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Continuing medical education: Methods of rapid diagnosis

Rapid diagnostic test for respiratory infections☆

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ABSTRACT

Acute respiratory infections are the second cause of morbidity and mortality in children and adults worldwide, being viruses, bacteria and fungi involved in their aetiology. The rapid diagnosis allows for a better clinical management of the patient, for adopting public health measures and for controlling possible outbreaks. The main etiologic agents can be diagnosed within the first hours after the onset of symptoms with antigen detection techniques, primarily immunochromatography. Results are obtained in 15–30 min, with 70–90% sensitivity and >95% specificity for the diagnosis of *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup O1 infections from urine, *Streptococcus pyogenes* from throat swabs and respiratory syncytial virus from nasopharyngeal aspirates. Worse results are obtained for influenza viruses and *Pneumocystis jirovecii* with these techniques; however, other easy-to-perform molecular techniques are available for the rapid diagnosis of these microorganisms. In general, these techniques should not be used for monitoring the outcome or response to treatment.

Métodos de diagnóstico rápido de las infecciones respiratorias

Palabras clave:
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RESUMEN

Las infecciones respiratorias agudas son la segunda causa de morbimortalidad tanto en niños como adultos a nivel mundial en cuya etiología se implican virus, bacterias y hongos. Su diagnóstico rápido permite un mejor manejo clínico del paciente, adoptar medidas de salud pública y controlar posibles brotes. Los principales microorganismos responsables pueden diagnosticarse en las primeras horas tras el inicio del cuadro con técnicas de detección de antígeno, fundamentalmente inmunocromatográficas. Se obtienen resultados en 15–30 min, con una sensibilidad del 70–90% y especificidad superior al 95% para el diagnóstico de infecciones por *Streptococcus pneumoniae* y *Legionella pneumophila* serogrupo O1 a partir de orina, *Streptococcus pyogenes* en exudados faríngeos y virus respiratorio sincitial en aspirados nasofaríngeos. En infecciones por los virus de la gripe y por *Pneumocystis jirovecii*, los resultados con estas técnicas son peores; no obstante, existen técnicas moleculares de fácil ejecución para el diagnóstico rápido de estos microorganismos. En general, estas técnicas no deben utilizarse para control evolutivo ni para valorar respuesta al tratamiento.

Introduction

Respiratory tract infections are one of the primary causes of morbidity and mortality and one of the principle reasons for medical consultation all over the world. As in other infectious processes, swift accurate diagnosis is associated with more targeted and effective treatment, lower transmission of the disease and, often, a reduction in its duration.

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The aim of this study is to provide a review of rapid diagnostic tests (RDT) in some of the most common respiratory infections (RI). Chronic evolution RIs, such as tuberculosis or those which affect patients in specific situations (e.g. pneumonia associated with respiratory support), have been excluded as they are addressed in other chapters.

RDTs have been considered as those whose result can be given in under 7 h (a standard work shift) in comparison with conventional bacterial or viral culture techniques (18–24 h and 48 h or more, respectively). Even though serological antibody detection techniques meet this temporal definition, they have not been included given that demonstrating seroconversion (appearance of antibodies in the serum) or seroreinforcement (increase in the initial titre of antibodies by a factor of 4) may take weeks or months to come about, with high levels of variability between individuals.

Given the simplicity and swiftness of their implementation and with which results can be obtained and interpreted, some of these RDTs may also be used as "*point-of care tests*" (POCT) with the subsequent benefits for the patient, who may receive the diagnosis and, depending on the result, the treatment in one single consultation.

In general, the use of RDTs in the diagnosis of RIs can help to:

- Reduce the use of antibiotics, given that many RIs are of a viral aetiology.
- Ensure the use of suitable anti-viral therapy in specific cases.
- Minimise the use of unnecessary diagnostic tests.
- Reduce the length of hospital stays.
- Permit the swift implementation of isolation measures to limit nosocomial infection, whenever necessary.

Moreover, in RIs of bacterial origin, on detecting the antigen of the target pathogen or its nucleic acids, RDTs are affected to a much lesser extent than culture in the diagnosis in the event that antibiotic treatment has already commenced.

