Washington University School of Medicine
Digital Commons@Becker

Open Access Publications

2006

Is influenza an influenza-like illness? Clinical presentation of influenza in hospitalized patients

Hilary M. Babcock
Washington University School of Medicine in St. Louis

Liana R. Merz
Washington University School of Medicine in St. Louis

Victoria J. Fraser
Washington University School of Medicine in St. Louis

Follow this and additional works at: http://digitalcommons.wustl.edu/open_access_pubs
Part of the Medicine and Health Sciences Commons

ORIGINAL ARTICLE

Is Influenza an Influenza-Like Illness?
Clinical Presentation of Influenza in Hospitalized Patients

Hilary M. Babcock, MD; Liana R. Merz, MPH; Victoria J. Fraser, MD

BACKGROUND.   Early recognition of influenza virus infection in hospitalized patients can prevent nosocomial transmission.

OBJECTIVE.   To determine the clinical presentation of influenza in hospitalized patients.

DESIGN.   Case series. Data were collected retrospectively from medical records and included demographic information, comorbidities, clinical symptoms and signs, microbiologic test results, and outcomes (including pneumonia and intensive care unit [ICU] admission).

SETTING.   A 1,400-bed teaching hospital.

PATIENTS.   A total of 207 inpatients who received a diagnosis of influenza virus infection during 3 seasons from 2000 to 2003.

RESULTS.   Over the course of 3 seasons, 207 patients received a diagnosis of influenza (186 were infected with influenza A virus, and 21 were infected with influenza B virus). The most commonly reported symptoms were cough (186 patients [90%]) and subjective fever (137 patients [66%]); 124 patients (60%) had a documented temperature of 37.8°C or greater before influenza was diagnosed. Sore throat was uncommon (44 patients [21%]). Centers for Disease Control and Prevention (CDC) criteria for influenza-like illness (ILI)—temperature 37.8°C or greater and either cough or sore throat—were met by 107 patients (51%). There were no differences in the proportion of patients who met ILI criteria with respect to age, sex, season, influenza virus type, or time to diagnosis in the hospital. Most patients (150 [72%]) received acetaminophen. Only 41 patients (20%) had positive results of clinical cultures; 178 patients (86%) received antibiotic therapy. Fifty-six patients (27%) had pneumonia: 36 (17%) required admission to the ICU, and 25 (12%) required ventilatory support. Patients with pulmonary disease were more likely to require ventilatory support (12 [26%] vs 13 [8%]; $P = .003$).

CONCLUSIONS.   Only half of hospitalized patients with influenza met CDC criteria for ILI. These criteria may be more appropriate in outpatient settings. A high index of suspicion is needed to recognize influenza in hospitalized patients.

Influenza epidemics in the United States result in an average of 36,000 deaths and 114,000 hospitalizations annually.[1] Early recognition in hospitalized patients prompts the institution of respiratory isolation precautions and prevents nosocomial transmission to other patients and to healthcare workers. It may also prevent the unnecessary testing and treatment of patients with influenza. This rapid identification is even more important when vaccine supplies are inadequate or when pandemic strains emerge for which there is no vaccine available. In these situations, rapid isolation and identification of the causal strain are crucial to control the spread of influenza.

The difficulties of identifying influenza virus infection on the basis of clinical characteristics have been well described for outpatients,[2-7] patients in the emergency department,[8,9] and residents of nursing homes.[10] There are fewer recent data regarding the clinical presentation of hospitalized patients with influenza.[11-15] The clinical presentation of influenza may be different in hospitalized patients than in ambulatory patients. More-severe symptoms may be expected in those who seek medical attention and whose illness warrants hospitalization. Conversely, more severe underlying illnesses and the medications used to treat them may affect the signs and symptoms of influenza infection. We performed a case series analysis over the course of 3 consecutive influenza seasons of all inpatients who received a diagnosis of influenza at a large tertiary care hospital, to better define their clinical presentations.

