MAJOR ARTICLE

Influenza-Associated Pneumonia Among Hospitalized Patients With 2009 Pandemic Influenza A (H1N1) Virus—United States, 2009

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Background. Pneumonia was a common complication among hospitalized patients with 2009 pandemic influenza A H1N1 [pH1N1] in the United States in 2009.

Methods. Through 2 national case series conducted during spring and fall of 2009, medical records were reviewed. A pneumonia case was defined as a hospitalized person with laboratory-confirmed pH1N1 virus and a chest radiographic report consistent with pneumonia based on agreement among 3 physicians.

Results. Of 451 patients with chest radiographs performed, 195 (43%) had pneumonia (spring, 106 of 237 [45%]; fall, 89 of 214 [42%]). Compared with 256 patients without pneumonia, these 195 patients with pneumonia were more likely to be admitted to the intensive care unit (52% vs 16%), have acute respiratory distress syndrome (ARDS; 26% vs 2%), have sepsis (18% vs 3%), and die (17% vs 2%; $P < .0001$). One hundred eighteen (61%) of the patients with pneumonia had ≥1 underlying condition. Bacterial infections were reported in 13 patients with pneumonia and 2 patients without pneumonia. Patients with pneumonia, when compared with patients without pneumonia, were equally likely to receive influenza antiviral agents (78% vs 79%) but less likely to receive antiviral agents within ≤2 days of illness onset (28% vs 50%; $P < .0001$).

Conclusions. Hospitalized patients with pH1N1 and pneumonia were at risk for severe outcomes including ARDS, sepsis, and death; antiviral treatment was often delayed. In the absence of accurate pneumonia diagnostics, patients hospitalized with suspected influenza and lung infiltrates on chest radiography should receive early and aggressive treatment with antibiotics and influenza antiviral agents.

In April 2009, the Centers for Disease Control and Prevention (CDC) confirmed the first 2 cases of human infection with the 2009 pandemic influenza A H1N1 [pH1N1] virus in the United States [1–3]. Since spring of 2009, the pH1N1 virus has spread throughout the world and continues to circulate globally [4]. In the United States, pH1N1 virus infection led to an estimated 61 million cases, 274 000 hospitalizations, and 12 500 deaths from April 2009 through April 2010 [5].

Pneumonia and bacterial coinfection are known complications of seasonal influenza [6–11]. Pneumonia has also been a commonly reported complication among patients hospitalized with pH1N1 infection in many parts of the world [12–18]. Detailed clinical information regarding influenza-associated pneumonia among hospitalized patients with pH1N1 infection is still emerging. This report summarizes clinical findings of influenza-associated pneumonia among hospitalized patients with pH1N1 virus infection during the 2 waves of the US pandemic in 2009.

METHODS

Patients and Study Design

Patient data included in this analysis were derived from 2 previously described national pH1N1 hospitalization case series conducted in the United States during the spring [12] and fall [15] of 2009. Patients included in these case series had laboratory-confirmed pH1N1 virus by real-time reverse-transcriptase polymerase chain

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reaction; testing was clinically driven. In the spring (1 May–9 June 2009), the first hospitalized patients with pH1N1 virus infection reported to the CDC were sequentially sampled; participation from 24 states where disease occurred yielded 25% of the total cases reported during the surveillance period [12]. In the fall (1 September–31 October 2009), patients were sampled based on probability of selection proportional to the number of hospitalized cases reported to the CDC; participation from 40 states yielded <2% of the total cases reported during the surveillance period [15]. Both the spring and fall case series were part of the emergency public health practice response to assess illness severity during the pH1N1 outbreak and were deemed not to be research in accordance with the federal human subjects protection regulations at 45 Code of Federal Regulations 46.101c and 46.102d and the CDC's Guidelines for Defining Public Health Research and Public Health Non-Research. Participation by the state and local health departments was voluntary.

For this analysis, a pneumonia case was defined as a hospitalized patient with pH1N1 virus and an admission chest radiographic report consistent with pneumonia. Using a standard form, demographic and clinical information was abstracted from medical records by infection control practitioners, physicians, nurses, or epidemiologists at state and local public health departments and reported to the CDC.

