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Original Article

Contribution of Rapid Influenza Antigen Test to Management of Febrile Young Infants without a Focus

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Abstract

Background: The aim of this study was to evaluate the application of the rapid influenza antigen test and the contribution of the test result to patient management in febrile infants aged 29–90 days.

Methods: The medical records of febrile infants without a focus who presented during influenza seasons from 2017–2019 were analyzed retrospectively. The study was carried out in the Department of Pediatric Emergency, Dr. Sami Ulus Maternity and Children's Training and Research Hospital. The demographic characteristics, clinical and laboratory findings, and management of the patients were examined. The patients were divided into two groups as 'with' and 'without' testing based on whether a rapid influenza antigen test was performed or not. Test results were categorized as positive or negative. Serious bacterial infection (SBI) risk and patient management were evaluated according to test results.

Results: A total of 173 patients (110 males/63 females) were evaluated. The influenza test was performed in 94 (54.3%) patients, and 31.9% were positive. SBI was present in 8.7% of all patients. The mean values of white blood cell (WBC), absolute neutrophil, platelet count, C-reactive protein (CRP) and, lumbar puncture, hospitalization, and initiation of antibiotic therapy were significantly lower in the positive group compared to the negative and without testing groups ($P<0.05$).

Conclusion: This study showed that using the influenza test in the emergency department in young febrile infants significantly reduced the use of antibiotics, hospitalization and the implementation of invasive procedures such as lumbar puncture, and the risk of SBI was not increased.

Keywords: Febrile infant, Influenza, Rapid test

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Introduction

Fever is one of the most common causes of emergency department visits in infancy. In febrile young infants, infections can range from mild viral infections to life-threatening bacterial diseases. Fever without a focus implies that the sole presenting feature in a well-appearing infant is a fever not exceeding five days. If the source cannot be detected, it is intended to identify infants who are likely to have occult bacteremia or serious bacterial infection (SBI). Fever may be the only symptom or finding in these infections. Many febrile infants have no obvious focus of infection on physical examination. Various protocols have been established to determine the risk of SBI.[1,2] However, no guide can precisely identify SBI in well-appearing infants in this age group.[3-5] Due to diagnostic challenges, various laboratory tests and lumbar puncture are performed, followed by commencing empirical antibiotic therapy.[6]

The aim of this study was to evaluate the contribution of the rapid influenza antigen test to patient management of young febrile infants without a focus during influenza seasons.

Materials and Methods

Patient Selection and Study Sample

The study was carried out in the Pediatric Emergency Department of Dr. Sami Ulus Maternity and Children's Hospital University of Health Sciences, which is a tertiary pediatric hospital in Ankara, Turkey. Emergency department physicians evaluate approximately 150 000 children per year and approximately hospitalize 4000 patients. The data records of febrile infants aged 29–90 days who presented during the two influenza seasons (between October and May) from 2017 to 2019 were analyzed retrospectively.

The well-appearing infants who had a body temperature ≥ 38°C, had a duration of fever of less than five days, had a gestational age of ≥ 37 weeks, were previously healthy, and had no history of antibiotic use in the previous 48 hours were included in this study. The well-appearing criterion was determined as stable according to the pediatric assessment triangle (PAT) and the vital signs (except fever) were within the normal range. PAT is used as a method of quickly determining the acuity of the child, and expresses the general impression of the patient admitted to the pediatric emergency department and provides guidance to determine the severity of the presentation. This tool includes appearance, respiratory and circulatory components. An abnormality in any component of the PAT indicates an unstable child and determines the urgency of the clinical intervention.[7] Patients who are considered

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as ill-appearing, had a history of vaccination within the past 48 hours and/or had taken antibiotics, had a history of chronic disease or whose data were not fully available were excluded from the study. Medical records were reviewed retrospectively for demographic information, clinical and laboratory data, and patient management. Return visits of patients who were sent home from the outpatient department were evaluated.

