Original Article

Accuracy and Utility of Rapid Antigen Detection Tests for Group A Beta-Hemolytic *Streptococcus* on Ambulatory Adult Patients with Sore Throat Associated with Acute Respiratory Infections at Siriraj Hospital

Visanu Thamlikitkul MD[1], Tantawan Rachata MD[1], Sukhonthip Popum BNS[2], Pornsiri Chinswangwatanakul BNS[2], Ananya Srisomnuek BNS[2], Chakkraphong Seenama BSc[1], Cheerasook Chongkolwatana MD[3], Sunun Ongard MD[3]

[1] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[3] Department of Otorhinolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: To determine the accuracy and utility of rapid antigen detection tests for group A beta-hemolytic *Streptococcus* [GAS] on ambulatory adult patients with a sore throat associated with acute respiratory infections at Siriraj Hospital.

Materials and Methods: The study was conducted on adult patients with a sore throat associated with acute respiratory infections within five days who visited the ambulatory care services at Siriraj Hospital between January 2016 and January 2017. All patients received regular care from their responsible physicians. Information on the patients' illnesses, physical findings, diagnoses and antibiotic prescriptions were collected. Throat swabs were obtained from each patient for culture for GAS and for rapid antigen detection tests for GAS (QuickVue Dipstick Strep A test, and Sofia Strep A+ FIA). On days 3 and 7 after their hospital visit, each patient received a telephone follow-up to ascertain the clinical course of the acute respiratory infections. Several months after their hospital visits, those subjects who had had a positive throat swab culture for GAS received another telephone call to ascertain any new illness suspected of being acute rheumatic fever. The medical records of all patients with positive cultures for GAS or positive tests for rapid antigen detection of GAS at enrollment were reviewed to identify any subsequent illness suggestive of acute rheumatic fever.

Results: Three hundred sixty patients with a sore throat as their chief complaint or an accompanying symptom of an acute respiratory infection were included. The mean age of the patients was 41 years, and most were female. The median duration of sore throat was two days. Acute pharyngitis or tonsillitis was diagnosed in 42.5% of the patients. The overall prevalence of GAS in the throat swabs was 3.3%. With the presence of GAS in a throat swab being considered the gold standard for diagnosis of a GAS infection, the sensitivity and specificity of the QuickVue Dipstick Strep A test were 58.3% and 95.7%, respectively, whereas the sensitivity and specificity of Sofia Strep A+ FIA were 44.4% and 97.1%, respectively. Fifty-seven patients (15.8%) received antibiotics, of which amoxicillin was the most commonly prescribed (35.1%). For most patients, the duration of the antibiotic treatment was five to seven days. The clinical outcomes of the acute respiratory infections on day 3 after the hospital visit were "cured" in 23.3% of cases, "improved" in 72.2%, "unchanged" in 3.9%, and "become worse" in 0.6%. However, on day 7 after their hospital visits, 91.4% of the patients were cured of their acute respiratory infections, while 8.1% and 0.6% had improved or remained the same, respectively. During the several months after the initial hospital visits for a sore throat, none of the patients with a positive throat swab culture for GAS (including two patients who were not prescribed antibiotics), and none of the patients with positive rapid antigen detection tests for GAS, had a subsequent hospital visit with an illness suggestive of acute rheumatic fever. If the study patients received a rapid test, the cost of the tests to detect a case of positive throat swab cultures of GAS was between 8,200 and 9,000 Baht. Antibiotics were administered to 57 patients, but two other patients with a positive culture of GAS did not receive antibiotics. If antibiotics had been prescribed to only those patients who had more than three clinical features of the Centor criteria in 360 patients, four patients with positive throat swab cultures for GAS would not have received antibiotics. If the QuickVue Dipstick Strep A test had been performed on all 360 patients and antibiotics had been prescribed to only those patients with positive test results, five patients with positive throat swab cultures for GAS would not have received antibiotics. If antibiotics had been prescribed to only those patients who had more than three clinical features of the Centor criteria in 246 patients, four patients with positive throat swab cultures for GAS would not have received antibiotics. If Sofia Strep A+ FIA had been performed on 246 patients and antibiotics had been prescribed to only those patients who had positive test results, five patients with positive throat swab cultures for GAS would not have received antibiotics.

Conclusion: The prevalence of GAS in the throat swabs of ambulatory adult patients with a sore throat associated with acute respiratory infections was very low. The sensitivity of the QuickVue Dipstick Strep A test and Sofia Strep A+ FIA for diagnosis of GAS infection in this population was modest. In this study population, using the rapid antigen detection tests to diagnose a GAS infection and to guide the prescribing of antibiotics for adult patients with a sore throat associated with acute respiratory infections seemed to offer no significant additional clinical benefits, and it was not cost-effective.

