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ORIGINAL PAPER

Diagnosis and management of acute pharyngitis in a paediatric population: a cost–effectiveness analysis

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Abstract Acute pharyngitis is one of the most frequent causes of primary care physician visits; however, there is no agreement about which is the best strategy to diagnose and manage acute pharyngitis in children. The aim of the current study was to evaluate the cost–effectiveness of the recommended strategies to diagnose and manage acute pharyngitis in a paediatric population. A decision tree analysis was performed to compare the following six strategies: "treat all", "clinical scoring", "rapid test", "culture", "rapid test + culture" and "clinical scoring + rapid test". The cost data came from the Spanish National Health Service sources. Cost–effectiveness was calculated from the payer's perspective. Effectiveness was measured as the proportion of patients cured without complications from the disease and did not have any reaction to penicillin therapy; a sensitivity analysis was performed. The findings revealed that the "clinical scoring + rapid test" strategy is the most cost-effective, with a cost–effectiveness ratio of 50.72 €. This strategy dominated all others except "culture", which was the most effective but also the most costly. The sensitivity analysis showed that "rapid test" became the most cost-effective strategy when the clinical scoring sensitivity was <91% and its specificity was ≤9%. In conclusion, the use of a clinical scoring system to triage the diagnoses and performing a rapid antigen test for those with a high score is the most cost-effective strategy for the diagnosis and management of acute pharyngitis in children. When the clinical scoring system has a low diagnostic accuracy, testing all patients with rapid test becomes the most cost-effective strategy.

Keywords Acute pharyngitis · Costs and cost analysis · Group A streptococcus · Rapid diagnostic tests · Streptococcal pharyngitis

Abbreviations

AP	Acute pharyngitis
GABHS	Group A beta-haemolytic streptococcus

Introduction

Acute pharyngitis (AP) is one of the most common causes for primary care physician visits, accounting for 20% of the visits in the paediatric population in Spain [5]. The majority of children presenting with AP have symptoms attributable to a viral infection, although many of them are infected with group A beta-haemolytic streptococcus (GABHS), which is the most important bacterium causing pharyngitis [18]. Spanish studies of GABHS prevalence report a range from 10% to 45% of AP cases [9, 14, 25, 28, 32].

GABHS is the only common form of AP for which antibiotic therapy is indicated [2, 5], but according to Spanish studies, a total of 80–90% of Spanish children with AP are being treated with antibiotics [4, 26]. The justification for treating GABHS pharyngitis among children is primarily based on trying to avoid the complications associated with GABHS, including rheumatic fever and suppurative complications [15, 29]. Also, antibiotic therapy

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reduces the rate of transmission and shortens the duration of symptoms [11].

Although penicillin therapy is accepted as the first line in AP treatment, it produces adverse reactions including anaphylaxis and death [2, 15] and it also has the potential of contributing to the emergence of drug-resistant bacterial strains [17]. Therefore, penicillin should not be prescribed indiscriminately.

Many strategies for the management of paediatric AP have been identified [27]. Treatment without testing of all patients who consult with a sore throat has the advantage that any GABHS pharyngitis case that is presented to primary care physicians is treated. However, it has the disadvantage that it unnecessarily treats a high number of patients with AP who do not have GABHS pharyngitis.

The use of a clinical scoring system based on clinical history and physical examination only, to triage the diagnosis, is a common practice in Spain [10, 26]. It saves testing costs but it has a low diagnostic specificity for streptococcal pharyngitis, which results in overdiagnosis with unnecessary prescribing of antimicrobial drugs [22, 32]. To date, some authors recommend using clinical scoring as a tool to increase sensitivity of the rapid antigen test or the culture [12, 30].

Throat culture is considered the standard method for establishing the diagnosis of paediatric GABHS pharyngitis [2, 15]. Performing a throat culture for all patients has the advantage of missing only a few cases of GABHS pharyngitis, but delays the onset of antibiotic treatment for at least 2 days.

Performing a rapid antigen test for the diagnosis of all children with AP has the advantage of identifying nearly all GABHS pharyngitis cases and allows for rapid antibiotic treatment. However, a few patients are missed, and they face the risk of the disease going untreated. Some institutions therefore recommend that the negative results be verified with a throat culture [2, 15].

There is no agreement about which is the best strategy to manage paediatric AP, and there are important issues to be considered when the different strategies proposed are assessed (complications of pharyngitis not optimally treated, over treatment and adverse effects of antibiotics, applications context, costs).

