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THE DIAGNOSTIC VALUE OF "CENTOR CRITERIA" IN CHILDREN WITH GROUP A BETA HEMOLYTIC STREPTOCOCCUS TONSILLOPHARYNGITIS

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ABSTRACT

Background: Centor criteria (fever >38.5°C, swollen, tender anterior cervical lymph nodes, tonsillar exudate and absence of cough) include a scoring system used to assess the probability of group A β hemolytic Streptococcus (GABHS) as the origin of sore throat, and it is developed for adults. Up till now, there's no graded scoring system established for children with suspected GABHS pharyngitis. Thus, it is important to evaluate the correlation between Centor criteria and presence of GABHS in children with sore throat. Objectives: This study was intended to test the Centor Criteria as a scoring system for GABHS in children and assess its diagnostic value to guide us toward whether to perform to a rapid diagnostic point of care (POC) test/throat culture in pediatric patients presenting with sore throat. In addition to assessing the impact of this scoring system with the support of practical laboratory tests: the WBC and the CRP. Methods: We proposed to carry out a retrospective cross-sectional study at the Makassed General Hospital in children (aged 3–15 years) diagnosed with tonsillitis. We recorded Centor scoring in addition to white blood cell count (WBC), C-reactive protein (CRP), rapid antigen detecting test and throat culture. Results: 484 children with tonsillitis were enrolled between 1st January 2010 and 31st July 2017. GAS was positive in 129 (26%) cases and negative in 358 (74%). In GAS cases, two of the Centor criteria were observed to be positive in 4 (3.1%), while 122 (94.6%) cases met three to four Centor criteria with a significant p-value (<0.001).The specificity of having three/four criteria was found to be 62 % and increased to 97% after including CRP and WBC. Conclusion: Centor criteria could be a tool to be used to reduce unnecessary rapid diagnostic point of care (POC) test/throat culture in children presenting with sore throat.

KEYWORDS: Centor critera; Group A Beta Hemolytic Streptoccocus, Tonsillopharyngitis.

INTRODUCTION

Pharyngitis symptoms are one of the most common causes for primary care visits.[1–3] Most of these cases are viral. Whereas, GABHS (Group A-beta Hemolytic Streptococcus) infections occur in children at a proportion of 15–30% and in adults 5–15%.[3-7] The global burden of GABHS disease predominantly relates to two complications: acute rheumatic fever (ARF) and chronic rheumatic heart disease (CRHD). The gold standard diagnostic method for GABHS pharyngitis is still the throat culture (sensitivity of 90% and above). However, results take up to 48 hours. Explaining this duration to parents of these patients is often difficult. Therefore, the use of a rapid antigen detecting test (RADT) by culture swab with enzyme-immunoassay methods, with a sensitivity of 80–90%, has become wide spread. A positive RADT is useful in establishing the diagnosis of GABHS pharyngitis.[3-5, 8-14] Diagnosis of GABHS tonsillopharyngitis by scoring clinical symptoms is an advised approach to guide towards performing RADT or culture. Many scoring systems have been suggested in evaluating the probability of GABHS pharyngitis based on clinical findings (Centor, Breese, Mc Issaac, Wald and Attia scores[16] WHO scoring system), but have not proven to be reliable enough to guide antibiotic prescription.[3,11,16,17] The Centor scoring method is a well-known method proven reliable in developed countries. Center for Disease Control and Prevention and the American College of Physicians–American Society of Internal Medicine approve application of the four-point Centor clinical scoring scale to guide management of acute pharyngitis in the adult population. Its interpretation consists of four clinical characteristics 'history of fever, exudative tonsillitis, anterior cervical adenopathy, and the absence of cough.[3,15-20]. While several studies[8-10,15-19,21-23] in developed countries have been conducted on the validity of the clinical scoring criteria, there are insufficient data from developing or underdeveloped countries. In addition, there's no graded scoring system for children below 15 years with suspected GABHS infection in guidelines up till now.[9,23,24]

The aims of the present study are to assess the diagnostic value of the Centor criteria by means of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV); and re-evaluate Centor scoring with the support of white blood cell count (WBC) count and/or C-reactive protein (CRP) in patients with GABHS pharyngitis. In addition to targeting who will undergo Rapid antigen testing or Throat swab culture. Therefore, reducing the cost and time, and to test new approaches regarding primary care.