Keywords: Rapid antigen detection test, Group A beta-hemolytic *Streptococcus*, Sore throat, Acute respiratory infections

J Med Assoc Thai 2018; 101 (4): 441-9
Website: http://www.jmatonline.com

Correspondence to:

Thamlikitkul V. Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone & **Fax**: +66-2-4125994
Email: visanu.tha@mahidol.ac.th

How to cite this article: Thamlikitkul V, Rachata T, Popum S, Chinswangwatanakul P, Srisomnuek A, Seenama C, et al. Accuracy and utility of rapid antigen detection tests for group A beta-hemolytic *Streptococcus* on ambulatory adult patients with sore throat associated with acute respiratory infections at Siriraj Hospital. J Med Assoc Thai 2018;101:441-9.

Sore throat is one of the most common presentations of adults with acute respiratory infections treated in ambulatory care settings. Acute pharyngitis has been shown to account for 1% to 2% of all visits to outpatient departments, physician offices, and emergency departments in the USA[1]. Acute pharyngitis is commonly caused by viruses, but approximately 5% to 15% of cases in adults are caused by the bacterium, group A beta-hemolytic *Streptococcus* [GAS][1].

Appropriate antibiotic therapy of acute respiratory infections caused by GAS is important to prevent rheumatic fever, acute glomerulonephritis, and suppurative complications, to decrease contagion, and to relieve symptoms[1]. A throat swab culture for GAS is considered the best diagnostic test for acute respiratory infections caused by GAS. However, throat swab cultures need several days for the test results to become available, which is not helpful if a patient needs antibiotic therapy at point-of-care.

It has been suggested that certain clinical features of patients with acute respiratory infections (namely, fever, tonsillar exudates, tender anterior cervical lymphadenopathy, and absence of cough, thus, the Centor criteria) be used to identify patients at risk of having GAS infections[1,2]. The Centor criteria have a high negative predictive value but a low positive predictive value, especially in a population with a low prevalence of GAS[3].

Given the limitations of the criteria, rapid antigen detection tests for GAS were developed. The higher-quality, immunochromatographic methods of the rapid antigen detection tests for GAS appear to be very sensitive (87% to 94%) and highly specific (92% to 95%) for diagnosis of GAS pharyngitis among adults[4]. Rapid antigen detection tests for GAS have therefore been recommended for use on patients with acute respiratory infections suspected of being a GAS infection[1,5,6].

GAS is an uncommon cause of acute respiratory infections among adult patients in Thailand[7-9]. Although some clinical features of patients with acute respiratory infections (namely, fever, tonsillar exudate/pustule, tender anterior cervical lymphadenopathy, and no cough) could identify some Thai patients at risk of having a GAS infection, up to 80% of Thai adult patients with acute respiratory infections, including acute pharyngitis, still routinely receive antibiotics[7-10]. The overuse of antibiotics for minor illnesses, including acute respiratory infections among ambulatory patients, is associated with an increased risk of adverse drug reactions, higher healthcare costs, and the development of antimicrobial resistance, even though the antibiotics are only used for a short duration[11,12].

Rapid antigen detection tests for GAS are available in Thailand, but they are seldom used in clinical practice. Therefore, the additional clinical benefit of using rapid tests on Thai patients is unknown. Two of the rapid antigen detection tests for GAS available in Thailand are the QuickVue Dipstick Strep A test and Sofia Strep A+ FIA[13,14]. The QuickVue Dipstick Strep A test employs an immunochromatography-based method, with a reported sensitivity and specificity of 92% and 98%, respectively. Sofia Strep A+ FIA utilizes a fluorescence-based immunoassay method, with a reported sensitivity and specificity of 94% each[13,14].

The objectives of the study were to determine the accuracy and utility of the rapid antigen detection tests for GAS on ambulatory adult patients at Siriraj Hospital who had presented with a sore throat associated with acute respiratory infections within five days.

Materials and Methods

The study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital. All participants signed informed consent forms. The study was conducted at the ambulatory care unit for patients under the social security scheme, the primary care unit for patients under the universal healthcare coverage scheme, and the ambulatory care unit at the Department of Otorhinolaryngology, Siriraj Hospital, Bangkok, between January 2016 and January 2017.

The eligible patients were adults who presented with a sore throat associated with acute respiratory infections within five days. All enrolled patients received regular care from their responsible physicians without using the results of the rapid tests or throat swab culture for management of those patients. Information on the patients' illnesses, physical findings, diagnoses and antibiotic prescriptions were collected.

