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Editorial

Severe viral infection and the kidney: lessons learned from the H1N1 pandemic

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Without Abstract

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Through the development and application of the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease (RIFLE)/Acute Kidney Injury Network (AKIN) criteria for acute kidney injury, uncertainties about definitions have finally ended [1]. However, the term acute kidney injury (AKI) shares some similarities with that of acute respiratory distress syndrome (ARDS) given that these 'definitions' provide no information as to the underlying specific aetiologies. Clearly the cause of AKI determines treatment but also has been shown to influence both prognosis and outcome [2]; for example, sepsis-related AKI is associated with particularly high mortality rates approaching 70% in some studies [3] and is usually attributed to bacterial infections, less so to fungal causes and rarely to a viral aetiology [4].

The Cinderella view of viral disease in the intensive care unit (ICU) has changed dramatically over the last decade with the initial appearance of severe acute respiratory syndrome (SARS) and more recently that of the pandemic influenza A (H1N1) infections during 2009, which have presented new challenges to intensivists. Two clinical studies in this current issue of *Intensive Care Medicine* specifically address AKI in the setting of severe influenza infection.

Pettil? and coworkers [5] from Australia and New Zealand present data from 628 critically ill patients which report an incidence of AKI in patients with H1N1 infection of approximately 34%. Eighteen percent of these reached RIFLE class failure, and approximately 5% required renal replacement therapy (RRT). In keeping with other studies, mortality was highest in the RIFLE failure group (ca. 40%) [6]; interestingly, however, mortality did not appear to be related to the need for RRT. Multivariate analysis revealed the usual suspects of increased age, any Acute Physiology and Chronic Health Evaluation (APACHE) III co-morbidity and mechanical ventilation as independent risk factors for hospital mortality as well as AKI of whatever stage. In addition, the authors found that elevated creatine kinase (CK) levels correlated with RIFLE stages in a subgroup of 120 patients (where CK levels were available), indicating that pigment nephropathy may play a significant role in the pathogenesis of H1N1-associated AKI.

The second study focusses on a more severe subgroup of patients, with Nin and coworkers [7] presenting data from 84 critically ill patients from 13 ICUs across Spain and South America. Only patients with viral pneumonia were included, and an incidence of AKI of around 50% was demonstrated, associated with higher mortality rates (40–78%). However, 30 patients were excluded from analysis through lack of data, which may have influenced the results significantly. In this study, 24% of patients required RRT and had an observed mortality of 74%, which is in keeping with data reported from studies in sepsis-associated AKI [3]. The majority of patients acquired AKI within 48 h of ICU admission. This cohort showed significantly better prognosis with higher reversibility and less requirement of RRT compared with those developing AKI later. Multivariate analysis revealed that late AKI (i.e. >48 h) but not RRT itself was associated with increased ICU mortality. The authors conclude that haemodynamic instability may be responsible for the AKI observed early and this is frequently 'reversible' after volume replacement. Late AKI represents rather persistent injury and is most likely influenced by co-morbidities or indeed a differing pathological process. Additionally, a letter by Nin and coworkers [8] describes the histological features from four deceased patients with H1N1 infection. Two patients with AKI showed the classical picture of acute tubular necrosis in the distal tubules, although the presence of viral nucleoprotein could also be demonstrated. In addition to tubular cells, periodic acid-Schiff (PAS)-positive intracytoplasmic granules could also be found in the parietal and visceral epithelia of the Bowman's capsule despite antiviral treatment. Endothelial lesions could not be detected.

The observation that critically ill patients with H1N1 also demonstrate a high prevalence of AKI is neither new nor unexpected [9–11]. The studies presented in this issue of *ICM*, however, do provide some answers to the question about the pathophysiology of viral-associated AKI. There is abundant data in the nephrological literature on viral disease presenting with significant renal manifestations; for example, chronic viral infections including hepatitis B and C or human immune-deficiency virus (HIV) usually manifest with glomerular disease with classical features including membranoproliferative glomerulonephritis (GN), membranous nephropathy or (collapsing) focal segmental glomerulurosclerosis. The pathological mechanisms behind these manifestations are either immune complex deposition or immune reactions resulting in glomerular membrane proliferation. Rarely do viral diseases result in the more severe form of rapidly progressive GN presenting as AKI. Rapid deterioration of renal function is seen with hantavirus-type infection (e.g. Hantaan, Dobrava, Puumala, Sin Nombre), often resulting in requirement of RRT [12, 13]. Fulminant organ failure has been described in these and other viral diseases, especially due to Balkan and Asian strains manifesting as haemorrhagic fever with renal

syndrome (HFRS) [12, 13]. Renal failure in this context appears to be based on severe coagulopathy, endothelial damage and increased vascular permeability, with some similarities to sepsis with disseminated intravascular coagulation resulting directly in impaired organ perfusion and subsequent tissue damage. Cytokine and humoral factor mediated acute interstitial nephritis may play a contributing role. Another frequent complication reported in many viral infections, including HIV, Coxsackie, Epstein–Barr, herpes simplex, adeno-, echo- and cytomegalovirus as well as parainfluenza and influenza A and B virus is that of severe myositis resulting in massive release of myoglobin and, as a consequence, pigment-associated AKI [11, 14, 15]. Perhaps the most recently, and comprehensively, studied viral infection in the critically ill prior to the H1N1 pandemic is that of the novel coronavirus (SARS-CoV) associated with the severe acute respiratory syndrome reported in Hong Kong and surrounding regions. Unsurprisingly, several similarities between H1N1 and SARS-CoV are demonstrated. In one large study on patients with SARS, renal involvement occurred in only 6.7%, but this included all hospitalized patients, whereas in those with SARS who developed renal failure the mortality was over 90% [16]. In keeping with the studies on H1N1 there appeared to be a significant pre-renal element, although again acute tubular necrosis with a predominantly distal tubule distribution was described, as was rhabdomyolysis associated with myositis [17]. The nature of the renal lesion was thought to be through an exuberant host response rather than through uncontrolled viral infection in the kidney. Furthermore, crude markers of tubular function including increased fractional excretion of uric acid coupled with hypouricaemia were observed in patients who subsequently developed AKI [18].

So what causes acute kidney injury in severe H1N1 infection? Analysis of the three studies described allows some conclusions to be drawn. Firstly, the high rate of 'early AKI' with less requirement for RRT and higher rates of recovery indicates an early haemodynamic component due to hypovolaemia or vasodilatory shock due to an exaggerated host response [7]. Secondly, the association between CK and RIFLE stage indicates rhabdomyolysis as an additional mechanism in those patients suffering from myositis [5]. However, the incidence and outcome of AKI do seem to be significantly influenced by co-morbidities and the requirement of mechanical ventilation. Furthermore, the role of supra-added infection, particularly in those patients with a longer ICU course, cannot be ignored and may have been significant in those developing 'late' AKI. Finally the histological investigation shows the classical picture of acute tubular necrosis (with predominantly distal tubular involvement) and viral particles in epithelial cells as well as the Bowman's capsule. Clearly these findings differ significantly from those reported in patients dying from (bacterial) septic shock [19], where increased rates of apoptosis in renal tubular epithelia as well as leucocytic infiltration in glomeruli and capillaries are found. Hence, the role of direct viral infiltration in the pathogenesis of H1N1-associated AKI still remains to be further established.