MATERIALS AND METHODS

Study design: This study is a Retrospective Observational Cross-Sectional Study and was held at the Makassed General Hospital (Beirut, Lebanon). We analyzed the medical records of hospitalized children diagnosed with tonsillopharyngitis between January 1st, 2010 and December 31st, 2018.

The data was obtained from data sheets and the results of physical examinations, RADT, throat culture, WBC, CRP, antibiotic prescription were evaluated using Statistical Package for Social Sciences (SPSS, version 21).

First, the study group was divided into two subgroups preschoolers (3-5 years) and schoolers (5-15 years).

The accuracy of several rapid antigen tests has been deemed sufficient for diagnosis and management of GAS infections,18,19 including the **Alere™ Test Pack +Plus Strep A with OBC** that has been proven to perform with enough accuracy20,21 to be comparable with a throat culture.12 It was therefore used as the reference standard for this evaluation.

Inclusion/Exclusion criteria

Inclusion criteria

-Patients aged 3–15 years.

-All files of children who underwent a rapid strep test and/or throat swab for GABHS culture with the following ICD-10 codes: infectious mononucleosis, nasopharyngitis, pharyngitis, tonsillitis and sore throat.

Exclusion criteria

-Children with underlying chronic respiratory, cardiac, hematological or immunological diseases

-No Throat swab culture for GABHS or Rapid strep test obtained

Methodology

Data was recorded on the data sheet: age; gender; body temperature; the clinical symptoms and signs of the Centor criteria, WBC, CRP, throat swab culture result, and RADT result.

The variables of the Centor criteria include

Tonsillar exudates (1 point), swollen tender anterior cervical node (1 point), lack of a cough (1 point) and history of fever (1 point).

Score= 0: Risk of GABHS pharyngitis 1-2.5%
Score= 1: Risk of GABHS pharyngitis 5-10%
Score=2: Risk of GABHS pharyngitis 11-17%
Score=3: Risk of GABHS pharyngitis 28-35%
Score=4: Risk of GABHS pharyngitis 35-51%

Statistical analysis

When comparing throat culture and /or RADT as the gold standard diagnosis, the criteria for each symptom existing for each group, sensitivity, specificity, PPV, and NPV were calculated. The cut off value for total Centor score was considered to be 3 (Risk of GABHS pharyngitis 28-35%).The sensitivity, specificity, PPV, and NPV were calculated according to each ≤ 2 and ≥ 3 total Centor score positivity and together with WBC and/or CRP lab tests, and the changes in the values were investigated. Standard descriptive methods were used for statistical analysis.

A p-value of 0.05 was evaluated as statistically significant. During the evaluation of the significance of the relation between the Centor criteria and culture positivity or RADT, in patient group who has 3 and above total Centor score, WBC/CRP and culture positivity.

RESULTS

Table. 1: Demographics and clinical characteristics of all patients.

	Group 1 (3 till <5 years) (n=235)	Group 2 (≥5 years) (n=249)	P value
Male sex	137 (58.3%)	128 (51.4%)	0.13
Tonsillar exudates	165 (70.2%)	187 (75.1%)	0.23
Tender anterior cervical lymph node	68 (28.9%)	88 (35.3%)	0.13
Lack of cough	148 (62.9%)	149 (59.8%)	0.48
Fever	227 (96.6%)	237 (95.2%)	0.43
GAS Positive	57 (24.3%)	72 (28.9%)	0.25
WBC ≥ 10000	142 (60.4%)	166 (66.7%)	0.15
CRP (+)	170 (72.3%)	194 (77.9%)	0.16
Centor criteria score			
0	1 (0.4%)	0 (0.0%)	0.12
1	11 (4.7%)	21 (8.4%)	
2	105 (44.7%)	89 (35.7%)	
3	85 (36.2%)	94 (37.8%)	
4	33 (14.0%)	45 (18.1%)	
Antibiotic prescription	111 (47.2%)	131 (52.6%)	0.24

Table. 2: Centor score and GAS infection.

