Impact of Rapid Viral Testing for Influenza A and B Viruses on Management of Febrile Infants Without Signs of Focal Infection

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**Background:** The objective of this study was to assess the effect of rapid testing for influenza virus on management of febrile young infants.

**Methods:** During 2 influenza seasons (November to December 2003 and December 2004 to February 2005), we studied prospectively infants who were 0 to 36 months of age who presented to the emergency department (ED) with fever in the absence of signs of focal infection. The Directigen Flu A+B test was used to determine infection with influenza virus types A or B. Confirmatory viral cultures were not done.

**Results:** Rapid influenza testing was performed in 206 infants and 84 (40.7%) of them were influenza-positive. Infants with a positive and a negative influenza test showed a similar mean (standard deviation) age (6.86 [6.3] versus 6.55 [6.8] months) and mean temperature (39.38°C [0.6] versus 39.32°C [0.8]), but there were significant differences (P < 0.01) in the percentage of patients undergoing blood tests (33.3% versus 100%), urinalysis (80.9% versus 100%), chest roentgenogram (14.2% versus 32%), cerebrospinal fluid analysis (1.3% versus 21.3%), mean length of stay in the ED (116.2 [75.5] versus 192.9 [76.3] minutes), admission to the ED observation ward (8.3% versus 21.3%), inpatient care (2.3% versus 16.4%) and antibiotic treatment (0% versus 38.5%). All positive bacterial cultures occurred among influenza-negative patients.

**Conclusions:** The inclusion of rapid influenza testing for the evaluation of febrile young infants without signs of focal infection during influenza season decreases the need for additional studies and reduces the length of stay in the ED, the use of antibiotic treatment and unnecessary hospitalizations.

**Key Words:** rapid influenza diagnostic test, influenza, influenza antivirals, febrile infants
ment for the etiologic diagnosis of his or her illness were prospectively studied. Our institution is an acute care, 900-bed teaching hospital in Barakaldo, Bizkaia, Basque Country (Spain), serving a population of 1,500,000. The Department of Pediatrics has 100 beds, and approximately 60,000 children aged 0 to 14 years are evaluated in the pediatric emergency department annually by 11 staff medical personnel. Information on the beginning of influenza epidemics was facilitated by the Influenza Sentinel Physicians Surveillance Network of the Basque Country, which provides essential information about the "state of flu" in our autonomous community and nationwide. Morbidity data, including number of influenza virus isolations and the weekly incidence rate per 100,000 inhabitants, are reported by telephone or Internet on a weekly basis. Rapid influenza test was performed while influenza rate incidence was more than 100 per 100,000 inhabitants.

All infants less than 3 months of age with fever (rectal temperature >38°C) and no documented source after a carefully clinical examination underwent the rapid influenza test. Infants aged 3 to 36 months of age underwent rapid viral testing for influenza if they had a rectal temperature of 39°C or greater and the attending pediatrician considered necessary influenza virus testing to identify the cause of infection. The rapid influenza test was performed before any other workup study (such as urinalysis, blood cell count, serum C-reactive protein and blood culture). If influenza virus was detected, the pediatrician in charge was able to modify the protocol regarding the indication of diagnostic tests, administration of antibiotic treatment, admission to the observation ward of the pediatric emergency department or admission to the hospital (Fig. 1). If the rapid influenza test was negative, the standard protocol for the management of febrile young infants without focal signs of infection and in good general condition was followed.

The commercially available assay Directigen Flu A+B Test Kit (Becton Dickinson, San Agustin del Guadalix, Madrid, Spain) for the direct and qualitative detection of influenza A and B viral antigens was used. Total test time is less than 15 minutes with reactivity determined by visual color development. In all cases, rapid viral testing was performed by emergency department staff pediatricians. The test was performed using internal kit positive, negative and procedural controls for each test kit run. Confirmatory viral cultures were not done.

For each patient, the following data were recorded: demographics, symptoms and findings on physical examination, result of the rapid influenza test and of other workup studies, diagnosis, treatment and site of care. A follow-up phone call was made to all influenza-positive infants after discharge from the emergency room or the hospital.