Rapid diagnostic tests for group A *Streptococcus* (*Streptococcus pyogenes–S. pyogenes–*)

The RDTs for group A *Streptococcus* (GAS) are fundamentally aimed at determining the bacterial nature of the pharyngitis. Pharyngitis is the most common infection caused by GASs, and may be accompanied by suppurative sequelae (e.g. peritonsillar abscesses) or non-suppurative sequelae (e.g. rheumatic fever and acute glomerulonephritis), although nowadays these complications are rare in the majority of developed countries. Less frequently, they may also lead to serious infections, such as necrotising fasciitis, and other infections such as pneumonia, endocarditis or meningitis.

The majority of paediatric pharyngitis, particularly in children under 3 years of age, are caused by viruses whose symptomatology is very similar to streptococcal infections. It is estimated that only between 20% and 30% of cases of pharyngitis in children, and 10% of those in adults are due to GAS[1] and thus a very low percentage of patients will benefit from treatment with antibiotics. This explains why RDTs for the diagnosis of this minor illness are among the most regularly used and are under continual assessment, since they help to prevent the inappropriate use of antibiotics.

The *gold-standard* test for the diagnosis of GAS-induced pharyngitis continues to be bacterial culture in blood agar, either direct, after enrichment, or with selected plates incubated for between 24 and 48 h.

RDTs for the detection of the GAS antigen in pharyngeal swabs appeared at the beginning of the 1980s. Since then, there have been a number of generations of RDTs which have employed different methodologies. Initial techniques employed latex agglutination, followed by the ELISA and lateral flow tests and colorimetric immunochromatographic tests. Recently, molecular tests, such as DNA probes, PCR and in situ fluorescent hybridisation[2] have been marketed.

Immunochromatographic tests (ICT) are currently among the most frequently used RDTs owing to their ease of use and rapid results (15 min). There are a great many of these tests on the market, but they all detect the C carbohydrate in the GAS cell wall by means of specific monoclonal or polyclonal antibodies. In the majority of these tests, the carbohydrate must be extracted from the cell wall beforehand in an acid medium capable of dissolving them, for their subsequent detection on the immunochromatographic strip.

The optimum performance for these tests is attained in populations previously screened on the basis of certain pharyngeal infection clinical criteria.[3] Compared with culture as a reference method, the meta-analyses and studies performed for GAS RDTs in the pharynx give a mean sensitivity of 85% (varying between 70% and 90%) and a specificity of around 95%.[1,3–5] Generally speaking, sensitivity varies greatly between studies, but not specificity, which is usually very high. The relatively low sensitivity means that the majority of authors continue to recommend taking a culture in case the test is negative, in order to detect a greater number of cases.[6]

The great advantage of ICTs is that they can be performed in the presence of the patient, which, along with the high specificity, means that after a positive result no confirmatory culture is required, and specific antibody treatments can be recommended on the spot. Except under special circumstances, performing an RDT or control culture at the end of this treatment is not recommended.

Despite the advantages offered by RDTs, it should be remembered that the culture and isolation of the GAS will facilitate the subsequent performance of other tests, such as the antibiotic sensitivity test or the genotypic characterisation of the isolations. It should also be remembered that, even though its role is subject to debate, in a low percentage of bacterial pharyngitis, beta-haemolytic streptococci from other groups (above all from groups C and G) are isolated which cannot be detected by means of GAS RDTs since the composition of the carbohydrates in their cell wall is different.[7]

There are also commercial molecular RDTs for the diagnosis of GAS-induced pharyngeal infection through hybridisation and real-time PCR. Although their sensitivity and specificity are as high, or higher, than the culture method, and their limit of detection exceeds that of antigen detection techniques,[8] they are still techniques which take between one and two hours to perform, with the need for qualified staff and specific molecular biology equipment. All of this, along with the simplicity and sound diagnostic performance of RDTs for the ICT antigen, has meant that there are currently very few clinical laboratories routinely using molecular techniques such as RDTs for GAS-induced pharyngitis.

For invasive infections caused by GAS, the performance of RDTs has also been compared to culture, with the sensitivity of ICT antigen detection tests being similar to PCR and greater than culture.[8] Despite these tests not being recommended in the presence of antibiotic treatment, RDTs may be positive in these samples with negative culture, since they take longer to become negative.

Rapid diagnostic tests for infection by *Legionella pneumophila (L. pneumophila)*

Legionella is a group of bacteria which are ubiquitous in aquatic habitats, comprising more than 55 species and 70 serogroups. Exposure to aerosols containing Legionella can give rise to different clinical manifestations, from Legionnaires' disease (severe community-acquired pneumonia), to Pontiac fever (self-limited febrile syndrome), or even asymptomatic infection. Of all of