Original Article

Cost and effectiveness analysis of the diagnostic and therapeutic approaches of group A Streptococcus pharyngitis management in Iran

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ABSTRACT

Background: A sore throat is one of the common causes behind visits to the physician and antibiotic overtreatment in the world, especially in Iran. There are six ways of approaching pharyngitis patients. It is necessary to perform a cost-effectiveness analysis and find the best approach in all situations on group A *streptococcus* (GAS) pharyngitis management to propose a pharyngitis guideline. **Method:** The decision tree of managing pharyngitis and its complications was drawn. The probability of every status and the branches of the tree were derived from the literature, and the cost of related diseases and complications were calculated based on the dossiers of the patients in two main pediatric central hospitals in Tehran, Iran. Further, cost-effectiveness, sensitivity, and threshold analyses were conducted to find out the best management strategy. Moreover, for a situation analysis of pharyngitis management in Iran, a questionnaire was designed and given to general practitioners and pediatricians; 130 subjects responded to it. The results were then analyzed. **Results:** The rapid test antigen (RTA) and culture strategy were proved to have the highest effect on the quality-adjusted life year. In addition, a less expensive strategy was solely observed to be the RTA. The worst effect gained (most quality-adjusted lost days) was, however, from the "treat none" strategy. **Conclusion:** According to our cost-effectiveness analysis, the best management of pharyngitis occurs in RTA alone, followed slightly by culture strategies; the "RTA then culture if needed" and "RTA and culture" approaches become possible options after them. The "treat all" and "treat none" approaches, however, were not proper strategies in any case.

Keywords: Approaches, management strategy, pediatricians, *Streptococcus* pharyngitis

Background

Pharyngitis is the cause for the referral of 14% of child and youth patients, under the age of 15, to medical clinics, and nearly 69% of these patients receive antibiotic (AB) medication.[1-4] In a study, Khorshidi *et al.*[5] demonstrated that from a total of 400 patients referred for medical treatments, 306 patients were clinically diagnosed with streptococci pharyngitis; however, only 24 cases of the cultured tests were positive.[5] The sensitivity value of the clinical findings was 71%, the specificity value was 23%, the positive predictive value was 8%, and the negative predictive value was 89%.[5] In a similar research report, Vahdat *et al.*[6] showed that all the patients were clinically diagnosed for streptococci pharyngitis and received penicillin; however, only 6% of the test cultures tested positive for streptococci

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pharyngitis.[6] Based on numerous studies, it has been confirmed that the clinical signs of infectious pharyngitis are not reliable indications for the definite diagnosis of this disease;[5-7] thus, the routine prescription of an AB leads to increased bacterial resistance and a loss of its effectiveness in treating streptococcus pneumonia.[8,9] Another problem associated with the unfounded use of ABs is the emergence of allergy (3.8%), diarrhea (10–60%) in children, and anaphylactic death (2 per 100,000 cases).[10] Penicillin is the most common cause of anaphylaxis and allergy.[11] All these undesirable consequences of using ABs are tolerated while 28% of patients are healed after 3 days of no AB use and 82% are free from infection after 7 days of no AB use.[10] The result of an Iranian study showed that from a total of 441 prescriptions provided by the general practitioners, 285 (64.6%) were AB, 264 items were for oral use, 55 were of the injection type, and 3 were local. The most common ABs were amoxicillin, co-trimoxazole, and ampicillin.[12] In another study in Urmia, Iran, it was found that the rate of AB use was 53%, with penicillin as the most commonly used AB (64%). Such studies determine the type of medical treatment that decreases the burden of disease and the types of diseases that have the highest cost for medical authorities, insurance companies, and corporations.[13-16] Therefore, the aim of this study was the cost and effectiveness analysis of the diagnostic and therapeutic approaches of group A *streptococcus* (GAS) pharyngitis management in Iran.