We considered these issues adapted to our context. In the Spanish healthcare services, clinical scoring systems are often used to diagnose paediatric AP, treating those with a high score with antibiotics. However, previous cost–effectiveness analysis did not consider this strategy. Our study is the first to include this strategy to diagnose and manage paediatric AP.

Medical decision analysis may be useful to facilitate making complex treatment choices amid diagnostic uncertainty and to demonstrate efficiency. For this reason, in order to examine this issue in the Spanish healthcare system, we performed a cost–effectiveness analysis to determine which of the most commonly recommended strategies for the diagnosis and management of AP has the best cost–effectiveness relationship for the paediatric population in Spain, and if this relationship is modified by changes in GABHS prevalence, oral penicillin effectiveness and clinical scoring accuracy.

Methods

Literature search

The literature was reviewed to identify the most widely recommended strategies available to manage paediatric AP and the probability values needed to feed the decision analysis model. We identified publications from searches of Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database and NHS Economic Evaluation Database (from inception to February 2010), using the following MeSH terms: pharyngitis, costs and cost analysis; and search phrases: streptococcal pharyngitis, acute pharyngitis, sore throat, pharyngitis microbiological test, rapid diagnostic test, cost–effectiveness, cost–utility and decision analysis. We selected original studies, reviews, economic evaluations and clinical practice guidelines. Additional references were manually retrieved from the bibliography of the reviewed articles.

Decision analysis model

We constructed a decision model to estimate the short-term cost and cost–effectiveness associated with the following six strategies (Fig. 1):

1. Treat all. Treatment of all patients with antibiotics without testing.
2. Clinical scoring. Use of a clinical scoring system to triage the diagnosis and treat those with a high score with antibiotics.
3. Rapid test. Test all patients with a rapid antigen test and treat those with positive results with antibiotics.
4. Culture. Test all patients with a throat culture and treat those with positive results with antibiotics.
5. Rapid test + culture. Test all patients with a rapid antigen test, treat those with positive results, perform a culture for those with negative test results and treat those with positive results with antibiotics.
6. Clinical scoring + rapid test. Use a clinical scoring system to triage the diagnosis, ignore those with a low score, perform a rapid antigen test for those with a high score and treat those with positive test results with antibiotics.

