Research Article

Critical illness associated with 2013-2014 influenza A (H1N1): Postpandemic characteristics, presentation and outcomes

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Abstract

Introduction: The United States experienced a postpandemic outbreak of H1N1 influenza in 2013–2014. Unlike the pandemic in 2009 clinical course and outcomes associated with critical illness in this postpandemic outbreak has been only sparsely described. **Methods:** We conducted a retrospective analysis of all patients admitted to the Medical Intensive Care Unit with H1N1 influenza infection in 2009–2010 (pandemic) and 2013–2014 (postpandemic). **Results:** Patients admitted in the postpandemic period were older (55 ± 13 vs. 45 ± 12, *P* = 0.002), and had a higher incidence of underlying pulmonary (17 vs. 7, *P* = 0.0007) and cardiac (16 vs. 8, *P* = 0.005) disease. Mechanical ventilation was initiated in most patients in both groups (27 vs. 21, *P* = 1.00). The PaO_2/FiO_2 ratio was significantly higher in the pandemic group on days 1 (216 vs. 81, *P* = 0.0009), 3 (202 ± 99 vs. 100 ± 46, *P* = 0.002) and 7 (199 ± 103 vs. 113 ± 44, *P* = 0.019) but by day 14 no difference was seen between the groups. Rescue therapies were used in more patients in the postpandemic period (48% vs. 20%, *P* = 0.028), including more frequent use of prone ventilation (10 vs. 3, *P* = 0.015), inhaled vasodilator therapy (11 vs. 4, *P* = 0.015) and extracorporeal membrane oxygenation (ECMO) (4 vs. 2, *P* = NS). No significant differences in mortality were seen between the two cohorts. **Conclusions:** Compared to the 2009–2010 pandemic, the 2013–2014 H1N1 strain affected older patients with more underlying co-morbid cardio-pulmonary diseases. The patients had worse oxygenation indices and rescue modalities such as prone ventilation, inhaled epoprostenol and ECMO, were used more consistently as compared to the 2009 pandemic.

Keywords: Acute respiratory distress syndrome, influenza A, mechanical ventilation

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Introduction

The 2009 influenza A (H1N1) pandemic highlighted the differences of this strain from seasonal influenza, due to its higher incidence and virulence in younger individuals, obese patients, and pregnant women.[1,2] Affected patients developed rapidly progressive hypoxemia requiring significant ventilatory support[1-4] and the frequent utilization of extracorporeal membrane oxygenation (ECMO) as a rescue therapy.[3,4] Since the first reports of the pandemic, 3 subsequent waves were documented throughout the world, and similar clinical presentation, case mix, and fatalities were reported globally.[5,6]

North America saw a predominance of the H1N1 strain of the influenza virus during the winter season of 2013–2014.[7] The Center for Disease Control noted a

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heavy burden of predominantly H1N1 influenza viral infection in all 50 states in the United States.[8] Unlike the pandemic in 2009 clinical course and outcomes of critically ill patients infected with the 2013–2014 strain of H1N1 influenza virus has been only sparsely described.[9,10] We report the experience with critical illness associated with the 2013–2014 H1N1 outbreak at a quaternary referral institution. We also report the differences in the baseline characteristics, presentation, and the management of these patients compared to the 2009 pandemic and comment on any consequent differences in outcomes between the groups.

Methods

Patients

We included all patients with confirmed influenza A/H1N1 infection who were treated in our Medical Intensive Care Unit (MICU) between April 2009 and April 2010 (pandemic group), and then again from November 2013 to February 2014 (postpandemic group). We defined a case as being confirmed if the influenza A virus rapid antigen testing, Reverse transcription polymerase chain reaction, or viral culture from nasopharyngeal swabs, tracheal aspirates, or bronchoalveolar lavage (BAL) specimens was positive.

