

PREVALENCE OF GROUP A BETA-HEMOLYTIC STREPTOCOCCAL PHARYNGITIS IN CHILDREN WITH ACUTE SORE THROAT, NARESUAN UNIVERSITY HOSPITAL, PHITSANULOK, THAILAND (MAY 2016 - APRIL 2017)

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Abstract. Streptococcal pharyngitis is a common bacterial pharyngotonsillitis in a pediatrics outpatient department setting. A rapid antigen detection test (RADT) was used in a prospective study in diagnosing group A beta-hemolytic streptococci (GAS) in children 1-15 years of age with fever and sore throat. Throat swabs were collected for culture and RADT from children ($n = 134$, median age = 5 years) experiencing fever and sore throat within the previous seven days of symptoms onset, who were treated at the Pediatric Outpatient Department, Naresuan University Hospital, Phitsanulok, Thailand from May 2016 to April 2017. All patients received regular care from physicians and information on patients' illness, diagnoses and antibiotic prescribed were collected. Acute pharyngitis was diagnosed in 43% of the children and GAS detected in 7% of throat swab cultures, with a prevalence of GAS pharyngitis of 7% (95% confidence interval (CI): 3-12). All GAS isolates were susceptible to chloramphenicol, penicillin and vancomycin, and 70% resistant to tetracycline. RADT demonstrated a sensitivity of 90% (95% CI: 85-95) and specificity of 91% (95% CI: 86-96), with positive and negative predictive value of 45 and 99%, respectively. In conclusion, the study shows low prevalence of GAS in children with acute pharyngitis and empirical antibiotic treatment should be avoided until a definitive diagnosis of GAS infection has been made.

Keywords: children, group A streptococcal pharyngitis, rapid antigen detection test, sore throat

INTRODUCTION

Fever with sore throat is one of the

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most frequently reported complaints among pediatric outpatients and is usually of viral origin (DuBose, 2002). However, it is difficult to diagnose pharyngitis stemming from viral or group A beta-hemolytic streptococci (GAS) infection just from signs and symptoms (Esposito *et al*, 2004). The majority of cases related bacterial pharyngotonsillitis is due to GAS, with prevalence depending on age group, namely, 20-30% in children and

5-15% in adults, and rarely due to group C and G streptococci, *Corynebacterium diphtheriae* or *Fusobacterium necrophorum* (Carapetis *et al*, 2005; Lindbaek *et al*, 2005; Shulman *et al*, 2012; Cohen *et al*, 2016). Clinical signs and symptoms of pharyngitis due to GAS are generally nonspecific and difficult to diagnose from viral causes such as adenovirus and Epstein-Barr virus (Green, 1998). Infectious mononucleosis from Epstein-Barr virus infection presents with exudative tonsillitis, cervical lymphadenopathy and maculopapular rash (Johannsen and Kaye, 2015). Petechiae in palate and diffused scarlatiniform body rash are distinctive of streptococcal infection but otherwise are uncommon (Cohen *et al*, 2016). Appropriate treatment following detection of the causative agent can prevent subsequent suppurative and non-suppurative post-infection sequelae, such as acute rheumatic fever, post-streptococcal glomerulonephritis and other immunologically mediated pathologies (Gerber *et al*, 2009).

Throat swab culture and rapid antigen detection test (RADT) are able to distinguish difference between GAS and viral pharyngitis (Shulman *et al*, 2012). Accurate diagnosis enables appropriate antibiotic treatment to prevent complications and transmission, and shortens course of the disease (Wessels, 2011). The gold standard in confirming GAS pharyngitis diagnosis is examining throat swab cultures for beta-hemolytic colonies (Colletti and Robinson, 2005). Recent antibiotic use, culture procedures and specimen integrity are common factors, which can affect outcome of bacterial culture tests (Felsenstein *et al*, 2014). Tests based on cultures take up to 48 hours to obtain results, thereby delaying appropriate antimicrobial

treatment. RADT was introduced to provide a more rapid diagnosis of GAS pharyngotonsillitis, identifying group A bacterial cell wall carbohydrates from an immunological assay from throat swab sample within a few minutes (Armengol *et al*, 2004). RADTs have sensitivity of 70-90% and specificity >95%, allowing physicians to correctly and timely and prescribe antibiotics based on the positive results (Rimoin *et al*, 2010; Arnold and Nizet, 2012; Pelucchi *et al*, 2012). In children, overall sensitivity and specificity of RADTs is 86 and 96% respectively (Lean *et al*, 2014, Stewart *et al*, 2014). RADT has a negative predictive value of ~95%, which is sufficient to confidentially exclude GAS infection. Factors influencing RADT sensitivity include, but are not limited to, specimen integrity and personnel competency. On the other hand, a negative RADT prompts a culture test especially in regions with high prevalence of cardiac-related diseases (Leung *et al*, 2006).