In terms of prevention of AKI, these studies tell us that measures similar to early goal-directed therapy in sepsis to avoid prolonged hypoperfusion are of utmost importance [20]. Forced isovolaemic diuresis may be considered in cases of severe myositis to prevent haem pigment nephropathy. Risk factors for development of AKI should be avoided if at all possible (e.g. nephrotoxins). The role of antiviral therapy such as neuraminidase inhibitors in terms of protection against AKI remains unclear from these studies. Nin and coworkers showed that the ICU mortality in patients treated with neuraminidase inhibitors remained high at 53% (of 77 patients), slightly lower than the 71% mortality in those who were not treated, but this cohort included only 7 patients [7]. However, it may be that neuraminidase

treatment occurred too late in the course of disease to influence outcome.

Conflict of interest The authors declare no conflict of interest.

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Original

Acute kidney injury in critically ill patients with 2009 influenza A (H1N1) viral pneumonia: an observational study

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Abstract

Objective
To describe the incidence, risk factors, and impact on mortality of acute kidney injury (AKI) in patients with 2009 influenza A (H1N1) viral pneumonia requiring mechanical ventilation.

Design
Observational cohort study.

Patients and methods
AKI was defined as risk, injury or failure, according to the RIFLE classification. Early and

late AKI were defined as AKI occurring on intensive care unit (ICU) day 2 or before, or after ICU day 2, respectively. Demographic data and information on organ dysfunction were collected daily.

Results
Of 84 patients, AKI developed in 43 patients (51%). Twenty (24%) needed renal replacement therapy. Early and late AKI were found in 28 (33%) and 15 (18%) patients, respectively. Patients with AKI, as compared with patients without AKI, had higher Acute Physiology and Chronic Health Evaluation (APACHE) II score and ICU mortality (72% versus 39%, $p < 0.01$) and presented on admission more marked cardiovascular, respiratory, and hematological dysfunction. Patients with early but not late AKI presented on admission higher APACHE II score and more marked organ dysfunction, as compared with patients without AKI. ICU mortality was higher in late versus early AKI (93% versus 61%, $p < 0.001$). On multivariate analysis, only APACHE II score and late but not early AKI [odds ratio (OR) 1.1 (95% confidence interval 1.0–1.1) and 15.1 (1.8–130.7), respectively] were associated with mortality.

Conclusions
AKI is a frequent complication of 2009 influenza A (H1N1) viral pneumonia. AKI developing after 2 days in ICU appears to be associated with different risk factors than early AKI, and is related to a higher mortality rate.

Keywords Acute kidney injury – H1N1 influenza

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Introduction

Acute kidney injury (AKI) is a common complication in patients admitted to the intensive care unit (ICU), with a prevalence rate ranging from 16% to 35% in ICU patients, depending on the definition used, reaching 75% for patients in shock; it is associated with a high mortality rate [1–5].

There is very limited information concerning the incidence, risk factors, and impact on mortality of AKI in patients with 2009 influenza A (H1N1) viral pneumonia requiring mechanical ventilation [6–10]. Trimarchi et al. [11] found that AKI was present in 64% of ICU patients with pandemic 2009 influenza A (H1N1) and was associated with 83% mortality. Rello et al. [7] found, in a population of 32 patients with H1N1 influenza requiring ICU admission, that 21% required renal replacement therapy (RRT). Other studies have reported a prevalence rate of AKI in patients with H1N1 influenza virus infection of 25% and 33% [12, 13]. In an autopsy study of 21 fatal cases of 2009 influenza A (H1N1), 9 patients (43%) were reported to have developed AKI, 4 required dialysis [14], and all had mild to moderate renal acute tubular necrosis on microscopic examination.

The aim of this study is to evaluate the incidence, risk factors, and impact on mortality of AKI in critically ill patients with 2009 influenza A (H1N1) viral pneumonia requiring mechanical ventilation. In addition, we hypothesized that AKI diagnosed soon after ICU

admission had different clinical characteristics and impact on mortality than AKI diagnosed later in the course of the illness.

Patients and methods

Study design

We conducted an observational cohort study enrolling all consecutive patients older than 18 years of age, with the diagnosis of confirmed or probable pandemic 2009 influenza A (H1N1) viral pneumonia, diagnosed as defined by the World Health Organization [15], and requiring mechanical ventilation, admitted to 13 ICUs in Argentine, Chile, and Uruguay, from May 1, 2009 to September 31, 2009. The Ethics Committee of each participating institution approved the study protocol. From the original cohort, patients with chronic renal failure, missing data or unknown ICU discharge status were excluded from the analysis.

Data collection

Data were collected by accessing each patient's clinical records. For each patient, we collected demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score using the worst values within the first 24 h after ICU admission, and the presence of comorbidities. Although the use of more modern severity scoring systems would have seemed more advisable, the used score was widely available and still allows for group comparisons. We collected on admission and on daily basis at 8:00 a.m. information on arterial blood gases, serum creatinine and bilirubin concentration, blood platelet count, vasoactive drugs dosage, as well as development of bacterial pneumonia and requirement for RRT. Information was recorded daily until death, ICU discharge or day 28, whichever came first. Day 1 started at 8:00 a.m. on the first ICU day.

Nasopharyngeal swab specimens were collected on admission, and bronchial aspirate samples were obtained after tracheal intubation. Specimens were placed in transport medium and kept at 2–4?C. Reverse-transcription polymerase chain reaction (RT-PCR) testing was done in accordance with published guidelines from the US Centers for Disease Control and Prevention [15]. A positive RT-PCR test in a respiratory sample (nasopharyngeal swab or tracheal aspirate) was required for confirmation of the diagnosis of 2009 influenza A (H1N1) pulmonary virus infection.

Definitions

AKI was classified according to the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease (RIFLE) criteria with a modification of the urine output criterion [1–3]. For this study, the RIFLE outcome categories loss and end-stage kidney disease were not evaluated [3]. Baseline serum creatinine values were estimated using the Modification of Diet in Renal Disease (MDRD) equation, as recommended by the Acute Dialysis Quality Initiative (ADQI) Working Group (assuming a lower limit of normal baseline glomerular filtration rate of 75 ml/min) and similar to previous studies [1–3]. For analysis, patients were assigned their worst RIFLE category according to either serum creatinine (the maximum value over a given time period)

or urine output criteria. Early AKI was defined as that occurring on admission or on 8:00 a.m. data on day 1 or day 2. Late AKI was defined as that occurring after day 2 data.

Use of vasopressor was defined as the requirement for norepinephrine at any dosage or dopamine at dosage >5 μg/kg/min. Hematological dysfunction was defined as coagulation Sequential Organ Failure Assessment (SOFA) score higher than 2. Fluid balance was calculated as the difference between fluid input and fluid output. Fluid input included all fluids infused by intravenous or enteral routes. Fluid output included urine output, volume of gastric residue, and fluid loss from drains.

