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Evaluation of a rapid antigen detection test in the diagnosis of streptococcal pharyngitis in children and its impact on antibiotic prescription

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***Objectives*: To study the performance of the Becton-Dickinson Link 2 Strep A Rapid Test, a rapid antigen detection test (RADT) for diagnosing streptococcal pharyngitis in children presenting to private offices and to the Pediatric Outpatient Clinic of a university hospital, in relation to clinical criteria (fever, tender anterior cervical lymph nodes, tonsillar exudate and absence of cough), and its impact on antibiotic prescription.**

***Methods*: Children were enrolled in Group A (enrolment by private-practice paediatricians; diagnosis by clinical picture only), Group B (enrolment by private-practice paediatricians; diagnosis by RADT and culture) or Group C (enrolment by hospital-affiliated paediatricians in the Pediatric Outpatient Clinic; diagnosis by RADT and culture).**

***Results*: During a 2 year period, 820 children were enrolled [369 (45%) in Group A, 270 (33%) in Group B and 181 (22%) in Group C]. Streptococcal pharyngitis was diagnosed by RADT and culture in 146 (32.4%) of the 451 tested children. The sensitivity, specificity and positive and negative predictive values of the RADT were 83.1%, 93.3%, 82.4% and 93.6%, respectively. A stepwise increase in the sensitivity of the RADT was noted among children with one, two, three or four clinical criteria (60.9% to 95.8%). Paediatricians without access to laboratory tests were more likely to prescribe antibiotics compared with paediatricians with access to tests (72.2% versus 28.2%, $P < 0.001$). Private-practice paediatricians prescribed antibiotics more frequently compared with hospital-affiliated paediatricians (55.7% versus 19.9%, $P < 0.001$).**

***Conclusions*: Our findings support screening of all children with pharyngitis for Centor criteria and subsequently performing an RADT to guide decision for antibiotic administration. Such a strategy has an important impact on limiting throat culture testing and is associated with reduced antibiotic prescription.**

Keywords: clinical criteria, RADT, streptococci

Introduction

Acute pharyngitis constitutes a frequent cause of visits and antibiotic prescribing in primary healthcare facilities. It has been estimated that in the USA alone more than seven million cases of acute pharyngitis are diagnosed by paediatricians annually.[1] *Streptococcus pyogenes* is the cause in only 15% to 30% of

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them, but antibiotics are prescribed in 55% to 75% of the cases.[2–5] Accurate diagnosis of streptococcal pharyngitis is necessary, because prompt antibiotic therapy is associated with faster subsidence of symptoms, prevention of early and late complications and reduced spread of the strain to others,[1–3,6] and it may be a useful tool to guide decisions for antibiotic prescribing.

On clinical grounds, streptococcal pharyngitis is strongly suggested by the presence of fever, tonsillar exudate, tender enlarged anterior cervical lymph nodes and absence of cough (Centor criteria).[7] However, due to the fact that these findings are non-specific and commonly found in cases of viral origin, even experienced physicians may accurately diagnose streptococcal pharyngitis based on the clinical findings alone in no more than 75% of the cases.[8,9] For more than 50 years, culture of a throat swab has been the standard method for diagnosing streptococcal pharyngitis.[1,8,10] Within the last two decades, rapid antigen detection tests (RADTs) have become commercially available for the detection of *S. pyogenes* using throat swabs. These tests offer the advantage of diagnosing streptococcal pharyngitis within a few minutes with an associated sensitivity of 70% to 85% and a specificity of more than 95%, using culture as the gold standard method.[10] Starting in 2000, the American Academy of Pediatrics (AAP) recommended the laboratory confirmation of cases with clinical suspicion of streptococcal pharyngitis.[11] Due to the relatively low sensitivity of RADTs, AAP recommends obtaining a follow-up throat culture in children with clinical findings compatible with streptococcal pharyngitis and a negative RADT, with the disadvantage of having a definite diagnosis 1–2 days later. In this case, either antibiotics are prescribed empirically and discontinued following a negative culture result, or treatment decisions are made when culture results become available. In the case of a positive RADT, the diagnosis is considered accurate and follow-up culture is not required.[11] Although the AAP recommendations have been published since 2000, there are only a few published studies investigating them in the management of children with clinical findings suggestive of streptococcal pharyngitis in everyday practice.[12–16]

The current study investigated two strategies in the management of children with clinical suspicion of streptococcal pharyngitis: a non-laboratory confirmation strategy using clinical criteria only and a strategy using an RADT and culture for diagnosis. It evaluated the impact of the two strategies on antibiotic prescribing and the performance and validity of the RADT in real time and in relation to clinical criteria. The study was prospectively conducted in private-practice offices and the Pediatric Outpatient Clinic of the University General Hospital ATTIKON in Athens, Greece.