Centor score	GAS Positive	GAS Negative	Total	P value
0	0 (0.0)	1 (0.3)	1	<0.001
1	3 (2.3)	29 (8.2)	32	
2	4 (3.1)	190 (53.5)	194	
3	68 (52.7)	111 (31.3)	179	
4	54 (41.9)	24 (6.8)	78	

Table. 3: Diagnostic values of Centor criteria 0,1, 2,3 and 4 with additional basic laboratory tests in all children.

		GAS Positive (n=129)	GAS negative (n=355)	Specificity CI (95%)	Sensitivity CI (95%)	PPV CI (95%)	NPV CI (95%)
Centor	≤2	7 (5.4%)	220 (62.0%)	0.62 (0.57 - 0.67)	0.95 (0.89 - 0.98)	0.47 (0.41 - 0.54)	0.97 (0.93 - 0.99)
	≥3	122 (94.6%)	135 (94.6%)				
Centor ≤2 with wbc	Yes	5 (3.9%)	113 (31.8%)	0.68 (0.63 - 0.73)	0.04 (0.01 - 0.09)	0.04 (0.02 - 0.10)	0.66 (0.61 - 0.71)
	No	124 (96.1%)	242 (68.2%)				
Centor ≤2 with CRP	Yes	3 (2.3%)	139 (39.2%)	0.61 (0.55 - 0.66)	0.02 (0.01 - 0.07)	0.02 (0.01 - 0.06)	0.63 (0.58 - 0.68)
	No	126 (97.7%)	216 (60.8%)				
Centor ≤2 with wbc& CRP	Yes	3 (2.3%)	92 (25.9%)	0.74 (0.69 - 0.78)	0.02 (0.1 - 0.07)	0.03 (0.01 - 0.10)	0.68 (0.63 - 0.72)
	No	126 (97.7%)	263 (74.1%)				
Centor ≥3 with wbc	Yes	99 (76.7%)	91 (25.6%)	0.74 (0.69 - 0.79)	0.77 (0.68 - 0.83)	0.52 (0.45 - 0.59)	0.90 (0.86 - 0.93)
	No	30 (23.3%)	264 (74.4%)				
Centor ≥3 with CRP	Yes	8 (6.2%)	27 (7.6%)	0.92 (0.89 - 0.95)	0.06 (0.03 - 0.12)	0.23 (0.11 - 0.41)	0.73 (0.69 - 0.77)
	No	121 (93.8%)	328 (92.4%)				
Centor ≥3with wbc& CRP	Yes	6 (4.7%)	11 (3.1%)	0.97 (0.094 - 0.98)	0.05 (0.02 - 0.10)	0.35 (0.15 - 0.61)	0.74 (0.69 - 0.77)
	No	123 (95.3%)	344 (96.9%)				

Table. 4: Diagnostic values of Centor criteria 0,1, 2,3 and 4 with additional basic laboratory tests in Group 1.

GROUP 1 (3 till <5 years)		GAS Positive (n=57)	GAS negative (n=178)	Specificity CI (95%)	Sensitivity CI (95%)	PPV CI (95%)	NPV CI (95%)
Centor	≤2	0 (0.0%)	117 (65.7%)	0.66 (0.58 - 0.73)	1 (0.92 - 1)	0.48 (0.39 - 0.58)	1 (0.96 - 1)
	≥3	57 (100.0%)	61 (34.3%)				
Centor ≤2 with wbc	Yes	0 (0.0%)	55 (30.9%)	0.69 (0.62 - 0.76)	0 (0 - 0.08)	0 (0 - 0.08)	0.68 (0.61 - 0.75)
	No	57 (100.0%)	123 (69.1%)				
Centor ≥3 with wbc	Yes	43 (75.4%)	44 (24.7%)	0.75 (0.68 - 0.81)	0.75 (0.62 - 0.85)	0.49 (0.39 - 0.60)	0.90 (0.84 - 0.94)
	No	14 (24.6%)	134 (75.3%)				
Centor ≤2 with CRP	Yes	0 (0.0%)	72 (40.5%)	0.59 (0.52 - 0.67)	0 (0 - 0.08)	0 (0 - 0.06)	0.65 (0.57 - 0.72)
	No	57 (100.0%)	106 (59.6%)				
Centor ≥3 with	Yes	5 (8.8%)	15 (8.4%)	0.91 (0.86 -	0.09 (0.03 -	0.25 (0.10 -	0.76 (0.69 -

