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ORIGINAL ARTICLE

Detection of group a *Streptococcus* in pharyngitis by two rapid tests: comparison of the BD Veritor™ and the QuikRead go® Strep A

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Abstract

We compared the performance of two rapid antigen tests—QuikRead go® Strep A test (Orion Diagnostica, Espoo, Finland) and BD Veritor™ system (Becton, Dickinson and Company, Sparks, MD) with throat culture. Our aim was to evaluate each assay's performance and agreement compared to throat culture in order to choose one of the assays as a point-of-care test in the emergency room. One hundred throat samples were collected in triplicates from patients with suspected pharyngitis admitted to the emergency room. One throat swab was seeded for a throat culture. The other two throat swabs from each patient were analyzed at the emergency room by the QuikRead go® Strep A test, and by the BD Veritor™ system, according to each manufacturer's instructions. Agreement level between BD Veritor™ test and throat culture was 79%; sensitivity and specificity of this test were 80% and 78.7%, respectively. QuikRead go® Strep A test had an agreement level of 75% with throat culture; sensitivity and specificity of this test were 80% and 73.3%, respectively. Both tests have a good diagnostic performance. Other characteristics such as costs, size of instrument, and ease of implementation should be taken into consideration when choosing a point-of-care test.

Keywords Pharyngitis · Group A *Streptococcus* · Antibiotic treatment · Rapid tests

Introduction

Acute pharyngitis is one of the most common infections seen both at community health care facilities and emergency rooms [1]. It leads to physician visits of 20–30% of children and 5–15% of adults in the USA [2, 3]. The main diagnostic challenge is to differentiate bacterial pharyngitis, which is responsible for 15–30% and 5–15% of cases in children and adults, respectively, from viral pharyngitis, which shares the same clinical presentation [4]. Despite this, more than 60% of patients with sore throat are treated with antibiotics [5, 6]. Therefore, it is very important to distinguish between viral and bacterial pharyngitis in order to eliminate unnecessary antibiotic use and the development of resistant bacteria. On the other hand, treatment is critical when the pathogen is *Streptococcus pyogenes* (group A *Streptococcus* [GAS]), due to the possible complications it may cause, including rheumatic fever and invasive disease [7].

GAS is the most frequent bacterial pathogen responsible for bacterial sore throat. Currently, the standard method for the diagnosis of GAS pharyngitis is a throat culture. Although highly sensitive, the main disadvantage is time to identification—24 to 48 h [8]. Therefore, rapid tests for identification of GAS in throat swabs have been developed to minimize time-to-result. This advantage has further implications; for example, in cases of viral pharyngitis—reduction of inappropriate use of antibiotics, and in cases of GAS pharyngitis—rapid treatment of patients may reduce the risk and duration of contagion and consequently reduce the sick leave time [9].

One type of rapid tests is based on GAS antigen detection. These tests are easy-to-use and do not require special training or expertise in order to perform them, which means that they can be used in the clinic or at the bedside [10]. In the current

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study, we compared the performance of two rapid antigen tests—the QuikRead go® Strep A test (Orion Diagnostica Oy, Espoo, Finland) and the BD Veritor™ system (Becton, Dickinson and Company, Sparks, MD) with throat culture. Our aim was to evaluate each assay's performance and agreement compared to throat culture in order to choose one of the assays as a point-of-care test at the emergency room.

Methods

Sample collection

One hundred throat samples were collected in triplicates from patients with suspected pharyngitis admitted to the emergency room at the Poriya Baruch Padeh Medical Center, between May 2018 and September 2018. One throat swab from each patient was sent to the clinical microbiology laboratory for throat culture as part of the patient's routine care. The other two throat swabs from each patient were analyzed at the emergency room by the QuikRead go® Strep A test and by the BD Veritor™ system, according to each manufacturer's instructions. The study was approved by a Helsinki board—approval no. POR 0012-17.

Clinical and epidemiological data collection

The following clinical and epidemiological data was collected from the medical records of the patients: antibiotic treatment on the day of throat sample collection (yes/no), duration of symptoms in days, presence of fever (yes/no), tonsils status (graded 1–4 by the doctor according to swelling), exudate presence (no/still/dotted/rough/with wounds), lymph nodes presence (yes/no), difficulties in swallowing (yes/no), and health status (co-morbidities—yes/no).

