

■ Research Article

Variations in the frequency of streptococcal tonsillopharyngitis among children after COVID-19

Çocuklarda COVID-19 sonrası streptokokal tonsillofarenjit sıklığındaki değişiklikler

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ABSTRACT

Aim: Comprehensive data on the variations in the frequency of *Streptococcus pyogenes* (GAS) tonsillopharyngitis before and after the Coronavirus disease 2019 (COVID-19) pandemic are still insufficient. This study aimed to investigate the changes in the frequency of GAS in children before, during, and after the COVID-19 period.

Material and Methods: This retrospective study included 13,061 patients diagnosed with a pre-diagnosis of bacterial tonsillopharyngitis based on clinical findings, between June 2018 and June 2023. All patients were administered the Strep A antigen test, and throat swab samples were collected. Patients were divided into three groups based on their hospital admission dates. Group 1, pre-COVID-19 pandemic period (1 January 2018 – 10 March 2020); Group 2, during the COVID-19 pandemic when strict measures were enforced (11 March 2020 – 30 June 2021); and Group 3, the period after the lifting of COVID-19 pandemic measures (1 July 2021 – 30 June 2023).

Results: The prevalence of GAS in the entire population was 23.2% (n=3024). Among the groups, Group 3 had the highest ratio of GAS cases, followed by Group 1, and then Group 2 (Group 1: 18.1%, Group 2: 6.0%, Group 3: 29.6%, p < 0.001). During the period characterized by stringent measures against the COVID-19 pandemic, a significant reduction in the frequency of GAS was observed in comparison to the pre-COVID-19 era. However, with the relaxation of COVID-19-related restrictions, particularly in the last quarter of 2022 and the spring of 2023, there was a marked increase in the frequency of GAS.

Conclusion: In children, the frequency of GAS significantly decreases with COVID-19 isolation measures. However, a rebound increase is observed following the relaxation of these isolation measures.

Keywords: Group A β -hemolytic streptococcus; COVID-19; strep A rapid test; tonsillopharyngitis

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ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVID-19) pandemisi öncesi ve sonrasında *Streptococcus pyogenes* (GAS) tonsillofarenjit sıklığında yaşanan değişikliklere ilişkin kapsamlı veriler yetersizdir. Bu çalışmada, COVID-19 dönemi öncesi, sırası ve sonrasında çocuklarda GAS sıklığında meydana gelen değişiklikleri incelemeyi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Haziran 2018 ile Haziran 2023 tarihleri arasında klinik bulgularla bakteriyel tonsillofarenjit ön tanısı alan 13,061 çocuk hasta dahil edildi. Tüm hastalara Strep A antijen testi yapılmış ve boğaz sürüntü örnekleri toplanmıştır. Hastalar, hastaneye başvuru tarihlerine göre üç gruba ayrıldı: Grup 1, COVID-19 pandemisi öncesi dönem (1 Ocak 2018 - 10 Mart 2020); Grup 2, COVID-19 pandemisi sırasında sıkı önlemlerin uygulandığı dönem (11 Mart 2020 - 30 Haziran 2021); ve Grup 3, COVID-19 pandemisi önlemlerinin kaldırıldığı dönem (1 Temmuz 2021 - 30 Haziran 2023).

Bulgular: Tüm popülasyonda GAS prevalansı %23.2 (n=3024) idi. Gruplar arasında, Grup 3 en yüksek GAS sıklığına sahipken, bunu Grup 1 ve ardından Grup 2 izledi (Grup 1: %18.1, Grup 2: %6.0, Grup 3: %29.6, p < 0.001). COVID-19 pandemisine karşı katı önlemlerin alındığı dönemde, COVID-19 öncesi döneme kıyasla GAS sıklığında önemli bir azalma gözlemlendi. Ancak, COVID-19 ile ilişkili kısıtlamaların gevşetilmesiyle, özellikle 2022'nin son çeyreği ve 2023 ilkbaharında, GAS sıklığında belirgin bir artış saptandı.

Sonuçlar: Çocuklarda, GAS sıklığı COVID-19 izolasyon önlemleriyle önemli ölçüde azaldı. Ancak, bu izolasyon önlemlerinin gevşetilmesinin ardından ani bir artış gözlemlendi.

