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# Asymptomatic Group A Beta Hemolytic Streptococcal Pharyngeal Carriage in North Cyprus

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## Abstract

**BACKGROUND/AIMS:** Group A beta-hemolytic streptococcus (GAS) *Streptococcus pyogenes* can cause benign to life-threatening infections such as pharyngitis, rheumatic fever, and acute glomerulonephritis. Asymptomatic carriers of GAS are a reservoir for transmission. The main aims of this study were to ascertain rates of asymptomatic carriage in adults in North Cyprus to prevent outbreaks and fatal complications and to gain insight into the risk factors for carriage in individuals with rheumatic and cardiovascular disease.

**MATERIALS AND METHODS:** This prospective study included 307 participants and was conducted from April 2019 to December 2019. The pharyngeal samples were collected from five districts of North Cyprus. Throat cultures were performed followed by rapid strep A antigen tests, catalase tests, gram staining, Lancefield latex agglutination, pyrrolidonyl arylamidase, bacitracin sensitivity, and trimethoprim-sulfamethoxazole resistance tests on subcultures.

**RESULTS:** In 307 participants, an asymptomatic prevalence rate of 4.9% was found. A higher and statistically significant ($p<0.05$) risk of GAS carriage was found in participants with rheumatoid and cardiovascular disease and in health care workers aged 18-29.

**CONCLUSION:** In North Cyprus, this is the first study to randomly sample a broad selection of the population for GAS pharyngeal carriage A higher risk of GAS carriage was found among participants with rheumatic and cardiovascular disease, in healthcare workers, and in the 18-29 years old age group, indicating the possibility of GAS hospital outbreaks and emphasizing the importance for outbreak prevention of screening of individuals with underlying diseases, and in school and healthcare settings.

**Keywords:** Streptococci, *S. pyogenes*, GAS, asymptomatic carriers

## INTRODUCTION

Group A beta-hemolytic streptococcus (GAS) *(Streptococcus pyogenes)* colonizes the skin and oropharynx and can cause a significant illness in humans. It is a coccoid Gram-positive bacterium capable of causing illnesses ranging from self-limiting to life-threatening, making it an important organism for research. The annual rate of mortality from GAS-related infections is 517,000 and the rate of new cases is 1.78 million each year.[1] The transmission of GAS is exclusively human-to-human with respiratory droplets from the oropharynx largely being responsible.[2-4] Asymptomatic carriers are a reservoir for GAS transmission; therefore, it is crucial to identify carriers to prevent outbreaks and reduce the threat of serious infections acquired from these carriers.

The main virulence factor for GAS is the M protein, which is a major antigen and is therefore a target for vaccine development. However, it

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has a highly variable structure, which complicates antigenic targeting. The *emm* gene encodes M protein. The *emm* type is an important factor in what kind of disease is produced, and the *emm* type distribution varies by country according to geographical and economic position.[5,6] More than 200 *emm* types exist, which belong to two main divisions: Class 1 and class 2. M proteins belonging to class 1 are associated with acute rheumatic fever outbreaks. This is because antibodies targeting certain regions of M proteins can crossreact with cardiac myosin causing rheumatic heart disease (RHD). Specific M types are associated with serious complications including necrotizing fasciitis, sepsis, and rheumatic sequelae.[5,6]

M protein plays an important role in the inhibition of phagocytosis and opsonization of GAS. It can bind the Fc domain of antibodies and block the complement cascade through a variety of other mechanisms preventing complement C3b binding and formation of the membrane attack complex. M protein is also important in mediating the adhesion of GAS to the host cell.[5,6]

GAS causes suppurative and nonsuppurative infections. Pharyngitis, impetigo, scarlet fever, cellulitis, necrotizing fasciitis, toxic shock syndrome, and sepsis are suppurative infections. Non-suppurative post-sequelae include acute glomerulonephritis and rheumatic fever.[7]

Asymptomatic carriers were defined as having GAS in the posterior pharynx without illness, i.e., throat culture shows a positive result in the absence of symptoms. An additional criterion required in this study for a carrier to be considered asymptomatic is a negative test for the antibodies anti-deoxyribonuclease B, anti-streptolysin-O, and anti-hyaluronidase.[8] It is important to differentiate asymptomatic carriers from cases with symptomatic disease. This is crucial for correct treatment. For asymptomatic carriers, treatment may be necessary in special situations such as outbreaks in communities of GAS invasive disease, pharyngitis, rheumatic fever, or glomerulonephritis and in families with a history of rheumatic fever.

