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Original Article

The Impact of the COVID-19 Pandemic on Invasive Group A *Streptococcal* Infections in Children

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ABSTRACT

Aim: The aim of this study was to evaluate the impact of the coronavirus disease-2019 pandemic on the invasive group A *Streptococcus* (iGAS) infections in children. We also aimed to assess the demographic and clinical characteristics, and treatment outcomes of children with iGAS infections.

Materials and Methods: We conducted a retrospective analysis of the medical records for pediatric patients aged 1 month to 18 years who were diagnosed with iGAS infections and followed by a single pediatric infectious diseases department from January 2010 to December 2021. The study period was divided into two periods: the pre-pandemic period (January 2010-February 2020) and the pandemic period (March 2020-December 2021).

Results: A total of 40 patients (60% female) with a median age of 8 years (1-17 years) were included in this study. Among these, 20 had bacteremia, 13 patients had necrotizing soft tissue infection, 4 had pneumonia and empyema, 2 had septic arthritis, and 1 had acute bacterial meningitis. Two patients developed streptococcal toxic shock syndrome. In 6 patients, varicella infection, and in 4 patients, influenza infection preceded iGAS infection. The distribution of patients by year was as follows: 2 patients in 2010, 2011, and 2012; 3 in 2013; 0 in 2014; 4 in 2015; 6 in 2016 and 2017; 7 in 2018; and 8 in 2019, indicating a progressive increase in iGAS cases towards the last years of the pre-pandemic period. No cases were observed during the pandemic period. Three patients died.

Conclusion: Our study found that the number of iGAS cases progressively increased in the last years of the pre-pandemic period, while no cases were observed during the pandemic period. This may be attributed to a reduction in GAS transmission due to the preventive measures implemented during the pandemic, as well as a decrease in the incidence of infections such as influenza and varicella, which are significant risk factors for iGAS.

Keywords: Invasive group A *Streptococcal* infections, COVID-19 pandemic, children

Introduction

Invasive group A *Streptococcus* (iGAS) infections include bacteremia, pneumonia, osteomyelitis, septic arthritis, and any other infections in which GAS is isolated from a normally sterile body site. These infections also include necrotizing fasciitis (1). The clinical spectrum of iGAS disease in children differs from that in adults (2).

After the onset of the coronavirus disease-2019 (COVID-19) pandemic in March 2020, significant behavioral changes

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occurred in society. Many countries adopted hygienic measures such as handwashing and widespread face masking, along with school closures and social distancing. These actions led to notable shifts in the epidemiology of viral and bacterial infections (3). iGAS infections have been associated with antecedent viral infections, such as varicella and influenza (1). Therefore, the number of new diagnoses for various infectious diseases was impacted by the pandemic. Our aim was to evaluate the impact of the COVID-19 pandemic on the number of iGAS infections in children. We also aimed to assess the demographic and clinical characteristics, and treatment outcomes of these children.

Materials and Methods

Pediatric patients aged 1 month to 18 years, admitted to Gazi University Hospital with iGAS infection between January 2010 and December 2021, were analyzed retrospectively. This study was approved by the Gazi University Clinical Research Ethics Committee Non-Interventional Research (decision no.: 226, dated: 20.03.2023). The study period was divided into two periods: the pre-pandemic period (January 2010-February 2020) and the pandemic period (March 2020-December 2021). We collected data from medical records, the infectious diseases consultation database, and the microbiology laboratory database regarding the patients' demographics (age, sex), admission dates, infection sites, risk factors, presenting symptoms, laboratory findings, culture results, antimicrobial treatments, the need for surgical drainage, complications [e.g., *Streptococcal* toxic shock syndrome (STSS)], and mortality. iGAS infections were defined as bacteremia, pneumonia, necrotizing soft tissue infection, or any other infection associated with the isolation of GAS from a normally sterile site (1).

Microbiological Methods

Tissue samples were inoculated onto blood and eosin-methylene blue agar. The aerob/anaerob blood culture bottles were incubated for 5 days in BacT/Alert System (Biomeriux, France). The growing microorganism was identified using matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (Biomeriux, France). Antibiotic susceptibility testing for the bacteria identified as GAS was performed using the Vitek 2 automated system (Biomeriux, France).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences 21 (SPSS 21) (IBM SPSS Inc, Chicago, IL, USA). Data were analyzed by frequency and percentage (%) for qualitative variables, and median, minimum, and maximum values for quantitative variables. The Mann-Whitney U test was used to compare the median age values between the groups with and without bacteremia. Statistical significance was set at $p<0.05$.