Throat swabs were obtained from each patient by using two sterile rayon swabs, which were provided by the manufacturer of the rapid tests, to rub the posterior pharynx, both tonsils and any other area where there was redness, inflammation, or pus. One swab was immediately inoculated on to a sheep blood agar plate at point-of-care and transferred to a laboratory. The same swab was used for a rapid antigen detection test for GAS using the QuickVue Dipstick Strep A test. Another swab was used for a second, rapid antigen detection test for GAS with Sofia Strep A+ FIA.

All laboratory tests were performed at the

Infectious Diseases Laboratory of the Department of Medicine, Faculty of Medicine Siriraj Hospital. The inoculated sheep blood agar plate was incubated at 35°C in an atmosphere of 5% CO_2 for 18 to 24 hours. Identification of GAS was made by performing a catalase test and a bacitracin susceptibility test[15]. All tests for the rapid antigen detection of GAS were performed according to the manufacturers' instructions[13,14]. The QuickVue Dipstick Strep A test was performed on all patients, whereas Sofia Strep A+ FIA was performed on only 246 of the patients due to a limited budget to purchase Sofia Strep A+ FIA tests.

On days 3 and 7 after their hospital visit, each patient received a telephone follow-up to ascertain the clinical courses of their acute respiratory infections. The clinical responses could be "cured" (an absence of all, or nearly all, of the respiratory symptoms), "improved" (the respiratory symptoms were much better), "unchanged" (the respiratory symptoms remained the same) or "worse" (the respiratory symptoms were more severe). Several months after their initial hospital visit for sore throat, those patients who had a positive culture for GAS received another telephone call to ascertain any new illness suspected of being an acute rheumatic fever. In addition, to identify any subsequent illness suggestive of acute rheumatic fever, a review was conducted of the medical records of all those patients with either positive throat swab cultures for GAS or positive rapid antigen detection tests for GAS. The period of the review was from the time of enrollment in the study up to several months after the first hospital visit.

The sample size was calculated using nQuery advisor 6.01, version 5, based on the following information, 1) the sensitivity and specificity of the QuickVue Dipstick Strep A test were 92% and 98%, respectively, 2) the sensitivity and specificity of Sofia Strep A+ FIA were 94% each, 3) the acceptable variation of sensitivity and specificity of the tests for rapid antigen detection of GAS was ±7%, 4) the prevalence of GAS was 16%, and 5) the type I error was 5%. Therefore, 360 subjects and at least 58 subjects having a positive throat swab culture for GAS were needed.

Statistical analyses of the study results were carried out using descriptive statistics, Chi-square test, Fisher's exact test, or Student's t-test, as appropriate. A *p*-value of 0.05 or less was considered statistically significant.

Results

Analyses were made of 360 patients with sore throats associated with acute respiratory infections within five days. Those patients had had throat swab samples collected and had received telephone follow-up to ascertain the clinical courses of the acute respiratory infections on days 3 and 7 after their first hospital visits.

The demographics and clinical features of the patients are at Table 1. The mean age of the patients was 41 years, and most were female. The majority visited the ambulatory care unit for patients covered by the social security scheme. All patients either had a sore throat as their main complaint or an accompanying symptom of an acute respiratory infection. Other common concomitant symptoms were cough, rhinorrhea, and fever. One third of the patients had underlying diseases, e.g., hypertension, diabetes mellitus, allergic rhinitis.

Table 1. Demographics and clinical features of 360 patients

Parameters	Results, n (%)
Female	276 (76.7)
Age (years)	
Mean ± SD	40.9±12.9
Median (range)	39 (18 to 81)
Location of ambulatory care	
Social Security Service Unit	323 (89.7)
Department of Otorhinolaryngology	35 (9.7)
Primary Care Unit	2 (0.6)
Patients with underlying diseases	121 (33.6)
Symptom and sign of acute respiratory infections	
Sore throat	360 (100)
Fever	163 (45.3)
Nasal stuffiness	45 (12.5)
Rhinorrhea	175 (48.6)
Sneeze	36 (10.0)
Cough	233 (64.7)
Hoarseness of voice	42 (11.7)
Headache	101 (28.1)
Myalgia	102 (28.3)
Malaise	13 (3.6)
No injection of pharynx	88 (24.4)
Mild injection of pharynx	239 (66.4)
Moderate injection of pharynx	31 (8.6)
Severe injection of pharynx	1 (0.3)
Tonsillar exudate or pustule	12 (3.3)
Tender anterior cervical lymphadenopathy	11 (3.1)
Duration of illness prior to the current hospital visit (days)	
Mean ± SD	2.9±0.8
Median (range)	2 (1 to 4)
History of using antibiotic for the current illness prior to hospital visit	47 (13.1)
Diagnosis of acute respiratory infections	
Common cold	195 (54.2)
Pharyngitis/tonsillitis	153 (42.5)
Others (acute sinusitis, acute laryngitis, acute bronchitis)	12 (3.3)

On physical examination, most patients had a mild injection of the pharynx. Tonsillar exudates (or pustules), and tender anterior cervical lymphadenopathy were observed in 6.4% of the patients. The median duration of the symptoms was two days. Only 13% of the patients had a history of taking antibiotics prior to their hospital visit. The common cold was the most common diagnosis (54.2%) of the patients who presented with a sore throat associated with acute respiratory infections. Acute pharyngitis/tonsillitis was diagnosed in 42.5% of the patients. Other less common diagnoses (3%) were acute sinusitis, acute laryngitis, and acute bronchitis.