Anahtar Kelimeler: Grup A Beta-Hemolitik Streptokok; COVID-19; hızlı strep A testi; tonsillofarenjit

Introduction

Streptococcus pyogenes (Group A beta-hemolytic streptococcus [GAS]), the most common cause of tonsillopharyngitis in the childhood age group, is a significant cause of mortality and morbidity due to its ability to cause complications such as acute rheumatic fever and acute poststreptococcal glomerulonephritis following infection [1, 2]. It has been reported that infections caused by GAS lead to over half a million deaths worldwide annually [3]. The transmission of the disease often occurs through droplet infection from other patients with GAS tonsillitis, and occasionally from asymptomatic carriers [4]. Therefore, crowded environments play a significant role in the spread of the pathogen [5].

In fact, viral infections persist as the leading cause of acute tonsillopharyngitis cases [6]. The burden of GAS can be heightened by viral infections that become complicated with bacterial infections either simultaneously or afterward [7]. During the 1918 influenza pandemic, *Streptococcus pneumoniae* and GAS were the most frequently observed bacteria in lung biopsies [8]. In the 2009 H1N1 influenza outbreak, GAS, a significant cause of bacterial superinfection, was associated with high mortality rates [9, 10]. At the beginning of the Coronavirus Disease 2019 (COVID-19) pandemic, numerous countries reported a significantly

decreased incidence of invasive GAS disease cases during 2020 and 2021 [11-13]. However, during the years 2022 and 2023, several European countries reported an increase in invasive GAS disease cases [12-16]. This increase is attributed to the easing of non-pharmaceutical interventions (NPIs) such as wearing masks, adhering to social distancing rules, and closing schools, which were enforced to combat the COVID-19 pandemic [12, 13]. However, comprehensive data on the variations in the frequency of GAS tonsillopharyngitis before and after the COVID-19 pandemic are still insufficient.

We hypothesized that the measures taken at the onset of the COVID-19 pandemic and the subsequent relaxation of these measures in the following years could lead to variations in the frequency of GAS. This study aimed to investigate the changes in the frequency of GAS in children before, during, and after the COVID-19 period.

Material and Methods

This retrospective study was conducted on patients who admitted to the Department of Pediatric Health and Diseases of the Hisar Intercontinental Hospital, between June 2018 and June 2023. The study was approved by the Hisar Intercontinental Hospital Ethics Committee (Date: 22.09.2023, Decision No: 23-48) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision).

Due to the retrospective design of the study, the local ethics committee waived the necessity for informed consent.

In this study, 15,594 patients under the age of 18 who admitted to the hospital during the aforementioned years, and were suspected of having bacterial tonsillopharyngitis, were retrospectively evaluated. Suspicion of bacterial tonsillopharyngitis included symptoms such as sore throat, fever, hyperemia or exudate on the tonsils, headache, nausea, vomiting, abdominal pain, and petechial rashes on the soft palate. Inclusion criteria were patients under 18 years of age presenting with high fever and sore throat, who were found upon physical examination to have high fever, hyperemia in the tonsils and pharynx, and/or membranes detected in pediatric patients. Patients with a previous history of tonsillitis or related complications such as rheumatic fever and poststreptococcal glomerulonephritis, those who have recently used antibiotics or received immunosuppressive therapy, those who have received a tonsillectomy, and patients without a confirmed diagnosis through throat culture were excluded from the study. After applying the exclusion criteria, 13,061 patients who underwent a strep A antigen test and had their diagnosis confirmed by throat culture were included.

At the time of the patients' outpatient clinic visits, their demographic information and laboratory results were documented. All patients were administered the Strep A antigen test (QuickVue+, Quidel Corp, San Diego, California, USA), and throat swab samples were collected. Throat swabs were taken solely from both tonsils and the posterior pharyngeal wall, as recommended in the guidelines [17]. The sensitivity and specificity of the Strep A antigen test have been reported as 92% and 86%, respectively [18]. Concurrently, inoculation for throat swabs on sheep blood agar was carried out in the clinical microbiology laboratory. The culture plates were evaluated for beta-hemolytic colonies after an incubation at 37 °C period of 24-48 hours. After 24 -48 hours of incubation growth of typical beta-hemolytic colonies were observed. Presumptive identification of *S. pyogenes*, was performed by using Gram positive, catalase test negative, bacitracin susceptibility and PYR activity. A definitive diagnosis was made positive Lancefield group A antigen test. The frequency of GAS was calculated based on cases with positive throat swab samples.