Definitions or Findings

Occult bacteremia, occult (focal) pneumonia, meningitis, and urinary tract infection (UTI) were accepted as SBI. Occult bacteremia was diagnosed based on a positive blood culture, bacterial meningitis with the determination of a single bacterial pathogen by positive cerebrospinal fluid (CSF) culture, and UTI by detection of a single microorganism ≥ 50 000 colonies/mL in a sample collected through sterile bladder catheterization. Pneumonia was defined as a focal consolidation on chest radiography.

The patient's age, sex, symptoms, and history of contact with a person having respiratory symptoms within the last seven days were evaluated. Complete blood count, absolute neutrophil count (ANC), C-reactive protein (CRP), complete urine test, blood culture, urine cultures, CSF culture, and rapid influenza diagnostic test (RIDT) results were recorded. Influenza was diagnosed based on a positive result of the nasopharyngeal swab rapid antigen test. Some patients could not be tested due to lack of the RIDT kit. Patients were divided into two groups as 'with' and 'without' testing, depending on whether the RIDT was performed. Patients who were tested were also divided as either positive or negative according to their results.

Rapid Influenza Antigen Test

The commercial assay Acro Influenza A+B Rapid Test Cassette (swab/nasal aspirate) (Acro Biotech, Rancho Cucamonga, CA, USA), which is a rapid chromatographic immunoassay test was used. A nasopharyngeal sample was taken with a sterilized swab. The sample obtained reacts with antibodies to influenza A/B coated on the particles. The results were read after 15 minutes. For positive influenza A, two distinct colored lines appear. For positive influenza B, two distinct colored lines appear. For a negative result, one colored line appears in the control region (C), and no apparent colored line appears in the test line regions (A or B). The test was evaluated using antigen kit positive, negative and procedural controls for each test kit run.

Statistical Analysis

We categorized and analyzed the data according to the patients' rapid influenza antigen test results: positive or negative. Data are expressed as mean and standard deviation (SD) with 95% confidence intervals (CIs) 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 χ^2 test or the Fisher's exact test probability test. Statistical significance was considered as $P<0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 23.

Results

A total of 173 patients (110 males and 63 females) were evaluated during two seasonal influenza seasons. The mean age of the patients was 59.1 ± 17 (95% CI, 56.5-61.6) days. Ninety-two infants (53.2%) were 29 to 60 days old, and 81 infants (46.8%) were 61 to 90 days old. While the fevers of 56 patients (32.3%) was detected at home, the fever of 117 patients (67.7%) was determined in the hospital. One hundred twenty-one patients (69.9%) had a history of contact with family members who presented with flu-like symptoms. Respiratory symptoms were the most common symptoms: specifically, cough (n = 98, 56.6%), rhinorrhea (n = 76, 43.9%), and rhinorrhea with cough (n = 61, 35.2%). There was irritability in 32 (18.5%) patients, poor oral intake in 26 (15.0%) patients, and moaning in 6 (3.4%) patients.

In laboratory evaluation, the mean white blood cell (WBC) count was 9564 ± 4473/mm³ (2550–27500) (95% CI, 8893-10236), the mean absolute neutrophil count (ANC) was 4148 ± 2767 /mm³ (650–17000) (95% CI, 3733-4564), the mean hemoglobin value was 10.9 ± 1.28 g/dL (8.4–17.2) (95% CI, 10.8-11.2), the mean platelet count was 415294 ± 138708/mm³ (139 000–909 000) (95% CI, 394479-436111), and the mean CRP value was 13.9 ± 17.7 mg/L (0.7–91) (95% CI,11.3-16.6).

The rapid influenza test was performed in 94 (54.3%) patients. The test result was positive in 30 (31.9%) patients and negative in 64 (68.1%) patients.

