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Clinical and Laboratory Features of Invasive Group A Streptococcal Infections: 8 Years Experience

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What is already known on this topic?

- *Group A streptococci can cause a broad spectrum of infections and complications from non-invasive to fatal invasive diseases.*
- *Invasive GAS infections can cause significant morbidity and mortality, with a mortality rate that varies between 3.6% and 8.3% in children.*

What this study adds on this topic?

- *Most of the patients had no risk factors.*
- *The clinical course of invasive GAS infection was severe in patients with pneumonia and bacteremia.*
- *Clindamycin may be preferred more frequently in severe cases.*

ABSTRACT

Objective: Invasive infections caused by group A streptococci, including bacteremia, pneumonia, sepsis, necrotizing fasciitis, streptococcal toxic shock syndrome, and focal infections, are the significant causes of mortality and morbidity worldwide. This study aimed to assess the clinical and laboratory features and management of children with invasive group A streptococci infections.

Materials and Methods: A descriptive observational study was conducted on children younger than 18 years with invasive group A streptococci infection in a single center between 2012 and 2019. The clinical and laboratory features, treatment options, and patient outcomes were evaluated retrospectively.

Results: Forty-nine patients diagnosed with an invasive group A streptococci infection were analyzed. Among them, 28 (57.1%) were boys and 21 (42.9%) were girls, with a median age of 84 months (IQR: 48-150). Group A streptococci strains were found to be isolated mainly from the skin and soft tissue abscesses (60.7%). It was found that 21 (42.9%) of the cases were hospitalized, and the median duration of hospitalization was 7 (IQR: 5-11) days. It was noted that all of the cases were treated, and infection-related mortality was not observed in any patient.

Conclusions: For correct management of invasive group A streptococci infections, timely diagnosis, appropriate duration of antimicrobial therapy, and surgical intervention in selected cases are required. It is thought that examining this issue in future studies may provide clues regarding the localization, severity, management of the infection clinic, and treatment.

Keywords: Child, group A streptococci, invasive infection, Streptococcus pyogenes

INTRODUCTION

The group A β-hemolytic streptococci are gram-positive cocci and produce clear zones of hemolysis (β) on blood agar, differentiating them from streptococci producing partial (α) and non-hemolytic (γ) streptococci.[1] *Streptococcus pyogenesis* is the only organism within group A streptococcus (GAS). Group A streptococcus is categorized or typed based on serologically distinct surface proteins and essential virulence factors including a hyaluronic acid capsule, which protects GAS from phagocytosis.[2] It was estimated that a minimum of 18.1 million people were suffering from severe GAS diseases.[3] Also, at least 663 000 new cases of invasive GAS (iGAS) and 163 000 deaths are reported each year.[3] It has been reported that children aged 0-4 suffer the most significant burden of GAS disease.[4] Group A streptococcus transmission is via droplets from pharyngeal infection or colonization, direct contact, contaminated fomites, or foodborne contamination.[5] Group A streptococcus can cause a broad

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spectrum of infections and complications from non-invasive infections such as pharyngitis and impetigo to fatal invasive diseases such as streptococcal toxic shock syndrome necrotizing fasciitis post-infectious sequelae, such as rheumatic heart diseases, post-streptococcal glomerulonephritis.[5] Invasive GAS diseases are generally defined as clinical diseases associated with the isolation of *S. pyogenes* in sterile areas such as blood, cerebrospinal or pleural fluids, deep wounds, and muscles.[2] This study aims to evaluate the clinical presentation, laboratory features, and management of children hospitalized with iGAS disease in our hospital between 2012 and 2019.

MATERIALS AND METHODS

Study Design

Medical records of children admitted to our hospital and GAS-positive isolation from sterile field cultures between 2012 and 2019 were analyzed. Clinical and laboratory features, treatment options and, patient outcomes were evaluated retrospectively. The Ethics Committee approved the study of our hospital with the number 2019/18-6 (26/12/2019).