The laboratory test results of the patients are at Table 2. Of the 360 patients who had had throat swabs done for culture and a QuickVue Dipstick Strep A test, the overall prevalence of GAS in the swabs was 3.3%. As for the 246 patients who had had throat swabs done for culture and Sofia Strep A+ FIA, the overall prevalence of GAS in the swabs was 3.7%. This figure was not significantly different from the overall prevalence among the 360 patients ($p = 0.8$). The prevalence of a positive culture for GAS among the patients who had visited the ambulatory care unit for people covered by the social security scheme tended to be less than that for the patients who received medical care from the Department of Otorhinolaryngology (2.8% vs. 8.6%, $p = 0.1$).

The QuickVue Dipstick Strep A test was positive for 6.1% of the 360 patients, whereas Sofia Strep A+ FIA was positive for 4.5% of the 246 patients tested. Nevertheless, the difference in the prevalence for the positive QuickVue Dipstick Strep A test results and the Sofia Strep A+ FIA results was not statistically significant (6.1% versus 4.5%, $p = 0.3$). The number of patients with a positive throat swab culture for GAS, and/or a positive QuickVue Dipstick Strep A test, and/or a positive Sofia Strep A+ FIA, was 32. This figure was comprised of five patients with a positive culture alone, 13 with a positive QuickVue Dipstick Strep A test alone, five with a positive Sofia Strep A+ FIA alone, three with both a positive culture and a positive QuickVue Dipstick Strep A test, two with both a positive QuickVue Dipstick Strep A test and a positive Sofia Strep A+ FIA, and four with all three, a positive culture, a positive QuickVue Dipstick Strep A test, and a positive Sofia Strep A+ FIA. Recognizing that the presence of GAS in a throat swab is considered to be the gold standard for diagnosis of a GAS infection, the sensitivity and specificity of the QuickVue Dipstick Strep A test were 58.3% and 95.7%, respectively. The sensitivity and specificity of Sofia Strep A+ FIA were 44.4% and 97.1%, respectively. As for the negative rapid antigen detection test results, five out of the 12 patients (41.2%) with a positive culture for GAS had a negative QuickVue Dipstick Strep A result. Similarly, five out of the nine patients (55.6%) with a positive culture for GAS had a negative Sofia Strep A+ FIA result.

The antibiotic treatment and the treatment outcomes of all 360 patients are at Table 3. None of the 12 patients (0%) with a positive throat swab culture for GAS had a history of taking antibiotics prior to their hospital visits. By comparison, two out of the 22 patients (9.1%) with a positive QuickVue Dipstick Strep A test, and two out of the 11 patients (18.2%) with a positive Sofia Strep A+ FIA result,

Table 2. Laboratory test results

Findings	Results, n; % (95% CI)
Presence of GAS in throat swabs of 360 patients	12/360; 3.3 (1.9 to 5.7)
QuickVue Dipstick Strep A test of 360 patients	
Positive test	22/360; 6.1 (4.1 to 9.1)
Sensitivity	7/12; 58.3 (32.0 to 80.7)
Specificity	333/348; 95.7 (93.0 to 97.4)
Presence of GAS in throat swabs of 246 patients	9/246; 3.7 (1.9 to 6.8)
Sofia Strep A+ FIA of 246 patients	
Positive test	11/246; 4.5 (2.5 to 7.8)
Sensitivity	4/9; 44.4 (18.9 to 73.3)
Specificity	230/237; 97.1 (94.0 to 98.6)

CI = confidence interval; GAS = group A beta-hemolytic *Streptococcus*

Table 3. Antibiotic treatment and treatment outcomes of 360 patients

Parameters	Results, n (%)
Overall prevalence of antibiotic prescription	57 (15.8)
Amoxicillin	20 (35.1)
Coamoxiclav	14 (24.6)
Roxithromycin	12 (21.1)
Clarithromycin	9 (15.8)
Azithromycin	1 (1.8)
Duration of antibiotic prescription	
5 days	24 (42.1)
6 days	1 (1.8)
7 days	30 (52.6)
10 days	2 (3.5)
Clinical outcomes of the patients on day 3 after hospital visits	
Cured	84 (23.3)
Improved	260 (72.2)
Unchanged	14 (3.9)
Worse	2 (0.6)
Clinical outcomes of the patients on day 7 after hospital visits	
Cured	329 (91.4)
Improved	29 (8.1)
Unchanged	2 (0.6)