Data are expressed as mean and standard deviation (SD) for quantitative variables or numbers and percentages for categorical variables. Continuous data were compared with the Student t test. Categorical data were examined using the χ² test or the Fisher exact test probability test. The SPSS 10.0 for Windows (SPSS Inc., Chicago, IL) was used for all

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**FIGURE 1.** Rapid influenza testing (Directigen Flu A+B) included in the algorithm for diagnosis and management of febrile infants (rectal temperature >38°C) without documented source and in good general condition during influenza season.
statistical calculations. Statistical significance was defined as $P < 0.05$.

RESULTS

Rapid viral testing for influenza was performed in 206 infants; 84 (40.7%) of them were influenza positive (influenza A, n = 82; influenza B, n = 2). Infants with a positive and a negative influenza test showed a similar mean (SD) age (6.86 [6.3] versus 6.55 [6.8] months) and mean temperature (39.38°C [0.6] versus 39.32°C [0.8]). Characteristics of the study population according to results of the Directigen assay are shown in Table 1. There were no significant differences between the groups of positive and negative influenza test with regard to antipneumococcal vaccination status and mild respiratory symptoms that were considered unrelated to the infection source. However, influenza-like illness cases in the household was significantly more frequent among influenza-positive infants. On the other hand, workup studies were less frequently performed in the influenza-positive group with statistically significant differences ($P < 0.01$) in the percentage of patients undergoing blood tests, urinalysis, chest radiograph and lumbar puncture for cerebrospinal fluid analysis. The mean length of stay in the pediatric emergency department was also significantly shorter and a few infants admitted to the emergency room observation unit in the department was also significantly shorter and a few infants were observed in the subgroup of infants aged ≤3 months. No patients had received influenza vaccination.

At the time of diagnosis, none of the patients in the influenza-positive group received empiric antibiotic treatment compared with 38.5% in the influenza-negative group ($P < 0.01$). Two infants (2.3%) with a positive influenza test required admission to the hospital only for observation (an infant of 7 days of life with the diagnosis of influenza and a 6-week-old infant with the diagnosis of influenza and stenosis of choanae), but they did not receive antibiotics. In the group of negative influenza test, 20 infants were admitted to the hospital because of fever without documented source in 7, pneumonia in 5, meningitis in 3, urinary tract infection in 3 and bacteremia in 2. All 14 cases of positive bacterial cultures occurred among influenza-negative patients (Escherichia coli was isolated from urine cultures in 11 cases, S. pneumoniae from cerebrospinal fluid culture in one case, S. pneumoniae from blood culture in one case and group A beta-hemolytic Streptococcus from blood culture in one case).

A similar percentage of infants in both groups returned to the emergency department for consultation after a few days (11.9% versus 11.5%) and in 8 patients (4 in each group), the diagnosis was changed to otitis media and pneumonia in 4 cases each. All influenza-positive infants showed a favorable clinical course. A telephone contact was made to 78 (93%) of the 84 influenza-positive patients. The remaining 6 patients corresponded to those admitted to the hospital and/or who returned for consultation. In 8 of the 78 patients contacted by phone, the primary care pediatrician started antibiotic treatment as a result of a diagnosis of otitis media (4 cases), pneumonia (one case) and persistence of fever without focal signs of infection (3 cases).

DISCUSSION

This study demonstrates the advantages of including rapid viral testing for influenza in the standard guidelines for

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<td>Blood tests, no. (%)/hemogram, C-reactive protein and blood culture</td>
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<td>Length emergency department stay, min, mean (SD)</td>
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<td>Hospital admission, no. (%)</td>
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<td>Antimicrobial treatment, no. (%)</td>
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*Completed vaccination.

