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ARTICLE

An algorithm to diagnose influenza infection: evaluating the clinical importance and impact on hospital costs of screening with rapid antigen detection tests

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Abstract Rapid antigen detection tests (RADTs) are immunoassays that produce results in 15 min or less, have low sensitivity (50 %), but high specificity (95 %). We studied the clinical impact and laboratory savings of a diagnostic algorithm for influenza infection using RADTs as a first-step technique during the influenza season. From January 15th to March 31st 2014, we performed a diagnostic algorithm for influenza infection consisting of an RADT for all respiratory samples received in the laboratory. We studied all the patients with positive results for influenza infection, dividing them into two groups: Group A with a negative RADT but positive reference tests [reverse transcription polymerase chain reaction (RT-PCR) and/or culture] and Group B with an initial positive RADT. During the study period, we had a total of 1,156 patients with suspicion of influenza infection. Of them, 217 (19 %) had a positive result for influenza: 132 (11 %) had an initial negative RADT (Group A) and 85 (7 %) had a positive RADT (Group B). When comparing patients in Group A and Group B, we found significant differences, as follows: prescribed oseltamivir (67 % vs. 82 %; p=0.02), initiation of oseltamivir before 24 h (89 % vs. 97 %; p=0.03), antibiotics prescribed (89 % vs. 67 %; p=<0.01), intensive care unit (ICU) admissions after diagnosis (23 % vs. 14 %; p=0.05), and need for supplementary oxygen (61 % vs. 47 %; p=0.01). An influenza algorithm including RADTs as the first step improves the time of administration of proper antiviral therapy, reduces the use of antibiotics and ICU admissions, and decreases hospital costs.

Some of the results of this study were previously presented as a poster at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, USA, 5th September 2014.

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Introduction

During the winter season, the influenza virus constitutes a work overload, especially for the emergency department, healthcare workers, and for the microbiological department [1]. The diagnosis of influenza virus has improved rapidly since the 2009 pandemic, becoming currently a fast and accurate diagnosis with an elevated sensitivity and specificity [2]. The reference standards for laboratory confirmation of influenza virus infection are reverse transcription polymerase chain reaction (RT-PCR) or viral culture. These tests require trained personnel, take time to perform, and are expensive techniques. Rapid antigen detection tests (RADTs) are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens. These tests are simple to perform and produce

results in 15 min or less, yet they have been proven to have a low sensitivity (≈50 %), but a high specificity (≈95 %), especially during the influenza season [3]. The value of these tests as a diagnostic tool for influenza infection and the importance of an algorithm using RADTs as a first step test is not clear [4, 5]. Our hypothesis is that a simplified strategy would improve the time to diagnosis, reduce the work load, improve patient management, and, ultimately, help to reduce costs. Our study consists of the evaluation of the clinical and laboratory impact of a diagnostic algorithm for influenza infection using RADTs as a first-step technique during the influenza season.

Methods

Setting, study design, and population

Our institution is a 1,550-bed general teaching hospital attending a catchment population of approximately 715,000 inhabitants in a large city.

We performed a cohort study from January 15th to March 31st 2014. During this period, our microbiological department received upper and lower respiratory samples from children and adults who arrived at our hospital with a clinical suspicion of influenza. Upper respiratory samples consisted of nose-throat swabs or nasopharyngeal aspirates and lower respiratory samples consisted of endotracheal aspirates or bronchoalveolar lavages. The samples were taken by the nursing staff in the emergency department and the hospitalization wards.

Microbiological procedure

All respiratory samples received in our laboratory were broken into a vial containing transport medium. During the study period, we systematically performed on all respiratory samples an RADT. The RADT was performed following the manufacturer's instructions (Xpect™ Flu A & B, Remel Europe Ltd.). We also performed an RT-PCR assay and/or a shell vial assay on all the samples. RT-PCR was performed by extracting viral RNA from 200 μL of the sample in a NucliSENS easyMag device (bioMérieux, Boxtel, the Netherlands) following the manufacturer's instructions, eluted in 60 μL of elution buffer, and maintained at 4 °C if it was analyzed immediately or at −70 °C until the assay was performed. A water sample was co-extracted as a negative control in all cases. Influenza A H1N1 and influenza B were detected using real-time RT-PCR following the manufacturer's instructions (RT-PCR Flu A/B Typing Real-time Detection, Anyplex). For the shell vial assay, the samples were inoculated into two cell lines, MRC-5 and A549, the latter with immunofluorescence using specific fluorescein-conjugated monoclonal antibodies (SimulFluor® FluA/FluB, Light Diagnostics), as reported previously [2].