CRP	No	52 (91.2%)	163 (91.6%)	0.95)	0.20)	0.49)	0.81)
Centor ≤2 with wbc& CRP	Yes	0 (0.0%)	49 (27.5%)	0.72 (0.65 - 0.79)	0 (0 - 0.08)	0 (0 - 0.09)	0.69 (0.62 - 0.76)
	No	57 (100.0%)	129 (72.5%)				
Centor ≥3with wbc& CRP	Yes	4 (7.0%)	6 (3.4%)	0.97 (0.92- 0.99)	0.07 (0.02 - 0.18)	0.4 (0.14 - 0.73)	0.76 (0.70 - 0.82)
	No	53 (92.9%)	172 (96.6%)				

Table. 5: Diagnostic values of Centor criteria 0,1, 2,3 and 4 with additional basic laboratory tests in Group 2.

GROUP 2 (≥5 years)		GAS Positive (n=72)	GAS negative (n=177)	Specificity CI (95%)	Sensitivity CI (95%)	PPV CI (95%)	NPV CI (95%)
Centor	≤2	7 (9.7%)	103 (58.2%)	0.58 (0.50 - 0.65)	0.90 (0.80 - 0.96)	0.47 (0.38 - 0.55)	0.94 (0.87 - 0.97)
	≥3	65 (90.3%)	74 (41.8%)				
Centor ≤2 with wbc	Yes	5 (6.9%)	58 (32.8%)	0.67 (0.60 - 0.74)	0.07 (0.02 - 0.16)	0.08 (0.03 - 0.18)	0.64 (0.56 - 0.71)
	No	67 (93.1%)	119 (67.2%)				
Centor ≥3 with wbc	Yes	56 (77.8%)	47 (26.6%)	0.73 (0.66 - 0.80)	0.78 (0.66 - 0.86)	0.54 (0.44 - 0.64)	0.89 (0.82 - 0.93)
	No	16 (22.2%)	130 (73.5%)				
Centor ≤2 with CRP	Yes	3 (4.2%)	67 (37.9%)	0.62 (0.54 - 0.69)	0.04 (0.01 - 0.13)	0.04 (0.01 - 0.13)	0.61 (0.54 - 0.68)
	No	69 (95.8%)	110 (62.2%)				
Centor ≥3 with CRP	Yes	3 (4.2%)	12 (6.8%)	0.93 (0.88 - 0.96)	0.04 (0.01 - 0.13)	0.2 (0.05 - 0.49)	0.70 (0.64 - 0.76)
	No	69 (95.8%)	165 (93.2%)				
Centor ≤2 with wbc& CRP	Yes	3 (4.2%)	43 (24.3%)	0.76 (0.69 - 0.82)	0.04 (0.01 - 0.13)	0.06 (0.02 - 0.19)	0.66 (0.59 - 0.72)
	No	69 (95.8%)	134 (75.7%)				
Centor ≥3with wbc& CRP	Yes	2 (2.8%)	5 (2.8%)	0.97 (0.93 - 0.99)	0.03 (0.004 - 0.11)	0.29 (0.05 - 0.70)	0.71 (0.65 - 0.78)
	No	70 (97.2%)	172 (97.2%)				

There were 1 123 charts of children diagnosed with tonsillitis screened.639 children were excluded (148 had absent throat cultures and/or RADT, 108 had comorbidities, 220 were not included in the age group of our study,163 had missing WBC and/or CRP). So,484 children were included in this study.

There was no statistically significant difference between the 2 study subgroups regarding demographic, clinical findings, RADT/throat culture positive GAS result, WBC and CRP positive, Centor score, and antibiotic prescription (All p-values > 0.05). (Table 1)

The association between Centor score and the number of patients with GAS positive is listed in Table 2. As Centor score increased from 0 to 4 the number of GAS positive patients increased from 0 (n=0) to 42% (n=54) with a significant p- value ($p < 0.001$). (Table 2)

Tables 3, 4 and 5 summarize the specificity, sensitivity, NPV and PPV values and the 95% confidence intervals (95% CI) for those who met ≤ 2 and ≥3 Centor scores in all age groups, group 1 and group 2 respectively.