Patient Definitions

Records of *S. pyogenes* isolated from sterile body fluids or abscess materials in the pediatric age group (1 month to 18 year) were obtained from the microbiology laboratory of our hospital. Invasive GAS infection was defined as the isolation of *S. pyogenes* in the culture of a normally sterile site (e.g., blood, pleural fluid, joint fluid, and cerebrospinal fluid).[2] Patients with skin and soft tissue infections such as cellulitis, abscess and deep wound infection, and GAS isolation from a normally sterile body fluid were included in the study. In patients with multiple *S. pyogenes* isolated, the isolated samples were included if different sterile body fluids. Varicella-zoster virus or influenza infection, trauma, burns, surgery, immunosuppression or immunodeficiency, malignant neoplasm, age <5, intravenous drug use, and long-term hospitalization were accepted risk factors associated with the development of invasive GAS infection.[2,4,6]

Laboratory Investigations

Samples taken from patients with clinical suspicions were sent to the Medical Microbiology Laboratory of our hospital. If the materials taken from sterile body fluids were insufficient, they were incubated for 5 days in a fully automated blood culture system (BACT/ALERT, 5 Rue des Aqueducs, 69290 Craponne, France). Samples with inadequate quantity were added to 5% sheep blood agar, Eosin Methylene-blue Lactose Sucrose, and chocolate agar (Biomerieux, France) and incubated for 48 hours. A fully automated identification system (Phoenix, Maldi-TOF MS, Becton Dickinson, ABD) with beta-hemolytic colony morphology, gram staining properties, catalase, bacitracin susceptibility results were used to identify the reproductive bacteria end of incubation.

Microbiology Investigation Criteria for Reporting Objectively (MICRO) reporting guide was used.

Statistical Analysis

We performed the statistical analysis with the Statistical Package for the Social Sciences software version 24.0 (IBM Corporation, Armonk, NY, USA). Demographic and clinical data were analyzed descriptively and reported as proportions of total patients. The normality of distribution of the continuous variables was evaluated using the Shapiro–Wilk test and Q-Q plot. The mean ± standard deviation was used when the continuous data were compatible with the normal distribution. The median value and interquartile range (IQR) were used when the normal distribution was not compatible. Numbers (n) and percentages (%) were used for categorical data. Numerical data with normal distribution were compared with independent groups *t*-test (independent samples *t*-test), and data not showing normal distribution were compared with Mann–Whitney *U*-test. Comparisons for categorical variables were made using the Pearson chi-square test. Statistical significance level was accepted as $P < .05$ in the study.

RESULTS

There were 49 patients diagnosed with an iGAS infection. Of the patients diagnosed with an iGAS infection, 28 (57.1%) were male, 21 (42.9%) were female, and the median age of the patients was 84 months (IQR: 48-150). The male-to-female ratio was 1.3. Thirty-three (67.4%) patients were older than 5 years. Nineteen (38.7%) patients had risk factors: 16 were younger than 5 years, 2 had trauma, 2 had long-term hospitalization, 1 had varicella, 1 had influenza, and 1 received corticosteroid treatment. It was observed that the GAS strains were mainly isolated from skin or soft tissue abscess (60.7%), blood (13.7%), and mastoid abscess (11.7%).

When the laboratory data were screened, the mean value of hemoglobin was 11.8 ± 2.3 gr/dL. Leukocytosis was presented in 22 (75.8%, 22/29) patients, and the median value of the leukocyte count was 16.100/µL (IQR: 10.750-21.850). Leukocyte count was higher in those with risk factors and those hospitalized ($P = .047$, $P = .009$). Reactive thrombocytosis was present in 2 (6.8%, 2/29) patients, and the median value of platelet number was 328.000/µL (IQR: 261.500-410.500). Twenty-six (92.8%, 26/28) patients had C-reactive protein (CRP) levels higher than normal value (5 mg/L), and the median value of CRP was 75.8 mg/L (IQR: 6.0-153.7). The median value of the sedimentation rate was 19 mm/h (IQR: 29.5-77.2) (Table 1).

Group A streptococcus was most often isolated from aspiration material (71.4%). It was found that 21 (42.9%) of the cases were hospitalized and had received intravenous therapy. The most common reasons for hospitalizations were skin or soft tissue infections. The median duration of hospitalization was 7 (IQR: 5-11) days. The majority of patients (58.1%) had received parenteral (intravenous or intramuscular) treatment. The total duration of treatment (parenteral or oral) was 10 (IQR: 7-13) days (Table 1). The mean age and median leukocyte count were higher in patients who received parenteral therapy than patients who received oral therapy ($P = .037$ and $P = .014$, respectively). Drainage history was found to be significantly higher in patients receiving parenteral treatment ($P = .039$) (Table 2).

