

Impact of Rapid Antigen Detection Tests in the Diagnosis of Streptococcal Tonsillopharyngitis in Children

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Abstract

- Background** Tonsillopharyngitis among children considered as a major public health problem in the community, because of post-streptococcal complications, cost, time consuming diagnostic tests and unnecessary antibiotics.
- Objective** To determine the validity of Rapid Antigen Detection Test (RADT) in the diagnosis of streptococcal tonsillopharyngitis in comparison with clinical and bacterial culture method.
- Methods** Throat swabs were taken from 214 children with tonsillopharyngitis in Baghdad from 20th November 2015 to 30th May 2016. Tonsillopharyngitis diagnosed by clinical, culture on blood agar and RADT.
- Results** *S. pyogenes* were recovered from 116 (54.2%) cases. *S. pyogenes* infection alone or with overgrowth of other bacteria is associated with recommendation for tonsillectomy, and indices for MClSaac clinical prediction for Streptococcal pharyngitis. RADT detection of *S. pyogenes* revealed 83.62% sensitivity and 95.92% specificity. MClSaac clinical prediction 89.66% sensitivity and 44.9% specificity. The combined MClSaac-RADT algorithm had increased sensitivity with an increased point of score and specificity found to be inversely associated with points of score.
- Conclusion** For routine work, this study supports clinical screening with MClSaac score for all children with tonsillopharyngitis and subsequent testing by Strep A RADT to facilitate the decision for antibiotic use.
- Keywords** Rapid antigen detection, streptococcus pyogenes, tonsillopharyngitis
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List of abbreviation: ASOT = Anti-streptolysin O antigen, GABHS = Group A β Hemolytic Streptococci, RADT: Rapid Antigen Detection Test, RF = Rheumatic fever, RHD = Rheumatic heart disease

Introduction

Tonsillopharyngitis could be the most common reason among children attending primary health care centers ⁽¹⁾. It can be caused by wide spectrum of bacterial and viral pathogens ⁽²⁾. Among them, Group A β Hemolytic Streptococci (GABHS) or *Streptococcus pyogenes* (*S. pyogenes*) is the

common cause of tonsillopharyngitis in 20-30% of children, which left untreated can cause rheumatic fever (RF) and rheumatic heart disease (RHD) ⁽³⁻⁵⁾.

Despite improvements in antimicrobial prescribing for tonsillopharyngitis among children, a substantial number of patients continue to receive inappropriate antibiotic therapy ^(6,7). Therefore, physicians should be excluding the diagnosis of GABHS to prevent improper administration of antibiotics to large

numbers of patients. Such unnecessarily therapy exposes patients to several consequences to the development of antibiotic resistance among common pathogens⁽⁸⁾.

Several diagnostic procedures have been applied for diagnosis of streptococcal tonsillopharyngitis worldwide, ranging from clinical, serological, conventional and molecular methods with varieties in their advantages and disadvantages⁽⁹⁻¹¹⁾. Thus, high attentions have been paid worldwide for rapid and cost-effective method for proper diagnosis and effective antibiotic treatment were essential to prevent post-streptococcal complications⁽¹²⁻¹⁵⁾].

In Iraq, still difficult and time-consuming methods had been used in routine laboratory diagnosis of GABHS in health care centers and hospitals that associated with overuse/misuse of antibiotics from private pharmacies without physician consultation or definite diagnosis.

This study aimed testing rapid antigen detection test (RADT) as a valuable tool for diagnosis of GABHS in laboratory of Iraqi hospitals and health care centers to determine the diagnostic value of *S. pyogenes* by RADT in comparison with culture and clinical method.

Methods

Study design and population

A cross-sectional study was conducted on 214 children (3-18 years) suffering from tonsillopharyngitis at pediatric and ENT consultant clinic of (Al-Imamein Al-Kadhimein Medical City and Al-Zahra Primary Health Care Center during the period between (20th November 2015 to 30th May 2016). Inclusion criteria children from 3-18 years of age attending one of the ENT or pediatric specialist with evidence of fever, anterior tonsillar exudates or anterior cervical adenitis. Patients who had used antibiotics for the current illness were included in the study.

