ORIGINAL INVESTIGATION

Clinical Signs and Symptoms Predicting Influenza Infection

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Background: New antiviral drugs are available for the treatment of influenza type A and type B infections. In clinical practice, antiviral use has rarely been guided by antecedent laboratory diagnosis. Defined clinical predictors of an influenza infection can help guide timely therapy and avoid unnecessary antibiotic use.

Objective: To examine which clinical signs and symptoms are most predictive of influenza infection in patients with influenzalike illness using a large data set derived from clinical trials of zanamivir.

Methods: This analysis is a retrospective, pooled analysis of baseline signs and symptoms from phase 2 and 3 clinical trial participants. It was conducted in mainly unvaccinated (mean age, 35 years) adults and adolescents who had influenzalike illness, defined as having fever or feverishness plus at least 2 of the following influenzalike symptoms: headache, myalgia, cough, or sore throat who underwent laboratory testing for influenza. Clinical signs and symptoms were evaluated in statistical models to identify those best predicting laboratory confirmation of influenza.

Results: Of 3744 subjects enrolled with baseline influenzalike symptoms, and included in this analysis, 2470 (66%) were confirmed to have influenza. Individuals with influenza were more likely to have cough (93% vs 80%), fever (68% vs 40%), cough and fever together (64% vs 33%), and/or nasal congestion (91% vs 81%) than those without influenza. The best multivariate predictors of influenza infections were cough and fever with a positive predictive value of 79% ($P<.001$). The positive predictive value rose with the increase in the temperature at the time of recruitment.

Conclusion: When influenza is circulating within the community, patients with an influenzalike illness who have both cough and fever within 48 hours of symptom onset are likely to have influenza and the administration of influenza antiviral therapy may be appropriate to consider.

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INFLUENZA VIRUS infection is a major public health problem, occurring, typically, in the Northern Hemisphere, between the months of December and April. Epidemics of influenza are characterized by an increased morbidity and mortality in the community and result in increased absenteeism from school and work.[1-6] The classic influenza syndrome is sudden in onset and is characterized by fever, headache, cough, sore throat, myalgia, nasal congestion, weakness, and loss of appetite.[3-8]

Vaccines, the most cost-effective primary prevention for influenza, are effective and readily available but have their limitations.[9,10] Two antiviral agents with similar activity, amantadine hydrochloride and rimantadine hydrochloride, have been available many years for prophylaxis and treatment of influenza.[3,10-13] However, both of these agents are active only against influenza type A and not influenza type B, and resistance of influenza A viruses to these drugs can be a problem.[14,15] Zanamivir and oseltamivir, new, recently approved antiviral agents, are inhibitors of the influenza virus enzyme neuraminidase and are active against influenza type A and type B.[3,11,12,16] When administered early in the course of infection, both reduce the time to alleviation of clinical symptoms in individuals infected with influenza.[3,11,12]

To be maximally effective against influenza, antiviral therapy must be initiated as soon as possible after symptom onset, and clearly cannot await traditional laboratory diagnosis.[11,12,17,18] This analysis examined which clinical signs and symptoms are most predictive of influenza infection in patients with influenzalike illness using a large data set derived from clinical trials of zanamivir. Knowledge of the most predictive symptoms of influenza could be used by physicians to diagnose influenza more accurately and to begin an appropriate course of treatment in time to be of most benefit to the patient.

PATIENTS AND METHODS

STUDIES AND DESIGN

Eight double-blind, placebo-controlled studies involving 231 study centers in North America, Europe, and the Southern Hemisphere were included in this analysis (**Table 1**). These studies were phase 2 and 3 clinical trials designed to evaluate the use of the antiviral agent zanamivir vs placebo for the treatment of influenza type A and type B viral infections and were conducted during the fall and/or winter of 1994 through 1998.

Data regarding patients' signs and symptoms, collected at baseline (ie, prior to any treatment), were pooled across the 8 studies. All available study data were included in the analysis to minimize the potential for bias.