Data collection

We recorded demographic and clinical data including age, gender, height, weight, body mass index, symptoms on presentation to the emergency department, medical history, vital signs, presence of vasopressors, laboratory values, ventilator settings and respiratory parameters, Sequential Organ Failure Assessment (SOFA) scores on admission to the MICU, duration of mechanical ventilation (MV), duration of ICU and hospital stay, mortality, and the use of rescue therapies (namely inhaled nitric oxide or prostacyclin, prone position ventilation, high-frequency oscillatory ventilation, and ECMO).

We also recorded specific data in regards to the MV and respiratory parameters in these patients. We documented: (1) Mode of ventilation: The mode of ventilation that was used for the longest time for a given day; (2) PaO_2/FiO_2: Worst daily ratios were recorded; (3) positive end expiratory pressure (PEEP): The value corresponding to the highest PEEP for the day was recorded; and (4) tidal volume (Vt): The largest daily volume was recorded. Respiratory data was captured on the 1st day of intubation (day 1), and then on subsequent days 3, 7 and 14 of MV. We also collected ICU-specific interventions such as the use of vasopressors and the need for continuous dialysis on these days.

Statistical analysis

Descriptive statistics is reported as frequency analysis (percentages) for categorical variables and means (standard deviation), or medians (interquartile range) for continuous variables. We used a Student's *t*-test, or Wilcoxon's rank sum test as appropriate for continuous variables, and Chi-square test or Fisher's exact test for discrete variables. Confidence intervals and *P* values reflect a two-tailed α level of 0.05. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 62 patients were enrolled during the two study periods. 35 patients were admitted to the MICU in 2009–2010 (Pandemic group), and 27 were admitted in 2013–2014 (postpandemic group) [Table 1]. Patients in the postpandemic were older (55 ± 13 vs. 45 ± 12 years, $P = 0.002$), and had a higher prevalence of co-morbid pulmonary and cardiac conditions.

Table 1: Demographics and presentation of critically ill patients with confirmed Influenza A (H1N1) infection: 2009 pandemic compared to 2013-2014 postpandemic outbreak

	2009-2010	2013-2014	P
Age, mean (SD), years	45±12	55±13	0.002
Female sex	15 (43)	13 (48)	0.68
BMI (kg/m^2)	33 (28-41)	36 (27-41)	0.76
Comorbidities			
Chronic lung disease	7 (20)	17 (63)	<0.001
Cardiac disease	7 (20)	16 (60)	0.002
Chronic renal insufficiency	5 (14)	3 (11)	0.99
Tobacco use	17 (49)	8 (30)	0.13
Neurological disease	3 (9)	10 (37)	0.01
Severity of disease at admission			
Vasopressors on admission	6 (17)	10 (37)	0.07
AKI need for dialysis	19 (54)	8 (30)	0.05
SOFA score, day 1	8.7 (3.7)	8.4 (4.3)	0.81
Admission vital signs and laboratory values			
SBP (mm Hg)	130±26	122±27	0.27
Diastolic pressure (mm Hg)	69 (64-78)	71 (57-86)	0.88
Temperature (°C)	37.7±1.4	37.7±1.1	0.87
RR (breath/min)	24 (20-27)	24 (20-29)	0.57
HR (beats/min)	105±24	112±29	0.29
WBC (k/uL)	9.8 (3.9-15)	9.8 (6.9-11.9)	0.84
Platelets (k/uL)	163 (108-252)	179 (133-271)	0.34
Creatinine (mg/dL)	1.3 (0.8-2.7)	1 (0.7-1.7)	0.11
Bilirubin (mg/dL)	0.4 (0.2-0.8)	0.4 (0.3-0.5)	0.60
CK (U/L)	274 (94-1488)	169 (90-520)	0.16

Values expressed as number (percentages). All values are reported from the first documentation on admission to our facility. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; HR: Heart rate; WBC: White blood cell; CK: Creatinine kinase; AKI: Acute kidney injury; BMI: Body mass index; SD: Standard deviation; SOFA: Sequential organ failure assessment

Initial presentation

There was no difference in the initial laboratory studies between the groups [Table 1]. The rate of respiratory failure at the time of presentation to the ICU was similar in both the cohorts (78% and 82% for Groups A and B, respectively, *P* = NS). More patients in the postpandemic group required vasopressors on admission (37% vs. 14%, *P* = 0.07), and more patients in the pandemic group had acute kidney injury (AKI) (54% vs. 30%, *P* = 0.05). The SOFA scores on admission were comparable (8.7 and 8.4, respectively, *P* = NS). Similar numbers of patients in both groups required invasive and noninvasive positive pressure ventilation [Table 2].