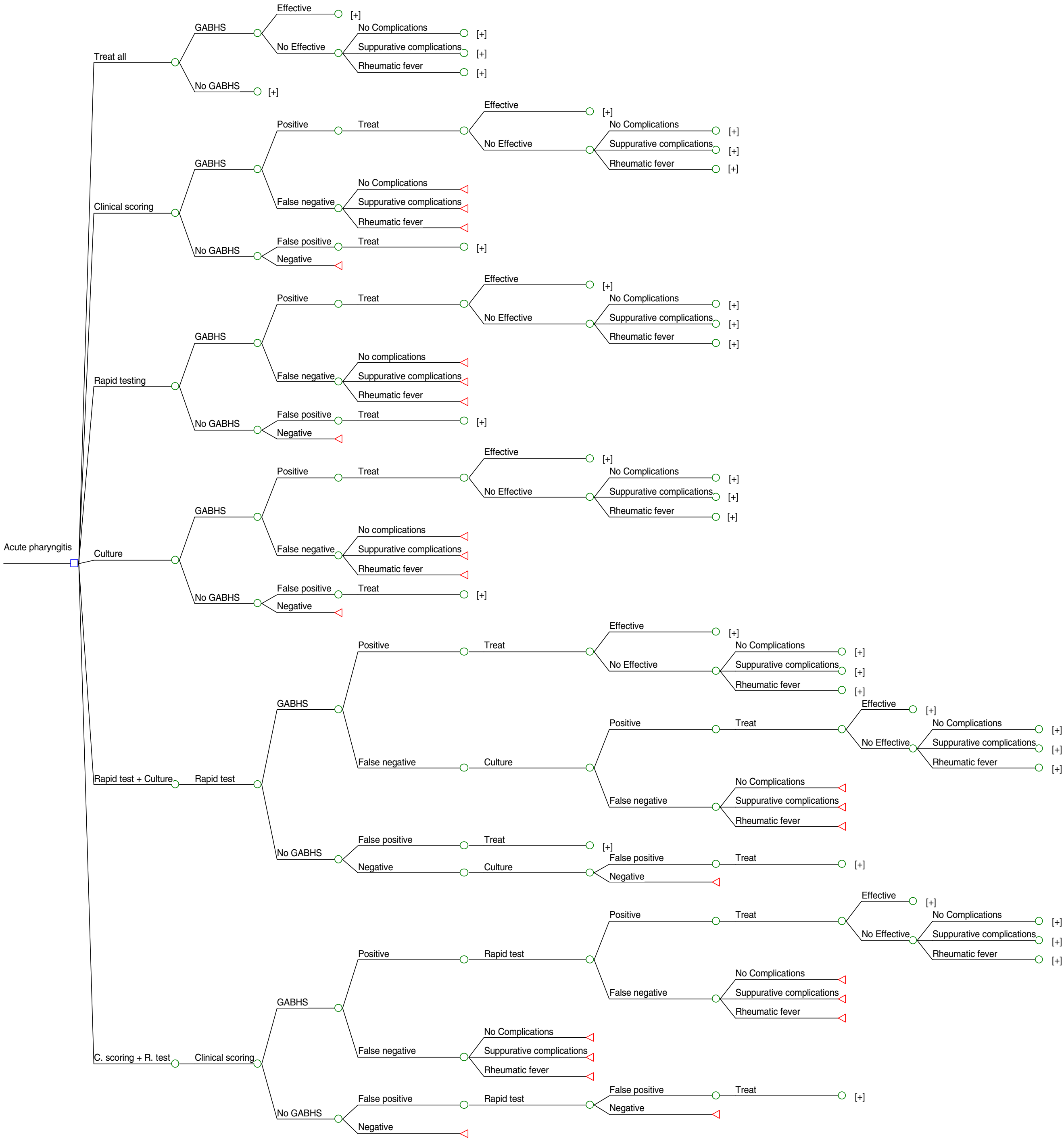

Fig. 1 Decision tree

The terminal branches of the decision tree that included antimicrobial therapy were extended to include the possible adverse reactions to penicillin (Fig. 2). Although previous decision analyses included the strategy of neither testing nor treating any of the patients [13, 31, 33], we did not include it because the treatment is recommended in Spain to

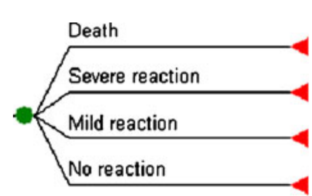

Fig. 2 Terminal branch of the decision tree

prevent the complications associated with GABHS infection in children.

Perspective

We calculated cost–effectiveness from the payer's perspective, considering the costs incurred by the Spanish National Health Service in implementing each of the strategies analysed.

Population

Patients between the ages of 2 and 14 years who consult with a primary care physician due to AP symptoms. We considered a hypothetical cohort of four million children, based on estimates of the number of paediatric consultations for sore throat that occur annually in the Spanish primary care centers [5].

Probabilities

Probability values used in the baseline analysis are summarized in Table 1. Regarding GABHS prevalence, we used 25% in the baseline analysis because GABHS prevalence that we found in Spanish epidemiological paediatric studies ranges from 10% to 45% [9, 14, 25, 28, 32]. Nonetheless, we considered both ranges in the sensitivity analysis.

The modified Centor score was the clinical scoring system considered in the model [24]. This system scores one point for each of the following five criteria: temperature >38°C, absence of cough, swollen or tender anterior cervical nodes, tonsillar swelling or exudates and an age range of 3–14 years. We considered a score of ≥3 points as high and <3 as low.

Table 1 Probabilities variables used in cost–effectiveness analysis

Variable	Probability
Prevalence of GABHS	0.25
Clinical scoring≥3 sensitivity	0.94
Clinical scoring≥3 specificity	0.11
Rapid test sensitivity	0.90
Rapid test specificity	0.78
Culture sensitivity	0.95
Culture specificity	0.99
Death from Penicillin allergy	0.00001
Severe allergic reaction to Penicillin	0.005
Mild allergic reaction to Penicillin	0.09499
Effective treatment	0.80
Suppurative complications	0.03
Rheumatic fever	0.0003

The rapid diagnostic tests considered were those based on optical immunoassay techniques because of their availability in Spanish healthcare centers. The mean sensitivity and specificity values of both the rapid test and the clinical scoring were taken from a recent study performed on paediatric patients in two Spanish primary care centers [14]. In addition, we included a range of values reported by other Spanish studies for the sensitivity analysis [9, 28].