Several theories have been presented to explain the asymptomatic carriage of GAS, including internalization of GAS into epithelial cells and growth of GAS in biofilms.[9,10] All these theories suggest mechanisms by which GAS can evade antibiotic treatment.

A total of 307 volunteers were selected from the five main districts of North Cyprus for this study and analyzed for GAS pharyngeal carriage. The purpose of this research is to determine the rate of GAS asymptomatic pharyngeal carriage in North Cyprus to better understand the risk of outbreaks and to reduce the risk of serious complications.

## MATERIALS AND METHODS

### Ethical Approval

This study was approved by the Near East University Institution Ethics Evaluation Board (approval number: YDU/2019/67-768 date: 28.03.2019).

### Participants and Study Design

This study is a prospective study conducted from April 2019 to December 2019. A total of 307 healthy adult participants were randomly selected from the five districts of North Cyprus: Nicosia, Famagusta, Kyrenia, Trigomo, and Lefke. Medical and non-medical salaried workers aged 18 to 65 years located in regional hospitals or medical faculties and long-term local residents of the five districts (regardless of occupation) were included in this study. Pharyngeal specimens were collected from all participants. Participants were presented with a questionnaire that asked for information including age, gender, nationality, area of residence, and occupation. Medical information was also required including whether they smoked, used alcohol, had any history of cardiovascular and rheumatic disease, had any respiratory or sleeping disorders, presence of tonsillectomy surgery, and had any usage of unprescribed antibiotics. All participants included in the study also signed a consent form.

### Laboratory Studies

Swab samples were taken from the posterior pharynx and tonsils of the participants using sterile swabs. The collected specimens were immediately transferred to the Başkent Private Hospital microbiology laboratory for screening and analysis of GAS using several standard microbiological and serological methods for detection of GAS carriage. Collected specimens were inoculated into 5% defibrinated sheep blood agar (SBA) (Condalab, Madrid, Spain) and incubated for 24-48 hours at 37 °C and tested with Vesrapido, an *in vitro* rapid immunochromatographic strep A antigen test (Vesta medikal, İstanbul, Türkiye). The test was performed according to the manufacturer's instructions. The manufacturer claims a sensitivity of 94,3% and a specificity of 100% for group bacteria in throat samples. After 24 h, the plates were examined for beta hemolysis, and positive colonies were considered as potential GAS and subjected to further analysis. Suspected colonies were subjected to a catalase test and Gram-staining (Premed, İstanbul, Türkiye). The catalase test differentiates catalase-positive *Staphylococcaceae* and *Micrococcaceae* from catalase-negative *Streptococcaceae* and *Enterococcus* spp. GAS are catalase negative and their morphology is gram positive with cocci arranged in chains. Catalase-negative colonies confirmed by Gram-staining were subcultured into 5% SBA for 24 h at 37 °C. The cultures were tested for sensitivity to the antibiotic bacitracin to differentiate beta hemolytic group A streptococci (*Streptococcus pyogenes*-susceptible) and susceptible micrococci from beta hemolytic non-group A Streptococci. These were used together with a sulfamethoxazole/trimethoprim (SXT) antibiotic disc susceptibility test to detect group beta hemolytic streptococci, which are SXT resistant.

Bacitracin Susceptibility Test Discs (Bioanalyse, Ankara, Türkiye) and in conjunction with it, SXT Susceptibility Test Discs (Bioanalyse, Ankara, Türkiye) were placed on subcultures growing on SBA and incubated for 24 hours at 37 °C. Colonies that were both bacitracin sensitive and SXT resistant were subsequently analyzed with a **pyrrolidonyl aminopeptidase** (PYR) **test kit** (Bioanalyse, Ankara, Türkiye). PYR is used for the detection of PYR (also called PYR) activity in group A strep *Streptococcus pyogenes*), *Enterococcus* spp., some coagulase-negative *Staphylococci*, and some *Enterobacteriaceae*.

PYR-positive colonies were classified using the Lancefield latex agglutination test (Strep Test Kit, Plasmatec, Bridport, UK) to assign group A beta-hemolytic Streptococci to Lancefield groups.

### Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences software demo version 26.0 (SPSS Inc, Chicago, USA).

