Rapid streptococcal antigen detection test in pharyngitis: impact on antibiotic use

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Abstract

Objective: to assess the impact of the use of rapid antigen detection testing for streptococcus on antibiotic prescription in children.

Patients and methods: retrospective observational cohort study through the review of the electronic health records corresponding to 10 paediatric caseloads in primary care centres in the province of Zaragoza (Spain) for years 2012 and 2013. We analysed the use of antibiotherapy and the complications that developed in the month that followed the pharyngitis episode, comparing cases where a rapid antigen detection test was performed versus cases where it was not.

Results: out of 17 455 possible cases, we selected 851 that met the inclusion criteria (3 or 4 Centor criteria). There was a 42% decrease in antibiotic prescription in the episodes where rapid antigen detection testing was performed (absolute risk reduction: 42%; 95% confidence interval [95 CI]: 37 to 48; p < 0.001). When we compared management by paediatricians who had access to rapid testing and made use of it (4), compared to those that did not use it (6), the absolute risk reduction was 29% (95 CI: 24 to 34; < .001). Infectious complications developed in 12% of treated patients and 8% of untreated patients (relative risk: 1.49; 95 CI: 0.88 to 2.52; = .178). Penicillin V was prescribed significantly more frequently than amoxicillin in episodes in which a diagnostic test was performed (relative risk: 1.30; 95 CI: 1.10 to 1.55; = .004).

Conclusions: in everyday clinical practice, the use of a rapid antigen detection test in paediatric patients selected based on clinical criteria for streptococcal pharyngitis contributed significantly to the rational use of antibiotics.

Key words:
- Antibacterial agents
- Children
- Drug evaluation
- Pharyngitis
- Diagnostic reagent kits

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INTRODUCTION

When it comes to the management of paediatric pharyngitis in the primary care setting, most recent clinical practice guidelines recommend that antibiotherapy be restricted to confirmed cases of streptococcal pharyngitis. Although there are a few exceptions that recommend treatment based on the severity of symptoms whether an aetiological diagnosis has been made or not, all others propose the use of a rapid antigen detection test (RADT) for streptococcus or, should it not be available, traditional culture. This recommendation is usually made on the condition that the patient has met a minimum set of criteria suggestive of a streptococcal aetiology. Thus, the ultimate goal is to initiate antibiotherapy only when the clinical suspicion of streptococcal pharyngitis is confirmed by either RADT or culture.

No sign or symptom of streptococcal pharyngitis in isolation has a high enough positive likelihood ratio to achieve a satisfactory post test-probability. Consequently, clinical criteria can only be useful in determining which patients are eligible for diagnostic tests, so that they are not performed in all patients presenting with any sign or symptom of pharyngitis. The use of a minimum set of data has been proposed; these data are often grouped in clinical prediction rules, of which the most widely used and validated in the paediatric age group are the Centor criteria and Centor criteria modified by McIsaac.

Very few studies, however, have assessed the diagnostic yield of RADTs in preselected patients in everyday clinical practice. In 2009, Ayanruoh published a study of patients that visited the emergency department of a hospital in New York that showed that the introduction of rapid testing was associated with a reduction of approximately 50% in antibiotic prescription in pharyngitis cases. Another large population-based study in the United States that used data from the National Ambulatory Medical Care Survey (NAMCS) from 1995 to 2003 found a significant reduction in the proportion of antibiotic prescription associated to the use of diagnostic testing. This study found that in cases with diagnosis codes for pharyngitis, tonsillitis or streptococcal sore throat, antibiotics were prescribed in only 57% of tested children compared to 73% of untested children. With the exception of studies focused on diagnostic testing that evaluated different RADTs, few studies have been conducted in primary care settings to assess their actual impact after their introduction in everyday clinical practice. De la Flor estimated a reduction of 54.5% in the prescription of antibiotics in cases of suspected streptococcal pharyngitis when this test was used in the paediatric population of Barcelona.

The aim of this study was to review electronic health records in order to assess the actual usefulness of RADT in the everyday practice of primary care paediatrics, evaluating its impact on antibiotic use and complications occurring soon after the episode of pharyngitis, based on whether the patient had or not received treatment.
MATERIALS AND METHODS

The study focused on the paediatric population of the province of Zaragoza (Spain). We conducted a retrospective observational analytic cohort study of data collected from the electronic health records corresponding to a random sample of 10 primary care pediatrics caseloads. A civil servant that was not acquainted with the study used a random number list to select the paediatric populations (caseloads) assigned to 5 paediatric clinics with access to RADT as a diagnostic test in 2012 and 2013, and another 5 caseloads managed by paediatricians that did not have access to this test. Two caseloads corresponded to clinics in rural areas and eight to clinics in urban areas. Medical health records in the public health system of the autonomous community of Aragon in Spain (which includes the city of Zaragoza) are kept in an electronic database, so that information on the episodes of disease experienced by each patient can be accessed regardless of the public health setting where the patient was managed (primary care centre, hospital, emergency department...). This allows access to information for different episodes and even assessment of patient outcomes, so we were able to obtain data on the potential complications of the episodes under study.