PATIENTS

To be eligible, study participants were required to have fever (body temperature ≥37.8°C or ≥37.2°C for patients ≥65 years old in NAIA/B3002 [the protocol report number]) or a symptom of feverishness, plus at least 2 of the following influenzalike symptoms: headache, myalgia, cough, or sore throat. Feverishness was defined as the patient's subjective symptom of feeling like they had a fever or chill. Specific influenzalike symptoms required for patient enrollment into each study are also summarized by study in Table 1.

A requirement for a study site to begin patient enrollment was the identification of at least 2 individuals with culture-confirmed influenza within a 7-day period prior to enrollment, who resided in the geographic region around the site. Geographic region was defined as the area within a 50-mile radius of the study location. This requirement was to improve the probability that influenza was actually present in the geographic region of the study.

DATA COLLECTION AND ANALYSIS

The following baseline signs or symptoms were analyzed as potential predictors of influenza infection: fever, feverishness, cough, headache, sore throat, myalgia, nasal congestion, weakness, and loss of appetite. Although the symptoms were collected using a 4-point severity scale, for this analysis they were analyzed as either absent or present. A diagnosis of influenza was defined either as a positive culture for influenza virus or as a 4-fold or greater increase in influenza antibody titer in convalescent vs acute serum samples as determined by hemagglutination inhibition. In some studies, influenza infection could also or alternatively be confirmed by polymerase chain reaction (NAIA/B3002 [the protocol report number]) or by immunofluorescence.[19,20]

Univariate and multivariate analyses were conducted to compare clinical signs and symptoms with the diagnosis of influenza. Demographic factors such as age, sex, high-risk populations (defined as having chronic respiratory disease, cardiovascular disease, or more advanced age [ie, ≥65 years old]), and hours from symptom onset to collection of the diagnostic specimen were also incorporated into the analysis. A stepwise logistic regression analysis was performed to determine which baseline symptoms and patient characteristics best predict influenza infection. The stepwise procedure selected the best explanatory variable into the model first, then selected the second best explanatory variable, and so forth. The stepwise procedure stopped selecting additional variables when they did not reach statistical significance at the $\alpha = .05$ level, given the other variables already in the model. The stepwise logistic regression model was tested for goodness of fit to determine the most parsimonious model. Odds ratios and their 95% confidence intervals were calculated for each variable in the logistic regression model. Measures of positive predictive value (PPV), negative predictive value, sensitivity, and specificity were calculated to also identify the best predictors of an influenza infection. Positive predictive values were compared for individual symptoms, as well as combinations of symptoms (SAS Statistical Analysis Software, version 6.12; SAS Institute Inc, Cary, NC).

RESULTS

A total of 3744 clinical trial participants with influenza-like symptoms were enrolled during the fall and/or winter of 1994 through 1998. Demographic information of study participants, the percentage who had been vaccinated against influenza, and the percentage with a positive diagnosis of influenza, are given in **Table 2**. Approximately two thirds of the patients recruited to this study were identified as being infected with influenza virus.

Among individuals with influenza, the most frequently reported symptoms were weakness (94%), myalgia (94%), cough (93%), and nasal congestion (91%) (**Table 3**). Among those individuals without influenza, weakness (94%) and myalgia (94%) were also commonly reported. Individuals with influenza were more likely than those without influenza to have baseline cough (93% vs 80%), fever (68% vs 40%), and cough and fever together (64% vs 33%).

As listed in **Table 4**, the stepwise logistic regression selected 9 baseline symptoms and characteristics into the model, with fever (odds ratio = 3.26; $P < .001$) and cough (odds ratio = 2.85; $P < .001$) as the 2 best explanatory variables. Headache, myalgia, and high-risk status were poor explanatory variables ($P > .05$) and were not selected into the model. Feverishness was not included since fever (body temperature ≥37.8°C) was already in the model. Both older age and onset over 36 hours from recruitment predicted positive influenza status. This may relate to the greater likelihood that such individuals would be seen by a physician for management of their symptoms. Sore throat negatively predicted the presence of influenza.

