Invasive Group A Streptococcal Infections in a Large Tertiary Center: Epidemiology, Characteristics and Outcome

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Abstract

Background: Invasive group A streptococcal (GAS) infections are increasing alarmingly worldwide.

Patients and Methods: To determine the clinical and epidemiologic characteristics of invasive GAS in a large tertiary medical center, we retrospectively surveyed microbiology and medical records of patients with invasive GAS infections (isolation of Group A *Streptococcus* from a normally sterile site) treated in our hospital from January 1995 to December 1997.

Results: 70 patients with a median age of 48 years (range 2 months–88 years) were identified. Of the 70 identified, 53 (76%) were adults (age ≥ 19 years). The most common co-morbid diseases for invasive GAS in adults were diabetes mellitus, congestive heart failure (CHF), malignancy and immunosuppression. A probable port of entry was identified in 31 (44%) of the cases. In children, varicella lesions were the major port of entry. Overall mortality rate was 17%: The difference in mortality between pediatric and adult cases was significant (0/17 vs 12/53, respectively; p = 0.03).Toxic shock syndrome (TSS) and necrotizing fasciitis were identified in 8.6% and 5.7% of the cases, respectively, with mortalities of 83.3% and 25%. Hyponatremia and hypocalcemia were more frequently observed among the severely ill.

Conclusion: Invasive GAS infections tend to have an unexpected course and a broad clinical spectrum, ranging from local skin or pharyngeal involvement to deeply invasive fasciitis with TSS and high mortality. The elderly and those with underlying medical conditions are at utmost risk for invasive GAS. Clear-cut guidelines for early therapeutic strategy, i.e. antibiotic administration and preemptive hospital admission are needed for community-based physicians.

Key Words

Streptococcus pyogenes · Toxic shock syndrome · Mortality

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Introduction

Invasive group A streptococcal (GAS) infections have been increasingly reported in the last two decades [1]. The most alarming clinical manifestations of these infections are quickly spreading necrotizing fasciitis and toxic shock syndrome (TSS) which, although rare, can be rapidly lethal [2]. Because of their association with significant morbidity and mortality, it is important to be aware of the diagnosis and management of GAS infections.

To determine the clinical and epidemiologic characteristics of invasive GAS, we retrospectively surveyed the microbiological and medical records of patients with invasive GAS infections (isolation of Group A *Streptococcus* from a normally sterile site) who had been treated in the Chaim Sheba Medical Center, a general 1,200-bed teaching hospital and regional tertiary referral center in the greater Tel-Aviv area, from January 1995 to December 1997.

Patients and Methods

The medical records of all patients suffering from invasive GAS infections presenting to our hospital over a 3-year period (January 1995 to December 1997) were retrospectively reviewed and the demographic and clinical data were extracted. Invasive GAS infection was defined by the isolation of *Streptococcus pyogenes* from blood, a normally sterile body fluid (spinal, synovial, peritoneal or pleural) or from pus obtained under sterile condition, e.g. aspirates, surgical incision and drainage [3]. Streptococcal TSS was defined according to the consensus definition of the Working Group on Severe Streptococcal Infections [4].

Categorical data were compared using Pearson's χ^2-test or Fisher's exact test where appropriate. Differences in means were assessed by Student's t-test (for normally distributed variables) or the Mann-Whitney test (for nominal data), using the BMDP statistical software [5]. A p-value of < 0.05 was considered significant.

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Results

Patient Characteristics

70 patients with invasive GAS infections were identified during the 3-year study period. Their median age was 48 years (range 2 months–88 years) and the male:female ratio was 43/27 (61%; 39%). Case distribution according to age-group, hospital length of stay (LOS) and the related mortality are presented in table 1. A total of 23 patients were referred from other medical facilities (peripheral hospital n = 7, community medical services n = 16) for further care due to the infection. All seven cases initially hospitalized elsewhere had a significant delay (> 48 h) before arriving for further care at the tertiary medical center. The mortality of these patients was significantly higher than for the other patients (3/7 vs 9/63; $p < 0.05$). These patients were generally older (mean 60 years, range 15–88 years) and in worse condition (six suffered from streptococcal bacteremia) than the others. No significant differences were found between LOS and age-group (Table 1).

Table 1
Case distribution, mortality, hospital length of stay and clinical characteristics according to age-groups of 70 patients with invasive GAS.