METHODS

Case Finding

All patients who received a laboratory-confirmed diagnosis of influenza through routine medical care at a 1400-bed tertiary-care teaching hospital in the Midwestern United States over the course of 3 influenza seasons were included in the study. Seasons were defined by the first and last case diagnosed at the hospital during the usual epidemic period. The first season was from January 28 to April 10, 2002; the second from January 16 to March 28, 2003; and the third from Oc-

TABLE 1. Inpatient Cases of Influenza, by Season and Virus Type

| Season | No. (%) of Influenza Cases, by Virus Type | | |
	Type A	Type B	Total
1 (2001-2002)	59 (84)	11 (16)	70
2 (2002-2003)	13 (59)	9 (41)	22
3 (2003-2004)	114 (99)	1 (1)	115
Total	186 (90)	21 (10)	207

tober 7, 2003, to February 18, 2004. Patients were identified through daily queries of our hospital informatics database, which includes microbiologic, medication, and hospital admission information for all inpatients. Two daily e-mail notifications were received by the investigators: one specified all patients who tested positive for influenza (by means of direct fluorescent antibody testing or viral culture) during the preceding 24 hours, and the other specified all patients for whom an order for amantadine, rimantadine, zanamavir, or oseltamivir had been written. Supplemental searches were performed retrospectively at the end of each season, to ensure that all patients had been identified. Patients who received their diagnosis in the emergency department but were never admitted to the hospital were not included in the analysis.

Laboratory Diagnosis

The virologic diagnosis of influenza at our hospital is made on the basis of analysis of a nasopharyngeal swab sample. The swab is transported in viral transport medium to the virology laboratory, where direct fluorescent antibody testing is performed. If results of the direct fluorescent antibody test are positive, no further testing is performed. If results are negative, then viral culture is performed for detection of influenza virus, respiratory syncytial virus, parainfluenza virus, and adenovirus. Cultures for detection of influenza virus are performed by plating the sample onto primary rhesus monkey kidney cell plates.

Data Collection and Analysis

For each identified case of influenza, data from the patient's electronic and paper medical records were recorded on a standardized data collection form by trained research assistants using standardized definitions. Data collected included symptoms and signs, as recorded in the doctors' notes, observed from the time of hospital admission until the date on which the nasopharyngeal swab sample was obtained. Data on demographic characteristics and comorbidities were also collected. Data on care variables included the use of antibiotics and antipyretics and performance of any additional microbiologic testing. The number and type of cultures performed from admission until 5 days after the nasopharyngeal swab sample was obtained (final culture results were reported on day 5) were recorded. Patients for whom culture of only a single specimen was positive for coagulase-negative *Staphylococcus* were excluded from the group with positive culture

results. Duplicate culture results (ie, those involving specimens from the same site that had the same result) were only counted once in the analysis of common organisms. All chest radiographs findings from 7 days before to 21 days after the swab sample was obtained were reviewed by one of us (H.M.B.). Patients were classified as having pneumonia by H.M.B. if new infiltrates observed on a chest radiograph were consistent with pneumonia.

Data were double entered into Access (Microsoft), cleaned, and converted for analysis with SPSS, version 12 (SPSS). Descriptive analyses were performed using means and medians for continuous data and proportions for categorical variables. Comparisons between groups were made with Student's *t* test, Kruskal-Wallis tests, and Mann-Whitney *U* tests, as appropriate, with $P < .05$ considered to be statistically significant on 2-tailed testing. The study was approved by the Human Subjects Committee at Washington University (St. Louis, MO).

RESULTS

Over the course of the study period, 207 inpatients received a diagnosis of influenza. Table 1 shows the distribution of the number of cases and influenza strains by year (1 case and 1 strain per patient). For approximately half of the patients (104), the diagnostic swab specimen was sent on the first day of hospitalization, and specimens from 90% of patients had been tested by the second hospital day. The remaining 10% of patients received a diagnosis of influenza between hospital days 3 and 26.

