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Evaluation of a direct test for seasonal influenza in outpatients

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ABSTRACT

Objective: To present our experience regarding the use of a rapid diagnostic test for seasonal influenza A and B.
Methods: We systematically collected and analyzed our data regarding the use of a rapid diagnostic test for seasonal influenza A and B in patients with specific respiratory symptoms that sought medical services, during the time period from 01/01/2009 to 30/05/2009, from a network of physicians (SOS Doctors) who perform house-call visits in the area of Attica, Greece.
Results: From the total of 16,335 house-call visits performed during the evaluated period, 3412 (20.8%) were due to respiratory/influenza symptoms; 197 (5.8%) patients were tested for influenza. From the 184 patients with available data regarding the test result, 97 (52.7%) were positive for influenza. Significantly more oseltamivir and less antibiotic treatment were prescribed to patients with positive test result compared with those with a negative test result. Additionally, the impact of the test in the participating physicians' decision making was obvious, as doctors who used the test systematically prescribed significantly more oseltamivir and less antibiotic treatment compared to the doctors who didn't use the test.
Conclusion: The use of a rapid test for seasonal influenza enabled the targeted treatment with oseltamivir, as well as a reduction in antibiotic treatment, in patients found positive for influenza in our clinical setting.

1. Introduction

Influenza is an important clinical entity with significant morbidity and mortality [1–3]. It is also a significant burden in the community as it is associated with both increased direct medical costs from excess hospitalizations, drug prescriptions, and outpatient visits [4,5], as well as indirect costs from work or school absenteeism and reduced production capacity [6,7].

The clinical symptoms of influenza tend to overlap with the symptoms of other respiratory, mainly viral infections, in pediatric and adult patients [8–10]. This makes the clinical diagnosis of influenza problematic. As a result, a rapid test, that enables the early recognition of patients with influenza, has many advantages, including the prevention of unnecessary antibiotic prescriptions, hospitalizations, and influenza transmission. It may also contribute in the reduction of the economic burden of influenza. In addition, early diagnosis of influenza may enable a proper use of antiviral agents. Literature provides evidence of the use of rapid direct tests for the detection of influenza in patients with respiratory symptoms in various settings, mainly in pediatric populations [11–18].

The use of a rapid direct test may aid considerably in the early detection of influenza cases and consequently enable a proper treatment during influenza pandemics [19,20]. In our study we aimed to systematically collect and analyze our data on the use of a rapid diagnostic test for seasonal influenza A and B in patients with specific respiratory symptoms that sought medical services from a network of doctors that performs house-call visits in the area of Attica, Greece.

2. Methods

2.1. Inclusion criteria

Eligible patients for inclusion in this study were patients of all ages that sought medical services from the network of SOS doctors in Attica, Greece during the time period from 01/01/2009 to 30/05/2009, that complained for respiratory/influenza-like symptoms, including fever >38 °C, cough, and at least one of the following: sore throat, nasal discharge, muscle aches, headache, or fatigue.

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2.2. Specimens' collection and testing procedure

The visiting physician obtained a nasal swab from the eligible patients during the house-call visit. The test used was the "Influ A&B Uni-Strip — Dry Swabs (C-1512)" test, which is manufactured by Coris BioConcept (http://www.corisbio.com). Specifically, this test is an acute-phase screening test that allows detection of both Influenza A and B in liquid swabs as it consists of two sides sensitized with a monoclonal antibody specific for influenza A and B, respectively. Directly after sampling the nasal swab was dipped in 15 droplets or in 500 μL of DS buffer. The Influ A&B Uni-Strip test was then dipped directly into this solution. After 15 min of incubation the results were read on wet strips.

2.3. Interpretation of the test results

For each of the two sides of the device, if 1 line (upper) appeared, the test was considered as negative; if 2 lines appeared, the test was considered as positive. If no line appeared, the test was considered as invalid and the sample was retested.

2.4. Patients' management

To the introduction of the rapid test for influenza as an additional diagnostic tool that enables the differentiation of patients with influenza from those who don't have influenza, and consequently aids in clinical decision making, the SOS doctors (internists, in particular) responded as follows: a) a group of doctors decided to use the test systematically (Group A), b) a group of doctors used the test occasionally (at least once but in less than 15% of the respective house-calls)-(Group B) and c) a group of doctors didn't use the test at all (Group C). The visiting physician performed the test during the house-call visit. The decision regarding the patient's treatment was left at the discretion of the visiting physician, based mainly on the clinical manifestations of the patients (particularly on the presence of fever and cough), along with epidemiological aspects, such as other confirmed or suspected influenza cases among household contacts (when available). The follow up of the patients included in the study was performed through a phone communication with the patient.