In the model, we assumed oral penicillin as the mode of treatment because of its low cost and proven effectiveness in the reduction of complications attributable to GABHS [2, 5]. The complications risks, treatment effectiveness and penicillin reaction risks were drawn from clinical studies conducted in other countries [13, 33] because they were not identified in the Spanish literature.

Costs

We included direct medical costs associated with testing, therapy and care of complications (Table 2). The cost of the rapid test was facilitated by the Microbiology Department of the "La Paz" University Hospital, a third level hospital of the Spanish National Health Service. The sale cost for a total dose of the oral penicillin V in Spain was 10.36 € [1], which we reduced to 40% because it must be paid by the patients. As a consequence, the total cost of oral penicillin V that we applied was 6.22 €.

The costs of primary care physician visits were taken from the official costs of public services and activities of health centers of the Madrid community [7]. We included a second visit to report results and prescribe appropriate treatment in all options that included the completion of culture. In these options, we also took into account an additional scenario, which replaced a second visit to report negative results by telephone contact. We assumed that the other options required only one visit to the physician because the "rapid test" would be performed immediately

Table 2 Cost variables used in cost–effectiveness analysis

Variable	Cost (€)
Visit (general practitioner)	37.00
Phone call	2.70
Rapid test	2.67
Culture	5.43
Penicillin (oral)	6.22
Azitromicin	7.51
Severe allergic reaction	1,249.58
Mild allergic reaction	44.51
Suppurative complications	1,373.16
Rheumatic fever	2,468.41

and the results made available rapidly enough to permit treatment at the initial visit.

The cost of suppurative complications, rheumatic fever and severe allergic reactions were taken from the provision rates of the Valencia Community Healthcare Service according to Diagnosis Related Groups to which they belong: 70, 137 and 451, respectively [8]. The mild allergic reaction cost included that of additional visits to primary care physicians and the charge for azitromicin.

Cost–effectiveness analysis

Effectiveness was measured as the proportion of patients cured without complications from the disease or from any adverse reaction to treatment with Penicillin. We calculated cost, effectiveness, the cost–effectiveness ratio of each alternative and the incremental cost–effectiveness ratio between the dominant alternatives. The effectiveness and cost of each strategy were also expressed per four million children annually (annual cost of disease).

Sensitivity analysis

We performed one-way sensitivity analysis to assess the impact of changes in assumptions for the following probabilities of the model: GABHS prevalence (0.10–0.45) and oral penicillin effectiveness (0.70–0.90). We also performed a two-way sensitivity analysis to assess the impact that changes in sensitivity (0.86–0.98) and specificity (0.06–0.17) values of clinical scoring could have over the cost–effectiveness ratio. The analyses were performed using the decision analysis software TreeAge PRO 2009™.

Results

The individual and the annual population cost and effectiveness, as well as the cost–effectiveness ratio associated with each strategy, are given in Table 3. The most cost-effective strategy was the “clinical scoring + rapid test”, which dominated to the other strategies except “culture” (Fig. 3). Moving from the “clinical scoring + rapid test” strategy to the “culture” strategy would have added an additional cost of 3,110 € per patient cured, without presenting complications from GABHS or any adverse reaction to penicillin (incremental cost–effectiveness ratio). The health benefits of each strategy in preventing suppurative complications and rheumatic fever, the number of unnecessary treatments and the number of allergic reactions including death resulting from each treatment strategy are given in Table 4.

The “treat all” strategy achieved the lowest rates of complications for GABHS. This option, however, is problematic from another perspective: reactions to treatment, including death, are unacceptably high. The “treat all” strategy resulted in 284,970 mild allergic reactions, 15,000 severe allergic reactions and 30 deaths among the three million patients who did not have pharyngitis attributable to GABHS and were therefore treated unnecessarily. Thus, the “treat all” strategy was the least effective. The “clinical scoring” strategy produced the second largest number of allergic reactions, including deaths, and a high number of patients treated unnecessarily.

The “rapid test” strategy resulted in an important reduction of unnecessary treatments. The number of allergic reactions to treatment was four times lower than for the “treat all” strategy, and this strategy was also the second least costly. The “culture” strategy was the most costly in the management of GABHS pharyngitis, at 344.1 million € for the study population. The “rapid test + culture” strategy was the second most costly and the third least effective. The numbers of allergic reactions were slightly higher than for the rapid test strategy. When the second visit to report negative results was replaced by telephone contact, the “culture” and “rapid test + culture” strategies show a cost–effectiveness ratio of 62.44 € and 57.36 €, respectively. The incremental cost–effectiveness ratio was reduced from 3,110 € to 1,003 €.