Results

We identified 40 children (n=24; 60% female) with laboratory-confirmed iGAS infections during the study period. The median age was 8 years (range 1-17 years). The distribution of patients by year was as follows: 2 patients in 2010, 2011, and 2012; 3 in 2013; 0 in 2014; 4 in 2015; 6 in 2016 and 2017; 7 in 2018; and 8 in 2019, indicating a progressive increase in iGAS cases towards the last years of the pre-pandemic period (Figure 1). Of these patients, 20 (50%) patients had bacteremia, 13 (32.5%) had necrotizing soft tissue infection, 4 (10%) had pneumonia and empyema, 2 (5%) had septic arthritis, and 1 (2.5%) had acute bacterial meningitis (Figure 1).

Bacteremia was present in 20 (50%) of 40 patients; 12 (60%) patients with bacteremia had a source of skin and/or soft tissue infection, and 8 (40%) patients had bacteremia without a focus. The median age of those patients with bacteremia was 4 years (range: 1-8 years), which was significantly lower than that of those patients without bacteremia (median age 9 years, range: 3-17 years) ($p=0.02$).

In 6 (15%) patients, varicella infection, and in 4 (10%) patients, influenza infection preceded iGAS infection. Two (5%) patients met the criteria for STSS; one had pneumonia and empyema, while the other had a retropharyngeal abscess. Both patients presented to our hospital with septic shock and rapidly developed multiple organ failure, resulting in death within 24 hours. Both patients were previously healthy and had no underlying diseases.

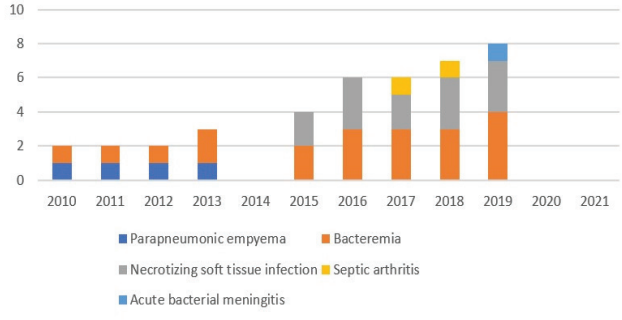

Figure 1. Annual numbers of children with invasive group A *Streptococcal* infections from 2010 to 2021

GAS meningitis was seen in a 7-year old boy who had a prior varicella infection and perforated otitis media. He presented with fever, headache, and signs of meningeal irritation. Cerebrospinal fluid (CSF) analysis revealed 1,250 cells/mm^3 with a glucose and protein concentrations of 20 and 232 mg/dL, respectively. Empiric treatment with intravenous (IV) ceftriaxone (100 mg/kg per day) and vancomycin (60 mg/kg per day) was initiated. A Gram stain of the CSF showed Gram-positive cocci, and CSF culture grew GAS (sensitive to penicillin). Blood and throat cultures remained negative. Vancomycin was discontinued, and since IV penicillin was not available at the hospital, the treatment was completed with ceftriaxone for 10 days. The patient was discharged in good condition on the 11th day of hospitalization.

The median white blood cell count was 15,670/mm^3 (790-42,000/mm^3) and C-reactive protein was 160 mg/L (40-240 mg/L). The median length of stay in hospital was 10 days (1-30 days). Four (10%) patients were admitted to the pediatric intensive care unit.

All patients were treated with antibiotic treatment: ampicillin-sulbactam+clindamycin (23 patients), ceftriaxone+clindamycin (10 patients), ceftriaxone+vancomycin (5 patients), and cefepime+teicoplanin (2 patients). Empiric treatment with cefepime+teicoplanin was initiated in 2 patients (1 patient with a retropharyngeal abscess and STSS, and another with necrotizing soft tissue infection with bacteremia) after a first dose of ampicillin- sulbactam+clindamycin, before the culture results were available. Both patients experienced rapid clinical deterioration, renal insufficiency, and eventual mortality.

All isolates were sensitive to penicillin. Clindamycin resistance was present in 7 (17.5%) patients, while erythromycin resistance was identified in 2 (5%) patients.