A nasopharyngeal swab was the diagnostic modality used most often to diagnose Influenza in the postpandemic group (23 patients). The other patients were diagnosed by BAL (*n* = 2) or a sputum sample (*n* = 2). Thirty percent of patients had at least one false negative test, including one patient who had a negative BAL but a positive nasopharyngeal swab. The data for Group A were unavailable.

Table 2: Ventilatory characteristics for critically ill patients (pandemic compared to postpandemic Influenza A/H1N1 outbreak)

	2009-2010 (*n*=35)	2013-2014 (*n*=27)	*P*-value
	n (%)	*n* (%)	
Mechanical ventilation at admission	27 (78)	22 (82)	0.78
Invasive	25 (93)	16 (73)	0.67
Noninvasive	2 (7)	6 (27)	0.11
Failure of noninvasive	1 (50)	2 (33)	
Ever ventilated	28 (80)	25 (93)	0.17
Patients requiring rescue therapies	7 (20)	13 (48)	0.028
Rescue therapies for hypoxemia			
Nitric oxide or inhaled epoprostenol	4 (11)	11 (41)	0.01
Prone ventilation	3 (9)	10 (37)	0.01
ECMO	2 (6)	3 (11)	
APRV	3 (9)	4 (15)	
HFOV	1 (3)	-	
Liberation from ventilation (60 days)	16 (57)	14 (56)	1

Values expressed as number (percentages); ECMO: Extracorporeal membrane oxygenation; HFOV: High-frequency oscillatory ventilation; APRV: Airway pressure release ventilation

Acute respiratory distress syndrome and mechanical ventilation

Acute respiratory distress syndrome (ARDS) was common on presentation in both groups, and most patients required invasive MV over the course of their hospitalization. Although the Vt and PEEP in both groups were similar, the PaO_2/FIO_2 ratio was significantly worse in the postpandemic group over the 1st week of MV [Table 3]. Patients in the postpandemic group had higher PEEP requirements on day 7 and 14 (16 vs. 10, and 17 vs. 10 cm H_2O, *P* < 0.05 and NS, respectively). Nonconventional therapies for severe hypoxia were used more frequently in the postpandemic group on days 3 and 7. Overall, more patients in the postpandemic group required nonconventional therapies (48% vs. 20%, *P* = 0.028) and more rescue therapies were utilized including more frequent use of prone ventilation (10 vs. 3, *P* = 0.015), inhaled vasodilator therapy (11 vs. 4, *P* = 0.015) and ECMO (4 vs. 2, *P* = 0.39) [Tables 2 and 4]. One patient in the postpandemic group underwent bilateral lung transplantation after demonstrating an inability to be liberated from ECMO. All patients (with one exception in the pandemic group) in both groups were treated with oseltamivir. Eighteen patients in the pandemic group and 3 patients in the postpandemic group received double dose therapy (150 mg twice a day).

Outcomes between the two groups were similar although the postpandemic group tended to have a longer ICU and hospital length of stay (18 vs. 13 and 24 vs. 17 days, *P* = NS for both, respectively) and higher mortality (41% vs. 26%, *P* = 0.28) [Table 5].