In all age groups: The specificity, sensitivity, NPV and PPV values for a Centor Criteria Score of 3 points or more and a positive GAS were 62% (95% CI 57 - 67), 95 % (95% CI 89 -98), 47% (95% CI 41 - 54) and 97% (95% CI 93 - 99) respectively. In patients who met ≤ 2 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity stayed the same 61% (95% CI 55 - 66) with CRP positivity, increased to 68% (95% CI 63 - 73) with WBC increase, and to 74% (95% CI 69 - 78) with both. Whereas sensitivity, PPV and NPV decreased with the addition of the lab tests of WBC and CRP and both. Furthermore, in patients who met ≥3 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity increased to 92% (95% CI 89 - 95) with CRP positivity, increased to 74% (95% CI 69 - 79) with WBC increase, and to 97% (95% CI 94 -98) with both. PPV increased to 52% (95% CI 45 -59) with WBC increase and decreased to 23% (95% CI 11 - 41) with CRP positivity and 35% (95% CI 15 - 61) with both. Moreover, sensitivity, and NPV decreased with the addition of the lab tests of WBC and CRP and both.

Similarly, in group 1: The specificity, sensitivity, NPV and PPV values for a Centor Criteria Score of 3 points or more and a positive GAS were 66% (95% CI 58 - 73), 100 % (95% CI 92 - 100), 48% (95% CI 39 - 58) and 100% (95% CI 96 - 100) respectively. In patients who met ≤ 2 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity decreased to 59% (95% CI 52 - 67) with WBC increase, stayed the same 69 % (95% CI 62 - 76) with CRP positivity, and increased to 72% (95% CI 65 - 79) with both. Whereas sensitivity, PPV and NPV decreased with the addition of the lab tests of WBC and CRP and both. Furthermore, in patients who met ≥3 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity increased to 91% (95% CI 86 - 95) with CRP positivity, increased to 75% (95% CI 68 - 81) with WBC increase, and to 97% (95% CI 92 -99) with both. PPV stayed the same 49% (95% CI 39 - 60) with WBC increase and decreased to 25% (95% CI 10 - 49) with CRP positivity and to 4 % (95% CI 14 - 73) with both. Moreover, sensitivity, and NPV decreased with the addition of the lab tests of WBC and CRP and both.

Moreover, in group 2: The specificity, sensitivity, NPV and PPV values for a Centor Criteria Score of 3 points or more and a positive GAS were 58 % (95% CI 50 - 65), 90 % (95% CI 80 -96), 47% (95% CI 38 - 55) and 94% (95% CI 87 - 97) respectively. In patients who met ≤ 2 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity increased to 67% (95% CI 60 - 74) with CRP positivity, to 62% (95% CI 54 - 69) with WBC increase, and to 76% (95% CI 69 - 82) with both. Whereas sensitivity, PPV and NPV decreased with the addition of the lab tests of WBC and CRP and both. Furthermore, in patients who met ≥3 of the Centor criteria, with the addition of the lab tests of WBC and CRP to these groups, the specificity increased to 93% (95% CI 88 - 96) with CRP positivity, to 73% (95% CI 66 - 80) with WBC increase, and to 97% (95% CI 93 -99) with both. PPV increased to 54% (95% CI 44 -64) with WBC increase and decreased to 20% (95% CI 5 - 49) with CRP positivity and 29% (95% CI 5 - 70) with both. Moreover, sensitivity, and NPV decreased with the addition of the lab tests of WBC and CRP and both.

DISCUSSION

Diagnosing GABHS by throat culture and RADT via culture swab is the most reliable way. However, the application of these tests can be cost and time consuming at a primary-care level. On the other hand, WBC and qualitative CRP are practical and cheap.[3,17,25] The widely recognized and easiest approach in terms of application at primary-care level is the clinical scoring method developed by Centor et al.

