Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Does This Patient Have Influenza?

EBEM Commentators
Barnet Eskin, MD, PhD
Robert Levy, MD

From the Department of Emergency Medicine, Morristown Memorial Hospital, Morristown, NJ.

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2006.08.016

[Ann Emerg Med. 2007;49:103-105.]

RATIONAL CLINICAL EXAMINATION REVIEW SOURCE

This is a rational clinical examination abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a rational clinical examination review from the *Journal of the American Medical Association* and a commentary by emergency physicians knowledgeable in the subject area.

The source for this rational clinical examination review abstract is: Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. The rational clinical examination: does this patient have influenza? *JAMA*. 2005;293:987-997. The *Annals'* EBEM editors assisted in the preparation of the abstract of this rational clinical examination review, as well as the Evidence-Based Medicine Teaching Point.

OBJECTIVE

To review and summarize the precision and accuracy of symptoms and signs for the diagnosis of influenza, as well as the operating characteristics of rapid diagnostic tests.

DATA SOURCES

The authors performed a MEDLINE search of English-language articles from 1966 to September 2004, using topic-specific search terms pertaining to the clinical diagnosis of influenza. They also manually searched the bibliographies of the retrieved articles. The authors limited their search to data from the period before the severe acute respiratory syndrome outbreak. In addition, the authors also searched MEDLINE from January 1996 to October 2004 for the most current and relevant rapid diagnostic tests available and obtained manufacturers' data on the specificities and sensitivities of the tests.

STUDY SELECTION

The authors selected studies that contained data on the operating characteristics of signs and symptoms of influenza diagnosis and met all of the following criteria: (1) prospective cohort, randomized controlled trial, or meta-analysis; (2) primary assessment of individual clinical signs and symptoms as predictors of diagnosis included; (3) a criterion standard of influenza diagnosis through culture, diagnostic antibody titer, polymerase chain reaction, or immunofluorescent antibody included; and (4) quality grade A or B using a previously published grading scheme in the Rational Clinical Examination series. They excluded studies for which primary data were not available.

DATA EXTRACTION AND ANALYSIS

Two authors independently reviewed and abstracted data and estimated the likelihood ratios (LRs) for clinical diagnostic findings using confidence profile method software FAST*PRO (Academic Press, Boston, MA).[1] Differences were resolved by discussion and consensus; κ values for interobserver agreement were not reported. Diagnostic odds ratios are reported for each of the findings, using a random effects/fixed effects model.

MAIN RESULTS

From 915 original citations, the authors included 6 articles describing clinical assessment of influenza-related illness in a total of 7,105 patients. The LR associated with each symptom is shown in the Table. In studies not restricting inclusion to specific age groups, no single clinical finding consistently had an LR high or low enough to clinically rule in or rule out influenza, respectively. The highest LR associated with a positive finding was 1.8, and the lowest associated with a negative finding was 0.4. "Feverishness," myalgias, malaise, sore throat, and sneezing each had LRs with confidence intervals (CIs) that include 1.0, rendering them useless in predicting the presence or absence of influenza infection.

The greatest LR reported (5.4) was for patients at least 60 years old who each had all 3 characteristics of fever, cough, and acute onset, found in 1 study. Among patients at least 60 years old, fever, chills, malaise, myalgias, feverishness, cough, headache, and nasal congestion had LRs associated with a positive finding greater than 1 whose 95% CIs did not cross 1 (see Table).

In the age-unrestricted group, among all clinical findings studied, fever and cough had the largest diagnostic odds ratios (see EBEM teaching point) at 4.5 and 2.8, respectively, implying that these findings may be the most useful for

Table. LRs of symptoms.*

Symptom	Age, y	LR+	LR–
Fever	All	1.8 (1.1–2.9)	0.4 (0.3–0.7)
	≥60	3.8 (2.8–5.0)	0.7 (0.6–0.8)
Chills	≥60	2.6 (2.0–3.2)	0.7 (0.6–0.8)
Malaise	≥60	2.6 (2.2–3.1)	0.6 (0.4–0.7)
Myalgias	≥60	2.4 (1.9–2.9)	0.7 (0.6–0.8)
Feverishness	≥60	2.1 (1.2–3.7)	NS
Cough	All	1.1 (1.1–1.2)	0.4 (0.3–0.6)
	≥60	2.0 (1.1–3.5)	0.6 (0.4–0.9)
Headache	All	NS	0.8 (0.6–0.9)
	≥60	1.9 (1.6–2.3)	0.7 (0.6–0.8)
Sore throat	≥60	NS	0.8 (0.7–0.9)
Sneezing	≥60	0.5 (0.2–0.9)	2.1 (1.4–3.1)
Nasal congestion	All	1.1 (1.1–1.2)	0.5 (0.4–0.6)
Fever and cough	All	1.9 (1.8–2.1)	0.5 (0.5–0.6)
	≥60	5.0 (3.5–6.9)	0.8 (0.7–0.8)
Fever and cough and acute onset	All	2.0 (1.8–2.1)	0.5 (0.5–0.6)
	≥60	5.4 (3.8–7.7)	0.8 (0.7–0.9)

