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Severe Influenza in 33 U.S. Hospitals, 2013-2014:

Complications and Risk Factors for Death in 507 Patients

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Abstract

Background: Influenza A (H1N1) pdm09 became the predominant circulating strain in the U.S. during the 2013-2014 influenza season. Little is known about the epidemiology of severe influenza during this season.

Methods: A retrospective cohort study of severely ill patients associated with influenza infection in intensive care units (ICUs) in 33 U.S. hospitals between September 2013 and April 2014 was conducted to determine risk factors present on ICU admission for mortality and to describe patient characteristics, spectrum of disease, management and outcomes.

Results: 444 adults and 63 children were admitted to an ICU in a study hospital; 93 (20.9%) adults and 4 (6.4%) children died. By logistic regression analysis, older age (> 65 years, OR 3.1 [1.4-6.9], p = 0.006 and 50-64 years, OR 2.5 [1.3-4.9], p = 0.007; reference age 18-49), male sex (OR 1.9 [1.1-3.3], p = 0.031), history of malignancy with chemotherapy administered within the prior 6 months (OR 12.1 [3.9-37.0], p < 0.001) and a higher Sequential Organ Failure Assessment (SOFA) score (for each increase by 1 in SOFA score, OR 1.3 [1.2-1.4], p <0.001) were significantly associated with mortality among adult patients.

Conclusions: Risk factors for death among U.S. patients with severe influenza during the 2013-2014 season, when influenza A (H1N1) pdm09 was the predominant circulating strain type has shifted in the first postpandemic season towards a more typical epidemic influenza season.

Introduction

Influenza is a common human viral disease that has killed an estimated 30,000 to 49,000 people in the US each year since 1976.[1] Influenza occurs in epidemics in the U.S. each winter, punctuated two to six times every century by pandemics, when a novel strain type of influenza A emerges and spreads rapidly around the globe. After each of the three pandemic seasons during the twentieth century (1918-1919, 1957-1958 and 1968-1969), the newly emergent strain type became the predominant circulating strain. During normal epidemic influenza seasons, the majority of deaths occur in young children and in adults > 65 years of age. The influenza pandemic of 1918 was the most severe infectious disease outbreak in history, causing 50 to 100 million deaths worldwide.[2] Unlike normal epidemic seasons, a great number of these deaths occurred in young adults.[3]

During 2009, the most recent pandemic year, a novel H1N1 influenza A virus (influenza A (H1N1) pdm09) was first recognized in Mexico in March and then rapidly spread to all 50 states in the U.S. by the end of the summer.[4-5] During the 2009 pandemic season, severe influenza infections and deaths were more common among children and healthy young adults than during typical epidemic seasons,[6] but the case fatality rate overall was not unusually high.[7] In contrast to the previous three pandemic years, the novel influenza A (H1N1) pdm09 virus did not become the exclusive circulating strain after 2009; instead, both it and influenza A (H3N2) virus circulated during the 2010-2011,[8] 2011-2012[9] and 2012-2013 seasons.[10] However, during the 2013-2014 season, the surveillance program of the U.S. Centers for Disease Control and Prevention (CDC) found almost exclusive circulation of the influenza A (H1N1) pdm09 virus.[11] It is not known whether the patient population at risk for severe illness and death during 2013-2014 was similar to the 2009-2010 season.

We conducted a retrospective review of patients with laboratory confirmed influenza infection hospitalized in intensive care units (ICUs) at 33 medical centers to determine the demographic characteristics, outcomes of infection and risk factors for death of this cohort during the 2013-2014 influenza season.

Methods

At each of the 33 study sites in the Severe H1N1 Influenza Consortium 2014 (SHIC 2014), collaborating specialists in infectious diseases or critical care prepared a list of eligible subjects. All patients who had a positive test from the clinical microbiology laboratory for influenza A and/or influenza B and were admitted to an ICU were included. Influenza testing may have used a PCR-based test, a rapid test or viral culture. Complete laboratory data were accessed by infection control records, an enterprise data warehouse or directly from the clinical microbiology laboratory. Subjects included all patients who both tested positive for influenza (at either the study site or an outside hospital) and were admitted to an ICU between September 1, 2013 and April 1, 2014. For inclusion, the patient must have been diagnosed with laboratory confirmed influenza during an ICU stay or within 30 days prior to ICU admission. Institutional review boards of each participating hospital approved the study.