gave a history of taking antibiotics. However, the differences in the frequency of taking antibiotics among the patients in these three groups were not statistically significant (0% versus 9.1% versus 18.2%, $p = 0.3$). Fifty-seven patients received antibiotics, giving an overall prevalence of antibiotic treatment of 15.8%. The prevalence of antibiotic prescription for the patients who visited the ambulatory care unit under the social security scheme was significantly less than that for patients who received medical care from the Department of Otorhinolaryngology (9.6% versus 74.2%, $p<0.001$). Amoxicillin was the most commonly used antibiotic (35.1%), followed by co-amoxiclav (24.6%), roxithromycin (21.1%), clarithromycin (15.8%), and azithromycin (1.8%). The duration of antibiotic treatment for the vast majority of patients who received antibiotics was five to seven days, with only two patients (3.5%) receiving a 10-day course of antibiotics. Antibiotics were given to 10 of the 12 patients (83.3%) with a positive throat swab culture for GAS. In contrast, eight of the 22 patients (45.5%) with a positive QuickVue Dipstick Strep A test, and five of the eleven patients (45.5%) with a positive Sofia Strep A+ FIA result ($p = 0.03$), received antibiotics.

On day 3 after the patients' hospital visit, the clinical outcomes of the acute respiratory infections were "cured" at 23.3%, "improved" at 72.2%, "unchanged" at 3.9%, and "become worse" at 0.6%. However, on day 7 after their hospital visits, 91.4% of the patients were "cured", while 8.1% and 0.6% had "improved" or "remained the same", respectively. Eight of the twelve patients with a positive throat swab culture for GAS (including two patients who did not receive antibiotics) were available for telephone follow-up several months after their hospital visits. None of them had had an illness suggestive of acute rheumatic fever during that period. A medical record review was also conducted of all 32 patients with positive throat swab cultures for GAS or with positive tests for rapid antigen detection of GAS. The review covered the period from enrollment up to several months after the initial hospital visits. No subsequent hospital visits by the patients for an illness suggestive of acute rheumatic fever were identified.

The hospital physicians decided to prescribe antibiotics for 57 patients, based solely on their judgement of the patients' conditions and without knowledge of the throat swab culture or rapid test results. Analysis of the study data shows that two patients with a positive throat swab culture for GAS did not receive antibiotics, while 45 of the 57 patients received unnecessary antibiotics.

If the decision to prescribe antibiotics had been based on a positive test result of the QuickVue Dipstick Strep A test (which was performed on all 360 patients), the total cost of doing those tests would have been approximately 108,000 Baht. This equates to 9,000 Baht to detect each case of positive throat swab culture for GAS. The 22 patients with a positive QuickVue Dipstick Strep A test would have received antibiotics. Only seven of those 22 patients had a positive throat swab culture for GAS, while five did not. Therefore, this means that 15 patients would have received unnecessary antibiotics. In addition, a further five patients who had a positive throat swab culture for GAS but who were not identified by the QuickVue Dipstick Strep A test would not have received antibiotics. Similarly, if the decision to prescribe antibiotics had been based on a positive test result of the Sofia Strep A+ FIA (which was performed on 246 patients of the 360 patients), the total cost of doing those tests would have been approximately 73,800 Baht. This equates to 8,200 Baht to detect each case of positive throat swab culture for GAS. The findings show that 11 of the 246 patients had a positive Sofia Strep A+ FIA result, so they would have received antibiotics. However, as only four of those patients also had a positive throat swab culture for GAS, the remaining seven patients would therefore have received unnecessary antibiotics. Moreover, five other patients who had had a positive throat swab culture for GAS but a negative Sofia Strep A+ FIA result would not have received antibiotics.

Among the 360 patients who had throat swab cultures and a QuickVue Dipstick Strep A test, 15 patients had three or more clinical features of the Centor criteria. Eight of those 15 patients had a positive throat swab culture for GAS, while the other seven had a negative throat swab culture. If the decision to prescribe antibiotics had been based solely on having three or more clinical features of the Centor criteria, 15 patients would have received antibiotics. On the other hand, four patients who had a positive throat swab culture for GAS but less than three clinical features of the Centor criteria would not have received antibiotics. By comparison, if the results of only the QuickVue Dipstick Strep A test had been used to guide the prescribing of antibiotics, i.e., without any consideration of the clinical features of the Centor criteria, five patients would not have received antibiotics. Of the 246 patients who had throat swab cultures and Sofia Strep A+ FIA performed, 10 patients had three or more clinical features of the Centor criteria.