Pneumonia Definition

Only hospitalized patients with available admission chest radiographic results were included in this analysis. We defined radiographically confirmed pneumonia based on modified World Health Organization criteria as the presence of a consolidation, infiltrate, or opacity that could be described as alveolar, interstitial, or lobar [19]. A positive, negative, or unknown diagnosis of pneumonia was determined by independent review of admission chest radiographic reports by 2 nonradiology physicians (S. J., S. B.) who were blinded to the opinion of the other (κ statistic, 0.76). In cases of discrepant opinions between the 2 reviewers, a third nonradiology physician (J. S.) independently reviewed the reports while blinded to the readings of the other clinicians. The final pneumonia diagnosis was based on agreement among all reviewers. Radiographic reports that were excluded from this analysis were those considered to be inconclusive either because reviewers agreed that pneumonia was unknown or because reviewers could not agree on a final diagnosis.

Statistical Analysis

We categorized variables using clinically and biologically relevant cutpoints. For time calculations, the day of admission was considered to be hospital day 0. We performed bivariate analysis to investigate associations with pneumonia, using the χ^2 test to compare categorical variables and the Wilcoxon rank-sum test for medians to compare continuous variables ($P \leq .05$).

We used multivariate logistic regression analysis to further investigate associations with pneumonia. The final model included factors that were clinically relevant, statistically significant in bivariate analysis, or potential confounders. For the regression models, we created a variable to represent severe illness on presentation that combined either shortness of breath or tachypnea, and tachycardia. All analyses were conducted with SAS software, version 9.1 (SAS Institute, Cary, North Carolina).

Table 1. Comparison of Characteristics of Patients Hospitalized With 2009 Pandemic Influenza A (H1N1) With and Without Pneumonia—United States, 2009 (N = 451)

Patient Characteristic	Patients With Pneumonia, No. (%) (n = 195)	Patients Without Pneumonia, No. (%) (n = 256)
Female sex	102 (52)	131 (51)
Median age (range)	29 y (1 mo–86 y)	25 y (1 mo–87 y)
Age		
0–23 months	17 (9)	30 (12)
2–17 years	53 (27)	71 (28)
18–49 years	84 (43)	104 (41)
≥50 years	41 (21)	51 (20)
Race and ethnicity		
Non-Hispanic white	70 (36)	100 (39)
Hispanic	52 (27)	52 (20)
Black	41 (21)	59 (23)
Other[a]	13 (6)	12 (5)
Unspecified	19 (10)	33 (13)

[a] Other race and ethnicity includes Native Hawaiian, Asian, or Pacific Islander; Native American; and multiracial.

RESULTS

Among 527 hospitalized patients with pH1N1 virus, 249 of 272 (92%) of spring and 225 of 255 (88%) of fall patients had an available admission chest radiographic report; 23 patients had inconclusive radiographic reports and were excluded from this analysis. We describe 451 hospitalized patients with pH1N1 and conclusive admission chest radiographic results.

One hundred and ninety-five patients (43%)—106 of 237 (45%) from spring and 89 of 214 (42%) from fall—had a radiograph consistent with pneumonia. The majority of patients with and without pneumonia were ≥18 years old (64% vs 61%) and were equally likely to be non-Hispanic white (36% vs 39%) or Hispanic (27% vs 23%) (Table 1). Among all patients with pneumonia, those from the spring were more likely to be Hispanic than those from the fall (37% vs 15%; $P < .0001$).