Data collected

At each center in this retrospective cohort study, a physician abstracted data from the electronic health record and entered them into a REDCap database.[12] Data included race and ethnicity; comorbidities; body mass index (BMI) (obesity defined as ≥ 30 kg/m^2); presenting symptoms; diagnoses, therapies and complications (reflecting the opinion of the treating physician); vital signs; Glasgow Coma Score at admission; laboratory, pathology, cytology,

microbiology and PCR diagnostic data; radiologic reports; prescription and nonprescription medications received; information on prior vaccination for influenza and *Streptococcus pneumoniae*; other pathogens isolated from clinical specimens; disposition and 30-day outcome; and autopsy reports. Data on underlying medical conditions specified by the Advisory Committee on Immunization Practices (ACIP) as risk factors for severe influenza were collected.[13] The Sequential Organ Failure Assessment (SOFA) score was calculated based on data in the first 24 hours of admission to the ICU.[14] Patients were not followed after hospital discharge.

Site-specific data were collected including the type of hospital (academic, community or Veterans Affairs [VA]), number of pediatric and adult beds, number of pediatric and adult ICU admissions during the 2013-2014 influenza season and the 2013 calendar year, and the type and brand name of the influenza test used during that season. Participating centers were located in 12 U.S. states (CA, CO, FL, IA, IL, IN, MI, NC, NE, NY, OH and TX) and included 20 academic, 10 community and 3 VA hospitals. Study sites had a median of 31 ICU beds (interquartile range [IQR], 18-90), a median of 373 total beds (IQR, 199-560), a median of 1,421 annual ICU admissions (IQR, 800-3,110) and a median of 16,087 annual hospital admissions (IQR, 10,014-24,384).

Statistical Analysis

Data were analyzed with STATA v12 (College Station, TX: StataCorp LP). Outliers were reexamined in the electronic medical record to ensure that data were accurate. No subjects with outlying values were dropped from any analysis. Descriptive statistics were tabulated for demographic data, symptoms, comorbidities, length of stay, laboratory test results, radiologic

studies, complications, treatment, SOFA score and support measures. An epidemic curve was generated. The case fatality rate was calculated.

Bivariable analyses compared potential risk factors for death < 30 days after ICU admission. A multivariable logistic regression model was developed to identify variables significantly associated in bivariable analyses at a $p < 0.05$ with death. In four sensitivity analyses, we ran the model without the SOFA score, only with influenza A (H1N1) pdm09 cases, excluding centers that used non PCR based diagnostic assays and excluding patients who were diagnosed with influenza > 7 days prior to ICU admission.

Results

Between September 1, 2013 and April 1, 2014, 507 patients with influenza infection were admitted to an ICU at one of the 33 study hospitals (median 22 patients per hospital [IQR, 11-37 patients]). Influenza A (H1N1) pdm09 was the predominant strain type, causing 311 (61.3%) infections in this cohort. Additionally, 170 (33.5%) infections were identified as Influenza A but were not subtyped (Figure 1). The remaining influenza strains identified included influenza A with an H1 subtype other than pdm09 (1.6%), influenza A with an H3 subtype (1.0%) and influenza B (2.6%).

The study population comprised 444 adults and 63 children. The 63 children were admitted at 10 of the 33 study hospitals. Baseline characteristics are displayed in Table 1. Notably, 213 (48.0%) of the adults were obese, 10/212 (4.7%) females were pregnant, and 25/502 (4.9%) patients tested positive for influenza > 48 hours after hospital admission. Fifty-eight of 184 adults (31.5%) and 11/45 (24.4%) children were known to have received the 2013-2014 vaccine 14 or more days before symptom onset, and 110/417 (26.4%) adults and 32/57 (56.1%) children received antiviral therapy within 48 hours after symptom onset. Ninety-seven

(19.1%) patients died within 30 days of ICU admission, of whom 93 were adults and 4 were children (Figure 2). Presenting symptoms among adults included cough (79.5%), shortness of breath (77.4%), fever (56.4%) and malaise (44.5%) compared with fever (76.2%), cough (73.0%), shortness of breath (68.3%) and nasal congestion (60.3%) among children (Figure 3a and 3b).

