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ORIGINAL ARTICLE

# Case-Control Study of Clinical Features of Influenza in Hospitalized Patients

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BACKGROUND.   The symptoms of influenza infection in outpatients are well described. The Centers for Disease Control and Prevention (CDC) definition of an influenza-like illness (ILI) includes fever and cough or sore throat. Few data exist on the clinical presentation of influenza in hospitalized patients, which may be distinct from the clinical presentation of influenza in ambulatory patients because of underlying medical conditions and medications.

DESIGN.   Retrospective case-control study.

SETTING.   A 1,250-bed urban teaching hospital.

PATIENTS.   A total of 369 patients were admitted to the general medicine wards during 3 consecutive influenza seasons (2001–2004): 123 case patients with laboratory-confirmed influenza that was diagnosed during routine medical care and 246 control patients with active surveillance culture results negative for influenza.

METHODS.   Data on demographic characteristics, comorbidities, and signs and symptoms were obtained from a review of the medical records of the case and control patients. Analysis included stratified analysis and logistic regression.

RESULTS.   Cough, coryza, sore throat, and fever were more common in patients with influenza infection. The CDC's definition of an ILI had a sensitivity of 43% and specificity of 86% in the study population, with a crude odds ratio (OR) of 4.7 (95% confidence interval [CI], 2.8–7.8). The sensitivity of the CDC's definition of an ILI decreased to 21% among asthmatic patients, who had similar rates of fever and/or ILI with or without influenza. By logistic regression, ILI was strongly associated with influenza infection in patients without asthma (adjusted OR, 7.5 [95% CI, 4.1–13.7]) but not in patients with asthma (adjusted OR, 1.1 [95% CI, 0.13–10]). The positive predictive value of an ILI in asthmatic patients was 50%.

CONCLUSIONS.   The CDC's definition of an ILI lacks sensitivity among hospitalized patients, and the presence of an ILI is not associated with influenza infection in asthmatic patients.

Influenza epidemics in the United States result in an average of 36,000 deaths and 114,000 hospitalizations annually.[1] The clinical characteristics of influenza infection have been well described for outpatients,[2-7] emergency department patients,[8,9] and nursing home residents.[10] Several different case definitions have been proposed for influenza in those populations.[2,4,5,11-14] The most commonly identified symptoms are fever and cough, but these symptoms are not seen in all cases. There are fewer data on the clinical presentation of hospitalized patients found to have influenza,[15-21] and many studies used symptom-screening criteria that may have resulted in an overrepresentation of common symptoms.

We hypothesized that hospitalized patients are less likely to have classic symptoms of influenza-like illness (ILI). We were specifically interested in the effect of age and chronic pulmonary disease, such as emphysema and asthma, for which the common presence of a cough could limit the discriminating ability of the traditional ILI criteria as defined by the Centers for Disease Control and Prevention (CDC).

## METHODS

*Study design.* We conducted a retrospective case-control study of patients hospitalized at a large, adult teaching hospital during the study period from 2001 to 2004, which encompassed 3 consecutive influenza seasons. Influenza seasons were defined as the period starting from the date of the first laboratory-confirmed case of influenza in the hospital each winter to the date of the last laboratory-confirmed case the following spring. Institutional review board approval for the project was obtained.

### Study Population

*Case patients.* Case patients ($n = 123$) were defined as inpatients admitted to the general medicine wards (2001–2004) who were found to have laboratory-confirmed influenza infection during routine medical care. Laboratory confirmation included a positive direct fluorescent antibody test from a nasal swab sample or, if that test result was negative, a positive culture result from a nasal sample plated onto a monkey kidney cell plate. All testing was performed at the virology laboratory of St. Louis Children's Hospital (St. Louis, MO).

*Control patients.* In the latter 2 years of the study period (2002–2004), an active surveillance program was started, in which all consenting patients admitted to the general medicine wards during influenza season were tested, regardless of clinical symptoms or diagnosis at admission. During a control patient's hospitalization, nasal swab samples were obtained for culture on admission and then on a weekly basis. Overall, 410 patients were approached for participation; 75 refused. No patients, other than those identified during routine care, had influenza virus infection diagnosed during surveillance testing. Of the 335 consenting patients known not to have influenza, 246 were randomly selected to serve as control patients, in a 2 : 1 ratio with case patients.

*Data collection and covariates.* Data on case and control patients were collected by retrospective chart review of electronic and paper medical records using a standardized data collection instrument. Age was dichotomized for analysis into less than 65 years of age and 65 years of age or older, according to CDC definitions of age groups at high risk for influenza. Data on race was categorized as white, African American, and other; data on sex were also collected.