We collected data from the 10 caseloads for the pharyngitis episodes recorded in 2012 and 2013 that met 3 or 4 Centor criteria. The Centor score\(^{15}\) can range from 0 to 4 based on the presence of the following criteria: fever > 38°C, tonsillar exudate, swollen and tender anterior cervical nodes and absence of cough. In the current regional primary care electronic health records system (OMI-AP\(^*\)), the diagnoses for each episode of disease are coded according to the International Classification of Primary Care (ICPC-2).\(^{20}\) We reviewed all cases with a relevant diagnosis managed by the paediatrician in charge of each selected caseload (streptococcal sore throat, acute tonsillitis, acute upper respiratory infection; ICPC-2 codes R72, R76 and R74, respectively). In the subsequent analysis, we included the episodes diagnosed with any of these codes that met 3 or 4 Centor criteria, managed by the paediatrician in charge of the caseload, and occurring in patients with no underlying disease or not under immunosuppressive therapy, factors that would require a different approach to the management of pharyngitis. We excluded episodes where there was a justifiable reason to not perform the diagnostic test (collection of a sample was not possible, recent antibiotic treatment or heart disease). We also retrieved diagnoses made in these patients in the month following the episode that could be indicative of an infectious complication due to lack of treatment or a complication resulting from treatment.

The primary variables were prescription of antibiotics or lack thereof, and the presence or absence of complications in the month following the onset of the episode. Secondary variables included sex, age, rural or urban setting, diagnostic test, presence or absence of each of the Centor criteria, Centor score and prescribed antibiotic.

The available RADT was the same in every clinic. It was an immunochromatographic assay in cassette format (Alere TestPack Strep A\(^*\)), with a sensitivity of 97.6% [95 CI: 93.1 to 99.5] and a specificity of 98.4% [95 CI: 95.9 to 99.6], as reported by the manufacturer), performed on suitable throat swab specimens. When culture was required, samples were submitted from primary care centres in the appropriate media and under appropriate conditions for performance of traditional culture in one of two possible hospitals (microbiology laboratories of the Hospital Universitario Miguel Servet and the Hospital Royo Villanova, Zaragoza, Spain). We summarised qualitative variables as percentages with their corresponding 95 CI, and quantitative variables using appropriate measures of central tendency and dispersion based on whether or not they followed a normal distribution. We used the Kruskal-Wallis test to check whether there were significant differences in median age between caseloads, as the age variable did not follow a normal distribution. We used the Kruskal-Wallis test to check whether there were significant differences in median age between caseloads, as the age variable did not follow a normal distribution. To analyse the use of antibiotics comparing episodes where a diagnostic test was used versus episodes where it was not, we
calculated the relative risk (RR) and the absolute risk reduction (ARR) with their 95 CIs. We also calculated the RR of immediate infectious complications (defined as those occurring within one month from diagnosis) potentially associated with the use or lack of use of antibiotherapy in treated and untreated patients.

This study was conducted in the framework of the project “Evaluation and Updating of the protocol for the management of paediatric acute pharyngitis in the Zaragoza II health district,” which was selected in 2014 for one of the grant programmes of the public health system of Aragon (Department of Health of Aragon, Spain) to support initiatives for improving health care quality (project No. 314). To participate in this programme, the project met the necessary ethical criteria (consent for retrospective electronic data collection, and anonymization of data to ensure the confidentiality of the patients and providers included in the reviewed caseloads). The Director of Primary Care of the Public Health System of Aragon also signed an express authorisation for the retrospective extraction of data from the electronic health records database.

RESULTS

After reviewing 17 455 episodes corresponding to the previously listed codes in the 10 caseloads, we found 851 episodes that met the criteria for inclusion in the analysis (Figure 1). The episodes contributed by each caseload ranged from 39 to 163. In one of the caseloads, the paediatrician in charge had access to the RADT but did not use it. In total, the clinics that used the RADT contributed 435 cases, and the clinics that did not contributed 416 (Table 1).

In the overall sample, no diagnostic test was performed in 471 cases (55.4%). In the subset of clinics where the test was available and used, a diagnostic test (RADT) was performed in 78% of episodes that met 3-4 Centor criteria, while in the clinics that did not have access or did not use the rapid test, culture was performed in 12.4% of episodes meeting the criteria. Of the total cases where a diagnostic test was performed (378), the results were positive for in 51.6%. Out of all cases where the results of the RADT were negative, a culture was subsequently performed for confirmation in only one third. Among the total cases with negative RADT results where culture was performed for confirmation, the results of culture were positive in 2 and negative in the remaining 52.

