Rapid diagnostic methods for acute viral respiratory infections

Técnicas de diagnóstico rápido para infecciones respiratorias agudas de etiología viral

José M. Navarro-Marí

Servicio de Microbiología, Complejo Hospitalario Universitario de Granada, Instituto Biosanitario Granada, Granada, Spain

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.1,4

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).3

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...
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’ con-
sumption once the individuals return to be attended as outpatients
at their health centers. 7

Regarding RDTs for Flu detection, the poor sensitivity and nega-
tive predictive values make controversial their use in emergency
units. In this situation (excepting high-risk individuals), a diag-
nostic 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 detec-
tion 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 respi-
tratory 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. 16 An example
of the former method is mariPOCT, designed for antigen detec-
tion of RSV, Flu A and B, adenovirus, parainfluenza viruses 1–3,
human metapneumovirus and Streptococcus pneumoniae in respi-
atory 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 epidemiolo-
logical situation and the severity of the disease, it is necessary to
establish rational and cost-effective diagnostic algorithms for respi-
ratory 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.

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