Of those 10, five had positive throat swab cultures for GAS, but five had negative throat swab cultures. If antibiotics had been given only to the patients who had more than three clinical features of the Centor criteria, 10 patients would have received antibiotics; however, four patients who had a positive throat swab culture for GAS would not have received antibiotics. In comparison, five patients who had a positive throat swab culture for GAS but a negative Sofia Strep A+ FIA result would not have received antibiotics if the Sofia Strep A+ FIA test results had been used as the sole guide to the prescribing of antibiotics.

Discussion

The procedures for detecting GAS in the throat swabs appear to be appropriate since the swabs taken from the patients were immediately inoculated onto sheep blood agar at the point-of-care before transfer to a laboratory for identification of GAS. The prevalence of GAS infection in acute respiratory infections in this population was very low (only 3.3%, with a 95% confidence interval from 1.9% to 5.7%). This might be because most patients were middle-aged adults, and most had a sore throat as an accompanying symptom of a common cold. Nevertheless, the prevalence of GAS infection in acute respiratory infections observed in this population was comparable to the 3.8% found in a previous study on Thai patients[7].

The procedures for using the QuickVue Dipstick Strep A test and Sofia Strep A+ FIA also appear to be appropriate. The instructions for the tests provided by the manufacturers were strictly followed, and the instrument required for Sofia Strep A+ FIA was supplied by the manufacturer. Moreover, both tests for the rapid detection of GAS were performed by the same individual throughout the whole project. Therefore, the results from the throat swab cultures and from both of the tests for rapid detection of GAS are considered to be valid and reliable.

The number of positive throat swab cultures for GAS was less than the number of positive test results from the QuickVue Dipstick Strep A test and Sofia Strep A+ FIA, as described in the results section. This might be explained by the fact that the proportion of patients with positive rapid test results who had a history of taking antibiotics tended to be higher than the patients with positive throat swab cultures for GAS. While only GAS was identified in the throat swab cultures, the rapid antigen detection tests might have detected antigens of streptococci other than GAS that we were not looking for in the cultures. On the other hand, some GAS isolates from the throat swabs might have been colonizers without causing infections. However, we were unable to prove if the low prevalence of positive throat swab cultures for GAS was an underestimate or an overestimate, and we had to use it as the gold standard for the diagnosis of a GAS infection of acute respiratory infections in this population.

When we used the throat swab culture results for GAS as the gold standard for diagnosis of a GAS infection in this population, the negative results of the rapid antigen detection tests in the samples with a positive culture for GAS were considered "false negative", while the positive results of the rapid antigen detection tests in the samples with a negative culture for GAS were considered "false positive". There are many factors contributing to a "false negative" and "false positive" in the rapid detection of GAS tests. For instance, a false negative result can be associated with minute amounts of GAS antigen in the sample, and a false positive result may be associated with the presence of the antigen of a *Streptococcus* other than GAS or with the antigen of other bacteria.

The specificity values of both tests for rapid antigen detection of GAS (QuickVue Dipstick Strep A test and Sofia Strep A+ FIA) were high (95.7% to 97.1%), and they were comparable with the results from the studies (94.4% to 98%) referred to by the manufacturers in their instructions for performing the tests. However, the sensitivity values of both tests (44.4% to 58.3%) were much lower than the results from the studies (92% to 93.7%) also referred to in those instructions. This could be due to the small number of patients with a positive throat swab culture for GAS (only 12 cases instead of the 58 cases that were needed, according to the sample size calculation). Since the number of the patients with a positive throat swab culture for GAS was small, the upper bound of 95% CI of the sensitivity value of the rapid antigen detection test for GAS was up to 80.7% for the QuickVue Dipstick Strep A test and 73.3% for Sofia Strep A+ FIA. Nevertheless, the highest sensitivity values of the rapid antigen detection tests for GAS were still lower than the results from the studies cited by the manufacturers in the user instructions for the tests.

Because the sensitivity values of the QuickVue Dipstick Strep A test and Sofia Strep A+ FIA were low, the positive and negative predictive values of the QuickVue Dipstick Strep A test were 31.8% and 98.5%, respectively, whereas the positive and negative predictive values of Sofia Strep A+ FIA were 36.4%

and 97.9%, respectively. Therefore, the diagnostic parameters of the studied rapid antigen detection tests do not seem to be useful for the diagnosis of GAS infections in this population with a very low prevalence of positive throat swab culture for GAS. The QuickVue Dipstick Strep A test could not capture five out of 12 patients with a positive throat swab culture for GAS, whereas Sofia Strep A+ FIA could not capture five out of 9 patients with a positive throat swab culture for GAS.