Patient characteristics associated with mortality among adults (> 17 years of age) in bivariable analyses are shown in Table 2. The number of children in our cohort who died was too small to assess risk factors for mortality. By logistic regression, characteristics associated with mortality among adults included older age (> 65 years, odds ratio [OR] 3.1 [95% confidence intervals, 1.4-6.9], p = 0.006 and 50-64 years, OR 2.5 [1.3-4.9], p = 0.007; reference group 18-49 years), male sex (OR 1.9 [1.1-3.3], p = 0.031), history of malignancy with chemotherapy administered within the prior six months (OR 12.1 [3.9-37.0], p < 0.001) and a higher SOFA score (for each increase by 1 in SOFA score, OR 1.3 [1.2-1.4], p <0.001). Separate regression models 1) excluding patients infected with influenza B, influenza A of an H3 subtype or influenza A of an H1 subtype other than pdm09, 2) excluding centers that utilized only rapid influenza tests and 3) excluding patients diagnosed greater than 7 days prior to ICU admission all showed no change in the variables associated significantly with death (data not shown).

In a planned secondary sensitivity analysis, when the SOFA score covariate on day 1 of ICU admission was removed from the multivariable model, two additional covariates became significantly associated with death within 30 days of ICU admission: 1) having infiltrates on initial chest x-ray in two or more lung quadrants and 2) having been admitted to a hospital, a skilled nursing facility or a long-term extended care facility during the prior year (data not

shown). We chose to include the SOFA score in the final multivariable model because it is a proven predictor of mortality among adult ICU patients.[14]

Medical and supportive therapies provided for patients in the study cohort are shown in Figure 3c and 3d. Among adults and children, 94.8% and 87.3%, respectively, received antiviral medications. Of adults, 419 received oseltamivir, 10 received intravenous (IV) zanamivir, two received amantadine and one received inhaled zanamivir. Of pediatric patients, 57 received oseltamivir and one received IV zanamivir. Two hundred seventy two (61.3%) adults and 22 (34.9%) children were intubated and mechanically ventilated. Of these patients, 114 (41.9%) adults and two (9.1%) children had non-invasive positive pressure (NIPP) ventilation attempted first. Also, 77/172 (44.8%) adults and 6/41 (14.6%) children who were not intubated underwent NIPP ventilation.

Reported complications of influenza infection are shown in Figure 3e and 3f. In a secondary bivariable analysis, complications occurring after ICU admission associated with death among all adults in the cohort and those adults with influenza A (H1N1) pdm09 included sepsis, acute kidney injury, acute respiratory distress syndrome (ARDS), shock, bacterial pneumonia, myocardial infarction, cerebrovascular accident and disseminated intravascular coagulation (DIC) (data not shown). Encephalopathy was associated with death in the entire cohort and acute liver injury was associated with death among patients with influenza A (H1N1). By bivariable analyses, sepsis, shock, encephalopathy and acute liver failure were associated with death among all children and those with influenza A (H1N1) pdm09. ARDS and DIC were also associated with death among all children (data not shown).

One influenza A (H1N1) pdm09 isolate and one influenza A isolate that was not subtyped were susceptible to oseltamivir when tested at the CDC.

Autopsies were performed for 12 of 97 patients who died. Lung histology revealed classic diffuse alveolar damage (DAD) in eight, DAD with necrotizing bronchiolitis in three, DAD with extensive hemorrhage in three and bacterial superinfection in four patients.

Discussion

In our cohort of severely ill patients, older age, male sex, having received chemotherapy in the previous 6 months and higher SOFA score on ICU day 1 were significantly associated with mortality. In 2009, in contrast, age < 65 years,[6,15] pregnancy[16-17] and morbid obesity[18] were associated with severe disease and mortality. Several multinational and non-U.S. studies have documented an age shift of severe disease and death towards older adults in the second influenza A (H1N1) pdm09 season.[19-23] In our study of patients who were admitted to ICUs, persons 50-64 years old (36.5%) and those 18-49 years old (30.8%) accounted for nearly 70% of the cohort. However, the oldest patients, those ≥ 65 years of age, were at the highest risk for death. The percentage of school-age children, adolescents or young adults who were critically ill with influenza was greater in a 2009 study[24] than in the present study. Therefore, the age distribution of patients with severe influenza in our study demonstrated a shift to older adults as compared to the 2009 pandemic year. Given that the genome of the influenza A (H1N1) pdm09 virus circulating in 2013-2014 was similar to the virus circulating during 2009,[25] this age shift may reflect increased population-level immunity among younger people resulting from H1N1 infections or from vaccination during the preceding four years.