Potential risk factors for GAS carriage were identified using a questionnaire. Outcome measures were stratified using several

characteristics: participants age/s, gender, nationality, medical history of certain diseases such as cardiovascular and rheumatic diseases, occupational risk factors such as nature of work, factors of influence such as antibiotic usage, and the prevalence of asymptomatic GAS carriage alongside sociodemographic data. Outcome measures were expressed as summary point prevalence percentages (number of subjects having the diseases at a time point/total number of subjects in the population) with 95% confidence intervals (CIs). Chi-square test was used for statistical analysis (2 * 2 layouts). If any of the expected frequencies was less than 5, Fisher's exact chi-square test was used instead. Odds ratios related to variables were also calculated and given with 95% CIs.

## RESULTS

This study included 307 healthy adult individuals. Sample collection and data analysis were performed from April 2019 to December 2019. Participants were randomly selected from the salaried personnel (medical and non-medical) in the regional hospitals or medical schools and from long-term local residents regardless of occupation living in the five main districts of North Cyprus and tested for GAS pharyngeal carriage. Participants under 18 years were excluded from the study, while hospital personnel were included only within the age range from 18 to 65 years. Pharyngeal specimens were collected from the participants and analyzed in the Baskent Private Hospital microbiology laboratory for GAS.

All participants completed a questionnaire. Potential risk factors for GAS carriage were identified, documented, and analyzed by the questionnaire which included basic demographic data as well as questions regarding medical history.

The overall rate of group A beta-hemolytic streptococci pharyngeal carriage was found to be 4.9% (307/15) (Table 1). Among the participants, 102 (33.2%) were males and 205 (66.8%) were females. 4.9% of males and 4.8% of females were GAS positive. There was no significant correlation between gender and the rate of GAS carriage $p>0.05$, t-test) (Table 2).

Participants were divided into the following age groups: 18-29 years old (63, 20.5%), 30-39 years old (50, 16.3%), 40-49 years old (52, 16.9%), 50-59 years old (69, 22.5%), and >60 years old (73, 23.8%). GAS carriage differences between age groups were not statistically significant ($p>0.05$, t-test) (the groups are included in Table 2).

The majority of participants were of Cypriot nationality (268, 87.3%). Other nationalities were also included (39, 12.7%). Row percentage of GAS carriage for Cypriots was 4.1% and for other nationalities was 10.26%. Statistical analysis using a chi-square test showed that GAS carriage did not differ significantly between nationalities (Cypriot vs. other) ($p>0.05$). In contrast, the odds ratio [odd ratio (OR): 2.67] showed that there was a higher risk of GAS carriage in other nationalities.

Participants were distributed between districts as follows: Nicosia (155, 50.5%) had the highest rate of GAS positivity, Famagusta and Trigomo (54, 17.6%), Kyrenia (47, 15.3%), Lefke and Omorfo (51, 16.6%). Chi-square test results showed no statistical significance between the distribution of GAS carriage between different districts ($p>0.05$) (Table 2).

222 (72.3%) participants used prescribed antibiotics, while 85 (27.7%) participants used unprescribed antibiotics. The difference in rates of GAS pharyngeal carriage between these groups was not statistically significant ($p>0.05$) (chi-square test) (Table 2).

The risk of GAS carriage in participants with rheumatic disease (row percent of GAS positivity was 21.4%) or cardiovascular disease (row percent of GAS positivity was 15%) was found to be higher relative to other participants and each one was individually statistically significant ($p<0.05$) (Table 2). Participants with rheumatic disease were found to have a 6 times higher risk (OR: 6.386) and with cardiovascular disease a 4 times risk (OR: 4.044) of GAS pharyngeal carriage than participants who had neither rheumatic nor cardiovascular disease (Table 2). There were no cases with the presence of both conditions in a single individual, so the combined risk of GAS carriage could not be measured.

Participants were divided by occupation into healthcare workers (79, 25.7%) and other occupational areas (228, 74.3%). There was no statistical significance observed by the use of the chi-square test between the occupational areas and GAS carriage of the participants over the entire study group ($p>0.05$) (Table 2). However, there was a statistical significance observed ($p<0.05$) between the occupational status of the participants within the age group 18-29 years old and GAS pharyngeal carriage (Table 3). The p-value was found to be 0.04 using the Fisher's exact chi-square test, a statistically significant result.