The study was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University (No.56, in 18/11/2015).

Informed verbal consent for participation was obtained from the parents of the child.

Clinical pro-forma was completed for each participant who enter the study, in which socio-demographic and clinical features were recorded. Children were classified according to the McIsaac score⁽¹⁶⁾, which comprises the following criteria: history of fever or temperature > 38 °C; absence of cough; tender anterior cervical adenopathy; tonsillar swelling or exudates; age ≤15 years scored +1 each, and age ≥ 45 years scored -1 While the age range between 15-45 years will be gives 0 score.

Sample collection and processing

Three throat swabs were taken from tonsillopharyngeal region, posterior pharyngeal wall and when patient permits, the swab rubbed with the rotation over one tonsillar area, then the arch of the soft palate and uvula, without touching the tongue or buccal surface to avoid contamination⁽¹⁷⁾. Then were processed as soon as possible for gram staining, culture on blood agar and RADT. The identification of *S. pyogenes* using RADT made by CerTest Strep A kit purchased from Certest Biotec® Spain. This test based on the qualitative immunochromatographic assay for the determination of Group A Streptococcal from throat swabs.

Statistical analysis

Data of the study sample were entered and analyzed by using statistical package for social sciences (SPSS) version 20. Descriptive statistics were presented as frequencies, proportion (%), means and standard deviation (SD). Chi-square test was used to estimate the association between two categorical variables. T-test was used to compare the actual difference between two means in relation to the variation in the data. Level of significance of < 0.05 was considered as significant.

Validity and predictability of different screening tests were assessed in relation to gold standard test by calculating sensitivity,

specificity, predictive value of positive and negative test results.

Results

Identification of microbial causes tonsillopharyngitis

The results of current study showed no significant association between *S. pyogenes* infection and sociodemographic characteristics of patients with tonsillopharyngitis like: age, gender, residence, maternal education,

parent's occupation and crowding index. On the other hand, single *S. pyogenes* infection among tonsillopharyngitis patients was significantly associated with some clinical signs like: presence of exudate, tenderness of lymph nodes, body temperature above 38.5 °C and modified centor score (MClSaac score). Recommendation for tonsillectomy was significantly associated with mixed *S. pyogenes* infection (Table 1).

Table 1. Association between *S. pyogenes* infection with demographic and clinical characteristics of tonsillopharyngitis patients

<i>S. pyogenes</i> (Culture)		Total	Positive	%	P value
Duration of illness (days)	≤ 7 days	100	55	55.0%	0.981 ^{NS}
	> 7 days	114	61	53.51%	
Family history of tonsillopharyngitis	Yes	133	74	55.6%	0.590 ^{NS}
	No	81	42	51.9%	
Recurrent	Yes	169	96	56.8%	0.139 ^{NS}
	No	45	20	44.4%	
Antibiotic use	Yes	114	57	50.0%	0.187 ^{NS}
	No	100	59	59.0%	
Tonsillectomy	Yes	6	3	50.0%	0.834 ^{NS}
	No	208	113	54.3%	
Recommended for tonsillectomy	Yes	115	85	73.91%	<0.001**
	No	93	28	30.1%	
Exudate	Yes	147	95	64.6%	<0.001**
	No	67	21	31.3%	
Swelling	Yes	208	113	54.3%	0.834 ^{NS}
	No	6	3	50.0%	
Tenderness	Yes	141	88	62.4%	0.001**
	No	73	28	38.4%	
Cough	Yes	147	84	57.1%	0.201 ^{NS}
	No	67	32	47.8%	
Temp. over 38.5°C	<38.5	58	20	34.5%	<0.001**
	≥38.5	156	96	61.5%	
Mclsaac score	Score 0	12	3	25.0%	<0.001**
	Score 1	19	3	15.79%	
	Score 2	25	6	24.0%	
	Score 3	37	11	29.73%	
	Score 4	62	40	64.52%	
	Score 5	59	53	89.83%	
Total		214	116	54.21%	

NS: None statistical significance (p>0.05).