Discussion

Although other countries experienced earlier postpandemic waves of H1N1 influenza virus infection, the United States did not see a resurgence of this strain until the winter of 2013–2014. Reports of patients with H1N1 infection in 2009[1-4] noted a proclivity for severe infection in healthy patients with younger age and obesity. The 2013 cohort in our study still had a significant

Table 3: Ventilatory and oxygenation parameters on days 1, 3, 7, and 14 of mechanical ventilation (pandemic compared to postpandemic Influenza A/H1N1 outbreak)

	Mechanical ventilation parameters and oxygenation indices							
	Day 1		Day 3		Day 7		Day 14	
	2009	2014	2009	2014	2009	2014	2009	2014
Mechanically ventilated patients	27 (77)	22 (82)	25 (86)	18 (86)	23 (92)	15 (84)	11 (85)	12 (86)
PaO_2/FiO_2	167 (92-320)	66* (56-87)	170 (114-288)	98* (65-121)	184 (105-248)	95* (77-152)	146 (84-178)	151 (133-167)
PEEP (cm H_2O)	18 (12-20)	18 (8-20)	13 (5-18)	15 (8-18)	10 (5-18)	16* (10-20)	10 (8-12)	17 (6-21)
Vt (ml/kg)	8±1.6	7.2±1.4	8.3 (7-9.6)	8 (7-8)	8 (6.8-8.6)	7.8 (7.7-8)	7.7±1.8	7.5±1.1

Values expressed as number (percentages). SD: Standard deviation; IQR: Interquartile range; PEEP: Positive end expiratory pressure; Vt: Tidal volume

Table 4: Clinical course of patients in the ICU (pandemic compared to postpandemic Influenza A/H1N1 outbreak)

	Day 1 *n* (%)		Day 3 *n* (%)		Day 7 *n* (%)		Day 14 *n* (%)	
	2009	2014	2009	2014	2009	2014	2009	2014
Patients in ICU	35	27	29	21	25	18	13	14
Patients requiring dialysis	-	-	7 (24)	2 (10)	7 (28)	4 (22)	8 (62)	3 (22)
Patients requiring vasopressors	6 (17)	10 (37)	6 (21)	9 (43)	5 (20)	7 (39)	2 (15)	2 (14)
Mechanically ventilated patients	27 (77)	22 (82)	25 (86)	18 (86)	23 (92)	15 (84)	11 (85)	12 (86)
Use of rescue therapy*	5 (19)	5 (23)	4 (16)	8 (45)	3 (13)	8 (53)	4 (34)	4 (34)
Mortality			1 (3)	3 (11)	2 (6)	5 (19)	5 (14)	7 (26)

The numbers here reflect the percentage based on the patients in ICU for all the variables except rescue therapies which are based on the number of patients who are mechanically ventilate. ICU: Intensive Care Unit

Table 5: Comparison of outcomes associated with pandemic and postpandemic influenza A/H1N1 outbreak

	2009-2010 *n* (%)	2013-2014 *n* (%)	*P*
Overall mortality	9 (26)	11 (41)	0.28
Time from ICU admission to death			
Day 28	9 (26)	9 (33)	0.58
Day 60	9 (26)	11 (41)	0.28
Duration of ventilation (days)	20±15	18±14	0.55
Survivors	22.6±17.1	21.9±14.8	0.96
Nonsurvivors	12.8±8	11.6±11.9	0.5
ICU length of stay (days)	13±12	18±14	0.13
Survivors	12.4±13.1	20.2±14.8	0.03
Nonsurvivors	13.4±7.7	16.1±18.8	0.6
Hospital length of stay (days)	17±12	24±18	0.11
Survivors	23.3±18.4	28.5±16.8	0.27
Nonsurvivors	13.8±7.5	16.8±18.6	0.7

Values expressed as number (percentages). SD: Standard deviation; IQR: Interquartile range; ICU: Intensive Care Unit

number of obese patients, but there were significant differences from previously reported literature. The 2013–2014 outbreak affected older individuals with chronic medical conditions when compared to the 2009 pandemic cohort. Despite a statistically significant difference in age of the two cohorts, it was striking that both these disease outbreaks did not affect geriatric populations (>65 years of age), preexisting immunity from previous outbreaks in the 1950's and 1960's might explain this finding.[11] These features are more reminiscent of populations effected by seasonal influenza rather than the 2009 H1N1 outbreak. This might be due to the development of immunity in younger individuals as a result of exposure to the H1N1 strain in 2009. Moreover, a lower rate of vaccination during the 2013–2014 season in at-risk patients might explain the shift in the age of the effected population.[10]

Our data also suggests that available Influenza diagnostic tests are imperfect. Our false negative rate of 30% in the postpandemic group is similar to other published data on this topic,[12] and highlights the importance of continued diagnostic evaluation in situations of high clinical suspicion of influenza infection, even in the face of one or more negative results.