SD indicates standard deviation; NS, not significant.
febrile infants without a source and in good general condition during influenza seasons. The use of Directigen Flu A+B test kit at the bedside in the pediatric emergency care setting for 2 consecutive influenza periods in infants who were younger than 36 months of age presenting with fever without focus and in the absence of toxic signs significantly decreased the need of other workup studies and reduced the length of stay in the emergency department, the use of empiric antibiotic treatment and unnecessary hospitalizations. Despite reduction of the rate of occult bacteremia because of the widespread use of the conjugate pneumococcal vaccine,19–22 the evaluation of this entity and of serious bacterial infection in febrile infants who are younger than 36 months continues to consume healthcare resources, causing transient discomfort to the patient and contributing to antibiotic resistance. On the other hand, it has been shown that febrile children with confirmed influenza have a very low frequency of bacteremia (less than 1%).23 In the present study, 9 positive influenza patients had a clinical diagnosis of bacterial infection (pneumonia 2, otitis media 7) when returned to the emergency department for a second consultation (4 patients) or when evaluated by their primary care pediatrician (5 patients). Both diseases are well-known complications of influenza virus infection and none of the patients required hospitalization. Moreover, all cases of positive bacterial cultures occurred among influenza-negative patients.

In our series, none of the influenza-positive infants younger than 3 months of age showed urine positivity, but 3 influenza-negative infants had a diagnosis of urinary tract infection and were hospitalized. Likewise, none of the influenza-positive children aged 3 to 36 months had a diagnosis of urinary tract infection, although urine testing was not used in all of them; however, 8 influenza-negative infants had a diagnosis of urinary tract infection. None of the patients with influenza had simultaneous urinary tract infection.

In a review of the published evidence on clinically useful diagnostic tests for influenza virus infection in children,9 3 commercially available rapid diagnostic tests showed sensitivities of 72% and 95% and specificities of 83%, 84% and 76%, respectively. A study of 72 infants and toddlers between ages 2 and 24 months with a positive enzyme-linked immunosorbent assay test for influenza virus type A available before discharge form the emergency department demonstrated a decrease in ceftriaxone therapy use and the number of ancillary tests ordered compared with patients for whom the test results were available later.12 In another study of 96 influenza-positive patients (aged 2 months to 21 years) whose emergency department physician was aware of the result compared with 106 influenza-positive patients whose physician was unaware of the result, a significantly reduced number of laboratory tests and radiographs ordered, decreased antibiotic use and decreased length of time to discharge was found.13 The same results were observed in a subgroup analysis of patients aged 2 to 36 months.13 These findings are consistent with results of our study. The benefits of rapid diagnosis of influenza in the emergency care setting were also demonstrated in the subgroup of infants of less than 3 months of age, an age group not included in previous reports.12,13 Patients with positive rapid influenza tests were not eligible for antiviral therapy because of their satisfactory clinical course. Although one of the benefits of performing rapid influenza testing is to guide antiviral treatment, in our current practice, we only prescribe antivirals in hospitalized children with severe illness.

Rapid testing for influenza virus was performed with the Directigen Flu A+B test because of high diagnostic accuracy, the ability to distinguish between the 2 viruses and greater experience with the application of this tool in young infants.24,25 This test, in the setting of influenza season or high clinical suspicion, would be best used as a confirmatory test because the positive predictive value is greater than 95% and the number of false-positive cases are small.9 Obtaining laboratory tests and radiographs in any age group would be expected to increase length of stay in the emergency room, particularly during influenza periods with overcrowded, saturated emergency departments.10 In our study and others,13 infants with documented influenza infection, mainly because of a decrease in the practice of ancillary tests and the need of observation, had a shorter stay in the emergency room.

The present results should be interpreted taking into account some limitations of the study, including the lack of follow up for influenza-negative patients and the fact that urine testing for infection was not performed in all influenza-positive infants more than 3 months of age. On the other hand, during influenza season, the number of false-negative rapid influenza tests is high. Although in our study, some infants with negative rapid influenza test could have been really false-negative cases, this set of patients were considered for high risk of bacterial infection and managed following the standard protocol.

We believe that the use of rapid testing for influenza in children younger than 36 months during influenza seasons in the emergency department setting reduces the number of laboratory tests and radiographs ordered and decreases the length of stay in the emergency department, antibiotic use and unnecessary hospitalization.

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REFERENCES


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