Bacterial pneumonia as a complication of viral pneumonia was diagnosed in the presence of purulent sputum and significant growth of a potentially pathogenic microorganism in a tracheal aspirate sample culture accompanied by fever or an increase in white blood cell count. Bacteremia was diagnosed when a potentially pathogenic microorganism grew in more than one blood culture.

Statistical analysis

Outcome variables were compared between patients without AKI and patients with AKI, as well as between patients with early and late AKI. Continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range) and were compared using Student's *t* test or analysis of variance (ANOVA) with post hoc Scheff? test. For nonparametric variables, Kruskal–Wallis test was used. Categorical variables were expressed as proportions and were compared by the χ^2 or Fisher exact test. Multivariate analysis was performed using ICU mortality as the dependent variable, including in the maximal model the variables associated with mortality ($p < 0.1$) on univariate analysis. The odds for dying is expressed as the odds ratio (OR) and its 95% confidence interval (CI). Two-sided p value less than 0.05 was considered statistically significant.

Results

General characteristics

During the observation period, 115 patients were admitted to the ICU with the diagnosis of 2009 influenza A (H1N1) viral pneumonia requiring mechanical ventilation. Six patients were excluded because of chronic renal failure, and 25 because of missing data.

Characteristics of the 84 patients included are shown in Table 1. Diagnosis was confirmed by positive PCR test in respiratory samples in 56 (67%) cases. No patient was lost to follow-up to the specific time end points.

Table 1 Patient characteristics and clinical outcomes of patients with 2009 influenza A (H1N1) viral pneumonia and total, early, and late acute kidney injury

	No AKI (*n* = 41)	**AKI (*n* = 43)**	**Early AKI (*n* = 28)**	**Late AKI (*n* = 15)**

	No AKI (*n* = 41)	**AKI (*n* = 43)**	**Early AKI (*n* = 28)**	**Late AKI (*n* = 15)**
Age, years, mean (SD)	42 (16)	46 (13)	48 (13)	43 (15)
Male, *n* (%)	15 (38)	30 (72)*	21 (77)*	9 (60)*
Body mass index kg/m^2, mean (SD)	29 (7)	33 (2)	34 (9)	31 (11)
APACHE II, mean (SD)	17 (7)	20 (7)*	22 (7)*	16 (5)†
$APACHE\ II_{nonrenal}$, mean (SD)	17 (1)	18 (1)	18 (7)	15 (5)
Renal replacement therapy, *n* (%)	1 (2)	19 (44)*	9 (32)*	10 (67)*,†
Noninvasive ventilation, *n* (%)	23 (56)	10 (23)	6 (21)*	3 (20)*
Days of mechanical ventilation, median (IQR)	10 (2, 15)	8 (4, 16)	9 (3, 16)	15 (12, 20)
ICU length of stay, median (IQR), days	10 (5, 16)	11 (5, 16)	9 (4, 16)	15 (12, 18)
ICU mortality, *n* (%)	16 (39)	31 (72)*	17 (61)	14 (93)*,†
Hospital length of stay, median (IQR), days	17 (12, 23)	18 (11, 34)	15 (11, 37)	28 (28, 28)
Physiological and biochemical parameters				
Cardiovascular failure, *n* (%)	11 (27)	26 (60)*	17 (61)*	9 (60)*
PEEP (cm H_2O), mean (SD)	10 (4)	13 (5)*	13 (5)*	13 (4)*
PaO_2/FiO_2 ratio	194 (142)	126 (74)*	124 (71)*	128 (84)
Platelet count ? 1,000/ml, mean (SD)	223 (63)	186 (74)*	180 (81)*	185 (69)
Bilirubin, mg/dl, mean (SD)	0.6 (0.5)	0.9 (0.6)*	1.2 (0.8)*	0.6 (0.3)
Fluid balance (ml/24 h), mean (SD)	1,008 (1,010)	1,421 (2,017)	3,075 (1,428)*	735 (1,958)
Urine output (ml/kg/h), mean (SD)	1.1 (0.6)	0.9 (0.6)	0.8 (0.6)*	1.2 (0.61)

* $p < 0.05$ versus non-AKI

† $p < 0.05$ versus early AKI

AKI acute kidney injury, *ICU* intensive care unit, *IQR* interquartile range, *PEEP* positive end-expiratory pressure

Acute kidney injury

AKI developed in 43 (51%) of 84 patients with influenza A (H1N1) viral pneumonia, and 20 needed RRT. Patients with risk (5/43, 12%), injury (11/43, 25%), and failure (27/43, 63%) had mortality of 40%, 64%, and 78%, respectively.

Patients with AKI were, as compared with patients without AKI, more likely to be male and obese, and had higher APACHE II score and greater ICU mortality. Noninvasive ventilation (NIV) was used less often in patients with AKI than in patients without AKI. Organ dysfunction was also more severe in patients with AKI, as indicated by higher prevalence of shock, and lower PaO_2/FiO_2 ratio and blood platelet count (Table 1). As the observed difference in APACHE II score between patients without and with AKI could be due to the renal component of the score, we recalculated the APACHE II score without the renal component, finding it to be not significantly different between non-AKI and AKI ($p = 0.65$) or between early and late AKI ($p = 0.32$).

There was no difference (comparison between groups not shown) between the non-AKI and the AKI groups in (data presented as median [IQR], percentage or mean ? SD for the entire group of 84 patients) the prevalence of different comorbidities, the NIV failure rate (29 of 33 who received NIV [87.5%]), days from onset of symptoms to ICU admission (6 [7–9]), prevalence of bacterial pneumonia as a complication (27/84 [32%]) or prevalence of bacteremia as a complication (8/84 [9.5%]). In addition, mean arterial pressure (81 ? 21 mmHg), tidal volume delivered (480 ? 108 ml/kg), peak airway pressure (30 ? 7 cmH_2O), plateau airway pressure (25 ? 6 cmH_2O), arterial pH (7.25 ? 0.34), $PaCO_2$ (47 ? 19 mmHg), white blood cell count (11,159 ? 7,506 cells/μl), lymphocyte count (915 ? 852 cells/μl), serum lactate dehydrogenase (LDH) activity (1,185 ? 1,121 U/l), and lactate serum concentration (2.3 ? 2.1 mmol/l) were not significantly different between the two groups. Of 77 patients who received treatment with neuraminidase inhibitors, 41 (53%) died, whereas among 7 who did not receive treatment, 5 (71%) died ($p = 0.30$).

Early versus late AKI

Early AKI was found in 28 patients (33% of all patients), and late AKI in 15 (18% of all patients) (Table 1).

When comparing early versus late AKI, some differences not obvious in the AKI versus non-AKI comparison became evident. Male predominance, as compared with the non-AKI population, was observed in both early and late AKI. The APACHE II score, however, was higher than in non-AKI patients in early but not in late AKI.