The ability to use these findings to identify which patients are most likely to have influenza was examined in a sensitivity analysis (**Table 5**). Of particular interest is the PPV proportion of those with a symptom who are confirmed positive for influenza. The PPV for baseline fever and cough was 79%, with sensitivity and specificity values of 64% and 67%, respectively. The PPV for baseline cough and fever was even higher (PPV = 85%) in the subset of patients with time from onset between 36 and 48 hours; in those recruited closer to illness on-

Table 1. Study Features and Clinical Characteristics of the 8 Multicenter, Phase 2 and 3 Studies Evaluating the Safety and Efficacy of the Antiviral Zanamivir for the Treatment of Influenza Type A and Type B Infections

Protocol Report No., Source*	Study Location (Year)	Patient Age, y	Duration of Onset of Symptoms	Fever/Feverishness at Enrollment†	No. of Patients Randomized
NAIA/B2005[12]	North America and Europe (fall/winter 1994-1995)	≥13 in A2005, ≥18 in B2005	≤48 h	Fever (NAIA2005); feverishness (NAIB2005)	417
NAI/B2007[25]	Southern Hemisphere (fall/winter 1995-1996)	≥13	≤48 h	Feverishness	554
NAIA/B2008[26]	North America and Europe (fall/winter 1995-1996)	≥13	≤48 h	Feverishness	1256
NAI/B3001[3]	Southern Hemisphere (winter 1997)	≥12	≤36 h	Fever and feverishness	455
NAIA/3002[27]	North America (fall/winter 1997-1998)	≥12	Within 2 calendar days	Fever	777
NAI/B3002[28]	Europe (fall/winter 1997-1998)	≥12	Within 2 calendar days	Fever	356

*All protocols were double-blind, randomized, placebo-controlled, parallel group, multicenter studies.
†Fever was a body temperature of 37.8°C or higher, whereas feverishness was the patient's subjective feeling that they had a fever or chill. For NAIA/B3002, the fever criterion was a body temperature of 37.2°C or higher for patients 65 years or older.

Table 2. Baseline Characteristics of Pooled Participants

Characteristic	Patients With Laboratory-Confirmed Influenza (n=2470 [66])	Patients Who Tested Negative for Influenza (n=1274 [34])
Age, mean (SD), y	34.8 (14.6)	34.5 (13.0)
Sex, % male	50.5	45.3
Ethnicity, % of patients		
White	92	89
African American	3	4
Hispanic	2	3
Asian	2	2
Other	1	2
High-risk population*	13.7	12.0
Vaccination status, %†	5.9	3.8
Onset of symptoms		
Mean (SD), h	29.4 (10.9)	27.2 (10.9)
Proportion of patients, %, at		
≤24 h	38	47
>24-36 h	39	34
>36 h	23	19
Influenza type, % of patients		
A	86.8	. . .‡
B	12.4	. . .
Both	0.3	. . .
Unknown type	0.5	. . .

*High-risk was defined as having chronic respiratory disease, cardiovascular disease, or advanced age (≥65 years).
†Vaccination status was available in only 6 of 8 studies.
‡Ellipsis indicates not applicable.

Table 3. Proportion of Pooled Participants With Baseline Symptoms

Symptom	Patients With Laboratory-Confirmed Influenza, % (n = 2470)	Patients Who Tested Negative for Influenza, % (n = 1274)
Fever (≥37.8°C)*	68	40
Feverishness*	90	89
Cough	93	80
Nasal congestion	91	81
Weakness	94	94
Loss of appetite	92	86
Sore throat	84	84
Headache	91	89
Myalgia	94	94

*Fever was a body temperature of 37°C or higher, whereas feverishness was the patient's subjective feeling that they had a fever or chill.

set, the PPV was still 77%. Adding other symptoms did not improve the PPV substantially. However, as shown in the **Figure**, the probability of a patient having confirmed influenza increased with increasing baseline temperature and was consistently greater in patients with a cough than in patients without a cough. The proportion of patients who were confirmed positive for influenza exceeded 80% when their temperature was above 38°C.