## DISCUSSION

This study examined the rate of GAS asymptomatic carriage among 307 adult individuals living in North Cyprus. The overall carriage rate was found to be 4.9% (Table 1). To our knowledge, this is the first large-scale study conducted in North Cyprus to identify asymptomatic GAS carriers. One study of GAS carriage was previously conducted in North Cyprus. However, that study investigated the rate of GAS only among 140 pharmacy students from Iran, Syria, Iraq, and Nigeria in a particular university.[11] The carriage rate was found to be 4.6%, which was similar to the current study that sampled a more representative population.

In the existing literature, there are only a limited number of studies of GAS carriage in adults. In a meta-analysis study, membership status in the National Organization for Economic Cooperation and Development (OECD), which consists mostly of high-income countries, was used to classify populations by socioeconomic position.[4] The prevalence rate of GAS carriage among adults was compared at the country income level between OECD and non-OECD studies. In OECD studies, the adult prevalence of GAS was 2% and in non-OECD studies 4.6%.[4] This study

**Table 1. Rate of GAS carriers identified in 307 participants**

| GAS pharyngeal carriage | Frequency, (n) | Percentage, (%) |
|---|---|---|
| Negative | 292 | 95.1 |
| Positive | 15 | 4.9 |
| Total | 307 | 100.0 |

GAS: Group A beta-hemolytic streptococcus.

**Table 2. Description of GAS pharyngeal carriage among participants**

| Variable | $N_{total}$=307, (n, %) | GAS positive, $N_{GAS}$=15, (n, %)[a] | p-value[b] | Odds ratio |
|---|---|---|---|---|
| **Gender** | | | | |
| Female | 205 (66.8) | 10 (4.9) | 0.993 | 1.0052 |
| Male | 102 (33.2) | 5 (4.9) | | |
| **Age in years** | | | | |
| 18-29 | 63 (20.5) | 4 (6.3) | 0.953 | |
| 30-39 | 50 (16.3) | 3 (6.0) | | |
| 40-49 | 52 (16.9) | 2 (3.8) | | |
| 50-59 | 69 (22.5) | 3 (4.3) | | |
| >60 | 73 (23.8) | 3 (4.1) | | |
| **Nationality** | | | | |
| Cypriot | 268 (87.3) | 11 (4.1) | 0.096 | 2.6701 |
| Other nationality | 39 (12.7) | 4 (10.3) | | |
| **Region** | | | | |
| Nicosia | 155 (50.5) | 10 (6.45) | 0.429 | |
| Famagusta + trikomo | 54 (17.6) | 1 (1.85) | | |
| Kyrenia | 47 (15.3) | 1 (2.13) | | |
| Lefke + omorfo | 51 (16.6) | 3 (5.88) | | |
| Rheumatoid disease | 14 (4.6) | 3 (21.4) | 0.003 | 6.384 |
| Cardiovascular disease | 20 (6.5) | 3 (15) | 0.030 | 4.041 |
| **Occupation** | | | | |
| Healthcare | 79 (25.7) | 7 (8.86) | 0.057 | 0.374 |
| Other | 228 (74.3) | 8 (3.50) | | |
| **Antibiotic usage** | | | | |
| Prescribed | 222 (72.3) | 11 (4.95) | 0.928 | 1.056 |
| Unprescribed | 85 (27.7) | 4 (4.71) | | |

[a]Row percent, [b]Comparison of GAS positive against negative tested variables, GAS: Group A beta-hemolytic streptococcus.

**Table 3. Description of GAS pharyngeal carriage among occupational areas within the age group 18-29**

| Age range 18-29 | | | | | |
|---|---|---|---|---|---|
| **Occupational area** | **Frequency (n)** | **Percentage (%)** | **GAS frequency (n)** | **GAS percentage (%)** | **p/OR** |
| Healthcare | 16 | 4.8 | 3 | 20.6 | p<0.05 |
| Other | 47 | 1.6 | 1 | 73.0 | OR: 3.119 |

Odds of observing $GAS_{Negative}$ in other/healthcare=2.674, GAS: Group A beta-hemolytic streptococcus.

showed similarity with the GAS prevalence rate in studies conducted in non-OECD countries.[4]

In this study, participants were consulted for the presence of rheumatoid disease, cardiovascular disease, sleeping disorders, and respiratory illnesses. We analyzed the risk factors for GAS carriage in individuals with rheumatoid and cardiovascular diseases. Higher risk and statistically significant GAS carriage was found among participants with rheumatoid and cardiovascular diseases (Table 2). GAS carriage is mainly known to cause pharyngitis.