Data on the presence or absence on admission of the following signs and symptoms commonly associated with influenza were collected from each patient's medical chart: cough, sore throat, "feverish" (patient reported), runny nose and/or coryza, headache, muscle and/or body ache, chills and/or rigors, fatigue, and fever. ILI was defined as fever and cough or sore throat, according to the CDC's surveillance definition.[22] Inpatients' temperatures documented in the medical records were reviewed; patients were considered febrile if they had a documented temperature of 37.8°C or higher prior to the in-hospital diagnosis of influenza (case patients) or prior to obtaining nasal swab samples for culture (control patients). Data on the presence or absence of symptoms atypical for influenza, which included nausea, vomiting, and diarrhea, were also collected.

Medical covariates included congestive heart failure, asthma, chronic obstructive pulmonary disease (emphysema or chronic bronchitis), diabetes, renal failure, liver disease (cirrhosis), cancer (with treatment in the last year), and an immunosuppressed state (eg, due to receipt of oral steroids, receipt of a transplant, or HIV infection). The covariates were considered present if they were recorded in the admission history, in the past medical history, or in the diagnostic assessment and treatment plan.

*Analysis.* The percentage of case and control patients with specific demographic characteristics, comorbid medical conditions, and clinical signs and symptoms was calculated. Among case patients, differences in clinical presentation by influenza type (A, B, or C) and by the sex and age of the patient were examined. The $\chi^2$ or Fischer exact tests were performed to determine if any differences were statistically significant (2-tailed testing; $P < .05$). Crude odds ratios (ORs) were calculated to determine the strength of association between the CDC definition of an ILI and the laboratory-confirmed influenza; 95% confidence intervals (CIs) were calculated to estimate the precision of the crude OR. The sensitivity, specificity, and positive and negative predictive values of the signs and symptoms of an ILI for laboratory-confirmed influenza were calculated.

Effect modification by presence of asthma, presence of chronic obstructive pulmonary disease, and older age was assessed with the Breslow-Day test for homogeneity. Mantel-Haenszel adjusted ORs were calculated if confounding was detected. Multivariate adjustment for effect modification and confounding was made with logistic regression analysis. The Hosmer-Lemeshow test was used to assess the fit of the model. All analyses were performed with SPSS, version 12 (SPSS).

### RESULTS

There were 123 case patients with laboratory-confirmed influenza on the general medicine wards during the 3 influenza seasons. The total study population included those 123 case patients, who had influenza diagnosed during routine medical care, and 246 control patients. Control patients were randomly selected from patients whose nasal swab samples tested

TABLE 1. Demographic Characteristics of Case and Control Patients Admitted to the General Medicine Wards of an Urban Teaching Hospital During 3 Consecutive Influenza Seasons (2001–2004)

| | No. (%) of patients | | |
|---|---|---|---|
| Characteristic | Case group ($n = 123$) | Control group ($n = 246$) | P |
| Age ⩾65 years | 67 (55) | 105 (43) | .03 |
| Female sex | 80 (65) | 131 (53) | .03 |
| African American race | 72 (58) | 96 (39) | .04 |
| Disease or condition | | | |
| Asthma | 24 (20) | 24 (10) | <.01 |
| Immunosuppression | 29 (24) | 38 (15) | .06 |
| Diabetes | 34 (28) | 104 (42) | <.01 |
| Chronic kidney disease | 14 (11) | 83 (34) | <.01 |
| Congestive heart failure | 20 (16) | 69 (28) | .01 |
| COPD | 26 (25) | 54 (22) | .54 |
| Cirrhosis | 3 (2) | 18 (7) | .06 |
| Cancer | 10 (8) | 17 (7) | .67 |

NOTE. COPD, chronic obstructive pulmonary disease.

TABLE 2.   Clinical Characteristics of Case and Control Patients Admitted to the General Medicine Wards of an Urban Teaching Hospital During 3 Consecutive Influenza Seasons (2001–2004)

| | No. (%) of patients | | |
| --- | --- | --- | --- |
| Characteristic | Case group ($n = 123$) | Control group ($n = 246$) | $P$ |
| Cough | 112 (91) | 94 (38) | <.01 |
| Subjective fever (patient reported) | 81 (66) | 87 (35) | <.01 |
| Documented fever[a] | 61 (50) | 72 (29) | <.01 |
| Myalgias | 42 (34) | 38 (15) | <.01 |
| Coryza | 36 (29) | 35 (14) | <.01 |
| Sore throat | 27 (22) | 17 (7) | <.01 |
| Headache | 34 (28) | 56 (23) | .30 |
| Nausea or vomiting | 46 (37) | 111 (45) | .16 |
| Diarrhea | 23 (19) | 84 (34) | <.01 |
| Fever and cough | 53 (43) | 34 (14) | <.01 |
| Fever and sore throat | 9 (7) | 8 (3) | .08 |
| Fever and cough or sore throat[b] | 53 (43) | 34 (14) | <.01 |

[a]  Temperature $\geqslant 37.8°C$.
[b]  Symptoms of influenza-like illness.

negative for influenza during active surveillance on the general medicine wards. The demographic characteristics of case and control patients are displayed in Table 1. Case patients were more likely to be 65 years of age or older, female, and African American. Asthma was more common in case patients, although there was no difference between case and control patients in the proportion that had chronic obstructive pulmonary disease. Immunosuppression was slightly more common in case patients, although the difference did not reach statistical significance ($P = .06$). Congestive heart failure, diabetes, kidney disease, and cirrhosis were more common in control patients.