Specimens for blood culture and catheter urine culture were taken from all patients. *S. pneumonia* was reproduced in one patient's blood culture. Reproduction was detected in the urine culture of 14 (8.0%) patients. Reproduction of *E. coli* occurred in 11 urine cultures, and reproduction of *K. pneumonia* occurred in three urine cultures. Lumbar puncture was performed on 64 patients but was not considered necessary for 91 patients. It was not performed on 18 patients because the family did not allow the procedure. No reproduction was detected in the CSF culture of any patients.

None of the patients had any signs during lung auscultation. Chest radiography was performed on 160 (92.5%) patients. Focal pneumonia was not detected in any patient.

Positive SBI status was determined in a total of 15 patients (8.7%). SBI was detected in 6.3% of the patients in the non-tested group, 10.0% in the positive test group, and 10.9% in the negative test group. The length of hospital stay was 4.9 ± 2.6 days. Patients who were positive for influenza were observed for 24 hours in the pediatric emergency department, oseltamivir was started, and they were discharged. The results of the patients with and without RIDT are shown in detail in Table 1. A comparison

of positive and negative test results is presented in Table 2. A comparison of the positive test group and the without testing group is presented in Table 3.

The test results showed that the mean WBC, ANC, platelet, and CRP values were significantly lower in the influenza-positive group ($P<0.05$). Lumbar puncture, hospitalization, initiation of antibiotic therapy, and length of hospital stay were significantly lower in the influenza-positive group compared to the without RIDT group ($P<0.05$).

Sixty-four outpatients (69.6%) returned for follow-up after 24 hours, and four patients were hospitalized due to lower respiratory tract infections.

Discussion

Fever is common in young infants and usually occurs due to a self-limiting viral infection.[8] Influenza is a common viral cause of fever in infants during winter and may cause a wide range of symptoms and complications.[9,10] At this age, febrile infants often have no obvious focus of infection on physical examination, and it can be difficult to make a diagnosis.[11,12] Unlike other respiratory viruses, high fever in influenza may cause difficulties in distinguishing the clinic picture from SBI.[13] It was reported that fever (48%) was the most common reason for admission in 218 infants younger than three months of age with a diagnosis of influenza, and it was followed by respiratory symptoms (29%).[10] In the current study, approximately half of the patients had respiratory symptoms. In one-third, there were no signs or symptoms other than fever. These nonspecific symptoms can cause difficulties in distinguishing SBI from influenza in infants. For this reason, it may be necessary to perform extensive laboratory tests and initiate intravenous antibiotic treatment, which requires hospitalization, in infants younger than three months of age.[11] As a result; there is an increase in side effects, medical costs, hospital infections, resistance to antibiotics, and invasive evaluations.[14]

During the influenza season, a history of contact with individuals with respiratory symptoms can provide clinicians with important information to assess febrile infants. In a previous study, influenza-like illness cases in the family were significantly more common among influenza-positive infants compared with the influenza-negative.[15] In our data, we found that an influenza-like disease history in influenza-positive infants was significantly higher (83.3%) compared to influenza-negative infants (76.6%).

SBI was seen in approximately 10.0% of febrile infants younger than three months of age.[3,4,11,16] In the current study, SBI was identified in 8.7% of the patients, which is consistent with the literature. SBI was detected in 10.0% of the influenza-positive infants. Recently, the correlation of influenza with SBI was investigated. Studies showed that the rate of SBI was significantly lower in febrile infants with known influenza infections than in influenza-negative infants.[10,17,18] In a multicenter study on 844 febrile infants aged ≤ 60 days who were tested for influenza, a lower SBI rate was recorded in infants with confirmed influenza (influenza-positive: 2.5%; influenza-negative: 13.3%).[18] In another study on infants with confirmed influenza diagnoses, it was reported that the SBI rate was 2.3%. All of them were diagnosed with UTI except for one case of bacteremia.[10]