Throat culture

Throat samples were collected using an Amies Agar Gel Medium Bacteriology Swab Collection System (Copan Diagnostics, Inc., CA, USA). The throat swabs were inoculated on Select Strep TSA + Defibrinated Sheep Blood agar (Hy Laboratories Ltd., Rehovot, Israel), and a MASTDISCS™ ID Bacitracin Disc (0.1 IU) (Mast Group Ltd., Merseyside, UK) was added to the agar. Among beta-hemolytic streptococci, Group A *Streptococcus*/*Streptococcus pyogenes* is the only streptococcus that is sensitive to Bacitracin; thus Bacitracin test is used as a first sorting test to discriminate between Group A *Streptococcus* and other beta-hemolytic streptococci. The agar plates were incubated at 36 ± 1 °C in 5% CO_2 for 48 h. Following incubation, the agar plates were screened for beta-hemolytic streptococci. Beta-hemolytic streptococci groups were identified using the Oxoid Streptococcal Grouping Kit (Remel Inc., Lenexa, USA).

QuikRead go® Strep A test

This test is based on nanoparticles coated with antibodies directed against Strep A. When Group A *Streptococcus* is present in the throat sample, its antigen reacts with these antibodies, resulting in turbidity change which is read by the QuikRead go instrument. Throat samples were collected with a cotton swab provided with the kit. Then, the swab was placed into an extraction tube and two drops of each extraction reagent (extraction reagents 1 and 2) were added to this tube. The swab was swirled for 30 s and incubated for further 1.5 min at room temperature. Following incubation, the solution was transferred into a cuvette, which was introduced to the QuikRead go instrument. This instrument is fully automated and displays the result following the reading of the solution's turbidity.

Possible results for the assay were: positive/negative/invalid.

BD Veritor™ test

This test is a rapid chromatographic immunoassay for qualitative detection of Group A *Streptococcus* antigen, and it is used in conjunction with the BD Veritor System Reader. The test line contains antibody coated with Group A *Streptococcus* antigen. When Group A *Streptococcus* is present in the throat sample, it reacts with a specific antibody that is conjugated onto detector particles. This complex is captured by the antigen in the test well, resulting in a positive result. Throat samples were collected with a cotton swab provided with the kit. Prior to sampling, three drops of GAS Reagent 1 were added to GAS Reagent 2 tube. Then the throat sample was taken and the swab inserted into this tube. Following incubation for 1–2 min, the swab was plunged up and down for 15 s and then removed. Three drops of the solution were transferred into the sample well. Following incubation for 5 min at room temperature, the device was introduced into the BD Veritor System Reader which displays the test result. Possible results for the assay were: Strep +/Strep –/CONTROL INVALID. In cases of CONTROL INVALID, the sample was retested.

Data analysis

We used the throat culture as the reference method for calculating sensitivity, specificity, and negative and positive predictive values. Therefore, specimens that were found positive or negative by a throat culture were defined as "True Positive" or "True Negative", respectively. Overall agreement, sensitivity, and specificity rates were calculated with corresponding 95% CI (confidence intervals) for analyzing the agreement between

each of the tested methods vs. the reference (throat culture) for identifying positive diagnosis. All tests were two-tailed, and a *p* value of 5% or less was considered statistically significant. Data was analyzed using SAS® version 9.3 (SAS Institute, Cary, NC, US).

Results

One hundred throat swabs were collected in triplicates; 25 (25%) were found positive and 75 (75%) were found negative for Strep A by throat culture.

Overall agreement between methods

The results of 79 (79%) samples tested by BD Veritor™ test were concordant with their throat culture results (Table 1). Out of 100 samples tested by QuikRead go® Strep A test, 75 (75%) samples had a concordant result to the throat culture result.

Assay performance

Five (5%) samples had a false negative result and 16 (16%) samples out of 75 negative samples were false positive when analyzed by BD Veritor™ test. Therefore, the sensitivity and specificity of this test were 80% and 78.7%, respectively (Table 1). The QuikRead go® Strep A test had also 5 (5%) false negative results. This test had a higher proportion (20%) of false positive results, compared to the BD Veritor™ test. The sensitivity and specificity of QuikRead go® Strep A test were 80% and 73.3%, respectively. Both PPV and NPV of the BD Veritor™ test were higher compared to QuikRead go® Strep A test.

Assay performance in sub-groups

Antibiotic treatment

We further wanted to evaluate the assays' performance in sub-groups of the study population. For example, we compared the performance of the two tests between patients that received antibiotic treatment with patients who were not treated with antibiotics. Among 61 patients that were antibiotic-treated, 8 (13.1%) were positive by throat culture. The overall agreement between culture and BD Veritor™ test results was 72.1% (Table 2).