LR+, LR associated with a positive finding; *LR–*, LR associated with a negative finding; *NS*, not statistically significant.
*The 95% CIs are given in parentheses. Results are not shown if the 95% CIs crossed 1.0 or are indicated by "NS."

distinguishing patients with influenza from those without. However, as shown above, in the age-unrestricted group, the presence or absence of fever (the finding with the largest diagnostic odds ratio and LRs farthest from 1) is unlikely by itself to change a physician's clinical impression.

The sensitivities and specificities for rapid diagnostic tests ranged from 59% to 81% and 70% to 99%, respectively. The cost-effectiveness of the rapid diagnostic tests depended on the pretest probability of a positive influenza finding. The authors of one study of cost-effectiveness in unvaccinated patients older than 65 years concluded that testing was preferred for pretest probabilities only between 5% and 14% because with pretest probabilities greater than 14%, simply treating all patients empirically with the neuraminidase inhibitor oseltamivir was more cost-effective than testing first.

CONCLUSIONS

No specific symptom or combination of symptoms is diagnostic of influenza. The combination of fever and cough during the influenza season suggests a significantly increased likelihood of influenza among elderly individuals. Clinicians would benefit from using publicly available surveillance data to determine the influenza season in their geographic area.

Rational Clinical Examination Author Contact
W. Paul McKinney, MD
Department of Medicine
University of Louisville
Louisville, KY 40202
E-mail mckinney@louisville.edu

COMMENTARY: CLINICAL IMPLICATION

The influenza season in the United States occurs in the winter months, peaks around the beginning of February,[2] and results in greater than 110,000 excess hospitalizations and 10,000 to 70,000 excess deaths annually, depending on the severity of the influenza epidemic.[3] Although one study found no increase in emergency department (ED) visits associated with influenza,[4] a second[5] did: the annualized excess ED visit rates for influenza and pneumonia combined were 389, 42, and 190 per 100,000 age-specific population for ages 0 to 14, 15 to 64, and ≥65 years, respectively. In addition, influenza can contribute to ED crowding and ambulance diversion.[6] Therefore, during the influenza season, identifying a potentially helpful set of symptoms specific to influenza could assist in management decisions by helping to rule out more serious conditions, as well as offer patients reasonable expectations for course and duration of symptoms.

This rational clinical examination installment shows that individual history and physical examination findings are of minimal independent assistance in diagnosing influenza, particularly when we consider the breadth of alternate diagnoses in which these signs and symptoms are found. However, the prevalence of the disease will affect their utility. For instance, in a population with a 50% prevalence of influenza (disease prevalence is synonymous with pretest probability), the presence of fever would increase the probability of a patient's having influenza to 64%, and its absence would decrease the probability to 29%.

When the data reviewed in this rational clinical examination installment are applied to the ED setting, it is vital to consider the characteristics of the study populations. First, the time frames of the 6 studies reviewed centered around the influenza season, and in 2 of these studies well persons at least 60 years old (median ages of 66 and 70 years) were enrolled and then followed forward until some developed symptoms suggestive of influenza, at which point correlation between symptoms and presence of virus was studied. In these 2 studies, 7% and 8% of enrolled patients developed influenza. However, for the other 4 studies, patients were younger (for each study, the reported mean or median ages were from 26 to 35 years) and were enrolled after they developed symptoms suggestive of influenza. These symptoms included fever in all 4 studies and cough, sore throat, headache, and myalgias in at least 3 of the studies. Three of the 4 studies were in family practice offices in Oklahoma, Paris, and The Netherlands; the fourth reported results of multicenter clinical trials in North America, Europe, and the southern hemisphere. The remarkably high prevalence of influenza in these 4 studies (28% to 67%) leads the reader to ask how the authors selected patients with such a high prevalence of disease if clinical characteristics are not useful. It seems likely, therefore, that either the study populations were endemic for influenza infection or, more likely, that the clinical syndrome of influenza found in these studies is relatively identifiable when multiple suggestive factors are present.