We studied all the patients who were positive for influenza infection, dividing them into two groups: Group A in which the initial RADT was negative but the reference tests were positive, informing the clinician of this last result, and Group B with an initial positive RADT, in which the clinician was immediately informed of the result and the diagnostic algorithm was considered finished. These results were confirmed by reference tests afterwards.

Clinical data

The clinical data were retrieved from the electronic medical records of the patients. The data included age, gender, location of the patients at the moment of presenting with respiratory symptoms, and complications of influenza infection: admission to the intensive care unit (ICU), new or worsening heart failure, requirement of supplementary oxygen (nasal cannula or oxygen mask), and endotracheal intubation with mechanical ventilation. Additional data included: prescribed and time of prescription of antiviral (oseltamivir) and prescribed antibiotic, final outcome, and length of hospital stay. We also collected microbiological results that included RADT, RT-PCR, and shell vial results.

Statistical analysis

Categoric variables appear with their frequency distribution. Non-normally distributed continuous variables are expressed as the median and interquartile range (IQR). The association between categoric variables was evaluated by using the χ^2 test or Fisher's exact test. A *t*-test was performed on the equality of means between Groups A and B; Bartlett's test has been used to test the equality of variances before conducting the *t*-test. A *p*-value of 0.05 was considered statistically significant. Data were analyzed using Stata, version 12.

Ethics committee approval

This study had been evaluated and approved by the ethics committee of our institution and by the Spanish Drug Agency.

Results

During the study period, we had a total of 1,156 patients with suspicion of influenza infection. Of them, 939 (81 %) had a negative initial RADT and a negative reference test result; therefore, they were considered true-negatives. On the other hand, 217 (19 %) had a positive result for influenza. Of these patients, 132 (11 %) had an initial negative RADT, but had a positive reference test for influenza (RT-PCR/culture); therefore, they were categorized into Group A, and 85 (7 %) patients had a positive RADT and were categorized into Group B (Fig. 1).

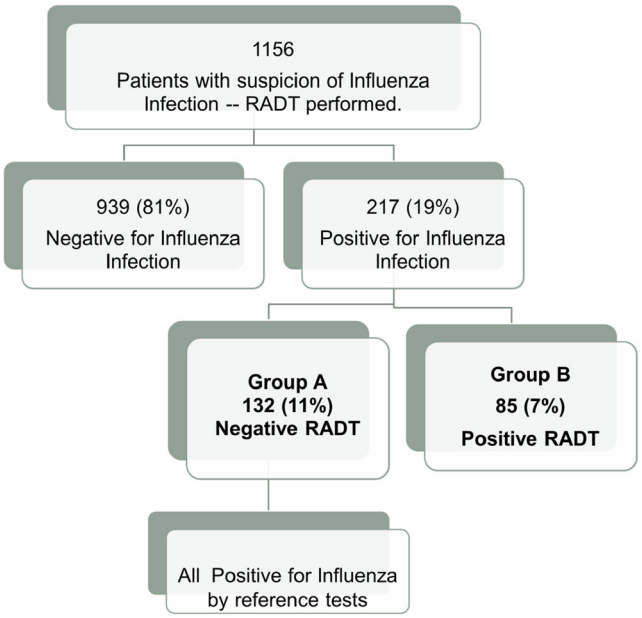

Fig. 1 Algorithm of patients included in the study

When comparing patients in Group A and patients in Group B, we found no significant differences regarding mean age (58 vs. 53 years; p=0.08), gender (59 % vs. 54 % male patients; p=0.76), first consultation in the emergency department (58 % vs. 53 %; p=0.43), and hospitalization units (p=0.67): ICU hospitalization (3 % vs. 2 %), general medicine (24 % vs. 22 %), cardiology (5 % vs. 5 %), oncology and hematology (4 % vs. 5 %), pediatric (3 % vs. 7 %), geriatric (2 % vs. 5 %), general surgery (1 % vs. 1 %), and obstetric wards (2 % vs. 0 %) (Table 1).