The median age of inpatients with influenza virus infection was 60 years (range, 15-99 years) (Table 2). Age and sex distributions were similar for all 3 influenza seasons. Influenza B virus infection was more common among patients younger than 65 years of age (18 [16%] of 116 vs 3 [3%] of

TABLE 2. Demographic Characteristics and Medical History of 207 Patients Who Received a Diagnosis of Influenza

Characteristic	Value
Age, median years (range)	60 (15-99)
Sex	
Female	124 (60)
Male	83 (40)
Race	
African American	106 (51)
White	97 (47)
Other	4 (2)
Medical condition	
Congestive heart failure	35 (17)
Asthma	38 (18)
Chronic obstructive pulmonary disease	46 (22)
Diabetes	55 (26)
Cancer (received treatment within past 12 months)	36 (17)
Immunosuppression[a]	71 (34)

NOTE. Data are no. (%) of patients, unless otherwise indicated.
[a] Immunosuppression includes human immunodeficiency virus infection, receipt of a solid-organ or bone-marrow transplant, immunodeficiency syndromes, and chronic steroid use or use of other immunosuppressive agents.

TABLE 3. Symptoms and Signs Reported by 207 Patients Before Influenza Diagnosis, by Age

Symptom	No. (%) of Patients, by Age			
	Aged Less Than 65 Years (n = 116)	Aged 65 Years or More (n = 91)	P	Overall
Cough	104 (90)	82 (90)	.85	186 (90)
Subjective fever	84 (72)	53 (58)	**.04**	137 (66)
Fatigue	52 (45)	56 (61)	**.02**	108 (52)
Chills and/or rigors	48 (41)	29 (32)	.13	77 (37)
Nausea and/or vomiting	51 (44)	25 (28)	**.02**	76 (37)
Myalgias	41 (35)	26 (29)	0.11	67 (32)
Coryza	42 (36)	21 (23)	**.05**	63 (30)
Headache	35 (30)	19 (21)	.12	54 (26)
Sore throat	35 (30)	9 (10)	**<.01**	44 (21)
Diarrhea	20 (17)	16 (17)	.98	36 (17)

NOTE. Data in bold type are statistically significant.

90 patients; $P = .003$). Most patients (167 [80.7%]) had at least 1 underlying medical condition (Table 2).

Clinical Presentation

The symptom most frequently reported across all age groups was cough (186 patients [90%]), followed by subjective fever and fatigue (Table 3). Sore throat was less common (44 patients [21%]). Sore throat, subjective fever, nausea or vomiting, and coryza were reported less frequently by patients younger than 65 years of age. Fatigue was reported more frequently by patients 65 years of age or older (Table 3).

There was little variation in symptom frequency by sex, although women more commonly reported headache than did men (40 [32%] vs 13 [16%]; $P = .01$). There were no significant differences in presenting symptoms between patients infected with influenza A virus and those infected with influenza B virus.

Fever, defined according to Centers for Disease Control and Prevention (CDC) influenza surveillance criteria (available at: http://www.cdc.gov/flu/weekly/fluactivity.htm) as a temperature of 37.8°C or higher, had been documented in the electronic medical record for 124 (60%) of the patients before influenza was diagnosed. Of the patients with documented fever, 106 (51%) of 208 also had cough or sore throat (Table 4) and, therefore, met all CDC criteria for influenza-like illness (ILI). When subjective fever was used instead of fever that was documented in the electronic medical record, 130 patients (63%) met ILI criteria. There was no significant difference in the presence of ILI-defining symptoms between patients with influenza A virus infection and those with influenza B virus infection (94 [50.5%] vs 11 [52.4%]; $P = .87$), between sexes ($P = .96$), among the 3 influenza seasons ($P = .17$), or by age group (<35, 35-49, 50-64, or ≥65 years; $P = .57$). Among patients with ILI-defining symptoms, there was no difference in the presence of ILI-defining symptoms

between patients who received influenza diagnosis within 2 days after admission and those who received influenza diagnosis later ($P = .688$).