Among non-treated patients, 17 (43.6%) out of 39 patients had a positive result by culture. The overall agreement between culture and BD Veritor™ test results was higher compared to the antibiotic-treated group (89.7% compared to 72.1%, respectively). Additionally, both sensitivity and specificity of the test were higher than those of the treated group (94.1% and 86.4%, compared to 50.0% and 75.5%, respectively). The PPV of the BD Veritor™ test was very low (23.5%) in the antibiotic-treated group. In contrast, the PPV of the non-treated group was high (84.2%). The NPV of both groups were high (90.9% and 95.0% for the treated- and non-treated groups, respectively) (Table 2). As for QuikRead go® Strep A test, the overall agreement with culture results among the treated group was 62.3% (Table 3), lower than the overall agreement of the BD Veritor™ test with culture results. The sensitivity and specificity of this test among antibiotic-treated patients were 50.0% and 64.1%, respectively.

Among the non-treated patients, the overall agreement between culture and QuikRead go® Strep A test results was higher compared to the antibiotic-treated group (94.9% compared to 62.3%, respectively). Additionally, it was higher than the overall agreement of the BD Veritor™ test with culture results in the same group, which was 89.7% (Table 2). Both sensitivity and specificity of the test were higher than those of the treated group (94.1% and 95.5%, compared to 50.0% and 64.1%, respectively) (Table 3). While the PPV of the QuikRead go® Strep A test was very low (17.5%) in the antibiotic-treated group, the PPV of the non-treated group was high (94.1%). The NPV of both groups were high (89.5% and 95.5% for treated- and non-treated group, respectively).

Disease symptoms duration

Another analysis of assays' performance was in regard to the duration of disease symptoms; we divided the patients into two groups—one for patients whose symptoms started 2 days

Table 1 Overall agreement and assay performance of the tested assays

Assay	Overall agreement[a]	Sensitivity[a]	Specificity[a]	PPV[a, b]	NPV[a, c]
BD Veritor™ test	79 (69.9–58.9)	80.0 (60.9–91.1)	78.7 (68.1–86.4)	55.6 (39.6–70.5)	92.2 (82.6–97.0)
QuikRead go® Strep A test	75 (65.6–82.5)	80.0 (60.9–91.1)	73.3 (62.4–82.0)	50.0 (35.2–64.8)	91.7 (81.5–96.8)

[a] Values are presented in percentages, 95% confidence interval is shown in parentheses

[b] *PPV*, positive predictive value

[c] *NPV*, negative predictive value

Table 2 Performance of the BD Veritor™ test in sub-groups

Sub-group (*N*)	Overall agreement[a]	Sensitivity[a]	Specificity[a]	PPV[a, b]	NPV[a, c]
Antibiotic treatment					
Yes (61)	72.1 (59.8–81.9)	50.0 (21.5–78.5)	75.5 (62.4–85.1)	23.5 (9.5–47.8)	90.9 (78.7–97.0)
No (39)	89.7 (75.8–96.5)	94.1 (73.0–98.9)	86.4 (66.7–95.2)	84.2 (61.6–95.3)	95 (74.6–99.9)
Disease duration					
Group A ≤ 2 d (43)	78.6 (63.8–88.5)	91.7 (64.6–98.5)	73.3 (55.5–85.8)	57.9 (36.2–76.9)	95.6 (77.3–99.9)
Group B > 2 d (57)	80.7 (68.5–89.0)	69.2 (42.4–87.3)	84.1 (70.6–87.3)	56.2 (33.2–76.9)	90.2 (76.9–96.7)

[a] Values are presented in percentages, 95% confidence interval is shown in parentheses

[b] *PPV*, positive predictive value

[c] *NPV*, negative predictive value

or less (Group A) before the throat sampling and the second for patients whose symptoms started more than 2 days prior to sampling (Group B). Among 42 patients from group A, 12 (28.57%) were positive by throat culture. Thirteen (22.81%) patients out of 57 from group B had a positive culture result. The overall agreement between culture and BD Veritor™ test results was similar in group A and group B (78.6% and 80.7%, respectively) (Table 2). The sensitivities and specificities of this test were 91.7% and 73.3% for group A and 69.2% and 84.1%, for group B, respectively. The PPV of the BD Veritor™ test was low in both groups A and B (57.9% and 56.2%, respectively). In contrast, the NPV of both groups were high (95.6% and 90.2% for groups A and B, respectively) (Table 2). As for the QuikRead go® Strep A test, the overall agreement between culture and the test results was higher in group A compared to group B (80.9% and 71.9%, respectively) (Table 3). The sensitivities and specificities of this test were 91.7% and 76.7% for group A and 69.2% and 72.7% for group B, respectively. Similar to the results of BD Veritor™ test, the assay performance was better when symptoms' duration was of 2 days or less. The PPV of the QuikRead go® Strep A test was much lower in group B compared to group A (42.9% and 61.1%, respectively). The NPV of both groups were high (95.8% and 88.9% for groups A and B, respectively) (Table 3).