Materials and Methods

Each comprehensive study on the cost of illness includes direct and indirect expenses. In the present study, two categories of nonmedical costs have been estimated: [a] losing potential production level of the patients and [b] cost of caregivers.[10,17,18] There are six different methods of approaching pharyngitis patients; these include[1] treatment for all,[2] no treatment,[3] treatment based on the rapid test for a streptococcal antigen (RTA),[4] treatment based on the culture test result,[5] treatment based on RTA plus culture, and[6] treatment based on the RTA result, and in the case of a negative result, culturing.[19-21] Owing to the insufficiency of data in Iran, the researchers had to prepare a questionnaire to collect the necessary data. After data gathering, statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS) 16.0 software [Figures 1 and 2]. In the initial step, through a systematic review, a flowchart of the disease accompanied by a flowchart of patients' referral was prepared [Figure 3]. Following the preparation of an outcome (decision) tree through a bottom-up approach, the cost of the disease was calculated by multiplying the cost of treatment (or cost of the illness itself) in its prevalence [Figure 4 and Table 1].[22] Then, a complete list of measurements was taken to diagnose (physician, lab, radiology, etc.) the treatment, and the cost of the work-loss time was also calculated. The costs were based on the tariff defined by the Ministry of Health and medical treatment. In this regard, no data of any disease cost or complication is available in documents of Iran ministry of health or other statistics centers; therefore, all the records of all the hospitalized patients between the years 2011 and 2015 were examined, and the cost of every patient was calculated based on the inflation rate that was announced by the Iran Center of Statistics central bank of Iran, and the Ministry of Health, and Treatment tariff table. Then, the median cost was calculated per patient [Tables 2 and 3]. The statistical value of life was based on the atonement set for a man according to Brajer's[23] study, which is often used to estimate the value. Considering the obsoleteness of this method, however, it was not possible to use other value of a statistical life **(**VSL) methods.[20] For the analysis purpose of the data and the determination of its effectiveness, a "treeage" software named DATA was employed.[24] In certain cases, when it was necessary to compare strategies and determine the net health/monetary benefit, a willingness to pay equal to one million rials (Iranian currency unit) was used, which is further explained in the Discussion section.

The willingness to pay method includes the costs that a person is willing to pay to decrease their likelihood of morbidity and mortality.[23,25]

Table 1: Evaluation of the risk of pharyngitis complications in various articles		
Complication	**Study**	**Probability**
Purulent complications	19	0.024
	11	0.01
	31	0.005
	30	0.0125
	4	0.015
	20	0.005
	30	0.0125
RHD	25	0.00036
	38	0.00016
ARF	39	0.004 in patient/year
	38	0.00039
	30	0.03
	31	0.0028
	11	0.0003
	19	0.0005
Complicated ARF		0.1*ARF
Complicated RHD	40	0.039
Death due to ARF		1% of ARF
	30	1% of ARF
Probability of ARF	32	0.0032
	40	0.0038
Death due to anaphylaxis	4, 19, 20, 30	0.00001
	31	0.000003
Mild allergy	20	0.1
	31	0.003
	39	0.02
	30	0.015
	11	0.05-0.01
	19, 20	0.1
Anaphylaxis	19	0.0001
Severe allergy	4, 31	0.0064

*ARF: acute rheumatoid fever; RHD: rheumatic heart disease

Table 2: Criteria used for the decision tree of diagnostic-therapeutic strategy for pharyngitis						
Complication	QALDs****	Min	Max	Probability	Min	Max
Peritonsillar abscess	5	1.65	11	0.018357*	0.005	0.2
Anaphylaxis	9	3	18	0.0001 **		
Severe adverse reaction	9	3	18	0.0064**		
Mild adverse reaction	0.62	0.15	1.5	0.02 *		
ARF	76.5	56	744	0.0032***	0.005	0.3
Untreated gas	0.25					
Recovery after treatment after RTA	0.15 (2 days symptom reduction)					
Recovery after treatment after culture	0.2 (2 days symptom reduction)					
Death	22995					
Death due to anaphylaxis				0.00001 (1% of anaphylaxis)****		
Death due to ARF				1% of ARF		
Probability of penicillin prevention of ARF				0.8		
Probability of penicillin prevention of PTA				0.87		
Probability of penicillin prevention of RHD				0.99		
Probability rate of pharyngitis being purulent				0.22	0	0.8

*The mean values of various articles were obtained. **The most reliable, the most frequently, and the most used. ***Buffering of data close together and authentic and the most used. **The NEUNER study was used for QALDs. *****From this part onwards, the numbers are accepted by a majority of studies. *ARF: acute rheumatoid fever; RTA: rapid test antigen ; RHD: rheumatic heart disease ; QALD: quality-adjusted life days

Results

The likelihood of infectious pharyngitis reported in Iranian research articles ranged between 18 and 22%; therefore, the maximum value was used to calculate the need to use ABs in the worst possible conditions, such as during winter, epidemics, etc., For the purpose of situation analysis, in our "decision analysis", a questionnaire was distributed among general physicians and pediatricians across the country to examine their opinions (n = 130). Overall, 80% of the physicians were pediatricians, 10% were general practitioners, and 7% held fellowships. Based on the analysis results of the questionnaire, the mean value of the pharyngitis cases referring to treatment centers during the spring and summer seasons were 13.6 per week [Figures 1 and 2].