** : Highly statistical significance (p≤0.001).

According to the culture characteristics and EPI 20 tests, *S. pyogenes* was isolated from 116/214 (54.2%) cases. *S. pyogenes* detected in 101/214 (47.2%) using Certest RADT (Table 2). Validity of RADT and modified Centor score (MCIIsaac) for detection of *S. pyogenes* infection were estimated in relation to the gold standard method (culture on blood agar). Regarding sensitivity, MCIIsaac score (89.66%) and the lowest was RADT (83.62%). On the other hand, RADT was highly specific (95.92%), while, MCIIsaac score had lower specificity

(75.51% and 44.9% respectively). Similarly, RADT had the highest positive predictive value (96.04%) while, MCIIsaac score shoed lowest PPV (65.82%) the lowest was MCIIsaac score (78.57%) (Table 2). The results showed the validity of combined MCIIsaac score and RADT (Table 3) in predicting *S. pyogenes* infection. The highest sensitivity had been increased with the increasing number of score in predicting *S. pyogenes* infection. Inversely, the specificity decreased by increasing the number of MCIIsaac score.

Table 2. Diagnostic performance of different methods in detection of *S. pyogenes*

<i>S. pyogenes</i>		Culture		Total	Sensitivity	Specificity	PPV	NPV
		Positive	Negative					
RADT	Positive	97	4	101	83.62 (75.83- 89.26)	95.92 (89.97- 98.4)	96.04 (90.26- 98.45)	83.19 (75.23- 88.96)
	%	83.60	4.10	47.20				
	Negative	19	94	113				
	%	16.40	95.90	52.80				
MCIIsaac score	Predict <i>S. pyogenes</i>	104	54	158	89.66 (82.79- 93.98)	44.9 (35.43- 54.75)	65.82 (58.13- 72.76)	78.57 (66.18- 87.29)
	Does not predict <i>S. pyogenes</i>	12	44	56				
		10.34	44.90	26.17				
Total		116 (54.04%)	98 (45.096%)	214				

PPV: positive predictive value. NPV: Negative predictive value.

Discussion

This study developed combined clinical and rapid point of care testing prediction guidelines in Iraqi primary health care centers and hospitals for improving clinical diagnosis of GABHS tonsillopharyngitis and prevention of post-streptococcal complications.

According to the results, the culture method reported a relatively high rate of isolation for GABHS among children with tonsillopharyngitis (116/214) 54.2%. This comes with agreement with Abd Al-kareem et al. 2014 whom reported comparable rate 142/376 (37.7%)⁽¹⁸⁾. Lower rate of *S. pyogenes* infection was also reported by Yousef et al., 2010 16/70 (22.9%)⁽¹⁹⁾. Unfortunately, few Iraqi studies were done on children with tonsillopharyngitis, or they utilize other methods for detection of *S. pyogenes* like

Anti-streptolysin O antigen (ASOT) serum titer^(20,21), or the study population were restricted to pharyngitis cases after tonsillectomy^(22,23). Other studies restrict their objectives to investigate molecular aspects like multidrug resistance genes^(24,25).

Rate of *S. pyogenes* isolation by culturing on blood agar like some Arabic studies Abu-Sabaah & Ghazi, 2006, in Saudi Arabia (19.4%)⁽²⁶⁾, Fourati et al. 2009, in Tunisia (20.2%)⁽²⁷⁾, Rimoin et al. 2010, in Egypt (24.8%)⁽²⁸⁾, and other global studies like Enright et al. 2011, in Scotland (21.5%)⁽²⁹⁾, Forward et al. 2006, in Canada (24.1%)⁽³⁰⁾, Subashini et al. 2015 in India (24.3%)⁽³¹⁾, Altun et al. 2015, in Turkey (24.7%)⁽³²⁾, Buchbinder et al. 2007, in France (26.4%)⁽³³⁾, Rogo et al. 2010, in USA using Quickvue test kit (28.5%)⁽³⁴⁾, Tanz et al. 2009,