Table 3 Cost, effectiveness and cost–effectiveness ratios of base case analysis

Strategy	Individual cost (€)	Effectiveness	Cost[a] (€)	Effectiveness[a, b]	C/E
Treat all	55.79	0.899	223,170,684	3,594,546	62.09
Clinical scoring	54.67	0.908	218,672,177	3,632,055	60.21
Rapid test	49.12	0.959	196,467,502	3,836,061	51.22
Culture	86.04	0.974	344,146,464	3,895,304	88.35
Rapid test + culture	74.70	0.957	298,786,412	3,826,582	78.08
Clinical scoring + rapid test	48.78	0.962	195,124,106	3,847,380	50.72

[a]Per four million children visiting for acute pharyngitis annually

[b]Number of patients cured without complications and did not have adverse reaction to penicillin therapy

C/E cost–effectiveness ratio

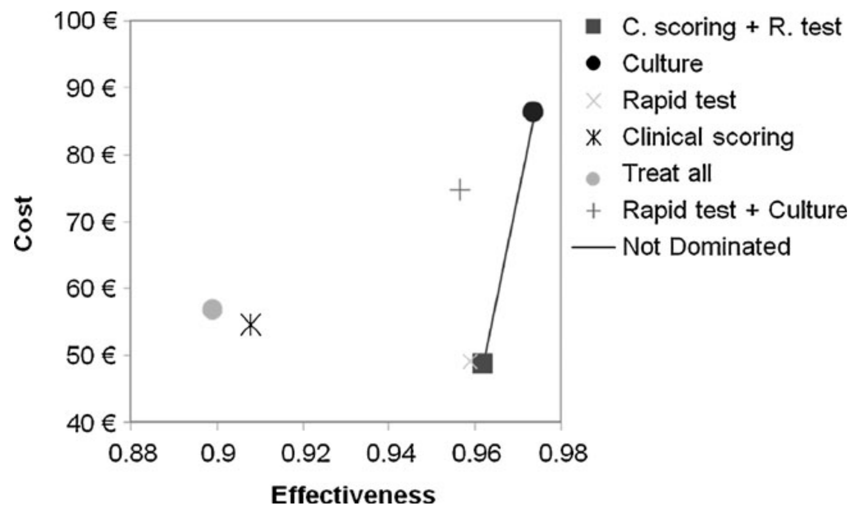

Fig. 3 Cost and effectiveness of the six strategies analysed

Sensitivity analysis

Changes in cost–effectiveness ratios when GABHS prevalence varies are noted in Fig. 4. The cost of all strategies became higher when GABHS prevalence increased because of higher rates of treatment and secondary complications. However, the cost–effectiveness ranking of the six strategies was the same when GABHS prevalence changed and did not change when the oral penicillin therapy effectiveness varied. Changes in sensitivity and specificity values for clinical scoring had an impact on cost–effectiveness ranking in such a way that the "rapid test" strategy would become the most cost-effective strategy if the clinical scoring of sensitivity and specificity would have been <91% and ≤9%, respectively (Fig. 5).

Discussion

This analysis sought to compare six diagnostic and therapeutic strategies in the management of AP to determine the most cost-effective method for the diagnoses and treatment of endemic GASBH pharyngitis in a paediatric population in Spain. The "clinical scoring + rapid test" strategy was the most cost-effective of the six strategies analysed. This relationship held up under all conditions studied in the sensitivity analyses except one: when the clinical scoring sensitivity was <91% and its specificity was ≤9%, the "rapid test" strategy became the most cost-effective of the strategies studied. Using a clinical scoring system to identify patients to be tested is one of the strategies currently recommended by primary

Table 4 Complications of GABHS, treatment unnecessary and adverse reactions to penicillin therapy[a]