Characteristic	Total	≤ 18 years	> 19 years
No.	70	17	53
Male gender	43	10	33
Mortality	12	0	12[a]
Median LOS in days (range)	18 (3–55)	12.5 (3–28)	18 (4–55)
Manifestations			
Bacteremia	38	10	28
TSS	6	1	5
Site of infection			
Skin infection	34	4	30
NEC	4	0	4
Bone and joint	10	3	7
Pelvic and abdominal	5	1	4
Bacteremia from unknown source	7	0	7
Co-morbid diseases			
Diabetes	14	0	14
CHF	12	0	12
Malignancy	12	5	7
Immunosuppression	8	2	6[b]
Renal failure	2	0	2
None	22	14	8
Portal of entry			
Blunt trauma	9	5	4
Surgical wound	7	2	5
Varicella	4	4	0

[a] $p = 0.03$; [b] one patient with AIDS; TSS: toxic shock syndrome; NEC: necrotizing fasciitis; CHF: congestive heart failure; LOS: length of hospitalization

Fatal Cases

Table 2 presents comparative data on survivors versus non-survivors. The crude mortality rate was 17% (12 patients), all occurring in the older age-group. All 12 non-survivors had positive blood cultures for the streptococci (Table 2). Bacteremia, necrotizing fasciitis and streptococcal TSS were more common in older patients ($p < 0.05$) (Mann-Whitney). The non-survivors had more co-morbidity and longer LOS.

Bacteriological Cultures

Group A streptococci were isolated from blood (n = 38 patients, 54%), pus (n = 33, 47%), pleural fluid (n = 5, 7%), spinal fluid (n = 2, 3%) and urine (n = 1, 1.4%). *Streptococcus* was isolated from more than one site in five patients. In both cases in which streptococci were isolated from the CSF, positive blood cultures were identified as well. The mortality of patients with positive blood cultures was 32%.

Site of Infection

Data on clinical characteristics and different sites of invasive GAS are presented in Tables 1 and 3. Skin was the most common site of infection, occurring in 34 patients. Their median age was 49 years (range 3–88 years) and the LOS was 18 days (range 3–73 days). Cellulitis, the most frequent condition, occurred in 23 patients. Other types of skin infection included pilonidal abscess (n = 6), postoperative wound infection (n = 4) and infected hematoma (n = 1). Among the patients with skin infection, 13 had co-morbid diseases which included diabetes (n = 6) and congestive heart failure (CHF, n = 7). Clinical manifestations included an elevated core temperature (n = 21), local redness and swelling (n = 27) and skin exfoliation (n = 3). Leukocytosis was present in 19 and leukopenia in two of the patients. Three patients had thrombocytopenia. Four patients with skin infection had shock and multiorgan involvement. Five patients needed surgical excision and debridement. The three

Table 2
Comparison between fatalities and survivors of invasive GAS.

Characteristic	Survivors n = 58	Non-survivors n = 12	P-value
Median age (range)	44 years (2 months–75 years)	70 years (20–88 years)	0.0001[a]
Bacteremia	26 (45%)	12 (100%)	0.0003[b]
TSS	1 (2%)	5 (42%)	0.004[b]
≥ 1 co-morbidity	36 (62%)	12 (100%)	0.013[b]
Probable port of entry apparent	25 (43%)	6 (50%)	0.75[b]
LOS in days(time to death for non-survivors)	16 (4-50)	31 (3-55)	0.003[a]

[a] Mann-Whitney U test; [b] Fisher's exact test; TSS: toxic shock syndrome; LOS: length of hospitalization

patients with skin infection who succumbed to their disease, suffered from a co-morbid condition as well.

Necrotizing Fasciitis

One male and three female patients (5.7%) suffered from necrotizing fasciitis due to invasive GAS infection. Their median age was 57 years (range 18–80 years) and all were treated surgically. The median LOS for this group of patients was 27 days (range 7–50 days). Clinically, they all presented with high fever and tachycardia, and one patient presented with stupor. Blood pressure was normal in all patients. Three patients had leukocytosis and one had leukopenia. Two patients suffered from thrombocytopenia. Renal functions were abnormal in one patient. Hypocalcemia and hyponatremia were present in two patients. The one patient who did not survive suffered from disseminated intravascular coagulation with severe rhabdomyolysis. He was 80 years old and had no co-morbid factors, but he had a fulminant course that rapidly culminated in progressive multiorgan failure.

Bone and joint infections included septic arthritis (n = 6) and osteomyelitis (n = 4). None of these patients died and only one patient suffered from co-morbid disease (CHF).