The first case of COVID-19 in Turkey was identified on March 11, 2020, followed by the implementation of strict measures to combat the pandemic. These measures included mandatory mask-wearing, social isolation, halting of air travel, curfews, shifting to online learning, the temporary closure of cafes and restaurants, and the cancellation of public events. Pandemic measures

began to be lifted on June 1, 2021, transitioning the country into a normalcy process after more than a year of restrictions and pandemic management efforts [19, 20]. Accordingly, patients were divided into three groups based on their hospital admission dates. Group 1, pre-COVID-19 pandemic period (1 January 2018 – 10 March 2020); Group 2, during the COVID-19 pandemic when strict measures were enforced (11 March 2020 – 30 June 2021); and Group 3, the period after the lifting of COVID-19 pandemic measures (1 July 2021 – 30 June 2023).

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean \pm standard deviation while non-normally distributed variables are given as median (min – max). For comparisons between groups, Kruskal-Wallis H test (post-hoc test: Dunn's test) were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Time series analysis was conducted to evaluate the changes and trends in the frequency of GAS. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

The study population consisted of a total of 13,061 pediatric patients, including 6,270 girls (48%) and 6,791 boys (52%). The median age of the patients was 5 years (range = 1 month - 17 years), with the majority being between the ages of 5-9 years (43.2%). It was determined that the majority of patients presented to the hospital during the winter season. The prevalence of GAS in the entire population was 23.2% (n=3024) (Table 1). The sensitivity and specificity of the Strep A antigen test were determined to be 93.1% and 89.2%, respectively.

The gender distribution among groups was similar. However, the median age of children admitted to the hospital (Group 1: 55 months vs. Group 2: 52 months vs. Group 3: 62 months, $p < 0.001$), and the ratio of children aged 5 and above were found to be higher in Group 3 compared to other groups. In the spring and summer periods, the rate of hospital admissions was higher in Group 2 compared to other groups, while the admission rate was lower in the winter. In the autumn, the rate of hospital admissions was found to be higher in Group 3 compared to other groups (Group 1: 15.9% vs. Group 2: 15.4% vs. Group 3: 20.3%, $p < 0.001$). The ratio of cases with GAS was higher in Group 2 compared to Group 1. In Group 3, the ratio of cases with GAS was higher than in the other groups (Group 1: 18.1% vs. Group 2: 6.0% vs. Group 3: 29.6%, $p < 0.001$) (Table 1).

Table 1. Demographic and clinical characteristics of patients.

Variables	All population n = 13061	Group 1 n = 6366	Group 2 n = 469	Group 3 n = 6226	p
Sex, n (%)					
Girl	6270 (48.0)	3032 (47.6)	219 (46.7)	3019 (48.4)	0.568
Boy	6791 (52.0)	3334 (52.4)	250 (53.3)	3207 (51.6)	
Age, months	60 (1-215)	55 (1-214)	52 (3-213)	62 (1-215)	<0.001*
<1 years, n (%)	702(5.4)	426(6.7)	27(5.8)	249(4.0)	<0.001*
1-4 years, n (%)	4159(31.8)	2280(35.8)	193(41.2)	1686(27.1)	
5-9 years, n (%)	5647(43.2)	2599(40.8)	165(35.2)	2883(46.3)	
10-14 years, n (%)	2062(15.8)	897(14.1)	72(15.4)	1093(17.6)	
15-18 years, n (%)	491(3.8)	164(2.6)	12(2.6)	315(5.1)	
Season of presentation, n (%)					
Summer	1488 (11.4)	732 (11.5)	120 (25.6)	636 (10.2)	<0.001*
Autumn	2346 (18.0)	1011 (15.9)	72 (15.4)	1263 (20.3)	
Winter	613 (47.6)	3475 (54.6)	41 (8.7)	2697 (43.3)	
Spring	3014 (23.1)	1148 (18.0)	236 (50.3)	1630 (26.2)	
GAS, n (%)					
No	10037(76.8)	5214(81.9)	441(94.0)	4382(70.4)	<0.001*
Yes	3024(23.2)	1152(18.1)	28(6.0)	1844(29.6)	

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * P <0.05 shows statistical significance. Bold characters indicate differences between groups. GAS, Streptococcus pyogenes.

The fluctuations in the frequency of GAS across different months and years are depicted in Figure 1. During the period characterized by stringent measures against the COVID-19 pandemic, a significant reduction in the frequency of GAS was observed in comparison to the pre-COVID-19 era. However, with the relaxation of COVID-19-related restrictions, particularly in the last quarter of 2022 and the spring of 2023, there was a marked increase in the frequency of GAS. Additionally, time series analysis revealed a sharp upward trend in the rate of GAS during the period when COVID-19 measures were relaxed (Figure 2).