Researchers continue to search for alternative methods to traditional investigations to identify infants at high risk of SBI and reduce unnecessary treatment and hospitalization of those at low risk. A rapid diagnosis of influenza caused a decrease in the performance of auxiliary tests. In febrile infants younger than three months of age, using RIDT reduced auxiliary tests, antibiotic prescriptions, and hospitalizations.[3,15,18,19] Similar results were obtained in the current study. In order to detect SBI in this age group, multiple screening methods have been developed. It was seen that many examinations or tests, including lumbar puncture, should be performed to allow for a

Table 1. Comparison of patient findings with and without the performed Rapid Influenza Antigen Test

Data	With RIDT ($n=94$)	Without RIDT ($n=79$)	Mean difference (95% CI)	*P*-Value
Gender (F/M)	30/64	33/46		0.180
Age:(days), mean ± SD	59 ± 16.2	59.2 ± 18	-0.236 (-5.38; 4.9)	0.928
WBC /mm³, mean ± SD	9359 ± 4403	9808 ± 4571	-449.732 (-1799.7; 900.2)	0.512
ANC /mm³, mean ± SD	4293 ± 2821	3976 ± 2709	317.734 (-517.2;1152.6)	0.454
PLT /mm³, mean ± SD	405414 ± 135056	427050 ± 142903	-21635.739 (-63421.3; 20149.9)	0.308
CRP (mg/L), mean ± SD	15.1 ± 19,07	12.5 ± 15,9	2.60 (-2.7; 7.9)	0.337
Lumbar puncture	29	35		0.063
Blood culture	0	1		0.457
Urine culture	10	4		0.218
Hospital admission	38	43		0.069
Antimicrobial treatment	38	45		0.033
Serious bacterial infection	10	5		0.309
Length of hospital stay: (days), mean ± SD	5 ± 3.3	4.9 ± 1.9	0.143 (-1; 1.33)	0,81

RIDT, Rapid Influenza Antigen Test; WBC, White blood cell; ANC, Absolute neutrophil count; PLT, Platelet; CRP, C-reactive protein; SD, Indicates standard deviation.

Table 2. Comparison of Rapid Influenza Antigen Test Results

Data	RIDT positive (*n*=30)	RIDT negative (*n*=64)	Mean difference (95% CI)	*P*-Values
Gender (F/M)	14/16	16/48		0.056
Age: (days), mean±SD	57.4±15.6	59.7±17	-2.319 (-9.48; 4.84)	0.522
WBC /mm³, mean±SD	6830±2129	10544±4697	-3713.865 (-5112.4; -2315.4)	<0.001
ANC /mm³, mean±SD	2953±1547	4922±3065	-1968.521 (-2914; -1023)	<0.001
PLT /mm³, mean±SD	347400±109127	432609±138168	-85209.375 (-142214; -28204.7)	0.004
CRP (mg/L), mean±SD	8.9±10.7	18±21.3	-9.118 (-15.69; -2.54)	0.007
Urine culture	3	7		1.000
Lumbar puncture	4	25		0.004
Hospital admission	4	34		<0.001
Antimicrobial treatment	4	34		<0.001
Serious bacterial infection	3	7		1.000
Length of hospital stay: (days), mean±SD	2.7±0.5	5.3±3.4	-2.51 (-6; 0.9)	0.155

RIDT, Rapid Influenza Antigen Test; WBC, White blood cell; ANC, Absolute neutrophil count; PLT, Platelet; CRP, C-reactive protein; SD, Indicates standard deviation.

Table 3. Comparison of patient findings positive and without the performed Rapid Influenza Antigen Test