2.5. Data collection and analysis

We prospectively collected, during the evaluated period, data regarding the patient's name, age (years), location and cause of the call, the visiting doctor's name, the result of the influenza test (positive/negative; influenza A/B in case of a positive result), the treatment prescribed (antibiotic/antiviral/symptomatic/other or combinations), as well as immediate hospitalization (at the same day with the house-call visit).

2.6. Data analysis

Comparisons regarding the number of anti-influenza and antibiotic agents prescribed, as well as regarding the number of hospitalizations between the patients that had a positive test result and those that had a negative test result for influenza were performed. In addition, in order to assess the impact that the introduction of the rapid influenza as an adjunctive diagnostic tool might have on the decision making of the participating physicians, we compared the number of antiviral, as well as antibiotic agents prescribed from the three groups of doctors. The chi square test was used to compare groups for dichotomous variables. A $p<0.05$ was used to denote statistical significance. All comparisons were performed with the use of the OpenEpi software [21].

3. Results

3.1. Study population

During the study period the network of SOS doctors performed a total of 16,335 house-call visits. The cause for 3412 (20.8%) of these 16,335 calls was a complaint for respiratory/influenza-like symptoms. Eight hundred and twenty three (24.1%) of these 3412 house-call visits were performed from doctors constituting Group A, 1181 (34.6%) house-call visits were performed from doctors constituting Group B, and the remaining 1408 (41.2%) house-call visits were performed from doctors constituting Group C (data are presented in Table 1).

One hundred ninety-seven patients (5.7%) of the 3412 patients seen with respiratory/influenza-like symptoms seen in the respective 3412 house-call visits were tested with the direct influenza test. Data regarding the number of patients tested per group of doctors are presented in Table 1. Data regarding the result of the test were available for 184 of the 197 tested patients. Specific data regarding the demographic characteristics, diagnosis, treatment prescribed, and immediate hospitalizations for these 184 patients as well as for the 3215 not tested patients with respiratory/influenza-like symptoms are presented in tabulated form (Table 2).

3.2. Patients tested for influenza

Eighty-five (46.1%) of the 184 patients with available data regarding the test result were women. The mean age of the 184 patients was 41.5 years; median was 35.5 years. Ninety-seven (52.7%) of the 184 patients had a positive test result for influenza, whereas the remaining 87 (47.2%) patients had a negative test result. Regarding the 97 patients that were found positive for influenza, 58 (59.7%) had influenza A, 38 (39.1%) had influenza B, whereas relevant data were not reported for the remaining 1 patient.

The visiting physicians prescribed significantly more anti-influenza agents, and significantly fewer antibiotic agents to the patients that had a positive test result for influenza A or B, compared to patients that had a negative test result. The observed difference between these subgroups regarding the number of hospitalizations that occurred was not significant. Specific data are presented in Table 3.

3.3. Impact of the test on physicians' decision making

A total of 79, 6, and 16 anti-influenza agents, specifically oseltamivir, were prescribed by the doctors from the groups A, B, and C, respectively (data are presented in Table 3). A statistical significant difference ($p<0.01$) was observed regarding the number of oseltamivir prescriptions in the comparison regarding all the 3 groups of doctors. In addition, the doctors who used the test systematically, prescribed oseltamivir treatment significantly more frequently

Table 1
Number of house-call visits and influenza tests performed from the 3 groups of doctors included in our study.

	No of house-call visits performed (%)	No of patients tested (%)
Group A: Doctors who used the test systematically ($n_1=7$)	823 (24.1)	163 (82.7)
Group B: Doctors who used the test occasionally ($n_2=8$)	1181 (34.6)	34 (17.2)
Group C: Doctors who didn't use the test ($n_3=13$)	1408 (41.2)	0 (0)
Total	3412	197

Table 2
Characteristics of the evaluated patients*.