Overall, 3 (6.1%) patients with an iGAS infection required admission to the intensive care unit. All 3 patients admitted to the intensive care unit had bacteremia, and 2 patients had pneumonia with pleural effusion. Additionally, all 3 patients had risk

Table 1. Clinical and Laboratory Characteristics of Patients with Invasive Group A Streptococcal Infections

Characteristics	**N (%)**
Demographics	
Age [median (IQR), in months]	84 (48-150)
<5 years	16 (32.6)
5-15 years	22 (44.8)
≥15 years	11 (22.6)
Male sex	28 (51.7)
Risk factors	19 (38.7)
Site of culture	
Skin	19 (37.2)
Soft tissue (peritonsillar and parotid abscess)	12 (23.5)
Blood	7 (13.7)
Mastoid abscess	6 (11.7)
Pleural effusion	4 (7.8)
Bone or joint fluid	3 (5.8)
Laboratory findings	
Hemoglobin [mean (SD), in gr/dL]	11.8 ± 2.3
Leukocyte number [median (IQR), in µL]	16.100 (10.750-21.850)
Platelet number [median (IQR), in µL]	328.000 (261.500-10.500)
C-reactive protein [median (IQR), in mg/L]	75.8 (6.0-153.7)
Sedimentation rate [median (IQR), in mm/h]	19 (29.5-77.2)
Patient disposition and outcomes	
Drainage	35 (71.4)
Admitted to Hospital	21 (42.9)
Admitted to ICU	3 (6.1)
Hospital length of stay [median (IQR), in days]	7 (5-11)
Total duration of treatment [Median (IQR), in days]	10 (7-13)

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit.

Table 2. Comparison of Clinical and Laboratory Characteristics of Patients Receiving Parenteral and Oral Therapy

	Parenteral Therapy, n = 25	**Oral Therapy, n = 18**	***P***
Age (months)‡	132 (48-192)	60 (36-84)	**.037***
Risk factors, n (%)	10 (40.0)	7 (38.9)	.941**
Drainage, n (%)	22 (88.0)	11 (61.1)	**.039****
Duration of treatment (days)‡	10 (8-14)	7 (7-9)	.366*
Hemoglobin (g/dL)⁺	11.8 ± 2.6	11.0 ± 0.8	.430***
Leukocyte number ($\times 10^3$/µL)‡	18.9 (15.6-23.3)	10.7 (8.9-13.7)	**.014***
Platelet number ($\times 10^3$/µL)‡	317 (259-411)	356 (324-369)	.915*
C-reactive protein (mg/L)‡	85.2 (45.4-158.6)	29.6 (11.6-38.4)	.198*
Sedimentation rate (mm/h)‡	49 (30-75)	45 (28-61)	.710*

*Mann-Whitney *U*-test; **Pearson chi-square; ***Independent groups *t*-test.
‡The median and interquartile range values were shown for the parameters that did not show normal distribution.
⁺The mean and standard deviation values were shown for hemoglobin due to normal distribution.
Statistically significant values were in bold.

factors. Case 1 was a 2-month-old infant with malnutrition and diaper dermatitis and had bacteremia. Case 2 had influenza B infection as a risk factor. He had bacteremia and pneumonia with effusion. Case 3 was receiving corticosteroid therapy for nephrotic syndrome. This case also had bacteremia and pneumonia with effusion (Table 3).

Most of the patients with invasive infections received empirical treatment with penicillin or second or third-generation cephalosporins. Four (8.1%) patients received empirical treatment with glycopeptide, and 10 (20.4%) patients received empirical clindamycin treatment in addition to penicillin treatment. Resistance to penicillin, clindamycin, and levofloxacin was not detected in the tested strains, 95.6% of the strains were susceptible to erythromycin, and the resistance rate to trimethoprim-sulfamethoxazole was 81.3% (Table 4). It was noted that all of the cases were successfully treated, and infection-related mortality was not observed in any patient.