Clinical characteristics differed between case and control patients (Table 2). The most typical symptoms of influenza were more commonly found in case patients than in control patients; these included cough, subjective and documented fever, myalgias, coryza, and sore throat. Cough was the most common symptom among case patients, and sore throat was the least common. Among case patients, there was no difference in clinical presentation between patients with influenza type A virus and patients with influenza type B virus, between men and women, between patients from each of the 3 influenza seasons, or between patients less than 65 years of age and patients 65 years of age or older. Control patients were more likely to have diarrhea than were case patients. There was no difference between groups in the proportion of patients with headache and nausea or vomiting.

The combination of fever and sore throat, although uncommon in both groups, was slightly more common in the case patients than in control patients (9 [7%] of 123 vs 8 [3%] of 246; $P = .08$). The combination of fever and cough was significantly more common in case patients than in control patients (53 [43%] of 123 vs 34 [14%] of 246; $P < .01$).

For case patients, the crude OR of having an ILI was 4.7 (95% CI, 2.8–7.8). By stratified analysis, asthma was found to be an effect modifier: for case patients with asthma, the adjusted OR of having an ILI decreased to 1.0 (95% CI, 0.2–4.0). Congestive heart failure and chronic renal disease were more common in control patients than in case patients and were found to be confounders on stratified analysis. Chronic obstructive pulmonary disease, age, race, and sex were not found to have any significant association with ILI.

A logistic regression model was built using ILI, asthma, congestive heart failure, and chronic renal disease as risk factors. According to this model, for case patients without asthma, the OR for meeting the case definition of an ILI was 7.5 (95% CI, 4.1–13.7). For case patients with asthma, however, the OR for meeting the case definition of an ILI was 1.1 (95% CI, 0.13–10.0). Further review of the 48 asthmatic patients (24 case patients and 24 control patients) revealed that, although cough was somewhat more common among case patients than among control patients (23 [96%] of 24 vs 18 [75%] of 24; $P = .097$), the prevalence of fever was the same for both case and control patients (5 [21%] of 24 vs 6 [25%] of 24; $P = .73$). The prevalence of ILI-defining symptoms was also identical (5 [21%] of 24 vs 5 [21%] of 24).

Overall, the use of ILI-defining symptoms to detect influenza in hospitalized patients has a sensitivity of 43% and a specificity of 86%, with a positive predictive value of 61% and a negative predictive value of 75% (Table 3). Cough alone had the best sensitivity (91%). Fever with sore throat had the best specificity (97%). Documented fever alone had a sensitivity of 50%. Among asthmatic patients, the sensitivity of the ILI definition was only 21%, with a specificity of 79%,

TABLE 3. Use of Symptoms of Influenza-Like Illness (ILI) to Detect Influenza in Patients Admitted to the General Medicine Wards of an Urban Teaching Hospital During 3 Consecutive Influenza Seasons (2001–2004)

| Patient group, symptom | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|
| Case and control patients ($n = 369$) | | | | |
| Documented fever[a] | 50 | 71 | 46 | 73 |
| Cough | 91 | 62 | 54 | 93 |
| Sore throat | 22 | 93 | 61 | 70 |
| Fever and cough | 43 | 86 | 61 | 75 |
| Fever and sore throat | 7 | 97 | 53 | 68 |
| ILI | 43 | 86 | 61 | 75 |
| Patients with asthma ($n = 48$)[b] | | | | |
| ILI | 21 | 79 | 50 | 50 |

NOTE.   NPV, negative predictive value; PPV, positive predictive value.
[a] Temperature ≥37.8°C.
[b] There were 24 case patients and 24 control patients.

and the positive and negative predictive values of the ILI-defining symptoms were both 50%.

## DISCUSSION

Our study reviewed the clinical presentation of influenza in hospitalized patients during 3 influenza seasons in a large midwestern teaching hospital using case-control methodology. This research builds on work reported previously[20] in which we described the clinical presentation of influenza in hospitalized patients by looking at a case series of 207 inpatients with influenza. The current study was limited to patients on the general medicine wards, to allow for comparison with a control population of patients on the general medicine wards known not to have influenza.