Early AKI did not impact duration of mechanical ventilation or ICU length of stay, and mortality was nonsignificantly higher than in non-AKI patients. Only patients with late AKI had, as compared with patients without AKI, a nonsignificant trend towards more prolonged duration of mechanical ventilation and ICU and hospital length of stay, and significantly higher mortality (Table 1).

Similarly, as compared with patients without AKI, in patients with early but not late AKI, the difference in PaO_2/FiO_2 ratio, blood platelet count, and serum bilirubin concentration on ICU admission reached statistical significance. ICU mortality was higher in late than in early AKI (Table 1).

Other variables [prevalence of comorbidities, bacterial pneumonia as complication, bacteremia, heart rate, mean arterial pressure, tidal volume delivered, peak and plateau airway pressure, white blood cell and lymphocyte counts, international normalized ratio (INR), and serum LDH activity] were comparable in patients with early versus late AKI (not

shown).

Among patients with early AKI ($n = 28$), 15 of 20 (75%) whose renal function did not improve over time died, whereas 2 of 8 (25%) whose renal function improved died (Fig. 1).

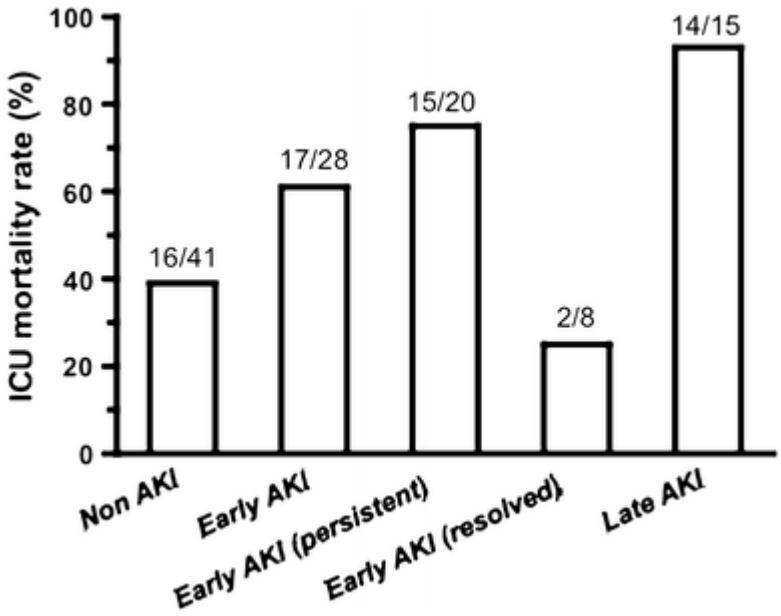

Fig. 1 ICU mortality rate in patients with non-AKI, early AKI (persistent or resolved), and late AKI. Numbers above columns indicate the number of deaths over the total number of patients with that condition. *AKI* acute kidney injury

The number of patients with AKI receiving RRT was 9 of 28 in the early AKI and 10 of 15 in the late AKI group. Of those, four (one before day 14 and three after day 14 of RRT) in the early AKI group and one (before day 14 of RRT) in the late AKI group came off RRT and survived. One additional patient without AKI received RRT in the context of multiorgan dysfunction as per the criterion of the attending physician.

Variables associated with mortality

Only the APACHE II score, the diagnosis of cardiovascular, hematological, respiratory failure, and the diagnosis of late AKI were associated with mortality on univariate analysis. Early AKI was not related to mortality. Since RRT is known to be associated with mortality, and RRT was used less frequently in early than in late AKI, it is possible that the difference in mortality observed in early and late AKI was due to the different mortality rate associated with RRT. Among 19 patients receiving RRT, 14 (74%) died, whereas among 24 patients not receiving RRT, 16 (67%) died ($p = 0.4$). Thus the impact of RRT on mortality did not reach statistical significance, and RRT was not associated with mortality on multivariate analysis.

On multivariate analysis, only APACHE II score on admission and the diagnosis of late AKI were associated with mortality (Table 2).

Table 2 Multivariate analysis of variables associated with ICU mortality in patients with 2009 influenza A (H1N1) viral pneumonia

	Patients who survived (n = 38)	Patients who died (n = 46)	Univariate analysis		Multivariate analysis	
			Odds ratio (CI 95%)	p Value	Odds ratio (CI 95%)	p Value
APACHE II, mean (SD)	17 (8)	20 (6)	1.1 (1.0–1.1)	0.04	1.1 (1.0–1.1)	0.04
Late AKI, n (%)	1 (2)	14 (23)	7.8 (1.1–52.4)	0.01	15.1 (1.8–130.7)	0.01

AKI acute kidney injury, *ICU* intensive care unit

Discussion

Several publications have reported the clinical characteristics and outcomes of critically ill patients with 2009 influenza A (H1N1). However, many aspects of the disease remain to be studied, including the prevalence and impact on mortality of organ dysfunction. Specifically, there is very limited information concerning the clinical characteristics of patients with 2009 influenza A (H1N1) and AKI.

The 51% prevalence of AKI in our series is somewhat lower than the 67% reported by Sood et al. in patients with pandemic H1N1 influenza admitted to the ICU [9], but similar to the prevalence reported for general ICU patients (20–75%) using the same RIFLE criteria [16]. Furthermore, the rate of AKI within the first 48 h (33%) is in line with the currently reported incidence in ICUs [1]. Although we cannot explain the difference from the previously reported incidence of AKI in pandemic 2009 influenza A (H1N1) [9], it is possible that different treatment strategies could be related to differences in the prevalence of AKI. In fact, most of the patients in Sood et al.'s study [9] had AKI by the urine output criterion and only 25% by the serum creatinine criterion, whereas in our series patients were nonoliguric on average (mean urine output 0.9 ml/kg/h). The prevalence of acute kidney injury in general ICU patients reported in the SOAP study [17] was lower than in our cases (36%), but in that study [17] diagnostic criteria indicative of more severe renal injury (serum creatinine >3.5 mg/dl or urine output <500 ml in 24 h) were used.

The distribution of patients in the different AKI classes (risk, injury, and failure) in patients with pandemic H1N1 influenza has not been previously reported. In the present report, it was 12%, 25%, and 63%, respectively. AKI class distribution reported in general ICU patients by Hoste et al. [18] was 18%, 40%, and 42%, respectively (recalculated from the original data).

The mortality of patients without AKI in the present series (39%) was much higher than the 5% [17] or 16% [18] reported in general ICU patients without AKI and the 17% in patients with pandemic H1N1 influenza [18]. Patients in those series [17, 18] were general ICU patients with less severity. For instance, in the SOAP study [17], about two-thirds of patients were on mechanical ventilation, less than one-quarter had respiratory failure, and only one-quarter had sepsis on admission. Our patients were all on mechanical ventilation, all had acute respiratory distress syndrome (ARDS), and 44% were in shock. Genetic background, date of censorship for mortality reporting, or nonobvious differences in treatment could also

explain to some extent the observed dissimilarities.