Process of Care

Many patients (150 [72.5%]) received acetaminophen before the diagnosis of influenza, although only 124 (60%) had an increased temperature. An even higher number (185 [89.4%]) received medications with antipyretic effects, such as nonsteroidal anti-inflammatory drugs or glucocorticoids. Twenty-five patients (12%) received anti-influenza medications (20 received oseltamivir, 4 received amantadine, and 1 received rimantadine). During the time between admission and the diagnosis of influenza, 648 clinical cultures were performed for 186 (90%) of 207 patients. These included 280 blood cultures, 162 urine cultures, and 131 sputum cultures. Forty-one patients had a clinical culture positive for a bacterial pathogen between admission and the diagnosis of influenza, 19 (46%) of whom had a total of 23 positive results of sputum cultures. The most common organisms detected were *Pseudomonas* species (9 [39%] of 23 cultures) and *Staphylococcus aureus* (7 [30%] of 23 cultures). Seven patients had positive results of blood cultures, not including 8 patients with only a single blood culture that yielded coagulase-negative *Staphylococcus* species. Two of these 7 patients were infected with coagulase-negative *Staphylococcus* species: one had the same organism isolated from a second site, and the other had 2 blood cultures with positive results. The other 5 patients were infected with oxacillin-resistant *S. aureus, Enterococcus faecalis, Klebsiella* species, *Streptococcus pyogenes,* and *Micrococcus* species.

Before the diagnosis of influenza was established, 178 patients (86%) received 482 courses of antibiotics. One patient with a sputum culture with normal flora and *Streptococcus pneumoniae* infection did not receive antibiotics; all other patients with positive cultures results did receive antibiotics, as did 137 patients without positive culture results. Of these 137 patients, 67 (49%) had abnormal chest radiograph findings, and 42 (31%) had radiographic evidence of pneumonia. The most commonly administered antibiotic overall was azithromycin (104 [21.6%] of 482 courses of antibiotics), followed by ceftriaxone (74 [15%]), cefepime (57 [12%]), and vancomycin (53 [11%]).

TABLE 4. Frequency of Influenza-Like Illness (ILI) Among Patients Found To Have Influenza Virus Infection

ILI Symptom	No. (%) of Patients
Temperature ≥37.8°C	124 (60)
Temperature ≥37.8°C and cough	106 (51)
Temperature ≥37.8°C and sore throat	25 (12)
Temperature ≥37.8°C and either cough or sore throat[a]	106 (51)

[a] Centers for Disease Control and Prevention definition of ILI.

Outcomes

The median length of hospital stay was 5 days (range, 0-68 days). Almost all patients with influenza (201 [97%]) had at least 1 chest radiograph obtained between 7 days before and 21 days after a nasopharyngeal swab sample was collected (mean, 3.97 radiographs; median, 2 radiographs [range, 1-33 radiographs]). Ninety-five patients (46%) had abnormal radiograph findings, with the most common abnormality being a focal infiltrate (60 patients [29%]). Fifty-six patients (27%) had pneumonia, as defined by a new infiltrate consistent with pneumonia detected on a chest radiograph. Of the patients with radiographic evidence of pneumonia, only 6 had positive results of sputum culture: *Pseudomonas* species were detected in 3 patients (1 of whom also had oxacillin-resistant *S. aureus*), *S. aureus* alone was detected in 2, and *Klebsiella* species were detected in 1. Seventy-six patients (37%) received a discharge diagnosis of pneumonia, as revealed by the *International Classification of Diseases, Ninth Revision* code recorded for that hospitalization.