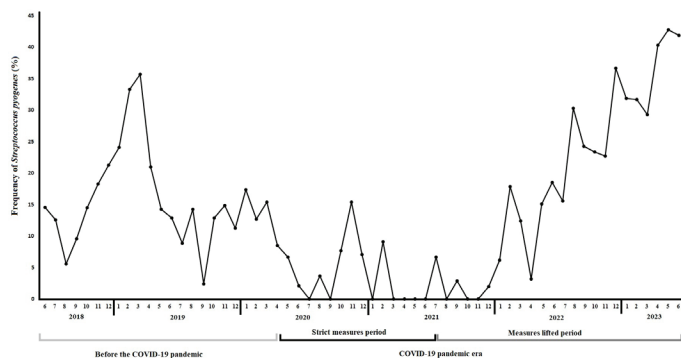


Figure 1. Frequency of Streptococcus pyogenes among children pre- and post-COVID-19 onset.

The 5-9 year age group exhibited the highest frequency of GAS infections before the COVID-19 pandemic's onset. During the period of stringent COVID-19 restrictions, an increase in the incidence of GAS infections was observed in the 1-4 year age group. Nevertheless, with the relaxation of COVID-19 precautions, the age demographics of GAS infections in children aligned with pre-pandemic observations (Figure 3).

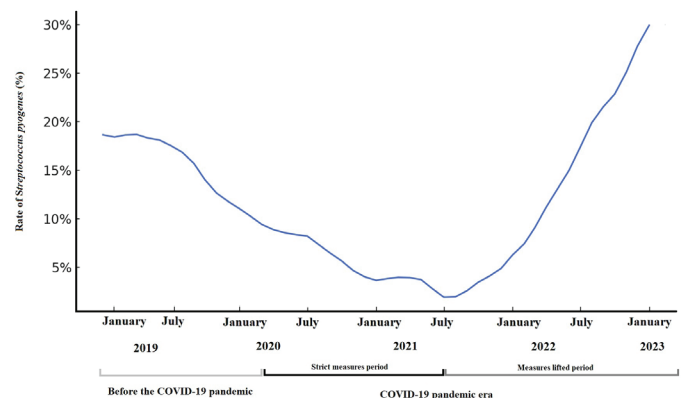


Figure 2. Trend of Streptococcus pyogenes ratios among children over time.

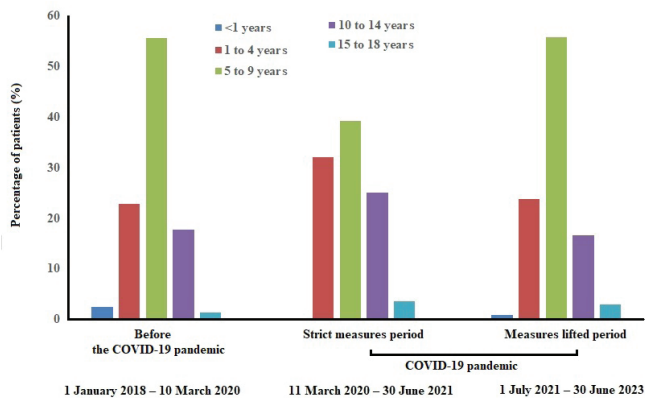


Figure 3. Age-wise distribution of cases with detected *Streptococcus pyogenes* pre- and post-COVID-19 onset.

Discussion

GAS is the most common bacterial cause of tonsillopharyngitis, although polymicrobial infections and viral pathogens can also lead to the condition [21]. To the best of our knowledge, this is the largest study to evaluate the differences in the frequency of GAS infections in the pediatric population in Turkey before and after the pandemic. This study revealed that GAS occurrences notably declined during the enforcement of strict COVID-19 protocols but surged past pre-pandemic levels once these measures were relaxed.

During the pre-pandemic period, the prevalence of GAS was around 18%, which falls within the previously reported range of 10-30% in Turkey [22-26]. However, the frequency of GAS infections showed a sharp decline in the early stages of the pandemic. Recent studies have shown that strategies to reduce COVID-19 infection have led to a decrease in the frequency of GAS pharyngitis [27, 28]. In a study conducted in the United States on children, it was reported that the frequency of GAS pharyngitis significantly decreased over the 21-month period since the beginning of the COVID-19 pandemic (Pre-mitigation period: 28.9% vs. Mitigation period: 17.3%, $p < 0.001$) [27]. A study conducted in France reported that the prevalence of GAS in children with tonsillopharyngitis was 43.4% before the COVID-19 pandemic, but it decreased to 23.7% in the early period following the pandemic [29]. This outcomes aligns with prior studies showing how COVID-19 preventive non-NPIs have affected children's respiratory infections, leading to a significant reduction in conditions like bronchiolitis and influenza during the pandemic's initial stages [30].