Strategy	Complications occurring		Treatment unnecessary	Allergic reactions[b]		Deaths
Treat all	SC	6,000	3,000,000	Severe	20,000 (15,000)	40 (30)
	RF	60		Mild	379,960 (284,970)	
Clinical scoring	SC	7,440	2,670,000	Severe	18,050 (13,350)	36 (27)
	RF	74		Mild	342,914 (253,623)	
Rapid test	SC	8,400	660,000	Severe	7,800 (3,300)	16 (7)
	RF	84		Mild	148,184 (62,693)	
Culture	SC	7,200	30,000	Severe	4,900 (150)	10 (0)
	RF	72		Mild	93,090 (2,850)	
Rapid test + culture	SC	6,120	683,400	Severe	8,392 (3,417)	17 (7)
	RF	61		Mild	159,431 (64,916)	
Clinical scoring + rapid test	SC	9,696	587,400	Severe	7,167 (2,937)	14 (6)
	RF	97		Mild	136,159 (55,597)	

SC suppurative complications, *RF* rheumatic fever

[a] Per four million children visiting for acute pharyngitis annually

[b] Number in parentheses denotes the number of allergic reactions in patients without pharyngitis due to GABHS and therefore treated inappropriately

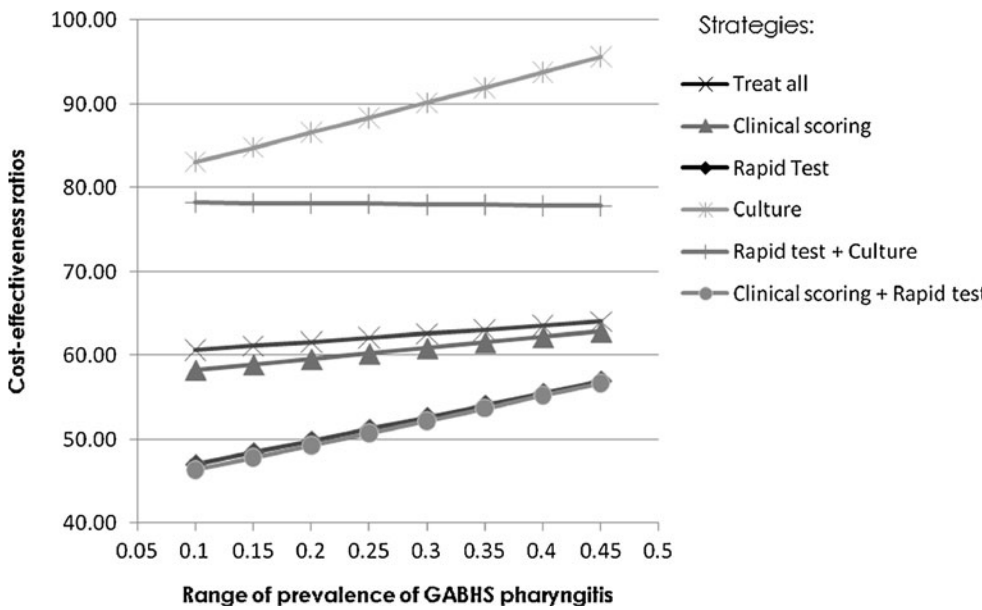

Fig. 4 Sensitivity analysis of the prevalence of GABHS pharyngitis

care physicians in Spain [20]. In addition, this strategy reported a lower number of patients treated unnecessarily and a lower number of allergic reactions to penicillin. Recent studies recommend this strategy, and note that it has an important impact in reducing antibiotic prescription [21, 30].

Using only a clinical scoring system to triage the diagnosis as well as treating those with a high score with antibiotics is the second least effective strategy. Indeed, this strategy may be generating a greater number of adverse reactions and a high number of patients treated unnecessarily. This strategy has not been included in previous decision analyses.

Treating all patients with antibiotics without testing is the least effective strategy. In the studies of Lieu et al. and Webb, this was actually the most effective strategy because both studies considered as the outcome only the prevention of streptococcal complications [19, 34]. The same authors noted that this strategy was associated with a much higher rate of allergic reactions than any of the other strategies studied. Therefore, they did not recommend it. In addition, this strategy may also lead to an increase in inappropriate treatment.