Data	RIDT Positive (*n*=30)	Without RIDT (*n*=79)	Mean Difference (95% CI)	*P*-Values
Gender (F/M)	14/16	33/46		0.645
Age: (days), mean±SD	57.4±15.6	59.2±18	1.815 (-5.48;-9.1)	0.623
WBC /mm³ mean±SD	6830±2129	9 808±4 571	2978.321 (1699.67; 4256.97)	0.001
ANC /mm³ mean±SD	2953±1547	3976±2709	1022.536 (196.91; 1848.16)	0.016
PLT /mm³ mean±SD	347400±109127	427050±142903	79650.63 (2243.2; 136869.1)	0.007
CRP (mg/L) mean±SD	8.9±10.7	12.5±15.9	3.60 (-2.64; 9.85)	0.255
Urine culture	3	4		0,391
Lumbar puncture	4	35		0.001
Hospital admission	4	43		<0.001
Antimicrobial treatment	4	45		<0.001
Serious bacterial infection	3	5		0.682
Length of hospital stay: (days), mean±SD	2.7±0.5	4.9±1.9	2.1 (0.17; 4)	0.033

RIDT, Rapid Influenza Antigen Test; WBC, White blood cell; ANC, Absolute neutrophil count; PLT, Platelet; CRP, C-reactive protein; SD, Indicates standard deviation.

febrile infant to be designated as "low risk". In the current study, the mean values of WBC, ANC, platelets, and CRP were found to be significantly lower in the influenza-positive group. Furthermore, these values were within the normal ranges considered low risk criteria for SBI. It is thought that these tests suggested in algorithms are not sufficient to distinguish patients with influenza from SBI patients. Lumbar puncture, hospitalization and initiation of antibiotic treatment were found to be significantly higher in the group without influenza testing. It is known that the negative predictive values of these parameters are primarily significant in the differential diagnosis of SBI.[20,21] Therefore, it is important to test for a diagnosis of influenza in 29–90-day old febrile infants.

This study provides additional rationale for developing a guideline for the RIDT that can optimize care, minimize damage, and increase parental satisfaction for febrile infants aged 29-90 days. It highlights the importance of diagnostic testing for influenza in infants younger than 90 days who present with fever.

In this study, as a result of the influenza rapid test, about 10.0% of positive and negative patients were diagnosed with a UTI, and there was no significant difference between the groups. This result showed that urine tests should be absolutely performed independent of influenza testing in this age group. The risk of bacteremia and meningitis has been found to be lower in young infants with identified viral infections. However, UTI continues to be seen as a cause of concern in infants aged 30–90 days.[2,18,22-24] Rapid Influenza test positivity provides an opportunity for clinicians to prioritize urine analysis and urine culture and thereby avoids the need for other tests.

Performing the rapid influenza test generally reduced the initiation of antibiotics. If the test result was positive, a significant decrease was observed in the performance of invasive procedures on patients compared to the without testing group and the negative influenza test group result. Only four patients with an influenza-positive test underwent lumbar puncture, were hospitalized, and were started on antibiotic treatment. In similar studies, based

on the low risk of SBI in infants with influenza, if influenza was diagnosed quickly and accurately, there was a decrease in hospital admissions and hospitalization time.[25-27]

This study has some potential limitations. It was conducted in a single center and had a limited number of patients over two influenza seasons. SBI was only found in 14 infants with UTI and one with bacteremia. More extensive studies with larger sample sizes are needed. The cause of all fevers could not be determined because other possible viral tests were not studied in non-SBI and influenza-negative patients.

In conclusion, the results of this study demonstrated that the application of the rapid influenza test reduced the initiation of antibiotic treatments. While hospitalization, antibiotic use, and invasive procedures, such as lumbar puncture, were significantly decreased, the risk of SBI was not increased, except for UTI. The importance of urine examination was emphasized in young febrile infants with influenza virus infections. The use of the test during the seasonal influenza season may be of benefit in management of febrile infants without a focus.

Authors' Contribution

NT, AT conceiving, designing and editing the manuscript. CDK, NT, AT search contributing to logical interpretation and presentation of the results. CDK, AT performed the statistical analysis. AAÇ, İB, BÖ data collection and literature. NT, CDK review and final approval of the manuscript.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest

Ethical Statement

The study protocol was performed in accordance with the Helsinki declaration of human rights. The study was reviewed and approved by the Keçiören Training and Research Hospital Ethics Committee (2012-KAEK-15/1992).

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