A Systematic Review of the History and Physical Examination to Diagnose Influenza

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Background: Although influenza is a commonly encountered condition in primary care, and diagnosis is increasingly important given the availability of new treatments, there has been no systematic review of the evidence on clinical diagnosis.

Methods: This was a systematic review of the literature with meta-analysis where appropriate. We included cohort studies and randomized trials that compared the history and physical examination with a reference laboratory test for the diagnosis of influenza A and/or B. The primary outcomes were the sensitivity, specificity, likelihood ratios, and area under the receiver-operating characteristic (ROC) curve.

Results: Seven studies reported the sensitivity and specificity for a total of 59 variables. We combined studies of influenza A or B alone with those of influenza A and B. Rigors [likelihood ratio (LR) +7.2], the combination of fever and presenting within 3 days of the onset of illness (LR +4.0), and sweating (LR +3.0) were best at ruling-in influenza when present. When absent, the following decreased the likelihood of influenza: any systemic symptoms (LR −0.36), coughing (LR −0.38), not being able to cope with daily activities (LR −0.39), and being confined to bed (LR −0.50). Cough, nasal congestion, and fever (subjective or objective) had the highest calculable areas under the ROC curve.

Conclusions: Individual signs and symptoms are of limited value for the diagnosis of influenza. Development of clinical decision rules that systematically combine symptoms may be a more useful strategy. (J Am Board Fam Pract 2004;17:1–5.)

The increasing availability of office and reference laboratory tests to diagnose influenza and the development of viable treatments for the disease make it more important than ever to make the best possible use of the history and physical examination (HPE) to accurately establish the pretest probability. Patients with a low likelihood of influenza based on the HPE and a negative in-office test have a very low likelihood of influenza, whereas those with a high pretest probability and a negative test may still have a clinically important likelihood of the disease. We have therefore systematically reviewed the literature on diagnosis of influenza using the HPE.

Methods

Search Strategy

We searched the Medline database in mid-2000 using the following strategy: “influenza/diagnosis” [MeSH Terms] AND (“sensitivity and specificity” [MeSH Terms] OR “predictive value of tests” [MeSH Terms] OR “medical history taking” [MeSH Terms] OR “physical examination” [MeSH Terms]). We also reviewed the bibliography of every identified study, contacted domain experts, and reviewed the Database of Abstracts of Reviews of Effectiveness. The Medline search was repeated in November 2001 to ensure that there had been no intervening publications.

Inclusion Criteria

We included articles that reported information about the accuracy of the HPE for the diagnosis of influenza A, B, or both sufficient to calculate both the sensitivity and specificity. We included only independent cohort studies and data from randomized trials that were the functional equivalent of independent cohort studies for the purposes of studying a diagnostic test and that used a reference
laboratory test as the reference standard for diagnosis of influenza.

**Study Protocol**

Two investigators reviewed all the abstracts of identified studies and by a consensus approach decided on the articles to review in full. Two investigators then read each article, first deciding whether the article met inclusion criteria and then abstracting relevant data to a standard data collection form. The decisions about inclusion and data abstractions were compared, and conflicts were resolved by consensus discussion with a third investigator. We felt that certain variables were similar enough that they could be combined: body aches were included under “myalgias”; feverishness under “fever (subjective)”; pharyngitis under “sore throat”; expectoration of sputum under “sputum”; and purulent nasal discharge with “nasal secretion (purulent).”

**Data Analysis**

Where data for a variable came from a single study, we calculated the sensitivity, specificity, and likelihood ratios using standard formulas. The positive likelihood ratio corresponds to how well a positive test includes the diagnosis and a negative likelihood ratio to how well a negative test excludes it. Test results associated with a likelihood ratio between 0.5 and 2.0 have little impact on the likelihood of disease. If more than one study reported data for a variable, we calculated summary estimates of the sensitivity and specificity using a random effects model (MetaTest 0.6; used by permission from Joseph Lau, MD) and we also reported the range. The likelihood ratio was then calculated from the summary estimates. The area under the receiver operating characteristic (ROC) curve7 [a measure of how well a test discriminates patients with disease from those without disease; scores range from 0.5 (worthless test) to 1.0 (perfect test)] was calculated by the MetaTest software.