The question of using rapid diagnostic testing for influenza does not have an easy answer for the practicing physician. Making influenza tests available in the ED during the influenza season appears to result in physicians ordering fewer tests overall and reduces ED length of stay,[7] but the effective use of testing is limited to a particular range of pretest probabilities, and individual physicians may have widely varying estimates of pretest probability in a particular patient.[8,9] The best inference may therefore be that physicians should familiarize themselves with prevalence of disease data throughout the influenza season to inform their choice of whether or not to use a rapid diagnostic test.

TAKE HOME MESSAGE

Distinguishing influenza from other febrile illnesses remains a vexing problem for the emergency physician, and combinations of typical signs and symptoms may be helpful. For patients younger than 60 years, the only individual finding useful in making the diagnosis of influenza is fever, and it is only marginally so (LR=2). For patients older than 60 years, the combination of fever and cough is more helpful (LR=5). Absence of any single symptom adds almost nothing. In summary, a combination of clinical signs and symptoms and knowledge of the influenza status at the local level is the best tool for the practicing clinician.

EBEM Commentator Contact

Barnet Eskin, MD, PhD
Residency in Emergency Medicine
Morristown Memorial Hospital
Morristown, NJ
E-mail phdmd@prodigy.net

EBEM TEACHING POINT

The diagnostic odds ratio is a single indicator of diagnostic test performance.[10] It is defined as the odds of finding a given result among individuals with disease divided by the odds of finding the same result among individuals without disease. It ranges from 0 to infinity, with higher values indicating better test performance. Although it can therefore be used to compare the performance of different tests, there are several concerns with using this test result. First, the actual value is of little clinical utility otherwise, because there is no recommended reference range for diagnostic utility and few physicians think in terms of odds or odds ratios. Second, it cannot be used to estimate the probability of disease in any individual patient. The LRs are much more useful for this because they can be used to translate a pretest probability in the individual patient into a posttest probability of disease.[11] Third, most clinicians do not have a firm grasp of the utility of diagnostic odds ratios. Finally, in the case of influenza clinical characteristics, even findings with the highest diagnostic odds ratios in age-unrestricted patients are associated with LRs that are not clinically useful in deciding whether a given patient has or does not have influenza.

REFERENCES

1. Egger M, Sterne JAC, Smith GD. Meta-analysis: meta-analysis software. *BMJ.* 1998;316. Available at: http://www.bmj.com/archive/7126/7126ed9.htm. Accessed October 9, 2006.
2. Centers for Disease Control and Prevention. CDC report: 2004-5 U.S. influenza season summary. Available at: http://www.cdc.gov/flu/weekly/weeklyarchives2004-2005/04-05summary.htm. Accessed July 10, 2006.
3. Simonsen L, Clarke M, Williamson G, et al. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health.* 1997;87:1944-1950.
4. Groll D, Henry B. Can a universal influenza immunization program reduce emergency department volume? *Can J Emerg Med.* 2002;4:245-251.
5. Menec VH, Black C, MacWilliam L, et al. The impact of influenza-associated respiratory illnesses on hospitalizations, physician visits, emergency room visits, and mortality. *Can J Public Health.* 2003;94:59-63.
6. Glaser C, Gilliam S, Thompson W, et al. Medical care capacity for influenza outbreaks, Los Angeles. *Emerg Infect Dis.* 2002;8:569-574.
7. Bonner AB, Monroe KW, Talley, et al. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. *Pediatrics.* 2003;112:363-367.
8. Richardson WS. Five uneasy pieces about pre-test probability. *J Gen Intern Med.* 2002;17:891-892.
9. Phelps MA, Levitt MA. Pretest probability estimates: a pitfall to the clinical utility of evidence-based medicine? *Acad Emerg Med.* 2004;11:692-694.
10. Glas AS, Lijmer JG, Prins MH, et al. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol.* 2003;56:1129-1135.
11. Hayden SR, Brown MD. Likelihood ratio: a powerful tool for incorporating the results of a diagnostic test into clinical decision making. *Ann Emerg Med.* 1999;33:575-580.