We determined culture positivity at ratios of 3, 4, 68, and 54 respectively, for 1, 2, 3, and 4 total Centor scores (Table 2). When the whole study group was examined, the ratio of cases in which GABHS was diagnosed with culture result was 94.6%,which is the highest compared to previous studies. McIsaac et al(10) determined 21.9% culture positivity in the group that included subjects >15 years of age and 34.1% culture positivity in the group including those ≤ 15 years of age. In that study,the researchers gave the ratio in children as 68.0%. Humair et al[26] found the GABHS positive ratio in their studies to be 37.6%, but their study was solely based on Centor 3 or 4 score positive cases; therefore, a high ratio is an expected result. In our study, the ratio of those with Centor 3 and 4 total score was 53 % (n=257). In this case, the sensitivity, specificity, PPV, and NPV values and CI (95% CI) of the Centor 3 and 4 total score were calculated as follows: 95% (89–98), 62% (57–67), 47% (41–54), and 97% (93–99), respectively. Bisno(4) gave the PPV for cases who met 3 or 4 of Centor criteria as 56.0% and, therefore, claimed that treatments planned according to these criteria lead to excessive antibiotic usage.

In a study performed by Maltezou et al.[27] using clinical scoring, RADT and culture positivity were found in 146 children out of 451, and they specified the sensitivity, specificity, PPV, and NPV values of the RADT as 83.1, 93.3, 82.4, and 93.6%, respectively. In that study, it was pointed out that RADT sensitivity varied from Centor 1 to 4 positive values with ratios between 60.9 and 95.8%. Therefore they claimed that all children with complaints of pharyngitis symptoms should be screened using the Centor criteria, and when the decision comes down to antibiotic prescription, it must be cross-checked with the RADT to decrease the unnecessary use of antibiotics.

Upon comparing our results to previous studies, we can notice that sensitivity of centor criteria was almost the same as that in Maltezou et al (93.6 %) and Alper et al(28)(86.1%).Moreover its specificity and consequently its positive predictive value was close to that in Alper et al (71.3%) but less than that in Maltezou et al (90%), since specificity affects PPV,and this is probably attributed to false positives in our study(who are the chronic GABHS carriers).In addition the negative predictive value was the same as that in Maltezou et al (96.6%).

Since culture decreases patient satisfaction and RADT is not economically viable, Alper et al tried to come up with a new approach. In this sense, to find an applicable approach that can be widely implemented in primary care, we tried to support the Centor criteria with simple lab tests, such as WBC and qualitative CRP.

Upon adding CRP with Centor scoring: Smeesters et al.[29] showed sensitivity of 71 % and specificity of 82 %. While In our study, sensitivity decreased (6 %).This may be explained by that CRP increases also with viral infection. In addition, we didn't tacle in our study the quantitative CRP.

WBC is an important parameter in the differentiation of bacterial and non-bacterial infections and it is a practical lab test easily performed at primary-care level.

Alper et al. showed sensitivity of approximately 81 % and specificity of 78 % when combining it with clinical scoring .However in our study, its sensitivity decreased to 77% and specificity was 74% .This may be due to that WBC may be high in some viral infections especially in adenoviral tonsillitis as reported by Putto et al.[30]

As it is known, in tests related to diagnosing an illness, sensitivity should be high for cases where an appropriate treatment exists and that does not lead to serious results. In addition, the specificity value must be kept high if unnecessary treatment of false positives leads to adverse reactions. Therefore, in cases where an illness has to be verified, we should choose a test with a high value of specificity. In particular, if a test has a high PPV that indicates the presence of the illness, then it can be used for diagnostic purposes.[31]

Limitations: It is a retrospective single center design study using a small convenience sample. However, this

small study demonstrates that testing and treatment decisions need to be tailored to the region. A larger, retrospective study on patients in the region presenting with sore throat is recommended, including following up those with sore throat and positive initial test to gain more information about chronic GAS colonization and asymptomatic GAS carriers; however, it would need appropriate funding.

CONCLUSION

As a result, in developing countries, the treatment of tonsillopharyngitis and unnecessary use of antibiotics are still serious issues. Guides based on clinical scores might be instructive for physicians. However we must take into consideration social factors, such as cost efficiency, expectations of the patient, time pressure, and the follow-up of the patient in order to make it implementable. Therefore, we propose that tonsillopharyngitis cases should be evaluated first with Centor clinical scoring to reduce unnecessary rapid diagnostic point of care (POC) test/throat culture in children presenting with sore throat.

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