Comparative analysis of positive results

In order to identify which clinical symptoms affect the result of each test to yield a positive result, we tested the correlations of the total number of positive results (by each test) and specific symptoms. Culture test results were affected only by the presence of fever; while 28.73% (25/87) of the patients who had a fever got a positive result, 0% (0/13) of the patients without fever had a positive result ($p = 0.0256$) (data not shown). BD Veritor™ test results were also affected only by fever, as positive result was obtained for 40.3% (35/87) of the patients with fever, compared to 7.7% (1/13) of patients without fever ($p = 0.0226$) (Table 4). In contrast, the presence of fever did not influence the results of the QuikRead go® Strep A test (Table 5). Both tonsils status and exudate presence affected test's results ($p = 0.016$, $p = 0.001$, respectively).

Discussion

The goal of this study was to evaluate the diagnostic performance and accuracy of two rapid antigen tests for the detection of GAS in throat swabs, compared with the gold standard method—culture. Overall, the sensitivities and specificities of the two assays, BD Veritor™ test and QuikRead go® Strep A

Table 3 Performance of the QuikRead go® Strep A test in sub-groups

Sub-group (*N*)	Overall agreement[a]	Sensitivity[a]	Specificity[a]	PPV[a, b]	NPV[a, c]
Antibiotic treatment					
Yes (61)	62.3 (49.7–73.4)	50.0 (21.5–78.5)	64.1 (50.7–75.7)	17.5 (6.4–37.7)	89.5 (75.3–96.4)
No (39)	94.9 (82.2–99.5)	94.1 (73.0–98.9)	95.5 (78.2–99.2)	94.1 (71.1–99.9)	95.5 (76.5–99.9)
Disease duration					
Group A ≤ 2 d (43)	80.9 (66.4–90.3)	91.7 (64.6–98.5)	76.7 (59.1–88.2)	61.1 (38.5–79.8)	95.8 (78.1–99.9)
Group B > 2 d (57)	71.9 (59.1–82.0)	69.2 (42.4–87.3)	72.7 (58.1–83.6)	42.9 (24.4–63.5)	88.9 (74.1–96.2)

[a] Values are presented in percentages, 95% confidence interval is shown in parentheses

[b] *PPV*, positive predictive value

[c] *NPV*, negative predictive value

test, were quite similar. Regarding the BD Veritor™ test, a previous study found lower sensitivity (76.2%) and higher specificity (93.6%) [8]. The sensitivity and specificity of the QuikRead go® Strep A test were lower than what we expected to find, according to a previous study that reported on a sensitivity of 91% and a specificity of 85% [11]. These differences may result from differences in the experience and expertise of the medical staff who collected the throat swabs. If patients had a small number of GAS colonies, inadequate sampling may have resulted in a negative result. It was found that the performance of rapid antigen detection tests (RADT) is correlated with the inoculum size in culture and the quantity of antigen; the higher the colony count, the higher the sensitivity [12–16]. It was suggested that a false negative RADT may represent chronic colonization with GAS rather than infection [9]. The sensitivity of RADT was also found to be influenced by the patient's clinical symptoms (called "spectrum bias"); the more clinical features, the higher the test's sensitivity [13, 17]. Lastly, differences in the study population may also explain the diverse values of sensitivity and specificity of RADT in different studies.

In the current study, we had a great number of false positive results detected by both BD Veritor™ test and QuikRead go® Strep A test (16% and 20%, respectively). It was suggested that these false positives result from the presence of other strains of Streptococci that share the group A carbohydrate antigen with GAS, such as some *Streptococcus milleri* strains [18, 19].

Table 4 Comparative analysis of positive results by the BD Veritor™ test

Clinical symptoms (*N*)	Positive (*N*, %)	Negative (*N*, %)	*p* value
Tonsils status			
1 (18)	4 (22.2)	14 (77.7)	0.093
2 (25)	6 (24.0)	19 (76.0)	
3 (47)	20 (43.0)	27 (58.0)	
4 (10)	6 (60.0)	4 (40.0)	
Exudate			
No (11)	2 (18.2)	9 (81.8)	0.410
Still (21)	9 (42.8)	12 (57.2)	
Dotted (12)	4 (33.3)	8 (66.7)	
Rough (53)	21 (39.6)	32 (60.4)	
With wounds (3)	0 (0)	3 (100)	
Lymph nodes			
Yes (64)	24 (37.5)	40 (62.5)	0.677
No (36)	12 (33.3)	24 (66.7)	
Difficulties in swallowing			
Yes (79)	28 (35.4)	51 (64.6)	0.821
No (21)	8 (38.1)	13 (61.9)	
Fever			
Yes (87)	35 (40.3)	52 (59.7)	*0.023*
No (13)	1 (7.7)	12 (92.3)	
Co-morbidities			
Yes (80)	30 (37.5)	50 (62.5)	0.532
No (20)	6 (30.0)	14 (70.0)	