in Chicago (30%)⁽³⁵⁾, Finger et al. 1999, in Vietnam (30.5%)⁽³⁶⁾, Pitetti et al. 1998, in Russia (31.3%)⁽³⁷⁾, Flores Mateo et al. 2010, in Spain (34.1%)⁽³⁸⁾, Camurdan et al. 2008, in Turkey (38.1%)⁽³⁹⁾, Omurzakova et al. 2010, in Kyrgyzstan (40%)⁽⁴⁰⁾, Comparable results were reported by Sheeler et al. 2001 in New York, (54%)⁽⁴¹⁾ and higher rate of *S. pyogenes* isolation reported by Kim, 2009, in Korea (66.5%)⁽⁴²⁾.

Table 3. Combined MCIsaac score and RADT diagnostic algorithm performance in detection of *S. pyogenes* infection

Score		Culture		Total	Sensitivity	Specificity	PPV	NPV
		Positive	Negative					
Score 0	RADT positive	0	0	0	0	100	0	75
	RADT negative	3	9	12	(0-56)	(70-100)	(0-100)	(47-100)
Score 1	RADT positive	1	0	1	33.34	100	100	89
	RADT negative	2	16	18	(1.7-88.2)	(80.6-100)	(5.1-100)	(67-98)
Score 2	RADT positive	3	0	3	50	100	100	86.4
	RADT negative	3	19	22	(19-81)	(83.2-100)	(44-100)	(67-95.3)
Score 3	RADT positive	7	1	8	64	96.2	87.5	86.2
	RADT negative	4	25	29	(35.4-85)	(81-100)	(53-99.4)	(70-94.5)
Score 4	RADT positive	38	2	40	95	91	95	91
	RADT negative	2	20	22	(83.5-99)	(72.2-98.4)	(83.5-99)	(72.2-98.4)
Score 5	RADT positive	48	1	49	90.6	83	98	50
	RADT negative	5	5	10	(79.6-96)	(44-99.2)	(89.3-100)	(24-76)
Total	RADT positive	97	4	101				
	RADT negative	19	94	113				

PPV: positive predictive value. NPV: Negative predictive value.

However, several broad studies reported lower Our results highlight the importance of GABHS as a potential human pathogen causing tonsillopharyngitis among Iraqi children. Furthermore, the incidence of *S. pyogenes* was the same in boys (55.6%) and girls (52.2%), affecting and no statistical significant association with any sociodemographic characteristics. In addition to that, no association have been reported with duration of illness or wither previously or recurrent infected. The incidence of *S. pyogenes* was associated among children whom recommended for tonsillectomy (73.9%), and clinical indices for MCIsaac clinical score like presence of exudate (64.6%), tenderness of cervical lymph nodes (62.4%), and body temperature over 38.5 (61.5%).

In clinical setting, MCIsaac scoring indices and score failed to differentiate between Streptococcal and non-streptococcal bacterial tonsillopharyngitis, which is meaningfully assumed that MCIsaac clinical score is sensitive to diagnose bacterial tonsillopharyngitis. This finding is supported by Steinhoff et al. 1997⁽⁴³⁾, Bisno et al. 2002⁽⁴⁴⁾, Martin & Green 2006⁽⁴⁵⁾, Ba-Saddik et al. 2014⁽⁴⁶⁾ whom reported that clinical assessment of streptococcal pharyngitis is unreliable method because of their indices were none specifically present in most bacterial tonsillopharyngitis. Furthermore, MCIsaac clinical score could not be employed to stratify children for immediate antibiotic treatment and suggesting a higher need for rapid and specific method for diagnosis of streptococcal pharyngitis.

According to the RADT, a higher rate of *S. pyogenes* antigen was detected 101/214 (47.2%). In comparison with gold standard method (culture on blood agar), the RADT showed 83.62% sensitivity and 95.92% specificity. These values come in agreement with several Arabic and global studies (summarized in table 4). The higher specificity

of the Certest kit attributed to that kit was designed to detect carbohydrate (CHO) antigens of streptococcus pyogenes, upon that several clinical practice guidelines have been recommended that all positive cases by RADT testing should not be cultured.