Table 2. Comparison of Clinical Characteristics of Patients Hospitalized With 2009 Pandemic Influenza A (H1N1 Virus) With and Without Pneumonia—United States, 2009 (N = 451)

Clinical Characteristic	Patients With Pneumonia, No. (%) (n = 195)	Patients Without Pneumonia, No. (%) (n = 256)	*P* Value
Median time from illness onset to admission, days (range)	4 (0–17) (n = 193)	2 (0–27) (n = 249)	<.0001
≤2 days from illness onset to admission	69 (36)	143 (57)	<.0001
Median length of stay from admission to death or discharge, days (range)	5 (1–73) (n = 190)	3 (0–57) (n = 252)	<.0001
Clinical symptoms at admission			
Fever	177 (91)	232 (91)	.96
Cough	174 (89)	225 (88)	.66
Shortness of breath	142 (73)	134 (52)	<.0001
Chills	80 (41)	83 (32)	.06
Fatigue and/or weakness	85 (44)	96 (38)	.19
Rhinorrhea	73 (37)	97 (38)	.92
Myalgias	68 (35)	84 (33)	.65
Wheezing	63 (32)	77 (30)	.61
Vomiting	59 (30)	77 (30)	.97
Sore throat	57 (29)	72 (28)	.80
Headache	53 (27)	76 (30)	.56
Diarrhea	52 (27)	46 (18)	.03
Chest pain	39 (20)	40 (16)	.23
Abdominal pain	29 (15)	28 (11)	.21
Underlying medical conditions[a]			
Any one condition	118 (61)	182 (71)	.02
Asthma or chronic obstructive pulmonary disease	54 (28)	97 (38)	.02
Asthma	46 (24)	79 (31)	.09
Chronic obstructive pulmonary disease	13 (7)	31 (12)	.05
Neurological disease	29 (15)	19 (7)	.01
Diabetes mellitus	27 (14)	35 (14)	.96
Chronic cardiovascular disease	28 (14)	31 (12)	.48
Immunosuppression	19 (10)	36 (14)	.17
Chronic renal disease	17 (9)	20 (8)	.73
Seizure disorder	15 (8)	13 (5)	.25
Pregnancy	13 (7)	16 (6)	.86
Current smoker[a]	29/175 (17)	44/232 (19)	.53
Obese or morbidly obese[a,b]	58/117 (50)	77/161 (48)	.77
Seasonal influenza vaccination	40/122 (33)	49/173 (28)	.41
Pneumococcal vaccination during lifetime	40/91 (44)	57/116 (49)	.46

[a] Patients who are pregnant, are immunocompromised (due to either medications or immune disorders including human immunodeficiency syndrome), or have chronic pulmonary (including asthma or chronic obstructive pulmonary disease), cardiovascular (excludes hypertension), renal, hepatic, hematological, neurological (neurocognitive, neuromuscular, or seizure disorder), or metabolic disease (including diabetes mellitus) are considered to be at high risk for influenza-related complications. Patients who are current smokers or obese were not included in groups considered to be at high risk for influenza complications.

[b] Body mass index (BMI) was calculated for a subset of patients for whom height and weight were available to determine obesity (BMI 30–39.9 in adults ≥18 years or BMI percentile 95–100 in children 2–18 years) and morbid obesity (BMI ≥40 in adults only); pregnant women were excluded from this calculation.

Patients with pneumonia were significantly less likely to be admitted within 2 days of illness onset than those without pneumonia (36% vs 57%) (Table 2). Among all patients with pneumonia, those from the spring were less likely to be admitted within 2 days of illness onset than those from the fall (29% vs 44%; $P = .04$). Patients with pneumonia were significantly less likely than patients without pneumonia to have an underlying medical condition (61% vs 71%), including asthma or chronic obstructive pulmonary disease (COPD; 28% vs 38%), but were more likely to have a neurological disease (15% vs 7%), including Down syndrome, cerebral palsy, developmental delay, and history of stroke (Table 2).