Acute severe hypoxic respiratory failure necessitating positive pressure ventilation was a cardinal feature of severe H1N1 infection in patients admitted to intensive care units in both 2009 and 2013,[1-4,10] and was common in both groups. However, patients in the postpandemic group tended to be more hypoxic, as evidenced by lower PaO_2/FIO_2 ratios and higher PEEP requirements. Rescue therapies for refractory hypoxemia were used in more patients in the postpandemic group, particularly on days 3 and 7 of the ICU stay. Despite worsening hypoxemia in this cohort, the mortality was similar to the pandemic cohort. The more frequent use of nonconventional therapies such as prone ventilation, inhaled vasodilators and ECMO in the postpandemic period likely reflects both the severity of hypoxemia, as well as the impact of newer studies changing clinical practice in critical illness since the 2009 pandemic.[13-15] Patients who required nonconventional therapies for refractory hypoxemia in the postpandemic period had good outcomes. Three of the 4 patients placed on ECMO and 6/10 patients who were ventilated in the prone position survived.

Abnormalities in liver function testing, noted in both groups, have been reported in association with H1N1 infection, with the hypothesis that the pandemic strain of Influenza has specific hepatotropic characteristics.[16] Influenza A infections have been associated with the development of AKI.[17] Although there is no clear evidence of the underlying mechanism, previous studies have shown an association of myoglobinuria and rhabdomyolysis with Influenza A infections.[17] High rates of AKI complicated the 2009 H1N1 pandemic, and the rates in our cohort are similar to previously reported numbers.[18] AKI was prevalent in both the groups in our study, but the rates were significantly lower in the 2013–2014 cohort. This is likely a reflection of more aggressive initial volume resuscitation due to the implementation of sepsis protocol and appropriate renal-protective doses of medications as a result of an antimicrobial stewardship program that were implemented over the last few years.

The mortality in both cohorts was high, although similar to reports of severe H1N1 Influenza infection in 2009 both globally[1-4] as well as in our institution.[19] This is most likely a function of a selection bias due to the quaternary nature of our institute and a high rate of referral for severe ARDS. The mortality rate of patients in our study was similar to that reported from previous observational cohorts and pragmatic trials in severe ARDS.[20-22]

Lung transplantation, although previously reported, is an uncommon rescue intervention in cases of severe ARDS.[23] It was utilized in one patient in our study who could not be liberated from ECMO. Its utility as a salvage therapy for ARDS after prolonged ECMO requires further clarification and study.

There are a number of limitations to our study. As a retrospective chart review, information culled for study purposes was at times incomplete. In addition, we understand the risk of selection bias due to the fact that our patient cohort represents only patients admitted to the intensive care unit of our specific tertiary referral center and may not be representative of the entire population. The small sample size further limits definitive statements regarding the generalizability of our findings. Moreover, it is challenging to distinguish whether observed differences were secondary to substantive differences between the cohorts or the result of clinical practice changes. Despite these limitations, the authors believe that the this study provides a meaningful and intuitive comparison between the two cohorts.

Conclusion

Our data indicate that there were clear distinctions in the "at risk" population during the two influenza A (H1N1) outbreaks. The 2009 pandemic clearly affected younger, healthier individuals, whereas the 2013–2014 outbreak behaved like seasonal influenza with a higher incidence in an older and more chronically ill population. Our data validate concerns that virulent influenza strains can have a significant burden on critical care resources and clinicians must maintain a high index of suspicion during influenza season, even in the face of negative diagnostic evaluations. Although there was a high rate of severe hypoxemic respiratory failure in both groups, recent studies have clearly changed practice patterns and have influenced the utilization of unconventional rescue therapies more often than in the pandemic of 2009.

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Conflicts of interest

There are no conflicts of interest.

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