The most commonly used drugs in cases of allergy to penicillin was erythromycin (79%), azithromycin (13%), and amoxicillin (12%); other drugs were used in less than 2% of the cases.

Cost-effective analysis

The most effective mean observed quality-adjusted life days (QALDs) was the simultaneous diagnostic treatment of RTA and culture; the highest amount of saving (monetary cost) was detected in RTA before treatment. The highest number of lost working days was observed in the case of no treatment. In case the analysis was performed based on the patients' willingness to pay (payers' prospective), if the cost/effect was calculated, the "no treatment" option had the highest quantity of the cost–effect value. However, with the inclusion of one million rials considered as "willingness to pay" (i.e. willing to pay a little portion of the expense in return for gaining higher health benefit), culturing was the most effective option provided that the cost of the fast antigen strop test was not paid by the insurance company and was paid without subsidy. Otherwise, including the insurance expense for this test, RTA was the right choice. From the perspective of
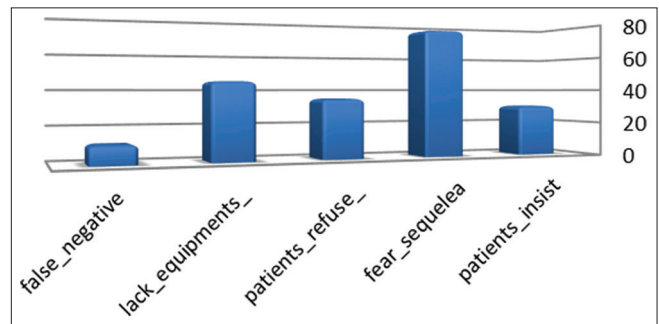

Figure 1: The cause of overtreatment

the insurance agent, a similar result, such as the one from the community prospect, was observed. This result is presented in Figure 5 and Table 4.

Based on the results of the questionnaire and the routine method of nearly all the cases of pharyngitis treatment in Iran, the advantage and disadvantage of other diagnostic treatments (in case of usage) have been prepared in Table 5. In fact, in this table, the difference in cost–effect in the different strategies for "treating all" is presented in QALDs/rial (currency unit).

Sensitivity analysis

Owing to the fact that a comprehensive approach including all factors was used in the analysis of patient treatment, the most effective variables were identified through a tornado diagram presented in Figure 6.

The selected strategy is RTA + culture when the peritonsillar abscess (PTA) following pharyngitis exceeded 0.08; it is RTA when it is less than 0.02; it is culture between these two values. In addition, the selected strategy is RTA in any AB medical treatment of pharyngitis (thus, for instance, whether to choose cephalosporin or macrolide is not an issue).

Discussion

The annual incidence rate of a sore throat in children ranged from 10–30%.[20,26,27] In addition, the probability of the streptococcal origin of the sore throat in Iranian studies ranged between 7.5 and 31%,[7,28,29] whereas the rate reported for other countries ranged between 20 and 36%.[10,11,19,20,26,30] Moreover, the effect of penicillin in reducing the symptoms of pharyngitis was 70–89%,[14,19,20,31,32] i.e. it decreases symptoms by 8–10 times. The percentage of penicillin resistance in Iranian articles was reported to be 6.5, 8, 18–21, and even 35.[7,33]

The age range of the patients referring for treatment was 4–12.5 years. Similar research results across the world have reported mean ages of 5–15 years for children and 30–35 years for adult populations[34,35]