According to our results, testing all patients with a rapid antigen test and then treating those with positive test results with antibiotics was the second most cost-effective strategy. The use of this strategy has been associated with a decrease in inappropriate prescription of antibiotics [3, 9]. Ehrlich et al. noted this strategy as the most cost-effective method of reducing the incidence of rheumatic heart disease from

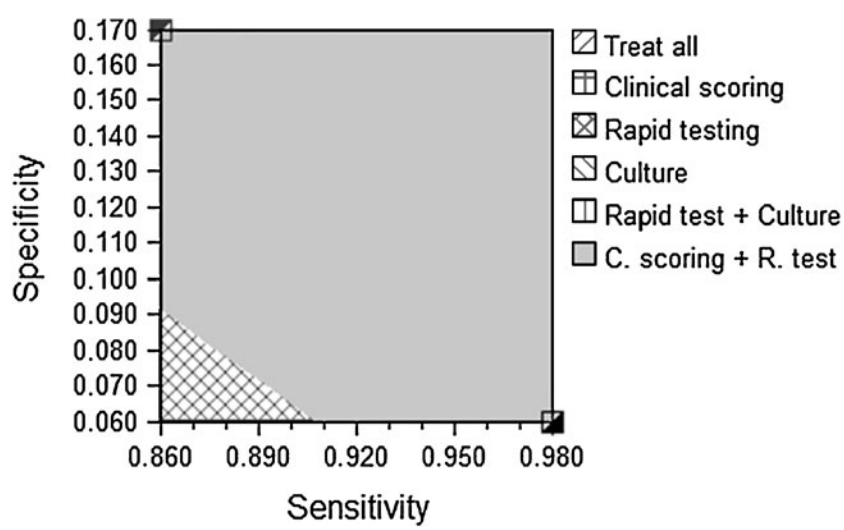

Fig. 5 Two-way sensitivity analysis of sensitivity and specificity of clinical scoring

GABHS infection in a paediatric population, although his model did not include the “clinical scoring + rapid test” strategy [13].

Testing all patients with a throat culture and then treating those with positive results with antibiotics were more effective, but also noticeably more costly than the “clinical scoring + rapid test” strategy. These results hold even if the visits are replaced by phone calls. This strategy, which was called “culture”, obtained the best cost–effectiveness relationship in the study performed by Tsevat et al., but with a different setting from ours [31]. The “culture” strategy, because it delays the onset of penicillin therapy for at least 2 days, could increase the rate of transmission of infection among school children. Reducing this transmission is currently considered as one of the goals of antibiotic therapy in GABHS pharyngitis.

The Spanish Committee that developed the consensus document of antimicrobial treatment of pharyngitis, the American Academy of Pediatrics, the American Heart Association and the Infectious Diseases Society of America recommend the strategy of testing all patients with pharyngitis with a rapid antigen test, treating those with a positive test result with antibiotics and performing a culture for those with negative test results. Lieu et al. also recommended this strategy [19]. However, this strategy turns out to be expensive in our analysis. Moreover, it is less effective than either of the single test strategies.

Gerber and Shulman assessed the effectiveness of the diagnosis of rapid streptococcal tests and have concluded that, with adequately trained personnel, negative rapid antigen test results may not always need to be routinely confirmed with throat cultures [16]. Other authors had noted that throat culture confirmation of rapid antigen test negative results may not be medically necessary for most patients, and it is costly [6, 23]. Webb et al. reported 2 years experience in the use of a high-sensitivity antigen test without culture confirmation and concluded that it has not been associated with an increase in suppurative and non-suppurative complications of GABHS [35].

The treatment of patients with pharyngitis is often driven by the pressure of the patients’ parents. It has been demonstrated that physicians can reduce unnecessary treatments by performing rapid antigen tests without compromising the patient’s satisfaction [9]. Although it would have been desirable to make an analysis from the societal perspective, we chose the healthcare system’s perspective because of difficulties in obtaining accurate indirect costs.

The results could be generalized to populations with epidemiological features and primary healthcare system similar to that of Spain.This analysis considers only endemic GABHS pharyngitis. Therefore, when public health institutions report epidemics, a more aggressive diagnosis and treatment strategy need to be guaranteed. Likewise, this decision analysis should not be applied to a special risk population, such as patients with personal or family history of complications of GABHS.

In conclusion, using a clinical scoring system to triage the diagnosis, ignoring those with a low score, performing a rapid antigen test for those with a high score and treating those with positive test results with antibiotics is the most cost-effective strategy for the diagnosis and management of acute pharyngitis in the paediatric population in Spain. When the clinical scoring system has a low diagnostic accuracy, testing all patients and treating those with positive results with antibiotics become the most cost-effective strategy. These strategies could improve the management of AP in primary healthcare because they allow the accurate diagnosis and optimal treatment of GABHS, prevent a large number of complications, minimize the unnecessary antibiotic prescription rate, and reducing the potential adverse effects of inappropriate antimicrobial therapy.

Conflict of interest The authors declare that they have no conflict of interest.

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