DISCUSSION

Although improvements in healthcare and the widespread use of antibiotics reduce complications, iGAS infection remains a significant public health problem. Children, especially under the age of 4, are at high risk and peak incidence occurs before 2 years.[4-8] However, pediatric literature is limited in managing children with infections caused by *S. pyogenes* and the effects of clinical involvement on the disease process in pediatric patients from Turkey. We planned this study because of limited publications except Ciftci et al[9] from our country. The median age of the patients was 84 months. Most patients (67.4%) were older than 5 years, and 44.8% were between 5 and 15 years. The median age was higher compared to the literature.[10-13] The reason for this may be that our patients had more skin and soft tissue infections.

Other than skin lesions in children, predisposing factors include burns, varicella, malignancy, immunosuppression, trauma, and a crowded environment.[14] Varicella and streptococcal pharyngotonsillitis were the main predisposing factors in the pediatric group.[15-17] In the multicenter trials conducted in the pediatric age group, risk factors between 15 and 70% have been reported.[17-20] Cancellara et al[18] determined the risk factor of 67%, and varicella constituted most risk factors. However, in most of these studies, the risk factor constitutes a small proportion of the patients in our study population. Ciftçi et al[9] reported the risk factor in 53.8% in their study, and varicella was written as a major risk factor in all patients. However, this study was published before the varicella vaccine was added to our national immunization program. In our research, it was observed that the most of the patients did not have any risk factors. The decrease may explain these findings in varicella incidence and herd immunity after including the varicella vaccine in the national immunization program in our country.[21] Early and improved treatment of skin infections, including impetigo, and burns could also reduce iGAS disease. However, prevention through effective vaccination will probably lower disease incidence the most, as has occurred for other pathogens, such as *S. pneumoniae* and *H. influenzae* type b. It might also be related to the fact that most of the patients in our study included outpatients.

Table 3. Demographic and Clinical Characteristics of Patients Required Intensive Care Unit

	Age, (Months)	Underlying Condition	Risk Factor	Site of Culture	LOI[1] (Days)	LOT[2] (Days)	LOH[3] (Days)	Treatment
CASE 1	2	Malnutrition and diaper dermatitis	Aged <5 years	Blood	3	10	10	Ampicillin+cefotaxime
CASE 2	132	-	Influenza B	Blood and pleural effusion	21	43	43	Vancomycin+ceftriaxone
CASE 3	204	Nephrotic syndrome	Corticosteroid treatment	Blood and pleural effusion	3	32	37	Teicoplanin+ceftazidime

LOI, length of stay in intensive care unit; LOT, length of treatment; LOH, length of hospitalization.

The most common GAS infection is acute pharyngotonsillitis, and the most common invasive diseases are bacteremia and skin or soft tissue infection.[22,23] Group A streptococci was most frequently isolated from skin and soft tissue infection in our study, mostly peritonsillar abscesses. The results were similar to those of Arrabal et al[20] from Spain and Tapiainen et al[24] from Finland. We attribute this to the frequency of suppurative complications of streptococcal tonsillopharyngitis due to not being treated with appropriate antibiotics at the correct time. Because skin or soft tissue infections can cause bacteremia in addition to suppurative complications, appropriate and timely treatment should be provided. There were no patients with necrotizing fasciitis and streptococcal toxic shock syndrome. Previous reports identified skin as a potential site where the primary trigger for clinical manifestation of bacteremia or sepsis happens.[18,25] Contrary to our findings, only 1 patient (14.8%,1/7) had skin or soft tissue infections as a predisposing factor. Also, despite the high frequency of skin and soft tissue infections, we detected none of the necrotizing fasciitis cases, which may again be under ascertainment from clinical information.

As with the clinical diagnosis, laboratory results were also highly variable among patients in this study; however, the CRP was consistently elevated in most of the patients (92.8%) in whom it was measured. Leukocytosis was also detected in most of the patients as CRP, suggesting that *S. pyogenes* infection is associated with relatively severe inflammation. High CRP and leukocytosis may be inflated because it was ordered in individuals who appeared sicker. This study confirms previous observations of laboratory features of invasive GAS. Some studies reported that high CRP and leukocytosis were commonly seen in patients with iGAS infections.[11,26] Studies should focus on developing a more sensitive clinical tool for identifying iGAS infections early in the future, whether through a clinical decision rule that considers patients' risk factors or through the bacteria's virulence factors.

