was too small to permit multivariate modeling or precise effect estimates. Multivariate analysis might have more accurately identified risk factors for kidney injury and failure in pandemic H1N1 and more accurately estimated the independent impact (ie, adjusted for confounding) of kidney failure on outcome in these patients. Although acute kidney failure was associated with mortality, the CI of the effect was wide (1.29-98.8), limiting its precision. Little information was available before ICU admission, and data for initial clinical presentation and type and timing of interventions might have shed further light on why kidney injury develops in some patients, but not others. Criteria for the initiation of dialysis therapy were not standardized; therefore, the incidence of dialysis may reflect local practice patterns to some degree, limiting generalizability. The study population is from a single region (Manitoba, Canada) and had a large proportion of First Nations (aboriginal) patients, factors that may limit generalizability to other centers and regions.

In conclusion, this study shows that kidney injury, kidney failure, and need for dialysis are common in critically ill patients with pandemic H1N1. Because of the strong association between kidney outcomes and both mortality and length of ICU stay, careful monitoring and characterization of kidney injury should be performed early in admission. These findings are of importance for clinicians in prognosticating their patients with suspected pandemic H1N1 infection, in addition to administrators planning for equipment and personnel training with this novel emerging infectious disease pandemic.

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