Admission white blood cell counts were available for 187 patients with pneumonia, 99 (52%) of whom had a white

Table 3. Comparison of Hospitalization Characteristics of Patients Hospitalized With 2009 Pandemic Influenza A (H1N1 Virus) With and Without Pneumonia—United States, 2009 (N = 451)

Clinical Characteristic	Patients With Pneumonia, No. (%) (n = 195)	Patients Without Pneumonia, No. (%) (n = 256)	*P* Value
Tachypnea[a,b]	90/177 (51)	78/237 (33)	.0002
Tachycardia[a,c]	135/179 (75)	164/240 (68)	.11
Leukopenia[a]	44/187 (24)	41/229 (18)	.16
Leukocytosis[a,d]	44/187 (24)	37/229 (16)	.06
Admitted to the intensive care unit	101 (52)	40 (16)	<.0001
Invasive mechanical ventilation	71/183 (39)	17/248 (7)	<.0001
Acute respiratory distress syndrome	45/171 (26)	4/242 (2)	<.0001
Diagnosis of sepsis at admission	30/169 (18)	7/242 (3)	<.0001
Treated with influenza antiviral agents	152 (78)	203 (79)	.55
≤2 d of illness onset	42/151 (28)	98/198 (50)	<.0001
Median time from onset to antiviral initiation, d (range)	4 (0–24)	3 (0–29)	<.0001
Treated with antibiotics	182 (93)	171 (67)	<.0001
Treated with steroids	74 (38)	89 (35)	.5
Death	34 (17)	4 (2)	<.0001

[a] Reference ranges of vital signs and laboratory measurements are based on Kleigman et al [51] and Fauci et al [52]. Leukopenia was defined as a white blood cell count of <5000 cells/μL; leukocytosis was defined as a white blood cell count of >11 000 cells/μL.

[b] Tachypnea was defined as increased respiratory rate based on age as follows: 0 to <3 months, >55 breaths per minute; 3 to <6 months, >45 breaths per minute; 6 to <12 months, >40 breaths per minute; 1 to <3 years, >30 breaths per minute; 3 to <6 years, >25 breaths per minute; 6 to <12 years, >22 breaths per minute; 12 years, >18 breaths per minute; >12 years, >24 breaths per minute.

[c] Tachycardia was defined as increased heart rate based on age as follows: 0 to <3 months, >150 beats per minute; 3 to <6 months, >120 beats per minute; 6 to <12 months, >120 beats per minute; 1 to <3 years, >110 beats per minute; 3 to <6 years, >110 beats per minute; 6 to <12 years, >95 beats per minute; 12 years, >85 beats per minute; >12 years, >100 beats per minute.

[d] Newborns <28 days of age were excluded from this analysis.

blood cell count within the reference range; 44 patients (24%) had leukopenia and 44 (24%) had leukocytosis (Table 3). Bacterial infection was confirmed in 13 patients with pneumonia and 2 patients without pneumonia. In patients with pneumonia, the organisms were identified at admission by blood culture (methicillin-resistant *Staphylococcus aureus* [MRSA], 2 patients; methicillin-sensitive *S. aureus* [MSSA], 2 patients; *S. aureus* of unknown sensitivity, 1 patient; *Escherichia coli,* 1 patient; *Streptococcus pneumoniae* and group A *Streptococcus* [GAS], 1 patient), sterile respiratory culture (*S. pneumoniae,* 3 patients; GAS, 1 patient; *Moraxella catarrhalis,* 1 patient), or urine antigen test (*S. pneumoniae,* 1 patient). Two patients without pneumonia were bacteremic with *S. aureus* (MRSA, 1 patient; MSSA, 1 patient). The majority of patients with and without pneumonia received antibiotics close to the time of specimen collection (96% vs 76%).

For 195 patients with pneumonia, radiographic findings included bilateral infiltrates (57%), an infiltrate limited to 1 lobe (31%), and multilobar infiltrates limited to 1 lung (7%). Descriptive terminology in relation to infiltrates included perihilar (13%), patchy (10%), interstitial (9%), alveolar (4%), and diffuse (3%). Additional descriptors included airspace disease (8%), pleural effusion (4%), and pneumonitis (3%).

Patients with pneumonia were equally likely as patients without pneumonia to receive influenza antiviral agents (78% vs 79%) (Table 3); the majority (91%) received oseltamivir. Patients with pneumonia were significantly less likely to receive antiviral agents within 48 hours of illness onset than those without pneumonia (28% vs 50%). For 151 patients with pneumonia and available antiviral treatment initiation date, receipt of antiviral agents in relation to day of admission was the following: before admission, 8%; on admission, 46%; within ≤48 hours of admission, 23%; and >48 hours after admission, 23%.