All patients suffering from pneumonia had an additional co-morbid condition which included underlying malignancy, immunosuppressive therapy, diabetes and CHF. The clinical manifestations included high fever and tachycardia in all patients as well as leukocytosis (n = 3) or leukopenia (n = 1). Three patients suffered from hyponatremia and two developed hypocalcemia. The non-survivor died due to multiorgan involvement. This 83-year-old patient suffered from diabetes and CHF. All patients with follicular tonsillitis had positive blood cultures and all survived. A neglected otitis media was the presumed cause for meningitis from which one patient died. Pelvic and abdominal infection included psoas abscess (n = 2), peritonitis (n = 2) and endometritis (n = 1); 60% of these patients did not survive. Streptococcal bacteremia without an identifiable port of entry occurred among the older age-group (median age 57 years, range 2–76 years) with all patients suffering from a background co-morbid condition which included diabetes (n = 2), malignancy (n = 2) and CHF (n = 3).

Table 3
Site of invasive GAS infection and special clinical manifestations in 70 patients.

Site of infection	No.	No. with bacteremia	No. with TSS	No. of deaths
Skin	34	12	4	3
Fascia	4	4	1	1
Joint and bone	10	2	-	-
Lungs	4	4	-	1
Pharynx	3	3	-	-
CNS	2	2	1	1
Pelvis and abdomen	5	3	-	3
Endocarditis	1	1	-	1
Unknown	7	7	-	1

TSS: toxic shock syndrome

Co-morbid Diseases and Predisposing Conditions

Co-morbid diseases associated with invasive GAS infection were identified in 48 (68%) of the patients (Table 1). The most prevalent were diabetes (20%), CHF (17%), underlying malignancy (17%) and prior immunosuppressive therapy (11%). Other co-morbid conditions included renal failure (n = 2) and AIDS (n = 1). A probable port of entry was identified in 31 (44%) patients, most prominently status post blunt trauma (n = 9, 13%) and postoperative wound infection (n = 7, 10%). Factors associated with invasive GAS infection in the 17 patients comprising the age-group ≤ 18 years were identified as blunt trauma (n = 5) and varicella infection (n = 4). In the 53 patients comprising the older age-group (> 18 years), 38 (71%) were identified as suffering from at least one co-morbid disease for invasive GAS infection. These included diabetes (n = 13, 48%), CHF (n = 10, 37%) and malignancy (n = 8, 30%).

Streptococcal Toxic Shock Syndrome

Six patients (8.6%) with a mean median age of 52 years (range 3.5–82 years) suffered from TSS; only one survived. All six patients exhibited at least one co-morbid disease related to invasive GAS infection, although they shared no common one. The LOS was 34 days (range 9–70 days), significantly longer than that for the other studied patients ($p < 0.05$). Clinically, all these patients suffered from stupor, high fever, tachycardia and reduced blood pressure. All were bacteremic. They all exhibited dermal signs of infection (erythema, swelling and skin bulla). Skin sloughing occurred in two patients (33.3%) 2 weeks after onset of the acute infection. Laboratory tests revealed leukocytosis (> 15,000 cells/mm^3) in four patients (66.7%) and leukopenia (< 2,000 cells/mm^3) in two (33.3%). A shift to the left of the WBC count was present in all six cases. In addition, all these patients continued to suffer from marked thrombocytopenia (< 100,000 cells/mm^3), impaired renal functions, hyponatremia, hypocalcemia, hypoalbuminemia and elevated serum creatinine kinase at 48 h following admission. Organ system failure included cardiorespiratory collapse and acute renal failure. Liver function tests and coagulation parameters were disturbed in all six patients.

Invasive GAS Infection and Varicella

Four children (two girls and two boys) whose ages ranged from 3–4 years suffered from varicella prior to the invasive GAS infection. Three of them needed surgical intervention and all of them survived. Their hospital LOS was 13 days (range 6–22 days). The types of infection included necrotizing fasciitis (n = 1), septic arthritis (n = 1), pneumonia

and empyema (n = 1) and TSS (n = 1). The skin varicella eruption, presumed to be the portal of entry, had occurred between 2–6 days before hospital admission. Bacteremia was present in two children. All the children presented with fever and tachycardia, and all had leukocytosis or leukopenia as well as thrombocytopenia. In addition, they all had hypoalbuminemia, hyponatremia or hypocalcemia.

Discussion

To determine the clinical and epidemiologic characteristics of invasive GAS in a large tertiary medical center, we evaluated clinical features and outcome of 70 patients with invasive GAS infection who had been hospitalized during a 3-year period in a large tertiary medical center in Israel.