As expected, AKI was generally diagnosed in sicker patients. Patients with AKI, as compared with patients without AKI, had higher APACHE II score and higher incidence of organ dysfunction (cardiovascular, respiratory, hematological) on admission. APACHE $II_{nonrenal}$ was not different between patients without and with AKI, indicating that it is the renal component of the score that determines the detected difference, and that risk factors not captured by the APACHE II score are related to the development of AKI.

According to our hypothesis, we found that the time of onset of AKI characterized two different populations. Patients with early AKI had only slightly and nonsignificantly higher mortality rate than patients without AKI, whereas patients with late AKI had significantly higher mortality than patients with either non-AKI or early AKI. In the study by Payen et al. [17], patients with early AKI had similar mortality rates to patients with late AKI. We cannot explain this discrepancy based on our results. Different availability of the use of RRT could explain these differences. Our results (higher mortality rate of late versus early AKI, and low mortality rate in those patients with early AKI whose renal function improves over time) are biologically plausible. Early AKI, probably determined to some extent by perfusion abnormalities in the context of insufficient or still ongoing resuscitation, is associated with a lower mortality rate than late AKI, which generally appears in combination with sepsis, multiple organ failure, and use of nephrotoxic agents. However, the lack of urinary indices or information concerning the response to fluid challenge makes our interpretation of the lower mortality rate of early versus late AKI purely speculative. It is very likely that the different mortality rate in early versus late AKI is due to the higher rate of resolution of renal dysfunction and the associated lesser requirement for RRT in early compared with late AKI.

There is a lack of information on the incidence and mechanisms of AKI in viral infections. Tentative explanations for AKI in patients with pandemic 2009 influenza A (H1N1) would be those proposed for AKI in general critically ill patients, including insufficient resuscitation and, in the context of the inflammatory response, perfusion failure and cell injury. Rhabdomyolysis, which certainly could contribute to AKI, has been reported in patients with pandemic 2009 influenza A (H1N1) [8, 19]. Whether there is virus present in renal tissue that could induce specific effects on renal function has not been reported as yet.

Patients with late AKI had a similar APACHE II score to patients without AKI. This result suggests that events taking place after admission (whose severity is not reflected in the admission APACHE II score) explain the development of AKI during the ICU course.

It is possible that, as RRT was used less frequently in early than in late AKI, the observed mortality difference in the two groups was due to the different use of RRT. In our study, the impact on mortality of the use of RRT did not reach statistical significance. Of 20 patients receiving RRT, 14 died and only 6 survived ($p = 0.09$). Consequently, although it is possible that this lack of significance is due to the small sample size, our results indicate that, regardless of the different use of RRT, early AKI is associated with a lower mortality rate than late AKI.

Limitations

A major limitation of this study is its observational nature, allowing only the study of

associations but precluding the assessment of cause and effect relationships. Second, the lack of information pertaining to many confounders (such as delay in oseltamivir treatment, availability, timing of renal replacement therapy, use of goal-directed sepsis therapy, ability to clear the virus, and use of nephrotoxic agents) forestalls the control of important variables that might play a role in the relationship between H1N1 influenza and AKI. In addition, this lack of information prevents us from speculating as to the causes of the development of late AKI. In addition, chronic renal failure, as self-reported or recorded in the patients' medical records, was an exclusion criterion. However, we could not determine whether elevated baseline serum creatinine was early AKI or rather indicated stable chronic renal failure. Finally, our results on the analysis of patients from a specific geographic area may not be generalizable to other areas.

Interpretation

AKI developing early after ICU admission that resolves over time is probably related to hemodynamic abnormalities rather than to inflammatory or sepsis-induced mechanisms. If this abnormal hemodynamics resolves (patients with early AKI that resolves over time), the mortality rate is comparable to that of patients with normal renal function. AKI that develops later in the course of the disease, appearing in the context of multiorgan dysfunction, is associated with a very high mortality rate. The severity of patients with late AKI is not captured on admission by the APACHE II score, suggesting that events taking place after ICU admission, and possibly amenable to preventive measures, are involved in the development of late AKI.

Conclusions

Patients with influenza A (H1N1) viral pneumonia have a high incidence of AKI. Late but not early AKI is associated with a large impact on mortality.

Participating units

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Intensive Care Medicine

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Kidney histopathological findings in fatal pandemic 2009 influenza A (H1N1)

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Without Abstract

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Dear Editor,

A new pandemic was originated by a novel influenza A (H1N1) virus [1–3]. Severe cases were characterized by acute respiratory distress syndrome (ARDS), shock, and acute kidney injury (AKI) [3]. Lung histopathological changes in fatal cases showed signs of diffuse alveolar damage, necrotizing bronchiolitis, and occasional alveolar hemorrhage [2]. However, histopathological changes in organs other than the lungs are not known. Here we report kidney histopathological findings and describe for the first time the specific kidney cell type targeted by pandemic 2009 influenza A (H1N1) virus infection.

With the approval of our Ethics Committee and with closest relative informed consent, renal biopsies from four patients who died in the intensive care unit (ICU) with diagnosis of

confirmed influenza A (H1N1) virus infection were studied by microscopy after hematoxylin and eosin (HE), Masson's or periodic acid-Schiff (PAS) staining. Cell nuclei were revealed by staining with 4',6-diamidino-2-phenylindole (DAPI). Localization of viral antigen and specific kidney cells was carried out by double immunofluorescence (IF) labeling [4] using antibodies (Santa Cruz) specific for either: (1) aquaporin 1, a marker of proximal tubular cells; (2) CD10, a marker of proximal tubular cells; (3) cytokeratin 7, a marker of distal tubular cells; or (4) CD34, a marker of endothelial cells, and a rabbit antiserum specific for influenza nucleoprotein (NP). This antibody was generated by immunization of rabbits with purified recombinant NP and validated by IF, Western blotting, and immunoprecipitation of control and influenza-infected human cells [5]. This antibody is cross-reactive with several influenza A virus subtypes (data not shown). Secondary antibodies were fluorescein isothiocyanate (FITC)-labeled goat anti-mouse immunoglobulin G (IgG) (Santa Cruz) and Alexa 546-conjugated goat anti-rabbit IgG. Sections were studied under confocal microscopy (Leica SP5), and single optical sections are presented.

Only cases 3 and 4 were diagnosed with AKI. Cases 3 and 4 had focal changes consistent with acute tubular necrosis (ATN) in the distal tubules (epithelial cell swelling, individual cell necrosis, and shedding of necrotic and viable epithelial cells into the tubular lumina). Although post mortem autolysis of renal tubules has features indistinguishable from ATN, we could not identify diffuse damage of proximal renal tubules attributable to autolysis, such as loss of tubular cell brush border or prominent cell vacuolization, in any of the cases reported here. Both biopsies had PAS-positive intracytoplasmic granules in tubular epithelial cells and in the parietal and visceral epithelium of the Bowman's capsule. Endothelial cell lesions were not seen in any of the cases. In cases 3 and 4 there was increased immunoreactivity for viral NP, specifically in the distal tubules and the Bowman's capsule epithelia (Fig. 1), and the level of NP suggested active virus replication in these cells. The predominant cytoplasmic localization of the NP signal suggests these cells are in a late phase of virus infection [5].