Proper diagnosis and treatment of symptomatic pharyngitis caused by GAS is important for prevention of post sequelae complications including rheumatic fever and RHD. ARF causes damage to the heart and is still a problem in low- and middle-income countries worldwide.[1,6,12] GAS carriage becomes important when there is a risk of a carrier developing these or other nonsuppurative complications such as acute glomerulonephritis or when there is a risk of the carrier spreading GAS to other people. Out of 33.4 million patients with RHD worldwide, 275,000 cases are fatal, while 9 million cases result in disability, with most of these cases occurring in developing countries.[1] In the world, there are 33.4 million patients with RHD.[1]

Therefore, it is important to carry out *emm* typing[8] to understand *emm* prevalence in North Cyprus. A reduced number of participants with clinical outcomes may have caused the lower accuracy in statistical terms.

The skin and the nasopharyngeal mucosa are the primary reservoirs for asymptomatic maintenance and transmission of GAS. GAS persists in saliva for an extended period or can reside in the skin tissue of an infected person. GAS is therefore transmitted from an infected person or an asymptomatic carrier by respiratory droplets or skin-skin contact.[6] Many participants in our study were identified as healthcare

workers (79, 25.7%). The GAS carriage of healthcare workers within the age range of 18-29 (4.8%) was statistically significantly different from other occupations ($p<0.05$, OR: 3.119). Odds of observing GAS-negative cases in other occupational groups were 2,674 times higher than in the health care occupational group, suggesting that young healthcare workers are at high risk of GAS carriage. The healthcare workers, due to their occupation, were normally in close contact with patients. Family members or patients admitted to hospitals are in close contact with health workers in clinical settings, leading to an increased risk of subsequent infection. Infection of health workers, even if asymptomatic, would can drive hospital outbreaks.[6] Eradication of GAS carriage in healthcare settings is therefore needed to prevent transmission to patients.[13] More studies should be conducted in healthcare occupations as the risk of outbreak is high. The risk of GAS carriage is higher in individuals with rheumatoid or cardiovascular diseases requiring additional precautions in these groups.

## CONCLUSION

We aim to gain insight into the high risk of GAS carriage in this community-level study of adult subjects. There are not many previous studies of adult asymptomatic GAS carriage. In contrast, many previous studies have investigated the asymptomatic carriage of GAS in children.[3] The asymptomatic carriage rate among adults provides crucial information needed to prevent outbreaks along with their potential for serious complications and for an epidemiologic understanding of GAS carriage.

GAS is a global health problem that can cause self-limiting to serious life-threatening complications. Mortality from GAS - related infections is at a critically important rate (about 517,000 annually) and 1.78 million new cases of GAS infection are reported each year.[1] More studies are needed, especially in healthcare settings and schools. To gain better insights into disease outcome and to understand the risk of GAS in North Cyprus, more studies including *emm* typing analysis should be conducted. The extension of such screening programs for GAS carriage to newcomers may serve as an effective preventive measure to avoid GAS transmission.

## MAIN POINTS

- The first large-scale study conducted in North Cyprus for identification of adult asymptomatic carriers of GAS (4.9%).
- Showed the importance of screening especially for prevention of outbreaks and fatal complications related to GAS.
- Analyzed the risk factors for GAS carriage in individuals who had rheumatoid and cardiovascular disease.
- Our findings suggest that more studies are needed in North Cyprus, especially in health institutions and schools to understand the prevalence of asymptomatic GAS.

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### Ethics

**Ethics Committee Approval:** This study was approved by the Near East University Institution Ethics Evaluation Board (approval number: YDU/2019/67-768, date: 28.03.2019).

**Informed Consent:** All participants included in the study also signed a consent form.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: R.K., E.Ç., Design: R.K., E.Ç., Supervision: R.K., E.Ç., Fundings: R.K., E.Ç., Materials: R.K., E.Ç., Data Collection or Processing: R.K., E.Ç., Analysis or Interpretation: R.K., S.Y., İ.E., Literature Search: R.K., S.Y., Writing: R.K., S.Y., İ.E., Critical Review: R.K., S.Y.

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