Data on admission to the intensive care unit and need for ventilatory support were recorded for the period between 7 days before and 21 days after the nasopharyngeal swab sample was collected. Thirty-six patients (17%) required admission to the intensive care unit, with a median length of stay of 4 days (range, 1-64 days). Twenty-five patients (12%) required ventilatory support, with a median time of ventilator use of 4 days (range, 1-60 days). Patients with a history of chronic pulmonary disease were more likely to require ventilatory support (12 [26%] vs 13 [8%]; $P = .003$). Overall, 7 patients (3.4%) died in the hospital. There were no significant differences in the prevalence of pneumonia, admission to the intensive care unit, need for ventilatory support, or death, according to age at the time of hospital admission.

DISCUSSION

In this case series of more than 200 inpatients who received a diagnosis of influenza over the course of 3 seasons, we found that only half (51%) of the patients met the CDC surveillance criteria for ILI. Only 124 inpatients with influenza (60%) had documented fever, and only 106 (51%) had an accompanying cough or sore throat. There was no difference in the prevalence of these symptoms by age, sex, season, or influenza virus type. The most common symptom was cough. Most patients received a diagnosis early during their hospital stay and had presumably been exposed and infected as outpatients.

The different clinical presentations in inpatients may have been due to more-severe illness or more-prevalent underlying conditions. In this study, 81% of patients had at least 1 underlying condition. Perhaps because of these conditions, a high proportion of these patients received medications with antipyretic effects, such as nonsteroidal anti-inflammatory drugs, corticosteroids, and acetaminophen-containing pain medications. The pervasive use of these medications may explain the low rates of increased temperature. CDC ILI criteria

may be more useful for detecting influenza in otherwise healthier, outpatient populations. If the influenza diagnosis for inpatients was based on increased temperature, with or without associated influenza symptoms, 40%-50% of diagnoses would have been missed in this group. The other clinical criteria used by the physicians who made the diagnosis are not known.

At the time of this study, rapid tests for detection of influenza virus were not routinely used in our hospital. The patients in this study underwent extensive testing for other infections that included blood, urine, and sputum cultures and, usually, chest radiography. They also received substantial antimicrobial therapy, although results of most clinical cultures were negative. Earlier recognition of and rapid testing for influenza virus might have avoided both the extra testing and extra treatment.

Many studies have described the clinical presentation of influenza in outpatient settings,[2-7] emergency departments,[8,9] and long-term care facilities.[6] Several meta-analyses have also addressed the clinical features of influenza in outpatients.[7,16] Findings of these studies vary, but most reported fever and cough, especially in combination, to be the symptoms most predictive of influenza. In outpatient studies, many recruitment strategies involve evaluating patients when they report ILI symptoms, such as fever and respiratory symptoms.[2-6] Not surprisingly, these studies observed high rates of fever and respiratory symptoms. Several reports have documented shortcomings of the definition of ILI in long-term care facilities, specifically because many patients did not have documented fever.[17] These differences have been attributed to the older age of the population. Our study found that the definition of ILI does not adequately capture hospitalized patients with influenza either, regardless of age. We found no difference in the frequency of fever across age groups, although this finding differs from findings reported elsewhere.[14] Perhaps the low rates of ILI symptoms among hospitalized patients and residents of long-term care facilities are more related to underlying medical illnesses and concomitant use of medication than to age.

Few studies have focused on the clinical presentation of inpatients, and most have found higher rates of fever than we did.[11,13,14] Two studies focused on older, hospitalized patients.[11,13] Both studies screened patients who were admitted to the hospital with classic ILI symptoms, as well as patients who were admitted with other acute cardiopulmonary conditions, and, as a result, may have missed patients with less classic presentations. One small case series from a single influenza season found a similar rate of cough and much higher rates of pneumonia (17 of 35 patients) and intensive care unit admission (10 of 35 patients).[12] The microbiologic profile of pneumonia in patients with positive results of cultures in our study showed that half were infected with *S. aureus* and half were infected with *Pseudomonas* species. Low rates of staphylococcal infection have been described elsewhere.[15] It is possible that some of the patients with pneumonia and

without a positive bacterial culture had primary influenza pneumonia. Although our study did not find higher rates of pneumonia among patients with chronic obstructive pulmonary disease, we did find a more frequent need for ventilatory support among such patients.