The winter of 2013-2014 was the first season since 2009 during which influenza A (H1N1) pdm09 was the predominant circulating influenza strain in the U.S., and the number of severely ill influenza patients was the highest since the 2009 influenza pandemic.[26] During the

pandemic year, mortality among patient cohorts with severe influenza ranged from 14.3% to 26%.[24,27,28] In our cohort during 2013-2014, 19.1% of patients died.

The influenza A (H1N1) pdm09 virus has caused increased morbidity and mortality among pregnant women.[6,16,24] While 10 pregnant women required ICU care in our study, none died. We observed a higher risk of death among males, which has been reported previously for seasonal influenza[29] and has been attributed to numerous behavioral, immunologic and comorbid factors.[30]

In our cohort, 93% of adults and 81% of children had underlying medical conditions included on the ACIP's list of factors increasing the risk of severe influenza. In California, 79% of severely ill influenza patients during 2009 and 93% during 2013-2014 had one of these conditions.[26-27] This suggests that a population with more comorbid conditions was severely ill with influenza infection in 2013-2014 compared with the 2009 pandemic year. This may mark 2013-2014 as the season when the influenza A (H1N1) pdm09 strain became, for the first time, the cause of a more typical, annual epidemic of influenza in the U.S.

While morbid obesity was a newly recognized risk factor for hospitalization and death from influenza during the 2009 pandemic[15,18] it was not associated with death in our study. Of note, an estimated 34.9% of all U.S. adults were obese during 2012[31] and roughly 50% of Californians ≥20 years of age hospitalized with 2009 H1N1 infection were obese.[15] In our cohort 48.0% of adult patients were obese; thus, obesity may still be a risk factor for severe influenza infection.

Nearly all patients in our cohort received an antiviral medication after symptom onset but only 26.4% of adults and 56.1% of children received an antiviral within 48 hours of symptom onset. A recent study has shown that there is a statistically significant survival benefit of starting

antiviral therapy within 5 days of symptom onset for critically ill influenza patients.[27] It is noteworthy that receiving antiviral therapy within 5 days of symptom onset was not associated with survival in a bivariable analysis ($p = 0.07$), however, it trended towards significance in our cohort. While our study may have been underpowered to determine an association between antiviral medication use and mortality, it may be that host factors were more important than the use of antiviral therapy for preventing death in our cohort.

Vaccination programs in the U.S. have not achieved adequate coverage, including among persons at high risk for complications.[32] For example, only 52.2% of pregnant women reported receiving the influenza vaccine before or during pregnancy during the 2013-2014 season.[33] In our cohort, 31.5% of adults and 24.4% of children were known to have received influenza vaccination in the 2013-2014 season 14 or more days before symptom onset. However, a history of vaccination was not associated with decreased mortality. The circulating influenza A (H1N1) pdm09 virus was antigenically similar to the vaccine component in the 2013-2014 Northern Hemisphere influenza vaccine.[25] This may suggest that the immunologic response to the vaccine may not have been adequate to prevent death in our severely ill cohort.

Data suggest that during the 1918 pandemic the majority of patients who died with influenza, died of secondary bacterial infection.[34-35] During the 2009 pandemic, bacterial pneumonia complicated roughly one-quarter of severe cases.[36] During the 2013-2014 season, 157 (31%) patients in our cohort were diagnosed with secondary bacterial pneumonia. This high prevalence of bacterial coinfection may justify the frequent administration of antibacterials in our population.

ARDS was diagnosed in 201 (39.6%) patients, which is similar to the 38% observed among severely ill patients in the 2009 pandemic year.[37] Consequently, aggressive rescue maneuvers and therapies were performed on both adult and pediatric patients (Figure 3c-d).

Our study had several limitations. First, while ICUs in 33 hospitals were included, the majority of subjects were treated at tertiary referral centers. Thus, our findings may not be generalizable to all critically ill U.S. patients. Additionally, patients with severe comorbidities or elevated age may have elected not be admitted to the ICU, which may affect risk factors for death. By collecting data only until April 1, 2014, we did not include the final part of the influenza season, likely excluding disproportionately patients with severe influenza B infection. Moreover, management of patients was not standardized and was determined in accordance with local protocols. Rapid diagnostic testing was the only method used in 3 of 33 hospitals, which may have resulted in some missing cases although risk factors for death did not change when these institutions were excluded. We also did not record which patients received high-dose vaccines, and vaccination data were only obtained from the electronic health record. While we used a standardized data-collection form, some variables were not available for some patients. Also, our cohort was likely not adequately powered to assess the associations of antiviral therapy or pregnancy with mortality. Finally, because this was a retrospective study, selection bias and immortal time bias may have affected our choice of subjects and our analysis, respectively.