In contrast to previous reports, most of our patients (n = 43, 60%) were younger than 55 years and free of specific co-morbid diseases [3]. All fatal cases occurred in older age-group patients: The difference in mortality between pediatric and adult cases is significant: 0/17 vs 12/53, respectively. Bacteremia, necrotizing fasciitis and streptococcal TSS were more prevalent in this age-group. In addition, all fatal cases suffered from one or more co-morbid states and their LOS was longer. Nevertheless, the other findings of our report confirm previously published data concerning risk factors, co-morbid diseases mortality rates and markers of severity of patients with invasive GAS infection [6, 7, 10, 14].

Although the apparent increase in frequency and severity of invasive GAS infections worldwide has been attributed to an increased prevalence of specific serotypes capable of producing virulent exotoxins [8], specific co-morbid diseases, such as underlying CHF, diabetes mellitus or old age, were noted as being related to invasive GAS infection [9]. In our study, older age was noted to be associated with a higher mortality rate and additional co-morbid diseases, i.e. diabetes, malignancy or CHF. These underlying medical conditions were present in the group of patients who suffered from bacteremia of unknown cause and were partially related to the patients' underlying medical condition or possible port of entry of the bacteria [10]. Invasive tissue infection or TSS were also more prevalent in older patients. Furthermore, all deaths occurred in patients older than 18 years.

In the younger age-group, previous traumatic injury or varicella infection were identified as predisposing to invasive GAS infection. Varicella is a particularly important risk factor for severe invasive GAS infections in previously healthy children; an increasing proportion of cases in recent years has been associated with varicella [10].

TSS has been previously reported with increasing frequency. Patients between the ages of 20–50 years are most commonly afflicted, and frequently do not have predisposing underlying disorders [7]. In our study, 8.5% of the patients suffered from streptococcal TSS and the only survivor was a 3.5-year-old child. The higher mortality from this fulminant type of infection is well known. In the adult population with invasive GAS infection, more than 15% of the patients can develop this rapidly progressive syndrome with a mortality rate of greater than 60% [11, 12]. The rapidly progressive deterioration of organ system function is a final common pathway for death in these cases.

The reported incidence of TSS among younger patients is low in our study and is similar to previous reports [11]. This is in contrast to the fact that noninvasive streptococcal infections are more prevalent in children. Indeed, repeated exposure to noninvasive community-acquired streptococcal pharyngitis or recurrent impetigo in childhood might confer better humoral immunity against streptococcal exotoxins or its M proteins due to the repeated exposure [11].

The described electrolyte disturbances, especially hyponatremia or hypocalcemia, are biochemical findings in patients with severe streptococcal infections which had been reported earlier by others [13]. Hypocalcemia was associated with hypoalbuminemia, a marker of the severity of organ system failure and infection-induced capillary leak that also caused dilutional hyponatremia in the severely affected patients [14].

The course of severe invasive GAS infections is often precipitous, requiring rapid diagnosis and initiation of appropriate therapy. Since initial signs and symptoms of streptococcal TSS are nonspecific, physicians who are likely to be called upon to treat patients with suspected infection must be alert to the invasive nature of streptococcal infections. The rapidly progressive and high lethality of invasive GAS infection mandates immediate diagnosis and rapid initiation of treatment. The limitations of resources and cost-containment considerations are, however, important factors in current health plans. Thus, it is essential to identify clinical predictors for outcome in these cases. From the present data it appears that the elderly and those with underlying medical conditions are at utmost risk for invasive GAS. Furthermore, the extent of the initial multiorgan involvement constitutes an important factor in determining the later course of patients with invasive GAS infection. Moreover, bacteremia was considered as being the most important positive culture source since it was demonstrated in all the fatal cases.

Several limitations of the current study need to be considered. The main limitation of our analysis is that due to the retrospective nature of the study, only limited clinical information could be collected during the course of hospitalization. In addition, the presented data represent a referral center series rather than a population-based study. Furthermore, we were unable to evaluate the role of specific clinical signs prior to admission, such as fever, signs of infection and data concerning administration of antibiotics prior to admission.

In light of the results that emerged from our investigation, a policy concentrating on early admission might prove beneficial in reducing mortality and morbidity, while careful surveillance in the intensive care unit will enable the

early detection and rapid intervention in cases of systemic deterioration. Additional studies involving greater numbers of patients are needed in order to establish more clear-cut guidelines for the community-based physician on initial therapeutic strategy for patients with mild to moderate streptococcal infection who present in the community. These should include recommendations for early administration of parenteral antibiotics or preemptive hospital admission.

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