Here, prevalence of children with group A streptococcal pharyngitis was determined employing both culture and a RADT (allowing validation) at Naresuan University Hospital, Phitsanulok Province, Thailand.

MATERIALS AND METHODS

Participants and study design

A prospective study involving children attending the Pediatric Outpatient Department, Naresuan University Hospital, Phitsanulok Province, Thailand, was carried out from May 2016 to April 2017. Inclusion criteria were children 1-15 years of age with fever and sore throat within the previous seven days. Exclusion criteria were children with lower respiratory tract infection, oral ulcer, herpangina, herpetic gingivostomatitis,

and immunocompromised status. Data were collected on the participants' illness, results of physical examination, diagnosis and type of prior antibiotic administered (if pertinent).

The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Naresuan University Hospital (COA no. 222/2015). Prior written consent was obtained from parents or legal guardian of each participant and assent from children 7-15 years of age.

Sample collection and laboratory tests

Each participant had two throat swabs taken by rubbing sterile rayon swab over both tonsils, posterior pharynx or in areas with exudates without touching tongue and lips. Samples for culture were immediately transported to the microbiology laboratory, Naresuan University Hospital, where they were plated onto 5% sheep blood agar (Biomedica (Thailand) Co Ltd, Nonthaburi, Thailand) and incubated at $35\pm 2^\circ\text{C}$ for 20-24 hours under a humidified atmosphere containing 5% CO_2 . Beta-hemolytic colonies were identified by Gram staining, catalase test and bacitracin susceptibility test (CLSI, 2017). The second swab was used for GAS antigen detection employing a Quicknavi™-Strep A kit (DenkaSeiken, Niigata, Japan).

Antibiogram profiling

Antimicrobial susceptibility test was carried out using disk diffusion method on Mueller sheep blood agar plate by measuring the zone of inhibition diameter according to the guidelines of Clinical Laboratory and Standards Institute (CLSI, 2017). Antimicrobial disks (Oxoid, Hampshire, UK and BD BBL™ Sensi-Disc™, NSW, Australia) contained penicillin (10 units), vancomycin (30 μg), erythromycin (15 μg), tetracycline (30 μg),

chloramphenicol (30 μg). The data were interpreted as sensitive (S), intermediate (I), or resistant (R) following CLSI criteria.

Statistical analysis

Data are presented as percent with 95% confidence interval (CI) and median with interquartile range (IQR). RADT accuracy was measured using an area under receiver operating characteristic (ROC) curve employing a STATA version 12.0 software (StataCorp, College Station, TX), with a *p*-value of 0.05 or less is considered statistically significant.

RESULTS

Children ($n = 134$), median age of 5 years (IQR = 3-8 years), 73 (54%) boys and 61 (46%) girls, were recruited (Table 1). Median duration of symptoms was 3 days (IQR = 2-3 days) and 27% of participants received antibiotic treatment prior to visiting the Hospital. Cough was the most common symptom (85%), followed by rhinorrhea (77%) and headache (45%). Physical examination revealed 84%, 28% and 27% of the children patients had tonsillar enlargement, tonsillar exudate or patch and palatal petechiae, with 43% diagnosed with acute pharyngitis (Table 1).

Following examination and diagnosis, children ($n = 92$) were treated with amoxicillin ($n = 68$; 74%), amoxicillin-clavulanate ($n = 8$; 9%), cephalosporins ($n = 7$; 8%), macrolides ($n = 6$; 6%), and other types of antibiotics (one person each received amoxicillin-clindamycin, cephalosporin-macrolide and meropenem).

Throat swab cultures indicated 21 patients (16%) with pathogenic growth, group A beta-hemolytic streptococci, *Staphylococcus aureus* and *Streptococcus pneumoniae* identified in 10 (7%), 6 (4%), and 5 (4%) of the samples, respectively.

Table 1

Demographic profiles, clinical presentations and diagnosis of children with acute sore throat attending the Pediatric Outpatient Department, Naresuan University Hospital, Phitsanulok Province, Thailand (May 2016 - April 2017).