Conclusions

We identified risk factors known on ICU admission that increased the likelihood of death among adult patients with severe influenza during 2013-2014. We did not find associations with

previously described risk factors for death among those infected with influenza A H1N1 pdm09 virus in 2009. Our findings suggest that risk factors associated with death from severe illness caused by influenza A H1N1 pdm09 virus may have shifted in this first predominant influenza A H1N1 pdm09 postpandemic season, after the virus had circulated at a relatively low prevalence over the previous three epidemic seasons and as the population acquired immunity to this virus through widespread infection or vaccination.

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Tables

Table 1: Characteristics of 507 patients with severe influenza infection in the U.S. diagnosed between September 1, 2013 and April 1, 2014, comparing adult and pediatric patients.

Characteristics [a]		Adults (N=444) No. (%)	Pediatrics (N=63) No. (%)
Sex	Female	223 (50.2)	28 (44.4)
Age group	0-23 mo	-	27 (5.3)
	2-4 yr	-	12 (2.4)
	5-9 yr	-	10 (2.0)
	10-17 yr	-	14 (2.8)
	18-49 yr	156 (30.8)	-
	50-64 yr	185 (36.5)	-
	≥65 yr	103 (20.3)	-
Race	American Indian or Alaska Native	2 (0.4)	0 (0)
	Asian	6 (1.4)	2 (3.2)
	Black	118 (26.6)	14 (22.2)
	Native Hawaiian or other Pacific Islander	1 (0.2)	1 (1.6)
	Other/Multiracial	24 (5.4)	3 (4.8)
	White	242 (54.5)	35 (55.6)
	Unknown	51 (11.5)	8 (12.7)
Ethnicity	Hispanic	56 (12.8)	19 (30.2)
	Non-Hispanic	346 (77.9)	42 (66.7)
	Unknown	41 (9.2)	2 (3.2)
Geographic region of hospital	Midwest	273 (61.5)	30 (47.6)
	Northeast	20 (4.5)	1 (1.6)
	South	95 (21.4)	4 (6.4)
	West	56 (12.6)	28 (44.4)
Current tobacco use		131 (29.6)	0 (0)
Body mass index kg/m^2	< 30	233 (52.4)	-
	30-39 (obese)	142 (32.0)	-
	≥ 40 (morbidly obese)	71 (16.0)	-
	Unknown	1 (0.2)	-
Pregnancy (N = 251)	Females: currently pregnant	10 (4.7)	0 (0)
Insurance status	Private	128 (28.8)	21 (33.3)
	Public	229 (51.6)	36 (57.1)
	Private and Public	33 (7.4)	3 (4.8)
	Uninsured	27 (6.1)	0 (0)
	Unknown	27 (6.1)	3 (4.8)
Influenza type and subtype	A – H1N1 pdm2009	274 (61.7)	37 (58.7)
	A – subtype not specified	150 (33.8)	20 (31.7)
	A – H1 subtype not pdm2009	6 (1.4)	2 (3.2)
	A – H3	3 (0.7)	2 (3.2)
	B	11 (2.5)	2 (3.2)
Initial influenza diagnostic test (N=506)	Polymerase chain reaction	369 (83.1)	38 (61.3)
	Rapid influenza test	61 (13.7)	18 (29.0)
	Viral culture	7 (1.6)	0 (0)
	Other	7 (1.6)	6 (9.7)
Exposures	Known health care exposure in the previous 12 mo (N=370)	150 (47.3)	25 (47.2)
	Recorded sick contact (N=505)	100 (22.6)	32 (50.8)
	Symptoms onset > 48 hr after hospital admission (N=502)	24 (5.5)	1 (1.6)
Vaccines	Received 2013-14 vaccine (N=258)	108 (51.4)	18 (37.5)
	Received 2013-14 vaccine ≥ 14 days prior to symptom onset (N=229)	58 (31.5)	11 (24.4)
Admission from	Home	311 (70.0)	46 (73.0)
	SNF/LTEC	28 (6.3)	0 (0)
	Other or Unknown	105 (23.6)	17 (27.0)
Discharge to	Home	214 (48.2)	53 (84.1)
	Morgue/Death	91 (20.5)	4 (6.3)
	SNF/LTEC	87 (19.6)	0 (0)
	Other/Unknown/Still in hospital	13 (2.9)	6 (9.5)
Coinfections	Bloodstream infection on admission	23 (5.2)	1 (1.6)
Antivirals	Received after symptom onset	421 (94.8)	57 (90.5)
	Initiated prior to hospitalization (N=478)	153 (36.3)	29 (50.9)
	Initiated ≤ 48 hr after symptom onset (N=474)	110 (26.4)	32 (56.1)
ACIP preexisting condition	Present	413 (93.0)	51 (81.0)
Days from diagnosis to ICU admission	> 7	14 (3.2)	0 (0)
	0-7	294 (66.2)	49 (77.8)
	Diagnosed after ICU admission	136 (30.6)	14 (22.2)
Died		93 (20.9)	4 (6.4)