Since there was no known Iranian research report regarding the willingness to pay for quality, the researchers considered the findings of the study by Hither *et al.* for comparison.[21] In the study, it was claimed that in the year 2000, quality-adjusted life year (QALY) saved USD 200,000. This figure is equal to six billion rials, regardless of the inflation rate in Iran and the increase in the health budget. In spite of the discrepancy in the GDP and the health budget between the United States and Iran, even when the one-twentieth of the amount is considered (300 million rials), the strategies of RTA, RTA + culture, and RTA followed by culture are still more effective than the "no-treatment" or "treatment-of-all" strategies. The "absence of treatment" is the best choice when the probability of streptococcal pharyngitis is less than 10%. The probability rate of acute rheumatoid fever (ARF) is no indication for use of the treatment-of-all or no-treatment strategies in streptococcal pharyngitis cases. In all amounts of reasonable fees (according to the review of hospitals expenditure records) for the treatments of pharyngitis and rheumatic fever as well as for severe and mild allergy medication with the cost of PTA (less than 27 million rials), the RTA strategy is the best option. Finally, in prevalence exceeding 36%, RTA + culture is the best option; and at a reasonable level of PTA prevalence, ARF is not the best option. Based on the strategy of comparison for the treatment of all (the original value of the variables), the option of culture (with a difference of QALDs = 0.05) requires 24 million rials per QALY; the option of RTA + culture requires 226 million rials per QALY; and the option of RTA followed by culture requires 197 million rials per QALY, and, according to the proposed standard, it is quite cost-effective. Considering the population pyramid in Iran and the prevalence of pharyngitis infection at different age groups in addition to the likelihood of streptococcal pharyngitis, it is estimated that 900,000 Iranian citizens are afflicted with GAS pharyngitis. Based on this figure and the likelihood of its complications, if no treatment approach is adopted, the number of patients who will suffer from rheumatoid fever may increase up to nearly 3,000 and the patients with infectious complications (e.g. different abscess) will rise to 16,000. Based on the result of the present study, employing the RTA strategy leads to the prevention of 1,900 cases of ARF and 11,300 cases of PTA. Meanwhile, conducting a diagnostic test prior to pharyngitis infection, instead of employing the "treatment-of-all" strategy, will prevent nearly 90,000 cases of mild drug allergy, 28,800 cases of severe allergy, 450 cases of anaphylaxis, and at least 4 cases of death. To avoid bias in sampling from physicians and the community, a total of 130 physicians were selected from different geographical regions and communities. Based on the result of the responses to the questionnaire, none of the physicians were familiar with the Centor Score Scale, and, therefore, they did not use it. Based

Table 3: Cost of treating complications of disease (in 2015)

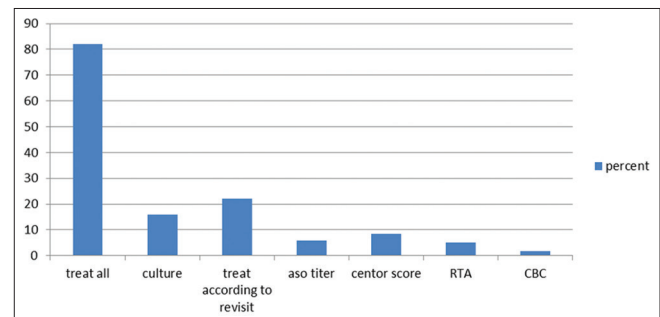| Complication	Cost as rials*	Min	Max
Peritonsillar abscess	16143	323	13175
Anaphylaxis	3670	155	28022
Severe adverse reaction	3454	431	35000
Mild adverse reaction	630		
Acute Renal Failure	4700	715	9692
Poststreptococcal Glomerulonephritis	18531		

rial=Iranian monetary unit (IRR)

Figure 2: The first approach to pharyngitis

Table 4: Analysis of cost-effectiveness of different diagnostic and treating strategies

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
RTA	94549		0.9250		102208	
Treat all	95728	1179	0.8765	-0.04854	109214	(Dominated)
Culture	99044	4494	0.9262	0.001164	106932	3860072
Treat none	99377	332	0.8518	-0.07433	116654	(Dominated)
RTA then culture, if needed	130760	31716	0.9415	0.015299	138881	2073101
RTA and culture	140332	9571	0.9490	0.007564	147859	1265439