Characteristics	Number (%) (n = 134)
Gender	
Male	73 (54)
Female	61 (46)
Age in years	
Median (IQR)	5 (3 to 8)
Age group	
1-5 years	72 (54)
>5-10 years	40 (30)
>10-15 years	22 (16)
Duration of symptoms in days, median (IQR)	3 (2 to 3)
History of antibiotic medication prior to hospital visit	36 (27)
Sign/symptom*	
Cough	114 (85)
Rhinorrhea	103 (77)
Headache	61 (45)
Malaise	51 (38)
Vomiting	37 (28)
Myalgia	36 (27)
Hoarseness of voice	35 (26)
Conjunctivitis	20 (15)
Diarrhea	12 (9)
Drooling	12 (9)
Tonsillar enlargement	113 (84)
Tonsillar exudates/ patches	38 (28)
Palatal petechiae	36 (27)
Lymph node enlargement	20 (15)
Conjunctival injection	11 (8)
Scarlatiniform rash	9 (7)
Tender at cervical lymph nodes	8 (6)
Diagnosis	
Acute pharyngitis	57 (43)
Acute exudative tonsillitis/acute tonsillitis	54 (40)
Influenza	9 (7)
Upper respiratory tract infection/ common cold	6 (4)
Scarlet fever	3 (2)
Infectious mononucleosis	2 (1)
Acute febrile illness	2 (1)
Acute lymphadenitis	1 (1)

*One child could have had more than one symptom; IQR: interquartile range.

Twenty (15%) throat swab samples produced positive GAS antigen RADT results, with one, nine and ten being from *Staphylococcus aureus*-positive, GAS-positive and pathogen-negative culture(s), respectively. Overall, prevalence of GAS in throat swabs was 7%. One of 10 children (10%) with positive throat swab culture and 5/20 (25%) with positive RADT results had a history of antibiotic use before the hospital visit, mainly treatment with amoxicillin (33%), amoxicillin-clavulanate (8%) and cephalosporins (8%).

Using a disc diffusion assay, among GAS isolates ($n = 10$), all were susceptible to chloramphenicol, penicillin, and vancomycin; seven were resistant to tetracycline and one was resistant to both erythromycin, and tetracycline.

Sensitivity and specificity of RADT was 90% (95% CI: 85-95) and 91% (95% CI: 86-96), respectively, with positive and negative predictive value of 45% (95% CI: 37-53) and 99% (95% CI: 97-100), respectively. Area under ROC curve of RADT was 0.90 (Fig 1).

DISCUSSION

The study shows a prevalence of children diagnosed with GAS pharyngitis at Naresuan University Hospital from May 2016 to April 2017 was 7%, comparable with a prevalence (6.5%) observed among primary care patients with GAS pharyngitis in northern Thailand (Greer *et al*, 2020), while a prevalence of 3.3% was reported in Bangkok among adults presenting signs of upper respiratory