Patients and methods

Study design and patients

In September 2005, 110 registered private-practice paediatricians working in South-West Attica, a region of the greater metropolitan area of Athens, were contacted by mail and invited to participate in the study. A total of 17 private-practice paediatricians accepted the invitation. In addition, seven hospital-affiliated paediatricians working at the Department of Pediatrics at University General Hospital ATTIKON (700 bed tertiary-care hospital), which is also located in South-West Attica and serves a population of approximately one million, agreed to participate in the study.

The study was prospectively conducted during 2 consecutive years (from 1 December 2005 through to 15 June 2006 and from 15 September 2006 through to 15 June 2007). Children aged 2–14 years attending the Pediatric Outpatient Clinic of the University General Hospital ATTIKON or the offices of the participating private-practice paediatricians with clinical evidence of pharyngitis including at least one of the following four criteria were eligible for the study: fever (>38.0°C), tonsillar exudate, tender enlarged anterior cervical lymph nodes and absence of cough. Children were excluded if they had received antibiotics within the previous week or were immunocompromised. At enrolment, patients were examined clinically, and their characteristics and clinical findings were recorded in an anonymous case report form [Figure S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

Private-practice and hospital-affiliated paediatricians were assigned into three groups and two different management strategies. Private-practice paediatricians were randomly divided into Group A (evaluation of children and decision to prescribe antibiotics by clinical criteria only, as in their usual everyday clinical practice) or Group B (application of the RADT in children with at least one clinical criterion and prescription of antibiotics only if positive; throat culture was also taken and if positive, but RADT-negative, prescription of antibiotics was done 48 h later). Hospital-affiliated paediatricians constituted Group C and managed children using the RADT/culture strategy (Figure 1).

In children enrolled from Group B and C paediatricians, following clinical examination, two throat swabs were vigorously rubbed over the posterior pharynx and tonsils. The first swab was tested through RADT by the paediatrician at his office or at the Pediatric Outpatient Clinic, whereas the second was transferred in liquid Stuart's transport medium within 24 h for culture at the Infectious Diseases Research Laboratory of the 4th Department of Internal Medicine, University General Hospital ATTIKON. Culture results were reported to paediatricians 2 days later by telephone. Group B and C paediatricians informed their patients about culture results and gave instructions regarding antibiotics, if required (modification or initiation of treatment). Paediatricians of all groups had a free

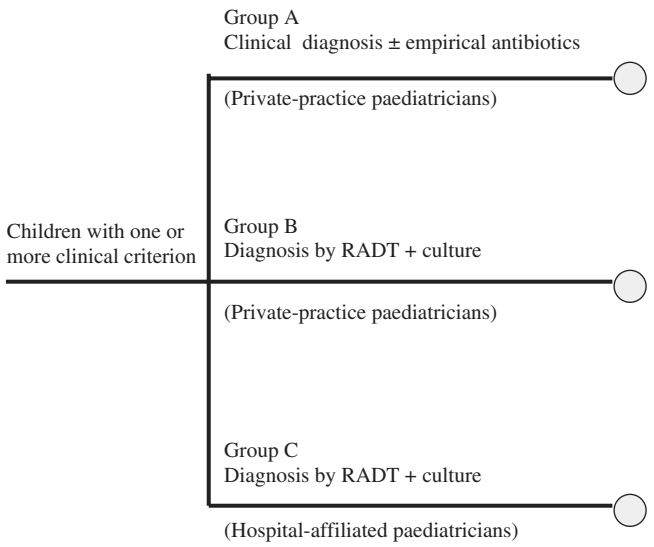

Figure 1. Distribution of children with pharyngitis per group of management.

choice in antibiotic type selection. Paediatricians of all groups called their patients ~3 weeks later for follow-up information (clinical course and complications, if any). The completed case report forms were sent to the Hellenic Center for Disease Control and Prevention, Athens, Greece for analysis. Informed consent was obtained from the parents or guardians of all children. The protocol was approved by the Ethics Committee of the University General Hospital ATTIKON and the Board of the Hellenic Center for Disease Control and Prevention.