*The strategy "treat none" is dominated by "culture". *The strategy "treat all" is dominated by "RTA". *Incr=incremental, Eff=effect; C/E=Cost/Effect; RTA=rapid test antigen. *Culture: throat swab culture. *Treat all: treat all patients with pharyngitis; Treat none: treat none of the patients with pharyngitis
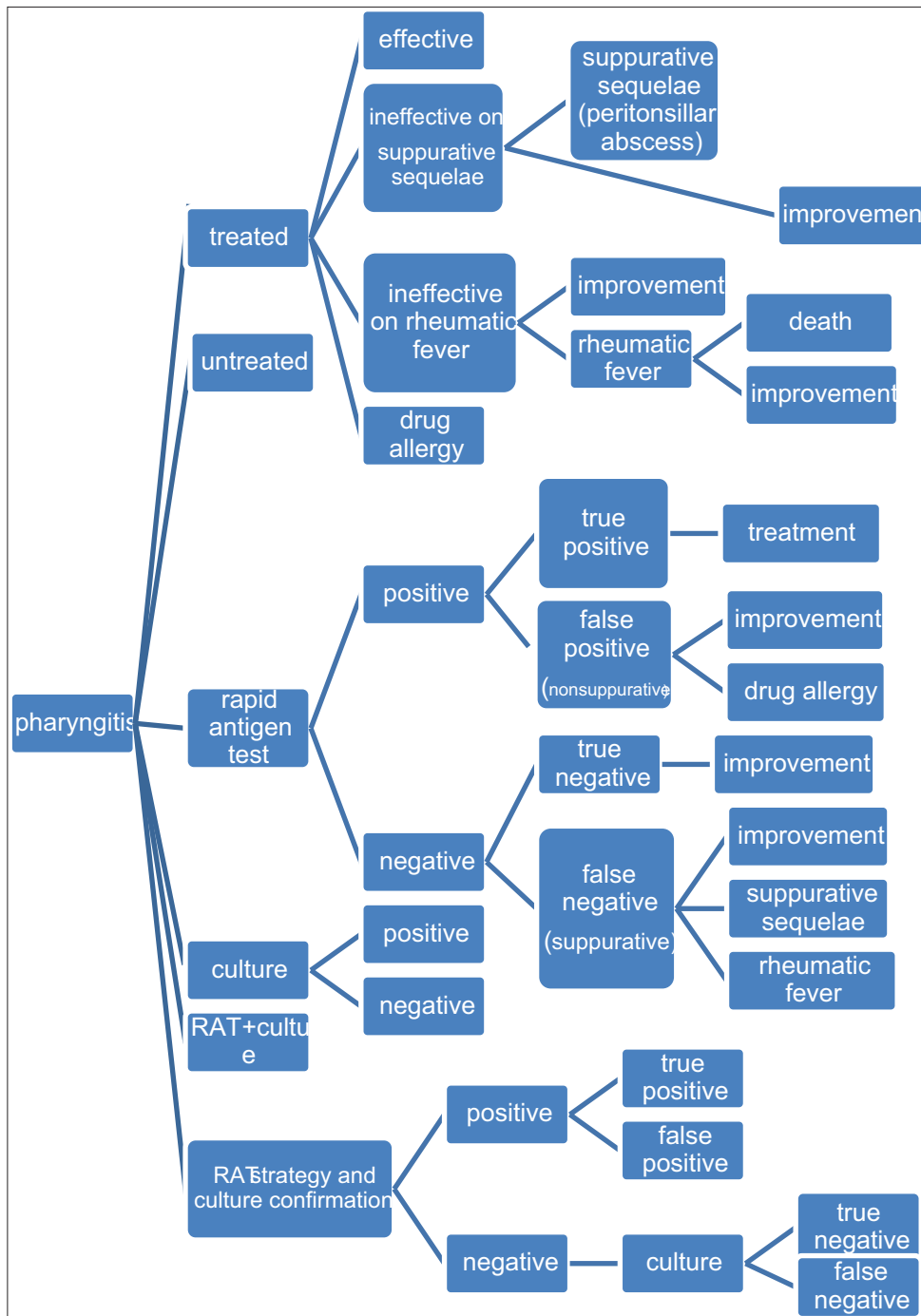
Figure 3: The flow diagram for pharyngitis