Patients with pneumonia were significantly more likely than patients without pneumonia to receive antibiotics (93% vs 67%) (Table 3). For 112 patients with pneumonia and available antibiotic initiation date, receipt of antibiotics in relation to day of admission was the following: before admission, 24%; on admission, 52%; within ≤48 hours of admission, 21%; and >48 hours after admission, 2%. Patients with pneumonia received a median of 3 antibiotics (range, 1–7). Commonly used antibiotics included ceftriaxone (50%), azithromycin (43%), vancomycin (42%), and levofloxacin (31%).

Patients with pneumonia were significantly more likely than patients without pneumonia to be admitted to the

Table 4. Multivariable Analysis of Select Characteristics Among US Patients Hospitalized With 2009 Pandemic Influenza A (H1N1) With Pneumonia as the Outcome (n = 421)

	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
Age, years		
<2	0.4 (.2–.9)	.03
2–17	0.6 (.3–1.1)	.10
18–49	1.0 (.6–1.7)	.90
≥50	Reference	…
Race and ethnicity		
Non-Hispanic black	1.1 (.7–2.0)	.65
Hispanic	1.4 (.8–2.5)	.22
Other	1.7 (.7–4.5)	.26
Unknown	0.9 (.4–1.9)	.76
Non-Hispanic White	Reference	…
Asthma or chronic obstructive pulmonary disease	0.4 (.3–.7)	<.01
Neurological disease	2.2 (1.2–4.4)	.02
Severe illness on presentation[a]	3.3 (2.1–5.2)	<.01
Spring vs fall season	0.8 (.5–1.3)	.38

[a] Defined as shortness of breath or tachypnea, and tachycardia.

intensive care unit (ICU; 52% vs 16%), require mechanical ventilation (39% vs 7%), have acute respiratory distress syndrome (ARDS; 26% vs 2%) and sepsis (18% vs 3%), and die (18% vs 2%) (Table 3). The median age of patients with pneumonia admitted to the ICU was 30 years (range, 1–86 years). Fifty-seven (56%) of 101 ICU pneumonia patients had an underlying condition. Eighty-seven (86%) ICU pneumonia patients received influenza antiviral agents and 98% received antibiotics. The median time from illness onset to antiviral treatment initiation was 5 days (range, 0–24 days), with 13% of ICU pneumonia patients receiving antiviral agents within 48 hours of illness onset.

Thirty-four of 195 (17%) patients with pneumonia died, 97% whom were admitted to the ICU and required mechanical ventilation. The median age of patients who died was 34 years (range, 1–70 years); the median time from illness onset to death was 16 days (range, 3–83 days). Twenty-one patients (60%) who died had an underlying condition. Of 34 patients who died, 88% received influenza antiviral agents and 97% received antibiotics. The median time from illness onset to antiviral treatment initiation was 5 days (range, 2–20 days), and 10% of patients received antiviral agents within 48 hours of illness onset.

In a multivariable model that included age group, race and ethnicity, asthma or COPD, neurological disease, severe illness on presentation, and season, the following factors remained significantly associated with a pneumonia diagnosis: neurological disease or severe illness on presentation (Table 4). Having asthma or COPD or being <2 years old was significantly associated with not having pneumonia.

DISCUSSION

During the 2009 influenza pandemic, among 2 national case series of patients hospitalized with pH1N1 virus infection in the United States, >40% had a chest radiograph consistent with pneumonia. Patients with pneumonia were more likely to have an underlying neurological disease or severe illness on presentation and less likely to have asthma or COPD. Patients with pneumonia had a more severe course of illness, including longer length of stay, ICU admission, mechanical ventilation, ARDS, sepsis, and death, than those without pneumonia. Patients with pneumonia were equally likely to receive influenza antiviral treatment as patients without pneumonia but treatment was often delayed; only one-fifth of the patients with pneumonia received antiviral agents within 2 days of illness onset.