COMMENTS

Acute respiratory illnesses are the leading cause of medical visits for outpatients of all ages. The precise origins for these illnesses are rarely identified.[8] This is largely because for most respiratory viral diseases, establishment of the specific viral cause is neither necessary (ie, does not direct therapy) and thus is not cost-effective. The situation is different for influenza virus infection, for which specific antiviral therapy has been available for many years. The introduction of the new neuraminidase inhibitors has made the need to be able to recognize influenza illness much more important.[3,10-12]

This analysis determined if there are clinical signs and symptoms that might help the clinician discriminate influenza infection from illness due to other respiratory viruses. The most common presenting symptoms among individuals with influenza in this cohort were feverishness (feeling of fever or chills), cough, myalgia, and

Table 4. Stepwise Logistic Regression Analysis of Predictors of Influenza Infection

Symptom	Stepwise Analysis Odds Ratio	95% Confidence Intervals	*P*
Fever (body temperature ≥37.8°C)	3.26	3.87-2.75	<.001
Cough	2.85	3.68-2.21	<.001
Nasal congestion	1.98	2.54-1.54	<.001
Age (≥55 y)	1.60	2.16-1.18	.003
Weakness	1.54	2.22-1.07	.008
Onset (>36 h)	1.53	1.90-1.24	<.001
Loss of appetite	1.43	1.86-1.10	.008
Sex (male)	1.27	1.50-1.08	.004
Sore throat	0.72	0.91-0.57	.01
Feverishness	. . .*	. . .	. . .
Headache	. . .	. . .	. . .
Myalgia	. . .	. . .	. . .
High-risk	. . .	. . .	. . .

**Ellipses indicate symptom was not selected in stepwise procedure.*

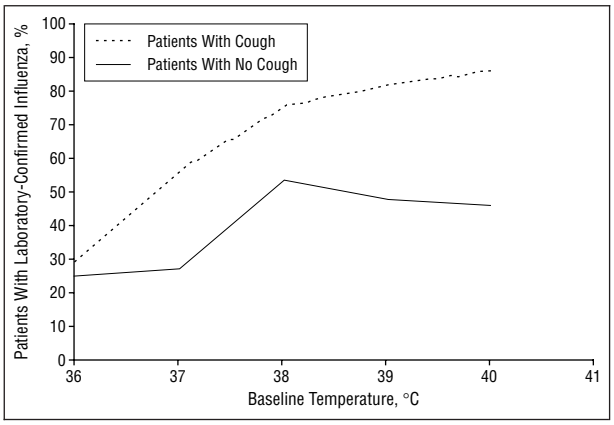
Table 5. Multivariate Predictors of Influenza Infection With Sensitivity and Specificity Analyses*

Symptoms	PPV	NPV	Sensitivity, %	Specificity, %
Fever	76.85	49.14	67.79	60.38
Cough	69.43	60.89	93.24	20.41
Fever + cough	79.04	48.91	63.81	67.19
Fever + cough when onset ≤36 h	77.28	51.35	63.32	67.54
Fever + cough when onset >36 h	85.37	42.33	50.30	80.89
Fever + cough + nasal congestion	81.45	48.21	59.03	73.94
Fever + cough + weakness	80.27	47.85	59.80	71.51
Fever + cough + myalgia	79.11	47.86	61.50	68.52
Fever + cough + loss of appetite	79.04	47.75	61.38	68.45
Fever + cough + sore throat	79.02	45.30	55.51	71.43
Fever + cough + headache	78.69	46.81	59.80	68.60

**PPV indicates positive predictive value, the probability of having laboratory-confirmed influenza when the symptom is present; NPV, negative predictive value, the probability of not having laboratory-confirmed influenza when the symptom is not present; sensitivity, the probability of having the symptom when the patient has laboratory-confirmed influenza; and specificity, the probability of not having the symptom when the patient does not have laboratory-confirmed influenza (ie, when the test result for influenza is negative).*

weakness, consistent with previous publications.[4-8,21] In this population, the PPV of cough and fever was 79%, compared with the 69% reliability of "practitioner intuition" as recently described.[7] The PPV rose even further as the height or degree of fever at recruitment increased. Thus, during periods when influenza virus is known to be present within a community, a high index of suspicion for influenza is warranted in patients who are seen with acute onset of cough and fever (body temperature ≥37.8°C).