Abbreviations: SNF, skilled nursing facility; LTEC, long-term extended care facility; ACIP, Advisory Committee on Immunization Practices.

[a] When there are missing data for a specific variable, the n for subjects with data on this variable is indicated in the far left column.

Table 2: Patient characteristics associated with mortality among 444 adult patients with severe influenza infection in the U.S. between September 1, 2013 and April 1, 2014: Results of bivariable analyses and a multivariable logistic regression model.[a]

Characteristic[b]		Survived; N=351 (%)	Deceased; N=93 (%)	Bivariable; P value	Multivariable; odds ratio (95% CI), P value
Age, years	18-49	137 (39.0)	19 (20.4)	**0.003**	**Reference**
	50-64	136 (38.8)	49 (52.7)		**2.5 (1.3-4.9), p=0.007**
	> 65	78 (22.2)	25 (26.9)		**3.1 (1.4-6.9), p=0.006**
Sex	Female	188 (53.6)	35 (37.6)	**0.006**	**Reference**
	Male	163 (46.4)	58 (62.4)		**1.9 (1.1-3.3), p=0.031**
Race (N=393)	White	184 (59.6)	58 (69.1)	0.080	
	Black	101 (32.7)	17 (20.2)		
	Other	24 (7.8)	9 (10.7)		
Ethnicity (N=403)	Hispanic	47 (14.7)	10 (12.1)	0.54	
	Not Hispanic	273 (85.3)	73 (88.0)		
Insurance (N=417)	Private	98 (29.6)	30 (34.9)	0.47	
	Public	184 (55.6)	45 (52.3)		
	Public and Private	25 (7.6)	8 (9.3)		
	Uninsured	24 (7.3)	3 (3.5)		
Body mass index, kg/m^2 (N=439)	< 30	184 (52.4)	49 (55.7)	0.30	
	30-39 (obese)	119 (33.9)	23 (26.1)		
	≥ 40 (morbidly obese)	48 (13.7)	16 (18.2)		
Documented sick contact (N=442)		87 (24.9)	13 (14.1)	**0.029**	0.79 (0.37-1.7), p=0.53
Admission to a hospital or SNF/LTEC stay in the prior year	Yes	111 (31.6)	39 (41.9)	**0.015**	Reference
	No	144 (41.0)	23 (24.7)		0.58 (0.29-1.2), p=0.12
	Unknown	96 (27.4)	31 (33.3)		0.69 (0.35-1.4), p=0.28
Comorbidities	Asthma	71 (20.2)	10 (10.8)	**0.035**	0.62 (0.26-1.5), p=0.27
	COPD or other chronic lung disease (N=443)	123 (35.1)	27 (29.0)	0.27	
	Cardiovascular disease	102 (29.1)	27 (29.0)	0.99	
	Diabetes mellitus	110 (31.3)	29 (31.2)	0.98	
	Chronic kidney disease	57 (16.3)	15 (16.1)	0.96	
	Liver disease	19 (5.4)	10 (10.8)	0.064	
	Malignancy, received chemotherapy in past 6 mo	10 (2.9)	17 (18.3)	**<0.001**	**12.1 (3.9-37.0), p<0.001**
	HIV infection	7 (2.0)	2 (2.2)	0.92	
	Dementia	12 (3.4)	2 (2.2)	0.53	
	Other neurologic diseases	40 (11.4)	9 (9.7)	0.64	
	History of transplant	24 (6.8)	12 (12.9)	0.057	
	Received steroid and/or biologic within the past month (N=443)	31 (8.8)	8 (8.7)	0.97	
	FTT or malnutrition (N=443)	13 (3.7)	5 (5.4)	0.47	
	Current smoker (N=442)	110 (31.4)	21 (22.8)	0.11	
	No PMH (N=438)	68 (19.6)	13 (14.3)	0.25	
	ACIP comorbid condition[c]	324 (92.3)	89 (95.7)	0.25	
Coinfection	Coinfection with viral respiratory pathogen within 48 hr of admission (N-441)	5 (1.4)	5 (5.4)	**0.023**	2.7 (0.56-13.1), p=0.21
	Bacteremia on admission[d]	15 (4.3)	8 (8.6)	0.094	
	Respiratory tract infection on admission[d,e]	31 (8.8)	14 (15.1)	0.077	
Antiviral therapy (N=417)	Antiviral administered within 48 hr of symptom onset	92 (27.7)	18 (21.2)	0.22	
Vaccine ≥ 14 d prior to symptom onset (N=189)	Yes	51 (31.3)	12 (46.2)	0.14	
	No	112 (68.7)	14 (53.9)		
White blood cell count, K/uL (N=443)	> 11 (Leukocytosis)	124 (35.3)	30 (32.6)	**0.043**	Reference
	3.5-11 (Normal)	200 (57.0)	47 (51.1)		1.1 (0.57-2.0), p=0.86
	< 3.5 (Leukopenia)	27 (7.7)	15 (16.3)		0.65 (0.23-1.9), p=0.42
SOFA score; mean (sd) (N=440)[f]		7.1 (4.0)	10.9 (4.2)	**<0.001**	**1.3 (1.2-1.4), p<0.001**
Initial chest x-ray quadrants with	≥ 2	173 (49.3)	60 (64.5)	**0.009**	1.4 (0.80-2.6), p=0.22