In our analysis, 43% of hospitalized patients with pH1N1 virus infection had pneumonia, which is midrange compared with other reports. In a California case series of pH1N1 hospitalizations, 66% of 833 patients had infiltrates on chest radiography [13]. In a pH1N1 hospitalization study conducted in Spain, 24% of 294 patients had multilobar infiltrates and 12% had bilateral infiltrates [16]. In a pH1N1 hospitalization study conducted in the United Kingdom, 35% of 106 children and 27% of 243 adults had findings consistent with pneumonia [17]. Each of these studies used different pneumonia case definitions, which may explain the range of proportions. Data from the CDC's Emerging Infections Program (EIP), which conducts US population–based active surveillance for laboratory-confirmed influenza hospitalizations, indicated that 36% of children (n = 2992) and adults (n = 4776) had influenza-associated pneumonia during seasonal epidemic periods prior to the 2009 pandemic [10, 11]. Our analysis differs from that of EIP in that we utilized physician reviews of radiographic reports into our final case definition, which cannot practically be incorporated into routine surveillance and may partially account for the difference in proportions between seasonal and pandemic periods. However, results from animal studies and human autopsy reports indicate that pH1N1 virus infection caused severe diffuse alveolar damage that likely led to more severe lower-tract respiratory disease and respiratory failure than was reported during previous seasonal influenza periods [20, 21].

The clinical features of pH1N1 pneumonia in this analysis are similar to those reported during seasonal influenza and past pandemics with acute onset of respiratory illness [22–25]. Interestingly, almost one-fifth of patients with pneumonia had

sepsis on admission compared with 3% of patients without pneumonia. Sepsis was recorded according to clinical judgment and may not have adhered to strict definitions as written in critical care guidelines [26]. Although sepsis is often associated with bacterial infection, the terminology is meant to encompass nonbacterial causes of systemic inflammatory response syndromes, including viremia [26]. Sepsis syndrome has previously been reported with influenza virus infection [27, 28]. Interestingly, neither leukopenia nor leukocytosis was associated with pneumonia. This analysis highlights the conclusion that during periods of influenza circulation, patients presenting with a chest radiograph consistent with pneumonia and a sepsis-like syndrome with or without bacterial coinfection, influenza, including pH1N1, should be considered in the differential diagnosis, especially in patients who also have a white blood cell count within the reference range.

Of the underlying medical conditions ascertained, only neurological disease was significantly associated with pneumonia. Patients with neurological disease are considered to be at high risk for influenza-related complications, including respiratory failure [29] and death [30], and a high-priority group for receipt of annual influenza vaccination [31]. Proposed mechanisms for increased risk of pneumonia include immobility, poor cough reflex, aspiration from impaired swallowing, gastroesophageal reflux disease, restrictive lung disease, and malnutrition [32–34]. Interestingly, in our analysis, patients with pneumonia were significantly less likely to have asthma or COPD. However, after examining asthma or COPD alone, there was no significant difference between patients with and those without pneumonia, likely due to inadequate power. Data from the CDC's EIP surveillance indicated that during seasonal influenza periods, children <18 years old with pneumonia were more likely to have asthma than those without pneumonia (24% vs 19%; $P < .01$) [35]. This study permitted the chest radiograph to be performed at any time during hospitalization as opposed to at admission, which could help explain the differences between these studies. Further clarity on the relationship between obstructive lung disease and influenza-associated pneumonia is needed to better understand who is at greater risk for pneumonia.

