



Enfermedades Infecciosas y Microbiología Clínica

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Editorial

Rapid diagnostic methods for acute viral respiratory infections



Técnicas de diagnóstico rápido para infecciones respiratorias agudas de etiología viral

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Acute respiratory infection (ARI) of viral etiology is the most frequent clinical syndrome affecting humans. Millions of people suffer from ARI, mainly during the colder seasons, every year. Fortunately, most cases are self-limited and evolve toward healing without the need for an etiological treatment. About twenty viruses have been involved as causative agents of ARI. Excepting infections caused by emerging viruses such as MERS-coronavirus (CoV), SARS CoV or new influenza viruses (Flu)], severe cases that require special attention and management rarely occur. Patients within the extreme stages of life, *i.e.* infants and elder adults, and/or individuals with underlying conditions or risk factors are mainly affected by a more severe infection. On the other hand, specific antiviral therapy is only available for Flu and respiratory syncytial virus (RSV) infections.

However, an overwhelming demand of healthcare services takes place yearly, coinciding with seasonal epidemics of Flu and RSV, which leads to an increase in visits to emergency units, in antibiotics use and in requests of laboratory and imaging tests.

Whenever a rapid detection test (RDT) is included in the portfolio of ARI diagnosis, appropriate sensitivity and specificity values must have been demonstrated so that the assay can be used for the purpose it was implemented. In this situation, the question is whether a RDT is cost-effective.

Mainly, it might reduce the use of antibiotics as serious bacterial co-infections are rare, minimize the need for ancillary tests, decrease the duration of hospital stay and, if necessary, allow the rapid implementation of a cohort in order to avoid nosocomial transmission.¹ Attending to these requirements, which technique should be used and when and how should it be used for the rapid diagnosis of ARI?

Many questions arise when one tries to implement a rational diagnostic algorithm: Should we investigate all viruses in all ARI cases or selected viruses in selected individuals? Should we investigate all viruses only in special cases? Should we use RDTs only in emergency units in all cases or only in hospitalized patients?..

Obviously, different clinical settings require different diagnostic procedures. A clinical diagnosis of ARI can be made in outpatients

and only in exceptional situations a rapid etiological diagnosis is needed, as has occurred with suspected cases of pandemic Flu in pregnant women and morbidly obese individuals, or to identify influenza virus infection as a cause of respiratory outbreaks in close institutions. Contrarily, all possible respiratory viruses should be investigated in situations of high risk for severe complications, *e.g.* in people with hematological malignancies.

In consonance with the wide spectrum of clinical situations that a physician can find, a significantly high number of RDTs are available, ranging from rapid antigen detection tests (RADTs) to automatic nucleic acids amplification techniques (NAATs). RADTs were primarily designed for RSV and Flu; being immunochromatographic assays (IC) the most widely employed because of their ease of use. However and specially with RADTs for Flu, variable sensitivity and specificity values have been observed depending on several factors, *i.e.* manufacturer, type of sample, patient's age, delay of sampling since the onset of symptoms, etc.² Overall, RADTs for Flu or RSV carried out in nasopharyngeal washes or aspirates, pediatric population and with samples collected within the first 72 h since the onset of symptoms have demonstrated the best results.^{3,4}

Recently a FDA-cleared RDT for Flu and RSV detection, the Sofia Influenza A+B and RSV fluorescent immunoassays (FIA) (Quidel Corp.), seems to improve the sensitivity and specificity of IC assays since they combine an immunofluorescence-based lateral-flow technology with automatic digital scan and interpretation of the test strip, which minimizes potential operator errors due to manual reading.^{5,6} Gómez et al. evaluate the Sofia Influenza A+B and RSV FIA, using cell culture and/or RT-PCR as reference methods, showing a good sensitivity and specificity. Especially for Flu detection, this assay enhances the diagnostic accuracy compared with classical IC assays. Higher sensitivity is obtained with nasopharyngeal aspirates vs exudates (90.6% vs 61% respectively) and with pediatric vs adult samples (87.8% vs 55.3% respectively).⁵

Nowadays, apart from the particular situations commented above, there is a consensus in order not to use diagnostic tests for detecting respiratory viruses in outpatients with ARI. In emergency units, RDTs are commonly employed, especially for RSV and Flu, although they have not demonstrated its utility in decreasing antibiotics' prescription and/or the use of ancillary tests in this setting.⁷ Even in the diagnosis of RSV infection, for which RDTs offer better sensitivities, the results from these assays may be

DOI of original article: <http://dx.doi.org/10.1016/j.eimc.2015.05.007>
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counterproductive and lead to a false sense of security in establishing cohorts of hospitalized patients. The use of RDTs in emergency units has only been associated with a reduction in antibiotics' consumption once the individuals return to be attended as outpatients at their health centers.⁷

Regarding RDTs for Flu detection, the poor sensitivity and negative predictive values make controversial their use in emergency units. In this situation (excepting high-risk individuals), a diagnostic test for Flu is not necessary if the patient is going to be discharged. If the clinical status of the patient makes necessary special healthcare and/or hospitalization, Flu should be directly investigated by NAATs. Besides, etiological diagnosis of Flu serves for prompt antiviral treatment and for the rapid implementation of control measures to prevent nosocomial outbreaks.^{8,9}

Currently, different commercial NAATs for Flu and RSV detection are available.¹⁰ Although they are not considered point-of-care assays as some RADTs are, automatic NAATs require a minimal hands-on-time and offer a rapid and more reliable result compared with the one obtained with RADTs.^{11–16} However, as NAATs can detect asymptomatic shedding or very low viral loads in the respiratory tract, the clinical significance of a NAAT-positive result in these cases is controversial. Also, there are no data supporting the use of NAATs for monitoring the outcome of the infection and/or the response to antiviral treatment.

Even more controversy is seen with the recommendation of use of rapid diagnostic tests for respiratory viruses other than RSV and Flu. Some commercial RADTs and automatic NAATs are available to detect a variable range of respiratory viruses.¹⁰ An example of the former method is mariPOC[®], designed for antigen detection of RSV, Flu A and B, adenovirus, parainfluenza viruses 1–3, human metapneumovirus and *Streptococcus pneumoniae* in respiratory samples. The potential cost-benefits of this technique have been recently reported.¹⁷ However, the real utility of this assay is still unclear. Furthermore, automatic multiplex NAATs for detecting an extended spectrum of respiratory viruses have demonstrated excellent performance,¹⁸ but the high costs of these assays limit their use in routine. For this reason, they are usually reserved for special situations, such as severely ill patients admitted to intensive care units.

In conclusion, according to the clinical setting, the epidemiological situation and the severity of the disease, it is necessary to establish rational and cost-effective diagnostic algorithms for respiratory viruses. Flu testing is recommended for hospitalized patients with influenza-like illness. However, empiric antiviral treatment should be initiated as soon as possible without the need to wait for any influenza testing results.

Acknowledgements

To Mercedes Perez and Sara Sanbonmatsu for their contributions and comments in the realization of this work.

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