Figure 2 shows the age distribution of the included cases (non-normal distribution, Kolmogorov-Smirnov test: maximum deviation of 0.053; = .017). The median age was 6.38 years and the interquartile range 4.08 to 8.99 years. Cases occurred in patients aged 10 months to 15 years and 11 months. Forty-eight percent occurred in girls and 52% in boys.

Table 1 shows the main characteristics of the cases managed by each paediatrician. There were no statistically significant differences in age distribution between caseloads (Kruskal-Wallis test). The clinics

![Figure 1. Flow chart showing the selection of the episodes included in the analysis](image-url)
that did not have access to the RADT had access to alternative diagnostic tests, as was the case of paediatrician no. 9, who ordered a culture in half of the cases. The table also includes the percentage of cases in each clinic where a diagnostic test was performed, the percentage of cases where antibiotic therapy was prescribed, and the percentage of cases in which infectious complications were documented in the month that followed diagnosis.

Table 2 analyses the proportion of antibiotic prescription based on whether patients did or did not undergo diagnostic testing, expressed as the RR and ARR for each comparison. Overall, we found the greatest reduction in antibiotic prescription in episodes where the RADT had been used (RR for not using vs using the test: 1.79 [95 CI: 1.63 to 1.97]; < .000), which amounts to an absolute reduction of antibiotic prescription of 42% when the test is used compared to when it is not (95 CI: 37 to 48). The use of culture was also associated with a significant reduction in antibiotic use: ARR of 18% (95 CI: 6 to 29).

In an analysis that took into account the specific circumstances of each paediatrician, we compared the caseloads of clinics where the RADT was either unavailable or not used, and those of clinics where the RADT was available and also used (six and four caseloads, respectively). The percentage of cases where antibiotic therapy was prescribed was of 92% (95 CI: 90 to 95) compared to 63% in the latter (95 CI: 59 to 68); RR: 1.46 (95 CI: 1.35 to 1.58; < .000); ARR: 29% (95 CI: 24 to 34).

Of the total cases where the RADT was negative (160), 8 (5%) were treated with antibiotics. Of the total of cases where the culture was negative (22), 13 (59%) were treated with antibiotics, in most cases because empirical treatment was initiated while
awaiting the results, and not discontinued due to the long time elapsed until results became available. Adverse events were reported in 2% of the cases treated with antibiotics (most of them gastrointestinal).

Infectious complications in the month following the diagnosis that may have resulted from antibiotic therapy or else from lack of treatment were documented in 12% of cases treated with antibiotics (95 CI: 10 to 15) and 8% of untreated cases (95 CI: 4 to 12). The risk was greater in the treated group, although the difference was not statistically significant: RR of 1.49 (95 CI: 0.88 to 2.52; = .178).

Penicillin V potassium (PCN VK) and amoxicillin amounted to 93% of antibiotic prescriptions (42% and 51%, respectively). The use of a diagnostic test was associated with a higher probability of PCN VK prescription compared to amoxicillin (RR: 1.30; 95 CI: 1.10 to 1.55; = .004). An antibiotic that would be considered inappropriate (an unjustified alternative to PCN VK, amoxicillin or a macrolide) was prescribed in 5% of episodes where a diagnostic test was not performed compared to 3% of episodes where a RADT was performed: RR of 1.86 (95 CI: 0.72 to 4.79; = .271).

**Table 2. Comparison of antibiotic use based on the performance or lack thereof of diagnostic tests (culture or RADT)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Antibiotic prescription (95 CI)</th>
<th>RR of prescription (95 CI)</th>
<th>ARR (95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No test</td>
<td>95% (93 to 97)</td>
<td>1.22 (1.06 to 1.41; p &lt; 0.007)</td>
<td>18% (6 to 29)</td>
</tr>
<tr>
<td>Culture</td>
<td>78% (67 to 89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No test</td>
<td>95% (93 to 97)</td>
<td>1.79 (1.63 to 1.97; p &lt; 0.000)</td>
<td>42% (37 to 48)</td>
</tr>
<tr>
<td>RADT</td>
<td>53% (48 to 58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No test</td>
<td>95% (93 to 97)</td>
<td>1.67 (1.52 to 1.82; p &lt; 0.000)</td>
<td>39% (33 to 44)</td>
</tr>
<tr>
<td>Any test</td>
<td>57% (52 to 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>78% (67 to 89)</td>
<td>1.47 (1.24 to 1.75; p &lt; 0.000)</td>
<td>25% (12 to 37)</td>
</tr>
<tr>
<td>RADT</td>
<td>53% (48 to 58)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARR: absolute risk reduction; RR: relative risk; RADT: rapid antigen detection test for streptococcus.
DISCUSSION

Many studies have assessed the usefulness of RADTs in paediatrics clinics for the purpose of diagnosis. As a consequence, there is an increasing agreement among clinical practice guidelines in recommending their use in patients previously selected based on a minimum set of clinical criteria and advising that antibiotherapy be restricted to patients with positive results. However, few studies have assessed the actual usefulness of rapid testing in everyday clinical practice.