Table 4. Rate of streptococcus pyogenes infection according to references diagnosed by culture on blood agar and rapid antigen detection test

Study number	Country (Ref)	Culture	RADT
1	Canada ⁽³⁰⁾	24.1	21.0
2	New York ⁽⁴¹⁾	54	46.0
3	Vietnam ⁽³⁶⁾	30.5	27.0
4	Russia ⁽³⁷⁾	31.3	27.0
5	Egypt ⁽²⁸⁾	24.8	26.4
6	Turkey ⁽³²⁾	24.7	20.4
7	Kyrgyzstan ⁽⁴⁰⁾	40	36.2
8	Turkey ⁽³⁹⁾	38.1	36.2
9	Scotland ⁽²⁹⁾	21.5	16.38
10	Spain ⁽³⁸⁾	34.1	45.0
11	Chicago ⁽³⁵⁾	30	21.3
12	Saudi Arabia ⁽²⁶⁾	19.4	23.5
13	France ⁽³³⁾	26.4	33.8
14	Tunisia ⁽²⁷⁾	20.2	24.7
15	India ⁽³¹⁾	24.3	13.5
16	USA (Acceava) ⁽⁴⁷⁾	39.3	39.8
17	Korea ⁽⁴⁸⁾	66.5	66.5

RADT: Rapid antigen detection test.

Giving the advantages of rapid test (Point of care test), increase the number of appropriately treated child's with tonsillopharyngitis, not only for avoiding unnecessary treatment with antibiotics but also avoiding the post streptococcal complications by treating those with positive *S. pyogenes* results ⁽⁴⁷⁾. Furthermore, point of care testing for *S. pyogenes* appears to reduce long-term costs by lowering the incidence of post-streptococcal complications especially rheumatic fever and post-streptococcal glomerulonephritis.

A number of commercial kits have been marketed and evaluated globally for detection of *S. pyogenes* antigen from throat swabs were

reviewed and used in statistical analysis (in addition to our results) for documentation of clinical utility of RADT to be used in clinical practice. However, the clinical utility score was 91.2% as an excellent for screening and good for case finding in clinical practice. With positive likelihood ratio 14.82. The authors believe this is the first study is that document the clinical utility of RADT for *S. pyogenes* among children with tonsillopharyngitis.

Many clinical diagnostic rules have been applied for identification of streptococcal tonsillopharyngitis since 1970 ^(44,48-53). We used MCIsaac clinical score in this study to identify ability to define cases caused by *S. pyogenes*. However, its diagnostic performance showed

low positive predictive value (65.8%) and low specificity (44.9%) and without microbiological testing, is in accurate testing method and have wrong prediction for proper antibiotic prescription.

Several clinical prediction criteria have been mentioned in the literatures. The majority of them were generated based on adults based on clinical and epidemiological variables. They varied in their applications according to populations. Some of the original clinical prediction rules including those by Centor, Breese, and Wald, although originally developed among adult populations, have been validated and modified in different age and geographic populations ^(16,48,49,52). Centor clinical scoring system is the best clinical prediction rule, based on presence of tonsillar exudate, swollen/tender cervical lymph nodes, absence of cough, and fever > 38.5 °C ^(5,60).

In the effort to make the diagnosis of streptococcal tonsillopharyngitis simple for use and selective diagnosis based on clinical findings, this study established combined clinical score and RADT results, in order to better predict infection. By another mean, the study claimed to introduce a simple point of care test method to increase the specificity of MCIsaac clinical score.

In this study, sensitivity, specificity, positive and negative predictive of RADT (Ceretest) where more the clinical score.

Conclusions

For routine work, our study supports clinical screening with MCIsaac score for all children with tonsillo-pharyngitis and subsequent testing by Strep A RADT to facilitate the decision for antibiotic use.

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Author contribution

Hadi was responsible for sampling and experimental works. Dr. Ghazi works concept design and statistical analysis of study. Dr.

Abdulla contributed by scientific advices and comprehensive editing and interpretation of data.

Conflict of interest

Authors declared there is no conflict of interest.

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