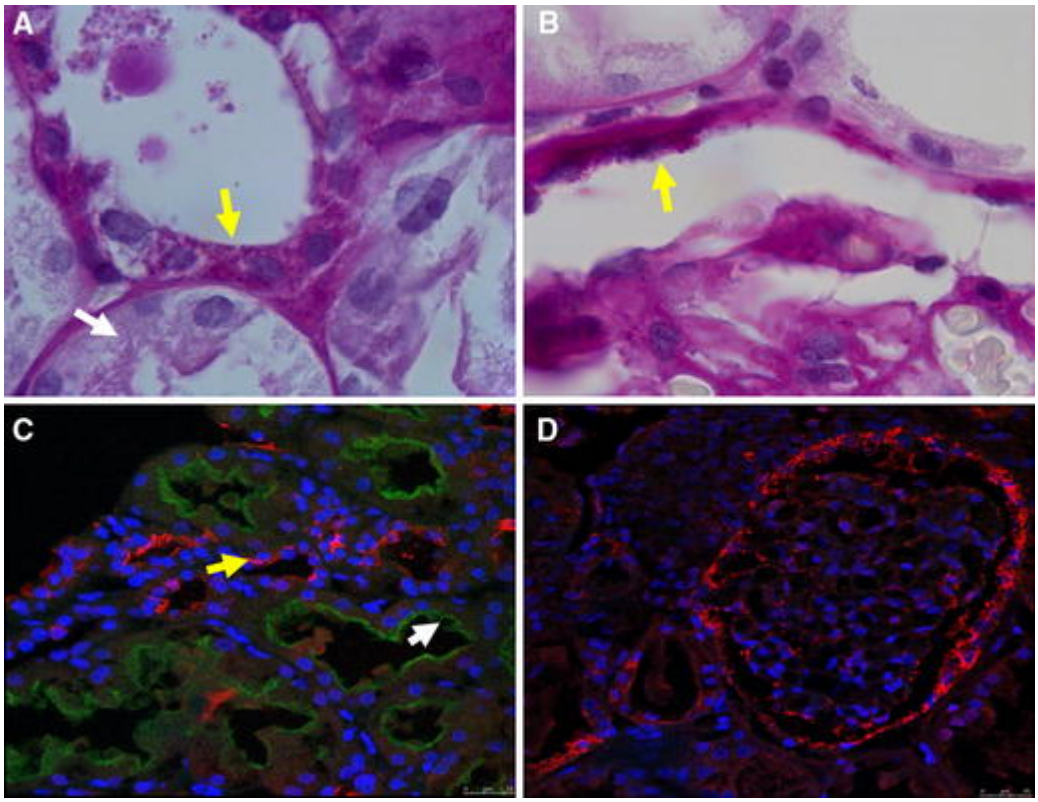

Fig. 1 Representative photomicrographs of kidney pathology (light microscopy), and demonstration of viral nucleoprotein. **a** (HE ?40) (case 3). Distal tubules with necrotic debris and shed necrotic tubular cells in their lumina. Red intracytoplasmic granules are widely seen in epithelial cells (*yellow arrow*). In contrast, a nearby undamaged proximal tubule with normal tubular epithelium and intact brush border is seen (*white arrow*). **b** (HE ?40, PAS stain) (case 3). The edge of a glomerulus shows the Bowman's capsule with numerous red intracytoplasmic granules in parietal cells (*arrow*). **c** Immunofluorescence for proximal tubular cells (CD10) (in *green*, *white arrow*) and viral nucleoprotein (in *pink*, *yellow arrow*) in tubular structures that are not proximal tubular cells. Nuclei are shown in *blue*. **d**. Immunofluorescence for viral nucleoprotein (in *red*) in a glomerular structure. Nuclei are shown in *blue*

In summary, kidney pathological changes in influenza A (H1N1) virus infection are consistent with ATN and persistence of viral infection despite antiviral treatment. Bowman's capsule epithelial cells and distal tubular cells seem to actively replicate the virus.

Conflict of interest None.

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Intensive Care Medicine

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Original

Acute kidney injury in patients with influenza A (H1N1) 2009

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Abstract

Objective

We aim to evaluate the incidence and outcome of acute kidney injury (AKI) among critically ill adult patients with H1N1 2009 infection.

Design and patients

From a prospectively collected influenza A (H1N1) 2009 bi-national, we identified 671 adult patients admitted to intensive care unit (ICU) from June 1 to August 31, 2009. Of these, 628 (93.6%) had admission and/or peak serum creatinine values during ICU stay. We defined AKI according to the creatinine criteria of the RIFLE classification.

Results

Of 628 adult patients, 211 [33.6%, 95% confidence interval (CI) 29.8–37.4%] had AKI: 41 (6.5%) risk, 56 (8.9%) injury and 114 (18.2%) failure. Of all 211 AKI patients, 76 [36.0% (29.4–42.6%)] died in hospital (36.6% in risk, 25.0% in injury and 41.3% in failure group) compared with 33 of 408 (8.1%) patients without AKI. Among the 33 AKI patients treated with renal replacement therapy, 13 died (39.4%). Mechanical ventilation [odds ratio (OR) 3.62 (2.07–6.34)], any severe co-morbidity (OR 2.36, 95% CI 1.15–3.71), age (OR 1.02, 95%

CI 1.01–1.03 per 1 year increase), and AKI (OR 6.69, 95% CI 4.25–10.55) were independently associated with hospital mortality.

Conclusions
Acute kidney injury appears common in H1N1 2009 infected patients and is independently associated with an increased risk of hospital mortality.

Electronic supplementary material The online version of this article (doi:10.1007/s00134-011-2166-8) contains supplementary material, which is available to authorized users.

Keywords Acute kidney injury – Influenza A – Pandemic – Critical illness – Mortality

On behalf of the ANZIC Influenza Investigators* [see appendix (as Electronic Supplementary Material)] and Australian and New Zealand Intensive Care Society Clinical Trials Group.

This article is discussed in an editorial available at: doi:10.1007/s00134-011-2196-2; related material can be found at doi:10.1007/s00134-011-2167-7 and doi:10.1007/s00134-011-2183-7.

Introduction

An influenza A (H1N1) 2009 pandemic emerged during 2009 and caused a significant burden of critical illness [1–3]. Little information is available on how such illness affected the kidney. Influenza A infections rarely cause acute kidney injury (AKI), mostly due to rhabdomyolysis [4, 5]. AKI has been reported in 17% of patients with avian influenza A (H5N1) [6], and, recently, a small single-centre case series of H1N1 2009 patients suggested a high risk (32%) of AKI [7]. More recently, a multicentre observational study of 50 critically ill patients with H1N1 infection reported a 67% incidence of AKI [8]. However, so far, the evidence is limited and no large, prospective, multicentre studies of H1N1 have reported on the incidence and outcome of AKI.

Accordingly, we used a prospectively collected influenza A (H1N1) 2009 bi-national [2] to evaluate the incidence and hospital outcome of AKI among critically ill adult patients with H1N1 2009 infection.