The overall prevalence of antibiotic prescriptions was 15.8%, which was much higher than the overall prevalence of GAS infection (3.3%). Nevertheless, two patients with positive throat swab cultures for GAS did not receive antibiotics. The prevalence of GAS infections among patients attending the ambulatory care unit of the Department of Otorhinolaryngology tended to be higher than that for the other ambulatory care unit. However, the prevalence of antibiotic prescriptions for patients attending the ambulatory care unit of the Department of Otorhinolaryngology was more than eight times higher than its prevalence of GAS infections, and it was much higher than that for patients attending the other ambulatory care unit. These observations will be provided to the Department of Otorhinolaryngology in order to improve the antibiotic prescribing practices for the patients with acute respiratory infections.

Although penicillin V, which is still active against all isolates of GAS, is recommended as the first-line antibiotic for GAS sore throat due to its narrow spectrum of activity, none of the patients in this study received it[1,5,6,16]. Amoxicillin is an acceptable alternative to penicillin V due to its more favorable pharmacokinetics and more convenient dosing regimen than penicillin V. Amoxicillin was prescribed to 35.1% of the patients diagnosed as having a common cold and pharyngitis/tonsillitis. Coamoxiclav was given to 24.6% of the patients even though this agent does not provide any more significant therapeutic benefits for GAS infections since GAS has never been resistant to amoxicillin. Coamoxiclav might be considered for use with patients with acute rhinosinusitis who do not respond to amoxicillin. Roxithromycin is also an acceptable alternative to amoxicillin in the case of patients with a penicillin allergy. Macrolides should not be used as a first line antibiotic since 20% of GAS infections are resistant to macrolides, and they are more expensive than penicillin[16]. Clarithromycin and azithromycin were prescribed to 17.6% of the patients. These antibiotics should be unnecessary for therapy of GAS infections since they are less active against GAS. At the same time, they are much more expensive than penicillin, and they are associated with severe adverse events, including cardiac death[17].

Only two patients (3.5%) received a 10-day course of antibiotics, whereas 96.5% were given antibiotics for seven days or less. If the patients who received antibiotics for seven days or less really had acute respiratory infections caused by GAS, they would not have received the benefit of the prevention of the non-suppurative complications of GAS infections, such as acute rheumatic fever, because a 10-day course of antibiotic therapy is needed to prevent such complications.

Most of the patients who received or did not receive antibiotics were either cured or their symptoms of acute respiratory infections had improved by day 3, and 91.4% of all patients (including the two patients with positive throat swab cultures for GAS who did not receive antibiotics) were cured by day 7. Overall, the use of antibiotics seemed to provide no significant effects on the clinical courses of the acute respiratory infections in this population, no matter whether the patients received antibiotics or not. Amoxicillin has been reported to confer no beneficial effects for patients with non-exudative pharyngotonsillitis[18]. In addition, the use of antibiotics in this study had no effect on the occurrence of non-suppurative complications of GAS infections in this population because most patients with a positive throat swab culture for GAS reported no illness suggestive of acute rheumatic fever during the follow-up telephone interviews conducted several months after their initial hospital visits. Moreover, the medical records of all patients with positive throat swab cultures for GAS or positive tests for rapid antigen detection of GAS revealed no subsequent hospital visits for an illness suggestive of acute rheumatic fever during the period from enrollment to several months later. Nevertheless, the number of the patients with positive throat swab cultures for GAS or positive tests for rapid antigen detection of GAS in this population who might have had acute respiratory infections due to GAS could have been too small to develop a single case of non-suppurative complications.

The observations from this study imply that antibiotics may not be needed by middle-aged adults with a sore throat associated with acute respiratory infections. Only symptomatic treatment should be sufficient, along with the provision of information to the patient on the natural history and clinical course of acute respiratory infections.

The simulation of the data using the Centor criteria, the results of the QuickVue Dipstick Strep A and Sofia Strep A+ FIA tests to guide antibiotic prescription among this population, and the very low prevalence of GAS in the throat swab cultures revealed that the number of the patients who had positive throat swab cultures for GAS but did not receive antibiotics based on the Centor criteria was comparable to the number of the patients who had positive throat swab cultures for GAS but did not receive antibiotics based on the rapid test results Moreover, the cost of detecting a case of GAS infection by using rapid tests on all patients in a population that has a very low prevalence of GAS infection is very high.

Therefore, in this study's population, basing the decision to prescribe antibiotics for adults with sore throats associated with acute respiratory infections on the results of the QuickVue Dipstick Strep A or Sofia Strep A+ FIA tests would not have been as cost-effective as using the Centor criteria alone.