In the current study, a sharp increase in the frequency of GAS infections was detected during the period when COVID-19 pandemic measures were relaxed. In the existing literature,

changes in the frequency of GAS infections before and after the COVID-19 periods have been rarely evaluated. A study in France reported that the frequency of GAS approached pre-COVID-19 ratio (43.4%) during the late COVID-19 period when NPIs were relaxed (39.3%) [29]. Studies carried out in Italy, Germany, and Spain have also documented comparable results [12, 31, 32]. The observed increase in GAS infections is thought to be associated with the concept of "immunity debt." Reducing long-term exposure to viruses or bacteria can lead to an increase in the number of individuals susceptible to infection and a decrease in collective immunity within the community, thereby raising the risk of outbreaks [33]. Additionally, co-infections can cause a significant increase in the incidence of GAS infections. In the influenza pandemic periods of 1918 and 2009, GAS infections were identified in a substantial fraction of cases [8-10]. Furthermore, respiratory viruses can increase the risk of secondary pathogens and, by breaking the respiratory barrier, can heighten the risk of invasive GAS [34]. A study in Australia on children reported that the incidence of invasive GAS infections was 3.7 per 100,000 before the pandemic, dropped below 1.0 per 100,000 during the pandemic period of NPIs restrictions, and increased to 4.9 per 100,000 during the pandemic period when NPIs were relaxed [13]. Additionally, this study reported that approximately 48% of the cases were positive for respiratory virus co-infection [13]. GAS studies conducted on children in England, an unusual increase in the rates of invasive GAS infections towards the end of 2022 was reported, and respiratory viral co-infection was diagnosed in approximately 50% of the cases [35, 36]. In the current study, although invasive GAS infections were not evaluated, the high prevalence of GAS infections observed during the period when COVID-19 measures were relaxed may be associated with respiratory viral co-infection.

A further important finding from this study is the detection of non-seasonal rises in GAS infection frequencies amid the easing of COVID-19 restrictions. Previous studies have shown that GAS infections peak during the winter and early spring, experiencing their lowest point in late summer and autumn [37, 38]. In this study, the frequency of GAS infections also peaked during the winter and early spring periods before the COVID-19 pandemic. Even though there was a significant drop in GAS infection frequency amidst the strict COVID-19 containment measures, GAS infections reached their peak in the late fall and end of winter. Despite observing seasonal rises in GAS infections during periods of relaxed COVID-19 restrictions, notable peaks were specifically observed at the end of summer 2022 and at

the beginning of summer 2023. Prior to the COVID-19 outbreak, there was a tendency for GAS infections to decline in the spring and summer; however, a significant surge was noted in these seasons of 2022 and in the spring of 2023. Previous studies in children have also reported that following the relaxation of COVID-19 restrictions, many pathogens caused non-seasonal outbreaks at higher rates than before the COVID-19 pandemic [15, 39]. The seasonal fluctuations in GAS frequency pre- and post-COVID-19 pandemic could significantly be influenced by age distributions. Studies conducted before the COVID-19 pandemic have shown that the frequency of GAS infections was highest among the 5-14 age group [40, 41]. Consistent with the literature, this study showed that the 5-9 year age group experienced the highest prevalence of GAS infections prior to the onset of the COVID-19 pandemic. However, a notable rise was observed in the 1-4 year age bracket during the strict COVID-19 containment measures. On the other hand, in the period when COVID-19 measures were relaxed, the age profiles of children diagnosed with GAS infections were akin to those observed before the pandemic. This underscores the dynamic nature of infectious diseases, where public health interventions can lead to shifts in disease patterns across different age groups. This study had some significant limitations. This study utilized a single-center, retrospective design, which may lead to variations in GAS prevalence across different geographic areas. Additionally, due to the retrospective nature of the study, long-term follow-up of the patients could not be conducted.

Conclusions

In children, the frequency of GAS tonsillopharyngitis significantly decreases with COVID-19 isolation measures. However, a rebound increase is observed following the relaxation of these isolation measures. It is our view that the escalation in GAS transmission might originate from an increase in droplet spread, owing to the lack of mask usage and lack of adherence to social distancing protocols.

Conflict of Interest/ Funding

The study received no financial support from any individual or organization, and the authors declare no conflict of interest.

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