Materials and methods

Patients

We have previously performed a multicentre inception cohort study in 187 ICUs in Australia and New Zealand comprising all adult, paediatric and combined adult and paediatric ICUs in Australia and New Zealand [2]. Each centre obtained Institutional Ethics Committee approval, and requirement for individual subject informed consent was waived at all sites. Between June 1 and August 31, 2009, all patients admitted to ICU with confirmed influenza A were identified. Influenza A was confirmed by polymerase chain reaction (PCR), antigen detection or serology. From this prospectively collected database, we then identified

all adult patients admitted with H1N1 2009. Of these patients, we selected those who had admission and/or peak creatinine values. We defined AKI according to the creatinine criteria of the RIFLE classification [9]. We report our findings according to the STROBE guidelines for observational studies [10].

Data collection

We collected the following patient-specific data: hospital and ICU admission date and time, age, gender, for women whether pregnant or postpartum <28 days, co-morbidities [any Acute Physiology and Chronic Health Evaluation (APACHE) III co-morbidity], history of chronic diseases, and airway status at ICU admission [2]. In addition, we collected data on daily use of renal replacement therapy (RRT) and mechanical ventilation, and serum creatinine and serum creatine kinase [normal values <200 IU/L] values at ICU admission and peak value during ICU stay. We recorded patient outcomes at hospital discharge status or as still in hospital as of November 23, 2009.

Data management and statistical methods

We collected data using electronic case report forms. The study-coordinating centre was the Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia. When the same patient was transferred between ICUs they were counted as a single ICU admission. We made no assumptions for missing data, and calculated all proportions as percentages of available data.

We identified AKI using the RIFLE [9] classification during ICU stay as recommended [11, 12] by the Acute Dialysis Quality Initiative group [9], and validated [13]. We identified the incidence of admission AKI using the first admission creatinine value, and defined "later" AKI if AKI developed during ICU stay in those patients with normal creatinine values at ICU admission. We used a cut-off value of 5,000 IU/L for markedly elevated creatine kinase as suggested previously [14].

We performed statistical analysis using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). We calculated descriptive statistics for all study variables. We report continuous variables as median with interquartile range (IQR) and categorical variables as percentage with 95% confidence interval (95% CI) where appropriate. We performed univariate analysis for hospital mortality using chi-square, Fisher's exact test or Wilcoxon rank-sum test as appropriate. We performed multivariate logistic regression analysis to identify factors independently associated with an increased risk of hospital mortality, using a multivariate model constructed using both stepwise selection and backwards elimination techniques. We included all variables with $p < 0.10$ in the univariate model in the model selection process. Two-sided p value <0.05 was considered to be statistically significant, except for the multivariate model where p value <0.01 was used.

Results

Incidence and severity of AKI

We identified 671 adult patients with H1N1 infection admitted to ICU from June 1 to August 31, 2009. Of these, 628 (93.6%) had admission (*N* = 589, 87.7%) and/or peak serum creatinine (*N* = 567, 84.5%) values measured during their ICU stay. Among these adult patients, we identified 211 (33.6%, 95% CI 29.8–37.4%) H1N1 patients with AKI according to the RIFLE classification: 41 (6.5%) risk, 56 (8.9%) injury and 114 (18.2%) failure (Fig. 1, Table 1).

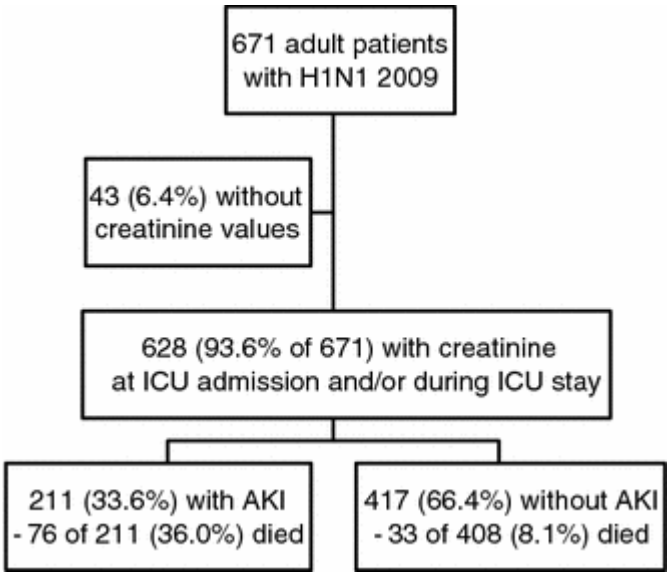

Fig. 1 Flowchart of adult influenza A H1N1 2009 patients admitted to Australian and New Zealand intensive care units

Table 1 Characteristics, treatment and outcome of adult patients with confirmed H1N1 2009-related critical illness (*N* = 628) according to presence or absence of acute kidney injury (AKI)

Characteristic	**AKI patients (*N* = 211)**	**Non-AKI patients (*N* = 417)**	***p*-Value**
Median (IQR) age (years)	47 (34–56)	44 (32–55)	0.06
Female sex, no. (%)	103 (48.8%)	228 (54.7%)	0.16
Pregnant women, no. (%)	12/103 (11.7%)	49/228 (21.5%)	0.047
Diabetes, no./total no. (%)	53/210 (25.2%)	63/405 (15.5%)	0.004
Chronic pulmonary disease, no./total no. (%)	60/209 (28.7%)	155/413 (37.5%)	0.03
Chronic heart failure, no./total no. (%)	34/209 (16.2%)	45/409 (11.0%)	0.06
Chronic renal failure, no./total no. (%)	12/211 (5.7%)	6/417 (1.4%)	0.006
APACHE III co-morbidity[a], no./total no. (%)	62/206 (30.0%)	91/399 (22.8%)	0.05
No known predisposing factors, no./total no. (%)	55/211 (26.0%)	127/417 (30.4%)	0.25

Characteristic	AKI patients (*N* = 211)	Non-AKI patients (*N* = 417)	*p*-Value
Time from first symptoms to hospital admission, median (IQR) days	4 (2–7)	4 (2–7)	0.64
Mechanical ventilation, no./total no. (%)	171/210 (81.4%)	237/410 (57.8%)	<0.0001
Vasopressors, no./total no. (%)	114/195 (58.4%)	94/367 (25.6%)	<0.0001
Corticosteroid treatment, no./total no. (%)	90/194 (46.3%)	153/365 (41.9%)	0.31

[a]Any condition that is defined within the chronic health evaluation component of the Acute Physiology and Chronic Health Evaluation III (APACHE III)

Of 211 AKI patients, 95 (45.0%) without chronic renal failure (CRF) and 2 (1%) with CRF had AKI on ICU admission, while 104 (49.3%) without CRF and 10 (4.7%) with CRF developed AKI during their ICU stay. Of 97 patients with admission AKI, 53 of 94 (56.4%) received vasopressors and 74 of 96 (77.1%) received mechanical ventilation (data missing for 3 and 1, respectively). The corresponding numbers for 114 patients with later AKI were 61 of 101 (60.4%) (data missing for 13) and 97 of 114 (85.1%), respectively.