Throat cultures

Throat cultures were inoculated in Columbia blood agar plates and examined at 24 and 48 h. *S. pyogenes* identification was confirmed by using 0.004 IU bacitracin discs (Becton Dickinson, Sparks, MD, USA) and a latex agglutination assay (Oxoid, Basingstoke, Hants, UK). Susceptibility testing was performed using the disc diffusion method according to the CLSI guidelines on Mueller–Hinton agar supplemented with 5% blood at 35°C in 5% CO_2.[17]

RADT

Based on sensitivity, specificity and cost data provided by the five companies that import RADTs in Greece, the Becton-Dickinson Link 2 Strep A Rapid Test was selected. Paediatricians of Groups B and C were trained in advance on the use of the test, in accordance with the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using SPSS 15 for Windows. All items were coded and scored, and the completed data were included in the analysis. The following parameters were determined: (i) prevalence of laboratory diagnosed streptococcal pharyngitis; (ii) sensitivity, specificity and positive and negative predictive values of the RADT using culture as the reference method; (iii) performance of the RADT in association with the number of clinical criteria; and (iv) impact of the RADT on antibiotic prescription. The χ^2 test was used between two nominal variables. One-way analysis of variance (ANOVA) was used to test for differences among two or more independent groups. P values of 0.05 or less were considered statistically significant.

Results

During the study period, 928 children were enrolled in the study: 474 during 2005–06 and 454 during 2006–07. Of them, 820 (88.4%) met the inclusion criteria (441 from 2005 to 2006 and 379 from 2006 to 2007), including 369 (45%) in Group A, 270 (33%) in Group B and 181 (22%) in Group C. Table 1 shows their characteristics.

Streptococcal pharyngitis was diagnosed in 123 (27.8%) of the 442 children tested by RADT and in 121 (27.4%) of the 441 children tested by culture. In total, streptococcal pharyngitis was laboratory-diagnosed in 146 (32.4%) of the 451 tested children (Groups B and C). Group B patients had more positive RADTs compared with Group C patients (31.7% versus 22.0%, respectively; $P = 0.026$) as well as throat swab cultures (28.8% versus 25.4%, respectively; $P = 0.438$). No statistically significant difference of laboratory-diagnosed streptococcal pharyngitis cases was found by comparing patients by age groups of 2–5 years old, 6–10 years old and 11–14 years old (29.8%, 38.25% and 24.67%, respectively; $P = 0.112$). The sensitivity, specificity and positive and negative predictive values of the RADT compared with culture as the gold standard were 83.1%, 93.3%, 82.4% and 93.6%, respectively, being statistically significant ($P < 0.001$). As shown in Table 2, a stepwise increase in the sensitivity of the RADT was noted among children with one, two, three or four clinical criteria. Table 3 shows antibiotic prescription per paediatrician group and accordingly managed patients. Paediatricians of Group A with no access to laboratory tests prescribed antibiotics more frequently compared with paediatricians of Groups B and C with access to tests, either considered together or separately (72.2% versus 28.2%, or 72.2% versus 33.7% and 19.8%, $P < 0.001$). Private-practice paediatricians of Groups A and B together prescribed antibiotics more frequently compared with hospital-affiliated paediatricians (55.7% versus 19.9%; $P < 0.001$), and this was also a significant event between private-practice paediatricians of Group B with access to diagnostic tests and hospital-based paediatricians (33.7% versus 19.8%; $P < 0.01$). Similarly, there were some differences in relation to the type of antibiotic prescribed between private-practice and hospital-affiliated paediatricians, as well as between paediatricians with access or not to laboratory

Table 1. Characteristics per group of patients

Characteristic	Group A ($N = 369$), n (%)	Group B ($N = 270$), n (%)	Group C ($N = 181$), n (%)	Total ($N = 820$), n (%)	P value[a]
Male	184 (49.9)	124 (46.1)	84 (46.7)	392 (47.9)	0.597
Mean age ± SD	7.71 ± 3.17	6.86 ± 3.27	6.69 ± 3.35	7.20 ± 3.27	<0.001
Fever	330 (89.4)	244 (90.4)	156 (86.2)	730 (89.0)	0.358
Tonsillar exudate	140 (37.9)	88 (32.6)	81 (44.8)	309 (37.7)	0.033
Tender cervical lymph nodes	139 (37.7)	120 (44.4)	84 (46.4)	343 (41.8)	0.084
Absence of cough	288 (78.0)	150 (55.6)	102 (56.4)	540 (65.9)	<0.001
Conjunctivitis	20 (5.4)	5 (1.9)	12 (6.6)	37 (4.5)	0.03
Rash	22 (6.0)	14 (5.2)	6 (3.3)	42 (5.1)	0.416
Enanthema	204 (55.3)	74 (27.4)	46 (25.4)	324 (39.5)	<0.001
Pharyngeal pain	341 (92.4)	231 (85.6)	139 (76.8)	711 (86.7)	<0.001
Rhinorrhoea	78 (21.1)	89 (33.0)	52 (28.7)	219 (26.7)	0.003

[a]One-way ANOVA was used to test for differences between groups.