*Italic, statistically significant

Table 5 Comparative analysis of positive results by QuikRead go® Strep A test

Clinical symptoms (*N*)	Positive (*N*, %)	Negative (*N*, %)	*p* value
Tonsils status			
1 (18)	4 (22.2)	14 (77.8)	
2 (25)	6 (24.0)	19 (76.0)	
3 (47)	23 (48.9)	24 (51.1)	
4 (10)	7 (70.0)	3 (30.0)	*0.016*
Exudate			
No (11)	0 (0)	11 (100)	*0.001*
Still (21)	8 (38.1)	13 (61.9)	
Dotted (12)	2 (16.6)	10 (83.3)	
Rough (53)	30 (56.6)	23 (43.4)	
With wounds (3)	0 (0)	3 (100)	
Lymph nodes			
Yes (64)	30 (46.8)	34 (53.2)	0.061
No (36)	10 (27.7)	26 (72.3)	
Difficulties in swallowing			
Yes (79)	33 (41.7)	46 (58.3)	0.483
No (21)	7 (33.3)	14 (66.7)	
Fever			
Yes (87)	37 (42.5)	50 (57.5)	0.182
No (13)	3 (23.1)	10 (76.9)	
Co-morbidities			
Yes (80)	31 (38.7)	49 (61.3)	0.610
No (20)	9 (45.0)	11 (55.0)	

*Italic, statistically significant

Both BD Veritor™ test and QuikRead go® Strep A test had a low PPV and a high NPV. From the point of view of a physician, a high NPV eases the decision-making with regard to antibiotic prescription. On one hand, physicians would not want to avoid treatment and thus expose their patient to possible complications [13]. On the other hand, a high NPV can allow reduction of the inappropriate use of antibiotics, which may expose the patient to drug side effects and bacterial resistance. It is important to mention that according to manufacturers' instructions of most RADT for GAS detection, negative results should be confirmed with throat culture. This is particularly important in cases of repeated pharyngitis cases, due to the fact that other streptococci such as streptococcus C and G rather than GAS, may cause the infection.

We further analyzed the tests' performance in sub-groups of our study population. To best of our knowledge, this is the first report that antibiotic treatment reduces the performance of RADTs. However, it is reasonable considering the fact that

RADTs are affected by inoculum size that is decreased following antibiotic treatment. Therefore, more accurate results are obtained when the patient has not yet started a treatment. One conclusion is to recommend performing RADT immediately with symptoms emergence in order to get a reliable result.

When we divided the study population according to disease duration, the sensitivities of both tests in the group of disease duration of ≤ 2 days (group A) were higher than tests' sensitivities in the group of disease duration > 2 days. These results reinforce our conclusion that RADT should be performed at the beginning of the disease for more accurate results. One possible explanation is that most patients are already treated with antibiotics that reduced the bacterial load in the throat sample, resulting in a negative result even in the presence of GAS.

Finally, we investigated the associations between clinical symptoms and positive result by any method. We found that both culture and the BD Veritor™ test results are affected by the presence of fever. This result is supported by a previous study, which showed that fever affects RADT's result [13]. In contrast, the QuikRead go® Strep A test results were not influenced by the presence of fever. Both tonsils status and exudate presence affected tests' results ($p = 0.016$, $p = 0.001$, respectively). To best of our knowledge, this is the first report with such a finding. Moreover, most studies did not test the effect of each clinical symptom separately. Instead, combined symptoms were classified according to Centor Score. Increased Centor Score was in correlation with increased sensitivity of RADTs [11, 17, 20].

BD Veritor™ test had a slightly better performance compared to QuikRead go® Strep A test in the overall study population. However, when we looked at the results in sub-groups, sometimes the QuikRead go® Strep A test had better results. Therefore, we cannot conclude unequivocally which of these RADTs is preferable. Other characteristics such as costs, size of instrument, and ease of implementation should be taken into consideration, when choosing a RADT.

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Compliance with ethical standards

The study was approved by a Helsinki board—approval no. POR 0012-17.

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

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