IV immunoglobulin was administered in 2 (5%) patients. Fifteen (37.5%) patients (13 with necrotizing soft tissue infection, 2 with septic arthritis) required a surgical procedure. Mortality was observed in 3 (7.5%) patients: 2 patients with STSS and 1 patient with a necrotizing soft tissue infection with bacteremia.

Discussion

In our study, we found that the number of iGAS cases increased progressively during the pre-pandemic period, while no cases were observed during the pandemic. This situation may be attributed to a reduction in GAS transmission due to the preventive measures implemented during the pandemic, as well as a decline in the incidence of infections such as influenza and varicella, which are significant risk factors for iGAS.

Similarly, data from the centers for disease control and prevention indicate that the number of reported iGAS cases in the United States remained high between 2015 and 2019, with annual rates of 100 to 200 cases. In 2020, during the pandemic, only 74 cases were reported, a decrease that may also be linked to COVID-19 pandemic measures such as isolation and infection control (4). A study conducted in the Netherlands evaluated the pre-pandemic and post-pandemic periods, and found that, similar to our study, no cases of iGAS were reported during the pandemic in 2020. However, a significant increase in cases was observed during the post-pandemic period (5).

Clinicians in several European countries and the United States have reported an increase in cases of iGAS infections in children after overall low incidence rates during the years of the COVID-19 pandemic (6,7). This increase is thought to be associated with an increased circulation of respiratory viruses which predispose individuals to GAS infection following the relaxation of COVID-19 measures. This increase may also indicate that the incidence of iGAS infections has returned to levels which were observed in the pre-pandemic period (8).

Previous reports have identified the skin as a potential source for GAS bacteremia (9,10). In our findings, 60% of the patients with bacteremia had skin and/or soft tissue infections as a predisposing factor, which is consistent with previous studies. Additionally, it has been reported that varicella and influenza infections are among the main predisposing factors in children, and our study supports this conclusion (5,11).

GAS is highly susceptible to beta-lactam antibiotics. However, clinical failures can occur with penicillin treatment alone, particularly in patients with iGAS infections in which a larger number of bacteria may be present (12,13). Clindamycin may be a more effective agent for the treatment of iGAS infections than penicillin, as its efficacy is not impacted by inoculum size or the stage of growth (12-14). Additionally, clindamycin suppresses bacterial toxin production (14). However, clindamycin should not be used as a monotherapy, because it is not bactericidal, and GAS resistance to clindamycin is rising in certain geographic areas (1). Therefore, a combination of penicillin/beta-lactam antibiotics and clindamycin is recommended for the initial treatment of iGAS infections (15). In our study, 82.5% of the patients were treated with a combination of clindamycin and beta-lactam antibiotics.

According to our study findings, the overall mortality rate was 7.5% (3 out of 40 children). In various studies conducted in different countries, mortality rates have ranged from 2% to 8% (16,17).

Study Limitations

This study has several limitations. First, as a single-center study, the findings may not be generalizable to other regions or healthcare settings with different epidemiological patterns. Second, the relatively small sample size limits the statistical power and the ability to detect subtle trends in iGAS incidence. Additionally, the absence of cases during the pandemic period may be influenced by changes in healthcare-seeking behavior, diagnostic practices. Lastly, the study did not assess potential changes in circulating GAS strains or the impact of variations in antibiotic use, which could have influenced the observed trends. Future multicenter and prospective studies are needed to validate these findings and further explore the factors influencing iGAS epidemiology.

Conclusion

Our study revealed a progressive increase in iGAS cases during the pre-pandemic years, while no cases were observed during the pandemic period. This decrease may be attributed to a reduction in GAS transmission due to pandemic-related preventive measures, as well as a decline in the incidence of infections such as influenza and varicella, which are important risk factors for iGAS. Prospective surveillance studies are needed in order to better evaluate any changes in the epidemiology of iGAS infections.

Ethics

Ethics Committee Approval: This study was approved by the Gazi University Clinical Research Ethics Committee Non-Interventional Research (decision no.: 226, dated: 20.03.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.Ü., M.P., N.K.U., E.G., T.B.D., H.T., A.T., Concept: N.A.Ü., M.P., N.K.U., E.G., Design: M.P., Data Collection or Processing: N.A.Ü., M.P., E.A.Ş., Analysis or Interpretation: N.A.Ü., M.P., Literature Search: N.A.Ü., M.P., Writing: N.A.Ü., M.P.

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