We know that when diagnostic tests are not used in paediatric cases of pharyngitis, there is a high probability of antibiotic prescription of up to 70-90%, a proportion that is unwarranted if we consider that the probability of a bacterial aetiology in this age group is approximately 35%. Rapid antigen detection tests are useful bedside tools that have allowed a more accurate diagnosis of this disease and proven effective to improve the therapeutic approach. Although they are limited in that they cannot differentiate between carriage and active disease (a limitation that also applies to traditional culture), it is estimated that the post-test probability of a positive result in a patient with clinical criteria suggestive of a streptococcal aetiology may be as high as 96%.

The few studies that have assessed the usefulness of rapid testing in children in clinical practice have reported significant reductions in antibiotic prescription. The study mentioned above by Ayanruoh, conducted in an emergency department, estimated a 50% reduction in prescription with the use of the test. Maltezou, in study conducted in children in Greece to validate the RADT, found a reduction of 44%. In Spain, no studies had been performed to assess the use of the test in everyday clinical practice: de la Flor estimated a reduction of 54.5% based on the results obtained with the test, but not on actual clinical practice. Contessotto estimated a reduction of 50% by comparing two different studies, and Regueras showed that in children with suspected streptococcal pharyngitis, use of rapid testing reduced unnecessary prescription by at least 29.5%. In a recent review on this subject that included two of the studies mentioned above, Cohen estimated a 30% reduction in the use of antibiotics associated with the use of the test.

In our series, the comparison of all episodes where RADT was used versus all episodes where testing was not performed found a 42% reduction in antibiotic prescription in the former, evincing a considerable difference compared to culture, as the reduction of antibiotic prescription in cases where only culture had been used was significantly lower (18%). However, a comparison of the actual figures in clinicians that used the test (prescription in 63% of episodes) versus those who did not (prescription in 92% of episodes) may be more illustrative of the status quo, showing a reduction in prescription with the use of the test of 29%. This percentage is close to the one found in the series published by Linder or the results summarised by Cohen, and may be due to the test having been performed in preselected patients that met 3 or 4 Centor criteria, in who the actual prevalence is higher. It is possible that the savings in antibiotic prescription would be greater if the test were applied to patients with fewer Centor criteria, but on the other hand the costs associated with testing would be higher, and it would be necessary to consider that the sensitivity is lower in patients meeting fewer than 3 criteria.

A recently published analysis of data on children managed in the emergency department of a hospital in Madrid suggests that the use of the test is essential to improve adherence to the recommendations of the main clinical guidelines. A relevant aspect of our review is that it allowed us to ascertain that the incidence of infectious complications in the days following diagnosis was not higher in untreated cases. The risk was actually lower in patients not treated with antibiotics compared to patients that received them (8% versus 12% of cases, respectively), although the difference was not statistically significant.

One of the strengths of the study, in our opinion, is that the use of data from medical records shows what is actually done in everyday clinical practice.
In this particular case, it also allowed us to assess the outcomes in each patient and even detect adverse events associated with treatment or subsequent infections, as our public health system has a unified medical records database, which reduces the risk of information and recall bias.

Some of the limitations of our study were those intrinsic to a retrospective review of medical records (in this case, electronic health records). Generally speaking, most of the important data were documented, but since a form specifically designed to document the clinical signs and symptoms was not used, there was a source of bias in the clinicians that entered the data in the records, as usually they record the manifestations that are present, but are less likely to specifically document manifestations that are absent. The health records system used in these clinics does not have a specific template for the documentation of clinical manifestations, which are entered as free text by each clinician, which may have led to detection bias.

**CONCLUSIONS**

Our study confirms that in everyday clinical practice in primary care, the use of the RADT for streptococcus is associated with a significant reduction in antibiotic prescription in paediatric cases of pharyngitis. This improvement in the appropriate management of streptococcal pharyngitis in the paediatric age group can reduce direct health care costs and prevent the development of antimicrobial resistance, especially in other bacteria that frequently colonise the upper respiratory tract of children and that are subjected to selective pressure with each antibiotic exposure. Furthermore, our data suggest that the lack of antibiotic treatment is not associated with an increase in the incidence of infectious complications in the first weeks after the episode.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare in relation to the preparation and publication of this article.

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**ABBREVIATIONS**

ARR: absolute risk reduction • CI: confidence interval • ICPC: International Classification of Primary Care • PCN VK: penicillin V potassium • RADT: rapid antigen detection test • RR: relative risk.

**REFERENCES**