on this result and the insufficiency of only relying on clinical diagnosis, the use of a diagnostic-treatment approach based on the Centor Scale is not possible in Iran. For this reason, it has not been discussed in this report. As reported by Singh *et al.*,[36] considering diagnostic-treatment based on the Centor Score approach (even when there is a high likelihood of streptococcal cases of sore throat) is not a proper choice. Another problem includes the failure to calculate the cost of increased AB resistance in case of overtreatment. However, this problem of drug resistance is important. In a study conducted by Salkind

and Wright[37] with regard to treating pharyngitis by the current clinical practice of American physicians (overtreatment) at USD 1.2 billion, 36% of drug resistance was related to AB resistance. While remaining committed to therapeutic guidelines (treating patients reasonably), this cost will be as high as USD 370 million, and only 1.4% of that cost will be due to AB resistance. The Infectious Diseases Society of America (IDSA) and American College of Physicians (ACP) guidelines do not consider the spread of infection as an important factor to treat and manage pharyngitis. However, in a study conducted by Pfoh,
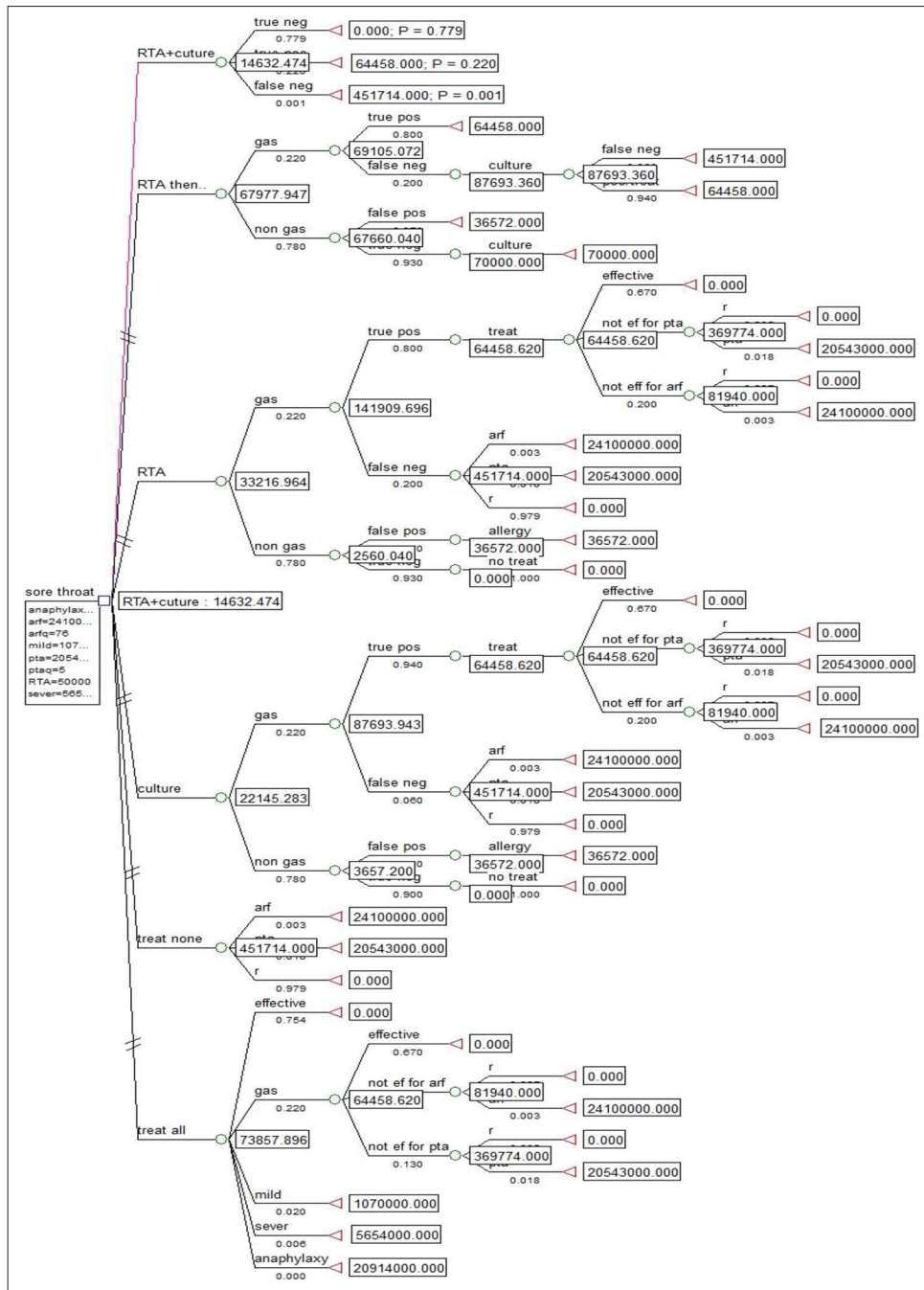
Figure 4: Detailed decision tree with probability and cost of each node