Table 1 Comparison of patients from Group A and Group B

	Group A, n=132 (%)	Group B, n=85 (%)	p-Value
Age, years (mean)	58.2	52.5	0.08
Gender			
Male	78 (59.1)	46 (54.1)	0.76
Location of patients at the moment of presenting with respiratory symptoms			
ED/outpatient consult	77 (58.3)	45 (52.9)	0.43
Inpatients:			0.67
Cardiology wards	6 (4.6)	4 (4.7)	
General surgery wards	1 (0.8)	1 (1.2)	
General medicine wards	31 (23.5)	19 (22.4)	
Geriatric wards	2 (1.5)	4 (4.7)	
Obstetric wards	2 (1.5)	0 (0)	
Oncology/hematology	5 (3.8)	4 (4.7)	
Pediatrics wards	4 (3.0)	6 (7.1)	
ICU wards	4 (3.0)	2 (2.4)	

ED emergency department; *ICU* intensive care unit

Comparing the clinical impact of the diagnostic algorithm between Group A and Group B, we found significant differences in the following: prescribed oseltamivir (67 % vs. 82 %; p=0.02); time of prescription of oseltamivir (p=0.03): before 24 h (89 % vs. 97 %), 24 h (2 % vs. 3 %), 48 h (5 % vs. 0 %), 72 h (2 % vs. 0 %), and more than 72 h (2 % vs. 0 %). Significant differences were also found in the antibiotics prescribed between both groups (89 % vs. 67; $p < 0.01$), specifically cephalosporins (13 % vs. 5 %; p=0.01) and quinolones (45 % vs. 33 %; p=0.04), and the following complications after the diagnosis of influenza: required ICU admission (23 % vs. 14 %; p=0.05) and required supplementary oxygen (61 % vs. 47 %; p=0.01). We found no significant differences in heart failure (22 % vs. 25 %; p=0.67), requirement of mechanical ventilation (11 % vs. 9 %; p=0.38), days of hospital stay (13.52 vs. 16.44; p=0.17), and mortality (7 % vs. 6 %; p=0.12) (Table 2).

The average time to diagnose influenza infection in Group A was 2 days, while the average time for diagnosis in Group B was 15 min. Reference tests could not have been purportedly avoidable in any patient of Group A, while they could have been avoided in all 85 (7 %) patients constituting Group B. Taking into consideration that performing RT-PCR in our laboratory accounts for 35€/per sample versus 12€/per sample for RADT, 3,000€ of expenses for RT-PCR could have been saved just in acquiring reagents. In addition to the above, we were able to save in antibiotic costs, since patients in Group B received less cephalosporins (the expenses of one vial of ceftriaxone of 2 g equals 17€) and quinolones (the expenses of one vial of levofloxacin equals 15€), and, most importantly, fewer patients in this group required ICU admission (a day of ICU admission accounts for ~1,100€ in Spain [6]).

Discussion

Our results prove that RADTs contribute to shortening the time of diagnosis of influenza infection in a high proportion of patients. Patients with a positive RADT receive more suitable management when compared to those patients whose RADT was negative and rely on the results of the reference tests (RT-PCR or culture). This is associated with a reduction in the time of diagnosis and hospital costs [7, 8]. The Centers for Disease Control and Prevention (CDC) consider RADTs to be useful in identifying influenza virus infection, particularly during the influenza season [9]. However, the role of RADTs in the era of molecular techniques is not clear.

In our study, we used RADTs as a first, easy to perform and low cost, step on all the respiratory samples received in our laboratory during the influenza season, followed by a reference test. However, these tests have been proven to have a variable sensitivity, depending on the prevalence of influenza infection, type of influenza virus, timing of the test and use in

Table 2 Comparison of evolution between patients in Group A and Group B

	Group A, n=132 (%)	Group B, n=85 (%)	p-Value
Prescribed oseltamivir	89 (67.4)	70 (82.3)	0.02*
Time of prescription since laboratory confirmation of influenza infection			0.03*
<24 h	79 (88.8)	68 (97.1)	
24 h	2 (2.3)	2 (2.9)	
48 h	4 (4.5)	0 (0)	
72 h	2 (2.3)	0 (0)	
>72 h	2 (2.3)	0 (0)	
Prescribed antibiotics during episode	118 (89.3)	57 (67.0)	<0.01*
Cephalosporins	17 (12.8)	4 (4.7)	0.01*
Quinolones	59 (44.7)	28 (32.9)	0.04*
Carbapenems	15 (11.3)	11 (12.9)	0.63
Complications after diagnosis of influenza infection			
Required ICU admission	30 (22.7)	12 (14.1)	0.05*
Onset of new or worsen heart failure	29 (21.9)	21 (24.7)	0.67
Required supplementary oxygen	80 (60.6)	40 (47.0)	0.01*
Required mechanical ventilation	14 (10.6)	8 (9.4)	0.38
Days of hospital stay (mean)	16.44	13.52	0.17
Final outcome			0.12
Cured	117 (88.6)	80 (94.1)	
Death related to influenza infection	9 (6.8)	5 (5.9)	
Death not related to influenza infection	5 (3.8)	0 (0)	