Our results corroborate those of Monto and Ohmit,[21] who reported that in individuals with influenzalike illness, the 2 best predictors of a laboratory-confirmed diagnosis of influenza are cough and fever, both for type A (H3N2) and type B viruses. The current results, analyzed



Percentage of patients with a positive influenza test result by baseline cough and temperature score.

from a much greater number of patients, show that cough and fever are better predictors of influenza infection than either symptom alone. Most isolates in the current analysis were type A(H3N2) viruses but based on the previous study, there is no reason to think that the situation with type B will be different. In contrast, Carrat et al[22] examined 610 patients, of whom only 168 (28%) were positive for influenza, mainly type A viruses. They found that fever and, for type A(H3N2) viruses, cough predicted influenza infection, but the PPV was not high with a variety of case definitions. The difference in conclusions may reflect the very different settings of the 2 studies, one derived from a surveillance program in which general practitioners were asked to collect a fixed number of specimens, and ours, derived from a clinical trial in which only patients with a predefined influenzalike illness were considered in the presence of circulating influenza. In any event, in 3 different studies, fever and cough have independently been found to predict influenza infection.

The clinical studies analyzed herein were performed in geographic regions where influenza was known to be present. Knowledge of the prevalence of influenza virus in the community can optimize the practicability of making the clinical diagnosis of influenza. First, there is the expected relationship between the PPV and the prevalence of a condition. Also, when influenza virus is prevalent, the incidence of illness due to other respiratory viruses tends to decrease, and because of this, the PPV of clinical signs and symptoms increases.[4] Although physicians are often informally aware of the arrival of influenza virus in the community, their knowledge could be increased with the help of better surveillance and rapid confirmation of infection. A problem arises at the start of an epidemic, when information is scanty and the PPV might be lower. Physicians might collect diagnostic specimens from patients who are seen at the start of the epidemic, not as much to direct therapy for these patients as to gather information about the local prevalence of the virus. These surveillance techniques, in combination with the symptoms of cough and fever, could improve the accuracy of physicians in making a clinical diagnosis of influenza.

There are limitations to the application of this information in everyday practice. Young children were not included nor were significant numbers of older individuals.

It is known that in elderly persons, living in the community and especially in nursing homes, outbreaks of agents such as respiratory syncytial virus can sometimes mimic those of influenza, so that identifications on the circulating viruses should be done in a small number of those affected to confirm the cause.[23,24] In the present analysis, fever or feverishness (a feeling of fever or chills) was an enrollment criterion for participation in these study protocols. In everyday practice, a diagnosis of influenza may be missed in individuals who do not have fever at the time of their office visit or clinical presentation. Furthermore, this analysis cannot consider altered (reduced) symptom presentation that may occur with antecedent vaccination (reducing or altering sensitivity and specificity of fever, cough, and other symptoms of influenza), since most participants were unvaccinated. Due to the selection of a patient population with defined symptoms of influenzalike illness such as fever, we may have overestimated the PPV that would actually be observed among practicing physicians in the community. The prevalence of laboratory-confirmed influenza infection in our study population of individuals with defined influenzalike illnesses was 66%; Cate[4] reported that at least 50% of throat swab specimens from patients with respiratory illness yielded influenza virus during a typical epidemic. However, these investigators suggest that this percentage might increase if specimens were collected only during the first few days of the disease.[4] Thus, if it is clear that influenza is prevalent within a practitioner's practice area, the PPV of all symptoms would increase and the threshold for intervention should be lowered.

Thus, the results of this study suggest that cough and fever are good predictors of infection among patients with an influenzalike illness when influenza is present within the community. To maximize their ability to diagnose and treat influenza, clinicians should work with community health officials and among themselves to keep apprised of influenza in the community. Education, better surveillance methods, an appropriate index of suspicion, and early treatment can reduce the time to alleviation of symptoms for patients suffering from influenza infection.

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