Table 2. Performance of the RADT per number of clinical criteria

No. of criteria	Total ($N = 432$[a]), *n* (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
One	118 (27.3)	60.9	96.8	82.4	91.1
Two	136 (31.5)	80.6	92.0	78.4	92.9
Three	118 (27.3)	91.4	94.0	86.5	96.3
Four	60 (13.9)	95.8	86.1	82.1	96.9

RADT, rapid antigen detection test; PPV, positive predictive value; NPV, negative predictive value.
[a]Number of patients with both RADT and culture performed.

Table 3. Prescription of antibiotics per paediatrician group

	n (%)		
Antibiotic category	Group A	Group B	Group C
Penicillin	183 (70.4)	60 (65.9)	27 (75.0)
Cephalosporin	36 (13.8)	5 (5.5)**	7 (19.4)**
Macrolide	41 (15.8)	26 (28.6)***	2 (5.6)***
Total (% of total patients)*	260 (72.2)	91 (33.7)	36 (19.8)

*$P = 0.004$.
**$P < 0.05$.
***$P < 0.01$.

tests. The antibiotics most commonly used were penicillin and amoxicillin followed by macrolides and cephalosporins (cefprozil, cefaclor and cefuroxime–axetil). Penicillin and amoxicillin were the most often prescribed antibiotics by all with no differences (66% to 75% of cases). Private-practice paediatricians (Groups A and B) prescribed significantly more macrolides compared with hospital-based paediatricians who preferred cephalosporins as the second choice. A stepwise increase in the prescription of antibiotics was noted among patients with one, two, three or four clinical criteria (16.1%, 45.4%, 63.5% and 68.7%, respectively; $P < 0.001$).

During the study period, allergic rash was recorded in one child treated with a cephalosporin; no other antibiotic-related adverse effect was noted. Overall, no streptococcal pharyngitis-related complications occurred.

Among the 121 throat swabs found positive for *S. pyogenes* by culture, 107 were available for susceptibility testing. Susceptibility testing showed 36.5% resistance to macrolides, whereas all isolates were susceptible to penicillins and cephalosporins.

Discussion

Greece is the leading country in Europe with regard to antibiotic consumption in ambulatory care (www.esac.ua.ac.be), exhibiting also the greatest seasonal variations. Consumption is highest during winter, indicating the overconsumption of antibiotics for upper respiratory illnesses. Macrolides, cephalosporins and broad-spectrum penicillins are the drugs mostly prescribed, with macrolides being the most consumed. Worldwide, efforts are being made to rationalize antibiotic use in upper respiratory tract infections and to reduce unnecessary antibiotic consumption. The target is the availability of reliable clinical scores and better diagnostic tools that can guide prescribing physicians to decide about the 15% to 30% of the bacterial pharyngitis cases that really need antibiotics.[5,18] The current study tried to investigate the contribution of RADT in such an effort, applied to a paediatric population, in a country where antibiotics are massively used and resistance rates are high.

Diagnostic tests and clinical criteria should be validated within the population and the setting where they will be employed before being recommended and introduced into everyday practice.[19] In addition, guidelines established at the local level may facilitate acceptance by physicians, and thus affect their prescription habits. In this context, the use of an RADT and of clinical criteria for diagnosing paediatric streptococcal pharyngitis in private-practice offices and in the Pediatric Outpatient Clinic of a University Hospital in South-West Attica was assessed.