	Patients tested (n = 184)#		Patients not tested
	Positive test	Negative test	
Demographic characteristics			
Number [females]	97 [44]	87 [41]	3215 [1526]
Mean age (years)	39.7	45.6	53.9
n/N (%)			
Diagnosis			
Influenza	85/92 (92.3)	5/81 (6.1)	58/3215 (1.8)
Viral respiratory infection	3/92 (3.2)	14/81	260/3215 (8.0)
Upper respiratory infection	0/92 (0)	27/81 (33.3%)	548/3215 (17.0)
Lower respiratory infection	4/92 (4.3)	9/81 (11.1)	630/3215 (19.5)
Tonsillitis	0/92 (0)	1/81 (1.2)	148/3215 (4.6)
Febrile episode	0/92 (0)	10/81 (12.3)	309/3215 (9.6)
Viral infection***	0/92 (0)	10/81 (12.3)	758/3215 (23.5)
Otitis media	0/92 (0)	1/81 (1.2)	4/3215 (0.1)
Not-allergic rhinitis	0/92 (0)	0/92 (0)	14/3215 (0.4)
Sinusitis	0/92 (0)	0/81 (0)	81/3215 (2.5)
Laryngitis	0/92 (0)	0/92 (0)	5/3215 (0.1)
Acute bronchitis	0/92 (0)	0/92 (0)	314/3215 (9.7)
Tracheobronchitis	0/92 (0)	0/81 (0)	30/3215 (0.9)
Pneumonia	0/92 (0)	1/81 (1.2)	54/3215 (1.6)
Other	0/92 (0)	3/81 (3.7)	0/3215 (0)
NR	5/97 (5.1)	6/87 (6.8)	NA
Treatment			
Antibiotics	4/91 (4.3)	32/64 (50.0)	1340/2194 (61.0)
Anti-influenza agents (oseltamivir)	*74*/91 (81.3)	*1*/64 (1.5)	25/2194 (1.1)
Other**	13/91 (14.2)	54/87 (62.0)	829/2194 (37.7)
NR	*6*/97 (6.1)	23/87 (26.4)	1021/2194 (46.5)
Hospitalization			
Yes	1/93 (1.0)	2/80 (2.5)	84/3215 (2.6)
No	92/93 (98.9)	78/80 (97.5)	3131/3215 (97.3)
NR	4/97 (4.1)	7/87 (8.0)	NA

Abbreviations: NR: not reported, NA: non-applicable.
#: A total of 197 patients were tested for influenza, yet data regarding the result of the test were available for 184 (93.5%) of these 197 patients.
*: In cases were data were reported for less than 10 patients, no percentages were displayed in Table 2.
**: Including anti-allergic, anti-asthmatic, analgesics, nasal anticongestants, *anti-cough drugs,* oral antiseptics, corticosteroids, *anti-emetic drugs,* anti-fever drugs, NSAIDs, and mucolytics.
***: This specific diagnosis was based on the patient's clinical manifestations, which were suggestive of a viral infection, but not adequate enough to support the diagnosis of influenza (for example absence of fever and/or cough).

($p<0.01$), in comparison to the doctors who used the test occasionally, as well as to the doctors that didn't use the test at all.

A statistical significant difference ($p<0.01$) was found between the 3 groups of doctors regarding the number of antibiotics prescribed (data are presented in Table 4). In addition, the doctors who used the test systematically prescribed significantly less antibiotics in comparison to the doctors who didn't use the test at all. On the contrary, no difference in antibiotic prescription was found in the comparison between doctors that used the test systematically and the doctors who used the test occasionally.

Table 3
Comparisons between patients with a positive and negative influenza test.

Patients to whom the influenza test was performed ($n_1 = 184$)			
	Patients with a positive influenza test ($n_3 = 97$)	Patients with a negative influenza test ($n_4 = 87$)	P value
Anti-influenza agents prescribed	74	1	<0.01
Antibiotics prescribed	4	32	<0.01
Hospitalizations	1	2	0.9

Table 4
Comparisons regarding the prescribing patterns between the three subgroups of doctors.

	Doctors who used the test systematically Group A	Doctors who used the test occasionally Group B	Doctors who didn't use the test at all Group C	P value
n/N′ (%)				
Anti-influenza agents (oseltamivir)	79/665 (11.8)	6/907 (0.6)	16/784 (2.0)	P_1: <0.01 P_2: <0.01 P_3: <0.01
Antibiotics	360/665 (54.1)	516/907 (56.8)	504/784 (64.2)	P_1: = 0.01 P_2: = 0.3 P_3: = <0.01

N′: Number of patients for whom data regarding the evaluated outcome were available.
P1: Refers to the comparison: Group A vs Group B vs Group C.
P2: Refers to the comparison: Group A vs Group B.
P3: Refers to the comparison: Group A vs C.

4. Discussion

The main finding of our study is that the use of a rapid direct diagnostic test for seasonal influenza A and B from a network of doctors performing house-call visits in the area of Attica, Greece resulted in significantly more oseltamivir but fewer antibiotic prescriptions to patients that were found positive for influenza in comparison to those that were found negative. Moreover, the introduction of the rapid influenza test as an adjunctive diagnostic tool had a considerable impact on the decision making of the participating physicians, as the doctors who decided to use the influenza test systematically prescribed oseltamivir significantly more frequently in comparison to those that decided to use the test occasionally or not to use the test at all. In addition, the doctors who decided to use the influenza test systematically prescribed significantly less antibiotic agents compared to the doctors that didn't use the test at all, whereas no difference was found in comparison with doctors that used the test occasionally.