Table 4. Resistance of *Streptococcus pyogenes* Strains

Antibiotics (N)	S (N, %)	R (N, %)
Penicillin (39)	39 (100.0)	0 (0.0)
Erythromycin (23)	22 (95.6)	1 (4.4)
Clindamycin (17)	17 (100.0)	0 (0.0)
Levofloxacin (8)	8 (100.0)	0 (0.0)
Sulfamethoxazole–Trimethoprim (16)	3 (18.7)	13 (81.3)

S, sensitive; R, resistant.

Invasive GAS infections can cause significant morbidity and mortality, with a mortality rate that varies between 3.6% and 8.3% in children.[26] In cases such as streptococcal toxic shock syndrome and necrotizing fasciitis, these rates increase twice.[16,27] In our study, the intensive care admission rate was 6.1%, lesser than other studies.[13,17-19,20,24] This may be because the study was conducted in a single center, and there were no patients with severe diseases such as streptococcal toxic shock syndrome and necrotizing fasciitis. Thielemans et al[19] in Australia reported that the rate of admission to the intensive care unit was found to be 40%, and it was observed that the majority of patients hospitalized in the intensive care unit were patients with pneumonia or bacteremia. Similar results were reported by Hua et al[17] in China. Similarly, we found that all 3 patients hospitalized in the intensive care unit had bacteremia and 2 patients had pneumonia with pleural effusion. Patients diagnosed with pneumonia or bacteremia due to *S. pyogenes* tend to be suffering from severe diseases and require intensive care admission.

After GAS has been determined, penicillin is still recommended as the first treatment option since penicillin resistance has not been detected until this time.[2] In addition, clindamycin is recommended for treating severe iGAS infections because it inhibits protein synthesis and the production of essential virulence factors of *S. pyogenes*.[2] It was determined that 4.4% of group A beta-hemolytic streptococci were erythromycin-resistant, higher than reported (1.3%) in Kara et al.[28] However, clindamycin and macrolide resistances have been reported at quite different rates between countries or regions. Hua et al[17] said that 88.9% and 81.4% of the tested strains were resistant to erythromycin and clindamycin in China. Maciá et al[11] reported a 10.6% prevalence of erythromycin resistance in Spain. Naseer et al[29] reported that 3% of *S. pyogenes* are erythromycin-resistant and 2% are clindamycin-resistant in Norway. Although it has been reported that the rate of macrolide resistance in our country is not high, the use of macrolide should be limited only to patients with a severe allergic reaction to penicillin.[30]

Our study is not without its limitations. This study was designed as a retrospective nature where patients involved were evaluated during 8 separate years. Another limitation is that we could not do a multivariable analysis because of low intensive care admission rates and no mortality. Hence, confounding or interactions between variables cannot be assessed. Furthermore, our study was based on data from a single center and the ensuing results cannot represent the general

Turkish population. The last limitation was that the genotype analysis of *S. pyogenes* could not be performed because of the study's retrospective nature. Therefore, we could not evaluate the effect of genotype on the severity of the invasive disease.

CONCLUSION

It was found that iGAS infections were most common between the ages of 5 and 15 and skin and soft tissue involvement were common. Most of the patients had no risk factors. It was determined that it could be clinically severe in the presence of pneumonia and bacteremia. The CRP was the most consistently abnormal laboratory investigation in patients with iGAS infection and should be evaluated when this disease process is suspected. Clindamycin resistance was not detected, and erythromycin resistance was relatively low compared to other countries. Clindamycin may be preferred more frequently in severe cases. Our data provide information about the *S. pyogenes* that cause invasive infections from our center in Turkey. Hereafter, nationwide data would be helpful to clarify the epidemiology, risk factors, clinical and microbiological characteristics of S. *pyogenes* invasion disease in children in Turkey.

Ethics Committee Approval: This study was approved by Ethics commitee of Health Sciences University Tepecik Training and Research Hospital, (Approval No: 2019/18-6).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – E.K.O.; Design – E.K.O.; Supervision – E.K.O., A.K.A., D.Y.C., N.Y.; Resource/Materials – A.S., N.Y.; Data Collection and /or Processing – A.S., N.C.Y., N.S.; Analysis and/or Interpretation – A.S., E.K.O., A.K.A.; Literature Search – A.S., E.K.O., N.C.Y.

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