The ILI symptom complex lacked sensitivity in this patient population. In contrast to other studies,[8,16,18,23] this study found no effect of age on presentation. Cough alone had the highest sensitivity (91%), while fever had a sensitivity of 50%. Our data suggest that, during influenza season, the presence of cough in a hospitalized patient should prompt testing for influenza, even in the absence of fever. We did not find any differences in the prevalence of the ILI-defining symptoms by season or influenza type (A or B).

For the asthmatic patients in this study, it was found that the ILI symptoms were simply not associated with influenza infection, by multivariate analysis. Contrary to our expectation, this difference appeared to be related to the low rates of fever in this population, not to high rates of cough. The low prevalence of fever in this population (21%) may be related to long-term use of steroids, either oral or inhaled; however, this information is unavailable because data on outpatient medication were not collected in this study.

Several outpatient studies have reported higher sensitivity for the ILI-defining symptoms of cough with fever, ranging from 50% to 95%,[4,6,7] with positive predictive values ranging from 40% to 87%.[2,4,6] The higher sensitivity of these symptoms for outpatients supports our hypothesis that hospital-ized patients may have less typical clinical presentations of influenza infection. Alternatively, the use of fever and/or upper respiratory symptoms as inclusion criteria for influenza testing in most of these studies may have resulted in them missing less typical presentations.

There are limited data on the clinical presentation of influenza in hospitalized patients. Two inpatient studies reported the clinical presentation of influenza among elderly patients.[15,17] One study found that 65% of the patients had a fever higher than 38°C,[15] and another found a sensitivity of 78% for the combination of fever, cough, and acute onset.[17] Both studies used inclusion criteria for influenza screening that included an ILI or a respiratory illness, which may explain the higher rates of those symptoms. A recent prospective cohort study in The Netherlands also found a low sensitivity of cough and fever (35%) in hospitalized patients.[21] All patients admitted during the study period were tested for influenza, including those without suspected ILI or respiratory illness. Similar to that of our study, this design provides an asymptomatic comparison group and more realistic calculations of sensitivity and positive predictive value.

Although the increased risk for influenza and for complications from influenza among asthmatic patients is well documented, there are few data that report the clinical presentation of influenza in those patients. One study performed prospective surveillance for viral respiratory infections with respiratory syncytial virus, adenovirus, parainfluenza, and influenza in 104 outpatient asthmatic and nonasthmatic children.[24] Viral testing was performed for both groups, regardless of whether there were current symptoms of an upper respiratory infection. The authors found that asthmatic children had a higher rate of viral infection than did nonasthmatic children, regardless of clinical symptoms at the time of the test.[24] This result supports our finding that clinical symptomatology may be an unreliable guide to the presence of influenza infection in asthmatics, although more studies are

needed of larger cohorts of asthmatic patients and of adult patients.

This study has several limitations. Because of the retrospective data collection, some data of interest could not be reliably obtained, including duration of symptoms, smoking history, and influenza vaccination status. The adequate capture of data on clinical symptoms relied on both the patient's reporting and the healthcare worker's recording of the information. A standardized data collection tool was used by trained data collectors to maximize our ability to find reported symptoms from the medical chart; the same system was used for case and control patients, to minimize any bias. Bias in the reporting of symptoms by patients or their healthcare providers cannot be detected.

In addition, the sensitivity of laboratory testing for influenza is dependent on the quality of the sample obtained, as well as on the timing of sampling during the clinical course of illness. Cases of influenza infection may have been missed if the sample was not obtained properly or if the sample was obtained late in the course of the disease. If this did occur, some case patients might have been analyzed as control patients, thus lowering the observed OR for an ILI. In addition, the low level of influenza activity during the study period may have influenced the positive predictive value of the influenza symptoms examined. Also, not all case and control patients were matched by year, because the surveillance program started in year 2 of the study. Although we did not find any differences in clinical presentation among case patients by year, differences between case and control patients by year could not be evaluated.

These findings have several important clinical implications. In the absence of reliable case definitions to identify hospitalized patients with influenza, vaccination remains an important measure to prevent the nosocomial spread of disease. Because vaccine mismatch with the circulating strain of the influenza virus may leave even vaccinated patients vulnerable, aggressive testing and early isolation are also critical to limit spread. Cough was the most sensitive symptom, indicating that a high clinical suspicion for influenza should be maintained for all patients admitted with cough during influenza season, regardless of other symptoms.

Among asthmatic patients, the presence of the ILI-defining symptoms had no correlation with influenza infection. Patients with asthma are at high risk for influenza infection and for complications from influenza. Vaccination remains the best defense, and screening criteria for influenza in asthmatic patients are needed. Until more data are available, consideration should be given to performing influenza testing on all patients with asthma admitted to the hospital during influenza season, regardless of suggestive symptoms. More work is needed to define predictive symptomatology for influenza infection among inpatients, in general, and among inpatients with asthma, in particular.

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