**Results**

We identified 93 studies in our initial survey Medline search, and 4 additional studies from the bibliographies of these studies. Of this group of 97 studies, 7 met our inclusion criteria.8–14 Study characteristics are shown in Table 1. All were independent cohort studies in the community or outpatient setting, largely primary care and during times of an influenza epidemic. None was explicit about blinding, but because of the usual timing of the HPE and reference laboratory tests, we assume that physicians performing the HPE were not aware of the results of the reference standard test.

The 7 studies reported the sensitivity and specificity for a total of 59 variables. Because there was no clear pattern regarding the accuracy of variables for influenza A versus influenza B, because it would reduce statistical power, and because this would introduce another layer of complexity into the analysis and presentation of data, we chose to combine studies of influenza A or B alone with those of influenza A and B.

Signs and symptoms with a positive likelihood ratio (LR+) greater than 2.0 or a negative likelihood ratio (LR−) less than 0.5 are shown in Table 2. Table 2 also summarizes the findings for all variables reported by more than 1 study, including the area under the ROC curve, when it could be calculated. Signs and symptoms with an LR− greater than 0.5 and an LR+ less than 2.0 are generally not useful clinically; those with likelihood ratios falling in this range that were measured only by a single study are not reported and include abdominal pain, antipyretics before consultation, any lower respiratory symptom, any other symptom, atopy, bronchiolitis, conjunctival injection, cold cough, earache, emesis, face ache, general practitioner consultation, gritty eyes, high risk condition, hoarseness, home visit by physician, lacrimation or conjunctival injection, loss of appetite, lower respiratory tract illness (age >65 years), male gender, moderate or severe fatigue, rhinorrhea, otitis media, pain on respiration, painful cervical adenopathy, received antibiotics, weakness, and wheeze. Monto8 reported on combinations of variables; only 2 combinations (fever, cough, and nasal congestion; fever, cough, and weakness) had a LR+ greater than 2.0.

The elements of the HPE that best ruled in influenza when present were rigors (LR +7.2), the combination of fever and presenting within 3 days of the onset of illness (LR +4.0), and sweating (LR +3.0). The signs and symptoms best able to rule out influenza when absent were having any systemic symptoms (LR −0.36), coughing (LR −0.38), not being able to cope with daily activities (LR −0.39), and being confined to bed (LR −0.50).

The area under the ROC curve could not be calculated for signs and symptoms or clusters of signs and symptoms reported by only a single study. The highest calculable areas under the ROC

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## Table 1. Design Characteristics of Included Studies (All Were Cohort and Independent, with Blinding Not Explicitly Stated)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Influenza</th>
<th>n</th>
<th>Population</th>
<th>Reference Standard</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholson et al 1997¹⁰</td>
<td>Community</td>
<td>A or B</td>
<td>291</td>
<td>Mean age, 73 years; 51.8% female</td>
<td>4× rise in titer for Influenza A</td>
<td>Respiratory infection (over age 60)</td>
</tr>
<tr>
<td>Carrat et al, 1997¹²</td>
<td>Primary care office and home visit</td>
<td>A or B</td>
<td>130</td>
<td>Mean age, 33.2 years; 59% female</td>
<td>Fluorescent monoclonal antibodies</td>
<td>Suspected influenza (influenza-like illness, upper or lower respiratory tract infection, and/or fever &gt;38°C without other evidence of infection within 36 hours of onset)</td>
</tr>
<tr>
<td>Carrat et al, 1999⁹</td>
<td>Primary care office and home visits</td>
<td>A</td>
<td>600</td>
<td>Mean age, 38 years; 58% female</td>
<td>DIF and ELISA; 25% culture + PCR</td>
<td>Suspected influenza (all patients over age 1 with ≥1 of the following: influenza-like illness, upper or lower respiratory tract infection syndrome, and/or temp &gt;38°C without any infectious signs or symptoms.)</td>
</tr>
<tr>
<td>Monto et al, 1996¹¹</td>
<td>Primary care office</td>
<td>A or B</td>
<td>897</td>
<td>NA</td>
<td>Viral culture or positive serology</td>
<td>Suspected influenza (influenza-like illness with fever and cough or sore throat presenting between November and April)</td>
</tr>
<tr>
<td>Lina et al, 1996¹³</td>
<td>Primary care office</td>
<td>A or B</td>
<td>340</td>
<td>NA (broad age range)</td>
<td>Culture or ELISA</td>
<td>Suspected influenza; data not available for patients without positive viral nasal swab.</td>
</tr>
<tr>
<td>Long et al, 1997¹⁴</td>
<td>Primary care office</td>
<td>A or B</td>
<td>788</td>
<td>Mean age, 76 in adults, 5 in children</td>
<td>Tissue culture, with ELISA to type the virus</td>
<td>Adults over age 65 and children with respiratory or febrile illness in community medical and pediatric practices.</td>
</tr>
<tr>
<td>Monto et al, 2000⁸</td>
<td>Outpatient</td>
<td>A or B</td>
<td>3744</td>
<td>Mean age, 34.7 years; 52% female.</td>
<td>Positive culture or ≥4× increase in influenza antibody titer in convalescent vs acute samples</td>
<td>Suspected influenza [fever (≥37.8°C; ≥37.2°C for patients ≥65 years in one study) or feverishness (subjective fever or chills) and 2 of the following: headache, myalgia, cough, or sore throat.</td>
</tr>
</tbody>
</table>

DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; NA, not available
curve were 0.679 for cough, 0.672 for subjective temperature, 0.654 for nasal congestion, and 0.653 for objectively measured temperature.

Discussion

Physicians have traditionally used information about the presence or absence of an influenza epidemic in the community and certain signs and symptoms such as sudden onset of fever, cough, myalgias, and chills to diagnose influenza. Our systematic review identifies 3 variables that, when present, help rule in influenza (rigors, sweating, and fever and onset of symptoms less than 3 days before) and 4 additional symptoms that rule it out (no systemic symptoms, not coughing, being able to cope with daily activities, and not being confined to bed). Other commonly used symptoms such as sore throat, chills, and myalgias were less useful.

A bias toward lower estimates of sensitivity and specificity may have been introduced by the fact that most studies only included patients with suspected influenza.8,9,11–13 For example, if fever was part of the inclusion criteria for a study, it will make it impossible for this variable to contribute to discriminating between patients with and without influenza. This bias particularly affects the estimates for fever, headache, myalgias, cough, and sore throat that were part of the inclusion criteria for the large Monto study.8

Our study had several limitations. The size of one study,8 a pooled analysis of the results of several randomized trials, meant that it often dominated the analysis. Any flaws in this study (eg, lack of blinding, an imprecise reference standard, selection bias) would therefore also dominate our analysis. There was considerable heterogeneity between studies, which is why we report the range as well as a summary measure of effect for sensitivity and specificity estimates based on data from more than one study. Finally, several of the variables that had the highest LR+/H1 or lowest LR−/H1 came from a single study; again, any flaws in that study’s design would have an important impact on our findings.

The literature review was repeated just before publication (February 2004) and identified only one additional article. This article studied patients over age 65 or with underlying cardiopulmonary disease who were admitted to the hospital with a respiratory diagnosis; approximately 20% had influenza.15 Despite the highly selected nature of the group, these findings were similar to ours. The best predictor of influenza A was the combination of cough,
temperature of 38°C or higher, and illness duration of 7 days or less (LR+ 2.9, LR− 0.3).

Previous studies have shown that individual signs and symptoms rarely include or exclude a disease. A more successful strategy is the use of several key symptoms in a clinical decision rule that stratifies patients into low-, moderate-, and high-risk groups. This information can be used in conjunction with the results of office laboratory tests and perhaps imaging studies to make a more accurate diagnosis while also limiting unnecessary testing and overtreatment. This strategy has been successfully implemented for sore throat, deep vein thrombosis, and pulmonary embolism. More than anything, this systematic review points out the need for well-designed studies in the primary care setting to develop and validate such a rule.

References