The accuracy of rapid direct diagnostic tests to detect seasonal influenza has already been evaluated in several studies that referred mainly to pediatric populations. The reported specificities were relatively high in comparison with the reference standard tests, whereas the reported respective sensitivities varied considerably [15,22–24]. Additionally, a considerable number of studies have also evaluated the impact of the use of a rapid influenza test on physicians' decision making, and patients' management. Specifically, according to these studies the use of the rapid influenza test in patients with influenza-like illness resulted in a reduction of further diagnostic tests and examinations, and consequently to a reduction of medical associated costs [11–14,25].

In our study, the subgroup of doctors that decided to use the influenza test as an adjunctive diagnostic tool systematically, prescribed significantly more antiviral agents and fewer antibiotics in comparison to the doctors that didn't use the test at all. This specific prescribing pattern might contribute to the reduction of unnecessary antibiotic treatment. Our findings are in accordance with a recent cross-sectional single-blinded study involving pediatric patients with influenza-like illness [26]. In this era of alarmingly increasing antibiotic resistance rates, the reduction of unnecessary antibiotic treatment (such as in patients with viral infections) is an issue of major importance in terms of both individual and public health perspectives.

The number of anti-influenza agents prescribed to patients that had a positive test either for influenza A, or B was also found to be significantly higher compared to those that had a negative test for influenza. These findings imply that the use of a rapid test and the awareness of a positive test for influenza resulted in a targeted prescription of anti-influenza agents to patients with influenza-like symptoms in this specific clinical setting. Of note, only one of the patients with a positive influenza test result required hospitalization. The benefit of early antiviral treatment on patients with influenza, regardless of the severity of the disease, has been pointed out in many studies. [27,28] The discussions regarding the benefits of early antiviral treatment were intensified during the latest influenza pandemic [29]. However, the effectiveness of neuraminidase inhibitors in preventing and treating influenza in healthy adults remains a debatable issue [30]. Yet, recent studies provide encouraging evidence regarding the effectiveness of neuraminidase inhibitors in reducing the time to symptoms' alleviation [31], as well as influenza complications in otherwise healthy and patients at-risk for influenza complications [32]. Consequently, patients with influenza of mild or moderate severity may also benefit from antiviral treatment.

The use of a rapid direct influenza test enables a timely and proper use of antiviral treatment, and simultaneously a reduction of unnecessary antibiotic treatment. Yet, one may consider that the use of rapid influenza test may potentially lead to over-prescription of antivirals. This may result in the emergence of viral strains that are resistant to the available antiviral agents [33]. Specifically, regarding the seasonal influenza during the evaluated period (winter 2009) in European countries, a considerably high rate of A/H_1N_1 viral strains (98%) resistant to oseltamivir was detected [34]. The use of rapid direct test could potentially be a useful tool during pandemic influenza outbreaks.[19,20] Even though the specific test used in our study is capable of detecting A/H_1N_1 swine flu cases, [29] no swine flu case was detected in our study population. Notably, the 1st swine flu case in our country was reported at May 18, 2009; the evaluated period of our study was from 01/01/2009 to 30/05/2009.

Our study has limitations that should be taken into consideration in the interpretation of its findings. Specifically, our findings derive from the analysis of data from a rather limited number of outpatients that sought medical services from a network of doctors performing house-call visits at a specific clinical setting, as well as at a specific time period. Consequently, the extrapolation of our findings to other clinical settings should be dealt with cautiousness. In addition, methods including viral cultures or polymerase chain reaction (PCR) were not performed in order to confirm influenza infection in the evaluated patients. On the contrary, the diagnosis of influenza was at the discretion of the visiting physician, based mainly on the patients' clinical manifestations, along with epidemiological aspects (if any). Consequently, we were precluded from assessing the accuracy of this specific test for the diagnosis of influenza infection in this clinical setting.

In conclusion, our experience with the use of a rapid diagnostic test for seasonal influenza A and B in patients with influenza-like clinical manifestations that sought medical services from a specific network of doctors that performs house-call visits in the area of Attica, Greece indicates that the use of the rapid influenza test resulted in a targeted use of anti-influenza agents, as well as in a reduction of unnecessary antibiotic treatment in patients that had a positive test for influenza. In this regard, clinicians may consider a rapid direct diagnostic test as a useful adjunctive tool for the diagnosis of influenza.

5. Learning Points

- Rapid influenza test may help in increasing targeted use of anti-influenza agents, as well as in reducing unnecessary antibiotic treatment in patients that had a positive test for influenza.
- Our data suggest that a rapid direct diagnostic test may be considered for use during seasonal influenza epidemics after taking into considerations its limitations.

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