Creatine kinase

The median (IQR) creatine kinase (CK) was 677 IU/L (254–2,295) in AKI and 413 IU/L (139–1,170) in non-AKI patients ($p = 0.006$). Median CK was 528, 638 and 918 IU/L in RIFLE classes R, I and F, respectively ($p = 0.04$). Of 120 AKI patients with available data on CK, 19 (15.8%) (2 in R, 3 in I and 14 in F class) had elevated serum creatine kinase exceeding 5,000 IU/L compared with 15 of 175 (8.6%) in patients without AKI ($p = 0.06$).

In-hospital mortality

Of all 211 AKI patients, 76 [36.0% (29.4–42.6%)] died in hospital (36.6% in RIFLE class R, 25.0% in I and 41.3% in F) compared with 33 of 408 (8.1%) H1N1 patients without AKI (Table 2). Of the 97 patients with admission AKI, 32 (33.0%) died in the hospital compared with 44 of 114 (38.6%) with later AKI (difference 5.6%, 95% CI 7.3–18.5%, ns). Of 33 RRT patients (15.6% of 211 AKI patients, 4.9% of all H1N1 patients), 13 (39.4%) died and 7 (21.2%) remained RRT dependent at hospital discharge. On multivariate analysis, mechanical ventilation, any severe co-morbidity and AKI were independently associated with an increased risk of hospital death (Table 3), but vasopressor use was not.

Table 2 Incidence and hospital mortality of acute kidney injury (AKI) in patients with H1N1 2009 infection according to different RIFLE criteria [9]

RIFLE class	*N* (%) of 628	Hospital mortality, *N* [%, (95% CI)][a]
R, risk	41 (6.5)	15/41 [36.6 (21.5–51.6%)]
I, injury	56 (8.9)	14/56 [25.0 (13.4–36.6%)]
F, failure	114 (18.2)	47/114 [41.3 (32.0–50.4%)]

RIFLE class	*N* (%) of 628	Hospital mortality, *N* [%, (95% CI)][a]
AKI R–F	211 (33.6)	76/211 [36.0 (29.4–42.6%)]
No AKI	417 (66.4)	33/408 [8.1 (5.4–10.8%)]

Urine output not available

[a]Hospital mortality available for all 211 AKI patients and 408 of 417 (97.8%) patients with no AKI as of November 23, 2009

Table 3 Variables independently associated with hospital mortality in adult H1N1 patients

	Odds ratio (95% CI)	*p*-Value
Age (per 1 year increase)	1.02 (1.01–1.03)	0.004
Any APACHE III co-morbidity	2.36 (1.51–3.71)	0.0002
Acute kidney injury	6.69 (4.25–10.55)	<0.0001
Mechanical ventilation	3.62 (2.07–6.34)	<0.0001

Discussion

In this prospective observational multicentre study, we identified 211 (34%) adult H1N1 2009 patients who developed AKI. We found that AKI patients had an increased risk of hospital death (36% versus 8%, adjusted OR 6.69) compared with patients without AKI. In adult H1N1 2009 patients, mechanical ventilation, any severe co-morbidity and AKI itself were independently associated with hospital mortality. AKI was associated with higher CK levels.

Few studies have reported cases of AKI associated with subtypes of influenza A [4–6, 15, 16]. Although the mechanism of AKI in influenza A infection remains unclear, evidence from case series has related it to rhabdomyolysis [14, 17]. Recent reports have also demonstrated elevated creatine kinase values in 62% [18] and approximately 75% [19] of critically ill H1N1 2009 patients. We found that creatine kinase exceeded 5,000 IU/L [14] in 16% of AKI patients, supporting the notion that muscle cell injury may contribute to the development of AKI in some H1N1 patients. Diabetes was also more common in AKI patients, as were use of vasopressors and mechanical ventilation, confirming that diabetes is a risk factor for AKI even in these patients and suggesting that, in some patients, AKI was part of multiple organ dysfunction.

An approximate assessment of the incidence of H1N1 2009-associated AKI has so far only been reported in 32% (9 of 28) of patients from a small case series in Argentina [7], and, more recently in 64% (32 of 50) of mechanically ventilated patients in Canada [8]. Furthermore, data from another larger case series, while not providing specific information, suggested a close to 10% incidence of AKI [19]. Given the sample size, our study provides the first robust estimate of the incidence of AKI (95% CI 30–37%) in adult critically ill patients with confirmed H1N1 2009 infection. This incidence is comparable to the 36% incidence of AKI reported in general ICU patients in the SOAP study [20], but lower than the 67% incidence of AKI in the cohort study by Hoste et al. [21], and lower than in critically ill

patients with confirmed or probable H1N1 infection (67%, 95% CI 53–80%) using RIFLE criteria with urine output data [8].

Our findings suggest that the severity of AKI in H1N1 2009 patients is comparable to in other ICU patients [22, 23]. Hospital mortality rates were higher in the R-group but lower in I- and F-groups than reported in other critically ill patients [22]. However, the mortality risk associated with AKI in H1N1 2009 patients seems to be comparable to that seen in other critically ill patients [20] (reported unadjusted ORs 2.4, 4.1 and 6.4 [22] according to different RIFLE classes, respectively).

We found that, in H1N1 2009 patients, RIFLE stages R, I and F were independently associated with hospital mortality, similarly to in other critically ill patients [23]. In addition, we found that severe chronic illness and mechanical ventilation on ICU admission were independently related to hospital death, in agreement with a previous study of AKI in general ICU patients [23].

To our knowledge, this is the only large, bi-national, multicentre study focussing on AKI in critically ill patients with H1N1 2009 infection. On the other hand, it has some limitations. First, creatinine values at admission were available in only 88% of patients. However, we did not detect any major differences between those with creatinine values available and those without. For those patients where the baseline creatinine value was missing, we estimated it as previously recommended [12]. Second, we did not have urine output data, which would have enabled us to use the complete RIFLE criteria. Other studies suggest that the urine output criteria have limited impact [24]. However, one recent multicentre study showed significant influence of urinary output on incidence of AKI [25]. Some patients may be oliguric without a significant increase in serum creatinine. Thus, the detected incidence of AKI without urine output in this study may be an underestimate. Third, data required for acute physiologic or organ dysfunction scoring were not available. Fourth, as an observational study, our results can only show association and no causal relationship. Fifth, we may have missed some possible confounding factors, such as additional infections, type of fluid resuscitation or lead-time bias. Finally, we did not gather data on dose or timing on RRT. However, our focus was simply to establish the burden and outcome of AKI in these unique patients.

In conclusion, we have demonstrated that one-third of critically ill patients with confirmed H1N1 2009 had AKI and that 4.9% required RRT. In addition, we found that patients with AKI had higher CK levels and that AKI was independently associated with increased risk of hospital mortality.

Conflict of interest The authors declared no competing interests.

Electronic supplementary material

Below is the link to the electronic supplementary material.
Supplementary material 1 (DOC 125 kb)

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