Few bacterial coinfections were detected but bacterial diagnostics were not obtained on all patients, and most received antibiotics near the time of culture collection, potentially reducing diagnostic sensitivity. Among patients who were hospitalized for and died of seasonal influenza, *S. aureus*, *S. pneumoniae*, and GAS have been the most commonly reported bacterial coinfections [10, 11, 36]. From April 2009 through January 2010, bacterial coinfections were identified among 46 of 156 children (28%) who died of pH1N1 virus infection and had available culture reports [37]. In addition, from May through August 2009, bacteria were identified in 22 of 77 (29%) deaths among adults and children with pH1N1 virus infection whose autopsy specimens were sent to the CDC for testing [38]. Amongst these fatalities, *S. aureus*, *S. pneumoniae*, and GAS were predominant [37, 38]. It is difficult to compare proportions of bacterial infections among patients with influenza who were hospitalized or died between different seasons and between different studies, due to variable clinical testing, antibiotic use, and study design. However, the relationship between influenza and bacterial pathogens is well described [25]. In addition to annual influenza vaccination for all persons ≥6 months old [31], the 13-valent pneumococcal conjugate vaccine is recommended for all children <5 years old and the 23-valent pneumococcal polysaccharide vaccine is recommended for all persons aged 2–64 years with certain health conditions and all persons aged ≥65 years [39].

Similar to our findings, in 2 radiographic pH1N1 hospitalization case series of 66 patients in Michigan [40] and 39 patients in Israel [41], bilateral airspace disease was the most common finding. In our case series, deep lung specimens were not available for correlation with radiographs to assess whether the predominance of bilateral airspace disease was specifically due to influenza, bacteria, or both, or whether the findings were more attributable to ARDS or other causes. In addition to improved use of existing diagnostics, development of more precise bacterial and viral pneumonia diagnostics and better studies to correlate radiographic findings with pneumonia etiology during influenza outbreaks are needed [42].

In our analysis, although patients with pneumonia were equally likely to receive antiviral agents as those without pneumonia, treatment was often delayed among those with pneumonia, especially those who were admitted to the ICU or who died. It is unclear whether the delayed treatment was due to delay in testing, ascertainment of results, or antiviral agent prescribing practice. Current guidelines of the Advisory Committee for Immunization Practices recommend oseltamivir or zanamivir for hospitalized patients with suspected or confirmed influenza, outpatients who are at higher risk for complications, and persons with suspected or confirmed influenza who have evidence of severe illness such as signs or symptoms of lower respiratory tract infection or clinical deterioration regardless of vaccination status [43]. Although evidence of benefit from the use of antiviral agents is strongest when treatment is initiated within <48 hours of symptom onset, observational studies have indicated a reduction in mortality and shorter duration of hospitalization with oseltamivir treatment, even when antiviral drugs were initiated >48 hours after symptom onset [44–46]. Observational data from the 2009 influenza A (H1N1) pandemic also suggested that early antiviral treatment was associated with increased

survival, including among pregnant women, children, and severely ill patients [12, 15, 47–50].

Our data are subject to limitations. The patients described were derived from 2 hospitalization case series that used different sampling methods [12, 15]. However, data from both periods were nationally representative of hospitalizations in areas in the United States where peak disease activity was occurring at the time. Participation was voluntary and therefore subject to reporting bias. Testing was clinically driven, and only patients with confirmed pH1N1 virus were included, who may not be representative of all hospitalized patients with pH1N1 infection because some may have not been tested. We do not have information on admission diagnosis therefore cannot discern if patients were admitted because of severe influenza, an underlying condition, or another reason. Although actual radiographs were not available for review and pneumonia was defined on the basis of chest radiographic reports, interobserver agreement was high. Despite use of a standardized data collection form, not all information was collected for all patients, including pneumococcal and influenza vaccination status (pH1N1 vaccine was not readily available during the study) This limits our ability to assess these interventions; however, the study was not designed to address these specific questions.

Pneumonia is the most common complication among patients hospitalized with influenza, including pH1N1, in the United States [10–13, 15]. Patients with influenza-associated pneumonia may present atypically with bilateral findings on chest radiography and a white blood cell count in the reference range. Patients with influenza-associated pneumonia are also at risk for bacterial coinfection, but without evidence of bacteria, influenza can still lead to sepsis, ARDS, and death. In the absence of accurate pneumonia diagnostics, patients hospitalized with suspected or confirmed influenza and lung infiltrates on chest radiography should receive both antibiotics and influenza antiviral agents [9]. The benefits of influenza antiviral treatment are likely greatest when started early, but antiviral agents should not be withheld if patients present >48 hours after illness onset [43].

Notes

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