infiltrate[g]					
Minimum PEEP at 24 h (N=245)	≥ 12 (high PEEP group)	41 (24.9)	17 (21.3)	0.53	
Tidal volume strategy at 24 h if volume mode used (N=149)	< 8 ml/kg of ideal body weight	82 (82.8)	44 (88.0)	0.41	

Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; FTT, failure to thrive; PMH, past medical history; ACIP, Advisory Committee on Immunization Practices; SOFA, Sequential Organ Failure Assessment; PEEP, positive end-expiratory pressure; sd, standard deviation.

[a] The multivariable analysis included all variables with $p < 0.05$ in the bivariable analysis.

[b] When there are missing data for a specific variable, the *n* for subjects with data on this variable is indicated in the far left column.

[c] ACIP conditions include children aged 6 through 59 months; all adults ≥ 50 years; adults and children with chronic pulmonary or cardiovascular, renal, hepatic, neurologic, hematologic or metabolic disorders; persons with immunosuppression; women who are or will be pregnant during the influenza season; children aged 6 months to 18 years who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome; residents of nursing homes and other long-term care facilities; American Indians/Alaska Natives; persons who are morbidly obese (BMI≥40)

[d] Were considered true infections by primary team based on documentation in the electronic medical record and appropriate antibiotic administered

[e] Included sputum, tracheal aspirate and bronchoalveolar lavage cultures

[f] SOFA score is determined by the following laboratory or clinical criteria: PaO_2/FiO_2; Glasgow coma scale; mean arterial pressure or requiring administration of vasopressor; bilirubin; platelet count; creatinine or urine output

[g] Determined by data abstracter by visual review of chest x-ray

Figure Legends

Figure 1. 507 patients with influenza admitted to intensive care units at 33 U.S. hospitals, by week, between October 1, 2013 and April 1, 2014, indicating influenza type and subtype.

Figure 2. Age distribution of 507 patients with severe influenza infection in the U.S. between September 1, 2013 and April 1, 2014, by outcome.

Figure 3(a-f). Symptoms present on initial hospital admission for 444 adult (3a) and 63 pediatric patients (3b) who were diagnosed with influenza infection and admitted to an ICU between September 1, 2013 and April 1, 2014. Therapies and supportive care utilized during ICU admission among these adult (3c) and pediatric patients (3d), by outcome before ICU discharge. Complications during ICU admission among adult (3e) and pediatric patients (3f), by outcome before ICU discharge.

Abbreviations: NIPP, non-invasive positive pressure; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; ICU, intensive care unit; DVT, deep vein thrombosis; CVA, cerebrovascular accident; *C. difficile*, *Clostridium difficile*; DIC, disseminated intravascular coagulation.