It should be noted that, in this study, the middle-aged adults with a sore throat associated with acute respiratory infections might not have needed antibiotics. This is because the prevalence of GAS infection in the present review was only 3.3%. An earlier study, which analyzed the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention, had recommended that in populations where the prevalence of GAS infections is less than 5%, the most appropriate course of action is not to treat patients with antibiotics[19]. Our study also found that patients who had three or more clinical features of the Centor criteria had a 53.3% probability of having a GAS infection. Research has established that antibiotics should be prescribed to all patients with three or more clinical features of the Centor criteria because treating all patients with penicillin is the most appropriate option when the prevalence of GAS infections is greater than 20%[19].

Still, the use of rapid antigen detection tests for GAS may prove to be both beneficial and cost-effective in a population with a higher prevalence of GAS as a causative agent of acute respiratory infections, such as adolescents and young adults. Therefore, a clinical study on the accuracy and utility of the rapid antigen detection tests for GAS on adolescents and young adults should be performed.

What is already known on this topic?

The guidelines for the management of ambulatory adult patients with a sore throat suggest that a rapid antigen detection test for GAS should be performed on patients suspected of having GAS infection, and that antibiotics should be prescribed if the test results are positive.

What this study adds?

The two rapid antigen detection tests for GAS that were examined (QuickVue Dipstick Strep A test and Sofia Strep A+ FIA) had a low sensitivity and were not cost-effective for use on Thai adult patients with a sore throat associated with acute respiratory infections, given that there was a very low prevalence of GAS in the throat swab cultures.

Acknowledgement

The authors would like to thank the personnel at the ambulatory care unit for the patients under social security scheme, the primary care unit for the patients under the universal healthcare coverage scheme, and the ambulatory care unit at the Department of Otorhinolaryngology, Siriraj Hospital, for their assistance. The authors are also grateful to Z-medic Co., Ltd. for providing some rapid tests and testing resources for use in the rapid antigen detection of GAS.

Funding disclosure

The study was supported by the Thai Health Promotion Foundation Fund, and by the Health Systems Research Institute (Thailand).

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Cooper RJ, Hoffman JR, Bartlett JG, Besser RE, Gonzales R, Hickner JM, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. Ann Intern Med 2001;134: 509-17.
2. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1981; 1:239-46.
3. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? JAMA 2000;284:2912-8.
4. Stewart EH, Davis B, Clemans-Taylor BL, Littenberg B, Estrada CA, Centor RM. Rapid antigen group A streptococcus test to diagnose pharyngitis: a systematic review and meta-analysis. PLoS One 2014;9:e111727.

5. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis 2012;55:1279-82.
6. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: Advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016;164:425-34.
7. Asawapokee N, Pruksachartvuthi S, Aswapokee P, Charoensuk B, Leelarasamee A. Differentiation of streptococcal and nonstreptococcal sore throat by clinical features. J Infect Dis Antimicrob Agents 1984;3:141-5.
8. Treebupachatsakul P, Tiengrim S, Thamlikitkul V. Upper respiratory tract infection in Thai adults: prevalence and prediction of bacterial causes, and effectiveness of using clinical practice guidelines. J Med Assoc Thai 2006;89:1178-86.
9. Boonyasiri A, Thamlikitkul V. Effectiveness of multifaceted interventions on rational use of antibiotics for patients with upper respiratory tract infections and acute diarrhea. J Med Assoc Thai 2014;97(Suppl 3):S13-9.
10. Thamlikitkul V, Apisitwittaya W. Implementation of clinical practice guidelines for upper respiratory infection in Thailand. Int J Infect Dis 2004;8:47-51.
11. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096.
12. Bryce A, Costelloe C, Hawcroft C, Wootton M, Hay AD. Faecal carriage of antibiotic resistant Escherichia coli in asymptomatic children and associations with primary care antibiotic prescribing: a systematic review and meta-analysis. BMC Infect Dis 2016;16:359.
13. Instructions for testing. QuickVue Dipstick Strep A test. San Diego, CA: Quidel Corporation; 2015.
14. Instructions for testing. Sofia Strep A+ FIA. San Diego, CA: Quidel Corporation; 2017.
15. Spellerberg B, Brandt C. Laboratory diagnosis of Streptococcus pyogenes (group A streptococci). In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic biology to clinical manifestations. Oklahoma City, OK: University of Oklahoma Health Sciences Center; 2016:1-16.
16. Kim S. Optimal diagnosis and treatment of group A streptococcal pharyngitis. Infect Chemother 2015;47:202-4.
17. Svanström H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: Cohort study. BMJ 2014;349:g4930.
18. Leelarasamee A, Leowattana W, Tobunluepop P, Chub-upakarn S, Artavetakun W, Jarupoonphol V, et al. Amoxicillin for fever and sore throat due to non-exudative pharyngotonsillitis: beneficial or harmful? Int J Infect Dis 2000;4:70-4.
19. Tompkins RK, Burnes DC, Cable WE. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med 1977;86:481-92.