Approximately one-third of the children with at least one Centor criterion tested positive for *S. pyogenes*, a prevalence comparable to previous reports.[4,5,14,20–22] The prevalence of streptococcal disease was also directly associated with the number of Centor criteria. McIsaac *et al.*[4,5] have also developed a score system (McIsaac score) for application in a mixed population of adults and children, giving points ranging from 1 to a maximum of 4 to symptoms such as fever $>38.0^{\circ}$C, absence of cough, tender anterior cervical lymph nodes, tonsillar swelling or exudate and age <15 years. Evaluation of this score system in real practice showed a stepwise increase in the prevalence of culture-proved streptococcal pharyngitis, from 0 (1%) to ≥ 4 points (51%).[4]

In our study, the overall sensitivity and specificity of the RADT when employed by paediatricians under office conditions was within the levels reported by others,[12–14,16,23,24] and, although less sensitive than culture, RADT is a useful and reliable diagnostic tool. The fact that throat swabs collected from hospital-affiliated paediatricians were positive by RADT less frequently ($P = 0.026$) compared with those collected from private-practice paediatricians may be attributed either to prevalence differences in the tested population or to improper collection of specimens due to the heavy work load encountered in the Outpatient Clinics. Regardless of the cause, these differences appear to have an impact on the performance of the RADT, as shown by the fluctuations in sensitivity and specificity depending on the personnel performing the test. Similar variations by setting and personnel have also been reported by others.[20,25,26]

Equally important, sensitivity of the RADT was directly associated with the clinical likelihood for streptococcal

pharyngitis, reflecting the association between prevalence of streptococcal disease and Centor criteria. Based on similar findings from a recent study, Edmonton and Farwell[27] propose the selective use of RADTs and back-up cultures, instead of the non-selective approach of the AAP recommendations.[11] In the same study, the authors recommend avoidance of testing children who lack clinical features of streptococcal pharyngitis, in order to preserve the overall RADT sensitivity.[27] A strategy using an RADT without back-up cultures has also been proposed as a cost-effective strategy by others.[23,28] Based on the results of our study, RADT testing is justifiable for all children with at least one clinical criterion. Children presenting with one or two clinical criteria should also be tested through throat swab cultures, following a negative RADT due to the low sensitivity of RADT in this group of patients, as shown in Table 2. However, in contrast to the AAP non-selective approach,[11] in children with three or four clinical criteria, diagnosis may rely on RADT only. Thus, our findings support screening of all paediatric pharyngitis cases for Centor criteria and subsequently performing an RADT in all children with at least one criterion, whereas cultures should be selectively performed in children with two or less clinical criteria.

In our population, diagnosis of streptococcal pharyngitis using clinical criteria only led to high rates of antibiotic prescription among children managed empirically (72.2%). Antibiotic prescription was reduced by 61% using the RADT compared with empirical management of patients. Similarly, McIsaac *et al*.[23] reported a 45% reduction in antibiotic prescription in adults using an RADT compared with empirical treatment. More specifically in our study, private-practice paediatricians using the diagnostic tests used 50% less antibiotics than those deciding on clinical grounds; this difference was higher in hospital-affiliated paediatricians and was still significant when both private-practice and hospital-based paediatricians used diagnostic tests. This could probably be attributed to better adherence of hospital paediatricians to guidelines and to less pressure on them for antibiotic use by parents. It is becoming evident that laboratory confirmation of paediatric streptococcal pharyngitis should be requested in order to avoid unnecessary prescriptions and should be valued as a tool to reduce antibiotic prescribing in upper respiratory infections.

Hospital-affiliated compared with private-practice physicians use significantly less macrolides, probably due to better knowledge of current resistance rates. Given the current high prevalence of macrolide resistance of *S. pyogenes* in Greek children,[29–31] as also shown in this study (36.6%), macrolides should probably not be used as empirical therapy for streptococcal pharyngitis. Penicillins remain the drug of choice with cephalosporins used as an alternative, but not preferred because of their broad spectrum. Fortunately, in this study, penicillins were the drug of choice in 66% to 76%, but hospital-affiliated and private-practice paediatricians deciding empirically showed a predilection for cephalosporins as an alternative choice. Antibiotic choice was up to each paediatrician in the study in order to simulate usual clinical practice, and we can offer no explanation for the differences recorded between groups concerning the second-choice antibiotic.

Our data indicate that antibiotic policies including provision of guidelines, offer of office-based rapid diagnostic tools, continuous resistance surveillance and educative interventions focusing at the primary healthcare level should be promptly implemented.

In conclusion, our study supports a new approach for the management of pharyngitis in the paediatric population, taking into account the clinical likelihood for streptococcal disease and the application of a targeted rapid diagnostic test. By screening all children with pharyngitis for the presence of the Centor criteria and subsequently performing an RADT, such a strategy has an important impact on limiting throat culture testing and unnecessary antibiotic prescription.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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