This study had several limitations. Patients received a diagnosed through routine care. By definition, we were unable to capture patients infected with influenza who did not receive their diagnosis during hospitalization. One might presume that those patients had an even less typical presentation, given that their physicians did not order diagnostic tests for detection of influenza virus. Also, the diagnostic tests for influenza are not 100% sensitive. We may have only included patients with higher viral titers in their nasal secretions. Whether these patients are more or less likely to have classic symptoms is unclear. Because it was a retrospective study, we relied on the list of symptoms reported in the doctor's notes, which is likely to have underrepresented actual symptoms. Temperature and medication reports, however, were retrieved from the electronic medical record and did not have the same limitation. The influenza vaccination status of the patients was not reliably recorded in the chart and so could not be taken into account.

In summary, in a large case series of hospitalized patients, a temperature of 37.8°C or higher was documented for only 124 patients (60%), and the classic ILI symptoms of fever with either cough or sore throat were only seen in 106 (51%). These criteria appear to be less useful for inpatients, because of underlying illnesses, concomitant medications, or other factors. A high index of suspicion and awareness of less classic presentations are necessary during influenza season, to facilitate the rapid identification of infected patients, early isolation to prevent nosocomial spread, and reduction in unnecessary testing and treatment.

Address reprint requests to Hilary M. Babcock, MD, Campus Box 8051, 660 South Euclid Avenue, St. Louis, MO 63110 (hbabcock@im.wustl.edu).

ACKNOWLEDGMENTS

REFERENCES

1. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA* 2000; 284:1655-1663.
2. Govaert TM, Dinant GJ, Aretz K, Knottnerus JA. The predictive value of influenza symptomatology in elderly people. *Fam Pract* 1998; 15:16-22.
3. Neuzil KM, O'Connor TZ, Gorse GJ, Nichol KL. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. *Clin Infect Dis* 2003; 36:169-174.
4. Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. *Clin Infect Dis* 2000; 31:1166-1169.
5. Carrat F, Tachet A, Rouzioux C, Housset B, Valleron A-J. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995-1996 epidemic in France. *Clin Infect Dis* 1999; 28:283-290.
6. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000; 160:3243-3247.
7. Ebell MH, White LL, Casault T. A systematic review of the history and physical examination to diagnose influenza. *J Am Board Fam Pract* 2004; 17:1-5.
8. Monmany J, Rabella N, Margall N, Domingo P, Gich I, Vazquez G. Unmasking influenza virus infection in patients attended to in the emergency department. *Infection* 2004; 32:89-97.
9. Friedman MJ, Attia MW. Clinical predictors of influenza in children. *Arch Pediatr Adolesc Med* 2004; 158:391-394.
10. Monto AS, Rotthoff J, Teich E, et al. Detection and control of influenza outbreaks in well-vaccinated nursing home populations. *Clin Infect Dis* 2004; 39:459-464.
11. Falsey AR, Cunningham CK, Barker WH, et al. Respiratory syncytial virus and influenza A infections in the hospitalized elderly. *J Infect Dis* 1995; 172:389-394.
12. Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. *Chest* 2001; 119:1717-1723.
13. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. *J Am Geriatr Soc* 2002; 50:1498-1503.
14. Bennett NM. Diagnosis of influenza. *Med J Aust* 1973; Special Supplement:19-22.
15. Bisno AL, Griffin JP, Van Epps KA, Niell HB, Rytel MW. Pneumonia and Hong Kong influenza: a prospective study of the 1968-1969 epidemic. *Am J Med Sci* 1971; 261:251-263.
16. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? *JAMA* 2005; 293:987-997.
17. Bradley SF. Prevention of influenza in long-term-care facilities. Long-Term-Care Committee of the Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 1999; 20:629-637.