Table 5: Analysis of all the strategies according to the "treat-all" option as reference				
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**C/E**
RTA	94549	−1179	0.9250	0.048541	102208
Treat all	95728		0.8765		109214
Culture	99044	3315	0.9262	0.049706	106932
Treat none	99377	3648	0.8518	−0.02463	116654
RTA then culture, if needed	130760	35031	0.9415	0.065005	138881
RTA + culture	140332	44603	0.9490	0.072569	147859

*Incr=incremental, Eff=effect; C/E=Cost/Effect; RTA=rapid test antigen

the rate of the overall secondary attack rate of streptococcal pharyngitis was reported to be 20%. Even by considering this estimation, the GAS prevalence rate can be equated as 26%. In addition, according to the analysis of the pharyngitis group a streptococcus (PGAS) variable, the RTA option followed by culture is still the most preferred option to manage the disease. Meanwhile, different authors have reported different results; for instance, studies such as Tsevat and Kotagal[31] have claimed that the culture was the best option, whereas Ehrlich *et al.*[20] proposed RTA as the best option.
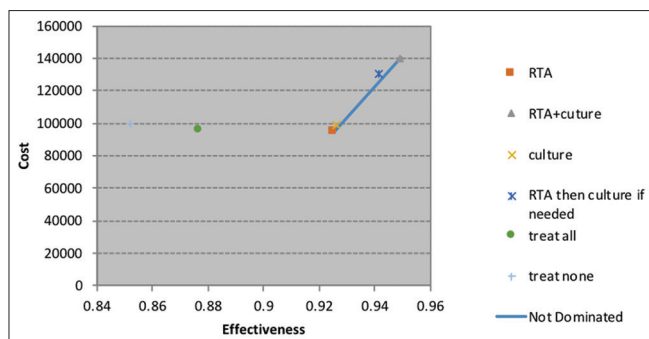
Figure 5: Cost-effectiveness analysis of sore throat

Figure 6: Most effective variables identified through a tornado diagram

Conclusion

Considering cost-effectiveness analysis, the best strategies for treating pharyngitis are as follows:[1] RTA followed by[2] culturing. The options of "treatment of all" and "no treatment" do not seem to be appropriate options.

Abbreviation

AB = antibiotic, ACP = American College of Physicians, ARF = acute rheumatoid fever, GAS = group A *streptococcus*, IDSA = Infectious Diseases Society of America, RTA = rapid test for a streptococcal antigen, QALDs = quality-adjusted life days, QALY = quality-adjusted life year, VSL = value of a statistical life, RHD = Rheumatic heart disease, PTA = Peritonsillar abscess, PGAS = Pharyngitis group a streptococcus.

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Availability of data and materials

Most patients' data were collected from hospitals related to Shahid Beheshti Medical University and Tehran Medical University of Science, chiefly Mofid and "Markaz Tebi" Children's Central Hospital of Tehran.

Ethics approval and consent to participate

The research has been approved legally and morally by the ethics committee of Shahid Beheshti Medical University of Science, where most case files were retrieved for this research.

Consent for publication

Not applicable.

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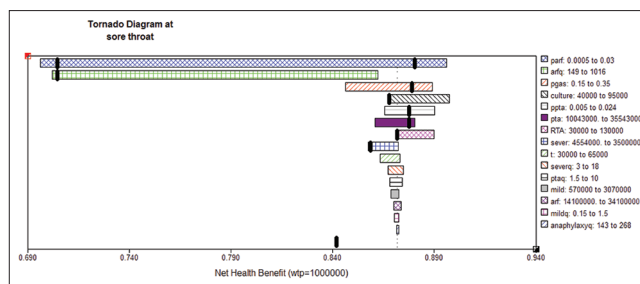Nil.

Conflicts of interest

There are no conflicts of interest.

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