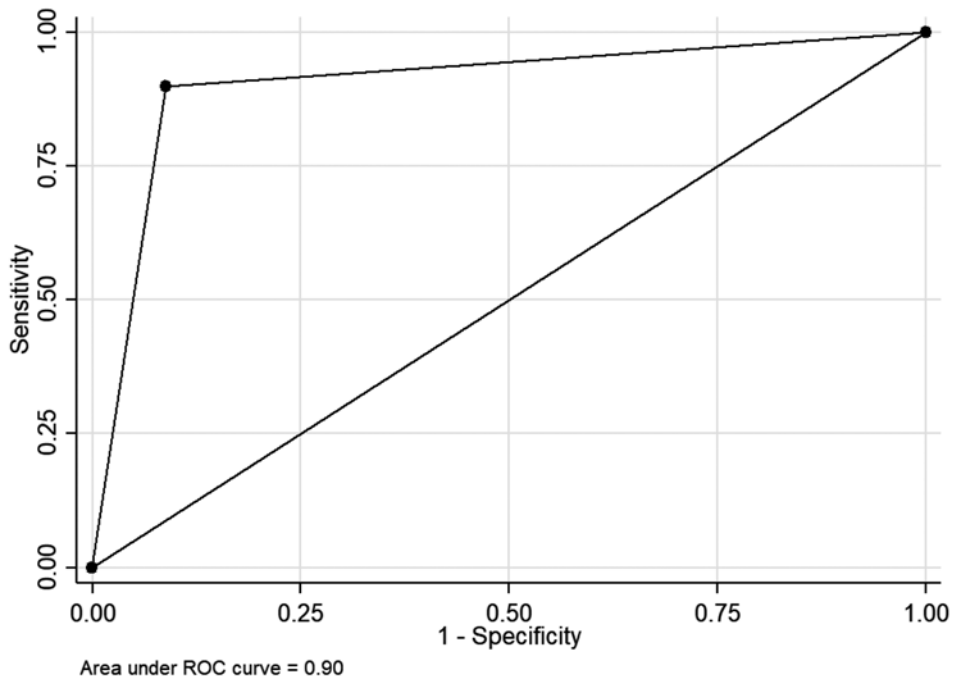


Fig 1-Receiver operating characteristic (ROC) curve for determination of accuracy of the rapid antigen detection test for group A streptococci used in the study.

X-axis: 1-specificity (false positive rate); Y-axis: sensitivity (true positive rate).

tract infection (Thamlikitkul *et al*, 2018). However, prevalence of GAS pharyngitis varies with country, region and age groups. A prevalence of 15% was reported among school-age children with GAS pharyngitis in developed nations (Carapetis *et al*, 2005) where there is an overall prevalence range 20-30% (Cohen *et al*, 2015). In a meta-analysis conducted in a previous study, prevalence of GAS pharyngitis is 37% among all children with sore throat and 24% among children <5 years of age (Shaikh *et al*, 2010).

The main reason for prescribing antibiotics is to treat GAS pharyngotonsillitis upon early diagnosis to prevent subsequent occurrence of suppurative and non-suppurative post-infection sequelae (Wessels, 2011). Although clinical manifestations are important for diagnosis of GAS pharyngotonsillitis, laboratory confirmation is necessary to clinically distinguish between viral and GAS pharyngotonsillitis (Kimberlin *et al*, 2018). In the present study, over half of the children presenting sore throat were prescribed antibiotics in the absence of any evidence of bacterial infection. Inappropriate antibiotic use leads to development of multi-drug resistant bacteria and consequently poses a serious challenge in pediatric practice (Tanz *et al*, 2004). A study conducted in Italy found GAS isolates resistant to clindamycin, erythromycin and tetracycline (Gherardi *et al*, 2015). In the present study, a high proportion of GAS isolates from children throat swabs were resistant to tetracycline but level of macrolide resistance was lower than that reported for erythromycin from China (>95% resistance) (Liu *et al*, 2009), France (22.4% resistance) (Bingen *et al*, 2004) and USA (48% resistance) (Martin *et al*, 2002).

Sensitivity and specificity of RADTs in

the diagnosis of streptococcal pharyngitis ranges 83.3-87.6% and 94.5-96.2%, respectively (Arnold and Nizet, 2012; Pelucchi *et al*, 2012). Variability in RADT sensitivity might be due to differences in laboratory kits, quality of specimen collection and personnel experience. Throat culture is 90-95% positive in GAS patients with active symptoms (Wessels, 2011), but requires 1 to 2 days to obtain results. The positive predictive value of RADT used in the present study was lower than the range (67.9-88.6%) previously reported (Oliver *et al*, 2018) and conversely negative predictive value higher than that (88.0-95.7%) reported earlier (Rimoin *et al*, 2010); but these results depend on the type of RADT employed. Although the high accuracy of RADT provides a precise test results in screening patients for GAS infection and thereby reduces unnecessary prescription of antibiotics, in Thailand, RADT is not recommended in routine practice because it is more expensive than blood agar plate culture, and there are limited available data regarding its cost-effectiveness; nevertheless, in private practice a combination of clinical presentation and RADT result provides rapid decision whether antibiotic should be prescribed in an outpatient setting.

The present study suffers from two major limitations. Firstly, the number of GAS isolates obtained was very small, and secondly, throat swab culture was not performed to detect other groups of streptococci, such as groups C and G, that could be the cause of sore throat in children.

In summary, the study shows a 7% prevalence of group A streptococcal pharyngitis among children with sore throat examined at an outpatient department, Naresuan University Hospital from May 2016 to April 2017.

All group A streptococci isolates were sensitive to chloramphenicol, penicillin and vancomycin, but most were resistant to tetracycline. While RADT for detection of group A streptococci is not routinely available in an outpatient setting, it provides valuable tool for ruling out group A streptococcal pharyngitis, thereby reducing unnecessary antibiotic treatment and potential development of drug resistance.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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