ICU intensive care unit

*p<0.05

adult patients, and other factors described previously [10–12]. On the other hand, viral cell culture and molecular techniques such as real-time RT-PCR are considered the reference methods for the detection of influenza A and B. The reference tests are becoming more accepted as gold-standard techniques for influenza viruses. However, molecular methods, at the present time, are technically demanding, laborious, and expensive, even though new and improved molecular detection tests, like those based on isothermal nucleic acid amplification, are being tested [13, 14]. Our results were consistent with the literature, in terms of the sensitivity and specificity of RADTs [3, 10, 15, 16]. Uyeki et al., in a study conducted in three different sites, compared the QuickVue Influenza A+B Test with RT-PCR as their "gold standard". Their results regarding sensitivity are one of the lowest found in the literature: 26.7 % (range, 18.9 %–32.3 %), with a median specificity of 97.2 % (range, 96.2 %–99.6 %) [16]. In our study, of the total of 217 patients who were positive for influenza, 132 (61 %) had an initial false-negative RADT, which was later confirmed positive by the reference tests (62 % sensitivity). Indeed, the sensitivity of these tests will vary, depending mainly on the setting and prevalence of influenza in a certain location; if the prevalence is high, the positive predictive value (PPV) will be high as well and the negative predictive value (NPV) will be low [17]; and also the type and performance of the different RADTs available, as described by Baas et al. [18] and Chan et al. [19]. For definite, each location would have to study whether RADTs could be a useful tool depending on the different factors discussed previously.

Because one of the main concerns of using RADTs as a screening tool is their low sensitivity, some authors recommend substituting them for molecular techniques [20]. An argument against this could be the saving in economic costs. In our study, of the 217 patients diagnosed with influenza infection, 85 (39 %) patients with a positive RADT could have been spared of a reference test. This means a high percentage of savings not only in laboratory costs, but also in prescribed antibiotics (especially cephalosporins and quinolones), human resources, and ICU admissions. González-Canudas et al. [7, found similar results when applying RADTs as a first-step technique; they saved 13$ per suspected case of influenza infection. Apart from economic savings, our algorithm has the advantage that it could easily be incorporated into the everyday clinical practice during the influenza season: every respiratory sample with a suspicion of influenza would first be tested by an RADT (easy-to-perform point-of-care bedside test with results in 15 min or less), and only negative results would then have to be processed and tested with a reference test (RT-PCR/culture).

Previous studies emphasize the importance of initiating antiviral treatment during the first several hours of the onset of respiratory symptoms [21–23]. A European study named

IMPACT (Immediate Possibility to Access Oseltamivir Treatment) investigated the relationship between time to intervention and duration of illness by treating with oral oseltamivir as early as possible after the onset of influenza symptoms. They concluded that an earlier intervention with oseltamivir was associated with shorter illness duration, reduced the duration of fever, severity of the symptoms, and the times to return to baseline activity and health scores [23]. Hayden and Pavia [21] also insist that oseltamivir has been shown to decrease antibiotic use, the number of hospitalizations, and, probably, the risk of death after influenza. Coincidentally, in our study, the patients with a positive RADT received earlier oseltamivir treatment (less than 24 h since the onset of symptoms) when compared to patients with a negative RADT, resulting in a better management of these patients and less ICU admissions.

Our study has the main limitation that it may not be possible to apply our algorithm in every setting, since RADTs are influenced by numerous factors, such as the prevalence of influenza infection in each population, as discussed previously.

Our algorithm for diagnosing influenza infection has a clinical impact in those patients diagnosed by a positive RADT, since these patients receive adequate and prompt antiviral treatment; receive less antibiotics, and present fewer complications than those diagnosed by standard reference tests.

Conflict of interest The authors declare no conflicts of interest.

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