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Characteristics of group A streptococcal bacteremia with comparison between children and adults

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This retrospective study aimed to compare the characteristics of group A streptococcal bacteremia in children and adults. A total of 76 (12 children and 64 adults) patients with group A streptococcal bacteremia treated from October 1995 through September 2000 at the Linko Chang Gung Memorial Hospital were included. The mean age was 47.6 years (range, 12 days-90 years). Forty-four (57.9%) patients had predisposing medical conditions. Malignant cancer (23.7%) and diabetes (22.4%) were the 2 most common conditions, which occurred only in adults. Two (16.7%) children had chickenpox associated with secondary group A streptococcal bacteremia. Skin and soft tissue infection (60.5%) was the most common clinical manifestation. The mortality rate related to group A streptococcal bacteremia was 25%. Twelve patients met the criteria of streptococcal toxic shock syndrome and 6 (50%) were children ($p<0.05$). Despite immediate and aggressive treatment, mortality due to streptococcal toxic shock syndrome was 66.7%. The incidence of streptococcal toxic shock syndrome was much higher in children (50%) than in adults (9.4%). Early diagnosis of invasive group A streptococcal infections and streptococcal toxic shock syndrome requires awareness of the presentations and a high level of suspicion. For fulminant group A streptococcal infection, a combination of a β-lactam antibiotic plus clindamycin and/or adjuvant therapy with intravenous immunoglobulin is recommended.

Key words: Bacteremia, group A *Streptococcus*, streptococcal toxic shock syndrome

Group A *Streptococcus* (GAS) (*Streptococcus pyogenes*) can cause several common diseases including pharyngitis, scarlet fever, and impetigo. Since 1987, a resurgence of invasive GAS infections (defined as the isolation of GAS from normally sterile sites) in the form of toxic shock-like syndrome has drawn widespread attention [1-4]. A rational, consensus definition of streptococcal toxic shock syndrome (STSS) was achieved by the Working Group on Severe Streptococcal Infection in 1993 [5]. An increase of GAS bacteremia and/or STSS has been reported in several studies in 1990s [6-12], but few of them included both children and adults [12].

This study investigated the clinical characteristics of GAS bacteremia in patients of all age groups over a 5-year period at the Linko Chang Gung Memorial Hospital, and compared the differences between children and adults.

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Materials and Methods

This 5-year retrospective study of group A streptococcal bacteremia was conducted from October 1995 through September 2000 at the Linko Chang Gung Memorial Hospital. A total of 78 patients with GAS bacteremia were identified from laboratory records on the basis of a positive blood culture for GAS. All GAS isolates were identified based on catalase-negative, gram-positive cocci exhibiting β-hemolysis on sheep blood agar plates, bacitracin susceptibility, and the pyrrolidonyl arylamidase test, and were confirmed by commercial latex agglutination (Oxoid, Basingstoke, Hants, England) [13].

A thorough medical chart review was performed for all cases, and data collected included age, sex, site of infection, presence of necrotizing fasciitis and/or STSS, treatments, and outcome. Data on conditions that may have predisposed patients to invasive infection was also collected, such as trauma, burns, varicella-zoster virus infection, and decreased body defenses (human immunodeficiency virus infection, cancer, diabetes, alcohol abuse, and corticosteroid therapy).

Case definitions

Streptococcal toxic shock syndrome was diagnosed according to the consensus definition of STSS proposed by the Working Group on Severe Streptococcal Infection in 1993 [5]. Patients with hypotension (≤90 mm Hg in adults and <5th percentile for age in children) in combination with at least 2 of the following were given a diagnosis of STSS: acute renal failure (creatinine ≥2 mg/dL or ≥2 times upper limit for age), coagulopathy (platelets ≤100 000 /mm^3 or disseminated intravascular coagulopathy), liver dysfunction (transaminases or bilirubin ≥2 times upper limit for age), adult respiratory distress syndrome, generalized skin rash that may desquamate, or soft tissue necrosis. Cases were also categorized according to whether infection was community acquired or nosocomial. Nosocomial infection was defined as an infection acquired after 72 h of hospitalization.

Statistical analysis

Statistical analysis was performed by using chi-square test with Yates correction or Fisher's exact test when an expected cell was less than 5. A p value of less than 0.05 was considered statistically significant.

Results

Demographic features

During the 5-year study period, 78 cases with GAS bacteremia were identified, but only 76 were included because of incomplete laboratory data in 2 cases. The age of patients ranged from 12 days to 90 years with a mean of 47.6 ± 25.1 years (median, 54 years). There were 12 (8 male and 4 female) patients aged below 20 years (range, 12 days-13 years; mean, 4.4 years), and 64 (35 men and 29 women) were adult patients (range, 20-90 years; mean, 55.7 years). Group A streptococcal bacteremia had the highest prevalence in children younger than 10 years (11 patients) and adults aged between 50 and 69 years (27 patients).

Underlying conditions

Forty-four (57.9%) patients had predisposing medical conditions, including malignant cancer in 18 (23.7%) patients, diabetes in 17 (22.4%), alcoholism in 7 (9.2%), chickenpox in 2 (2.6%), corticosteroid use in 2 (2.6%), and intravascular drug abuse in 2 (2.6%). Four patients had 2 underlying conditions–1 with diabetes and alcoholism, 3 with diabetes and cancer. Only 2 children had predisposing conditions–both were chickenpox, and they accounted for 16.7% of GAS bacteremia in children. High fever up to 40°C persisted for 4 days after the onset of skin lesions in both children before they were admitted to the hospital. One child presented with lethargy, submandibular cellulitis with necrotic change, and generalized petechiae. The vital signs in this patient revealed hypotension, tachypnea, and tachycardia. His conditions met the criteria for STSS and deteriorated rapidly, and he died within 10 h of admission. The other 10 children did not have any known predisposing or underlying conditions.

Clinical characteristics

The most common clinical manifestations were as follows: skin and soft tissue infection in 46 (60.5%) patients, bacteremia without septic focus in 21 (27.6%), septic arthritis in 3 (3.9%), necrotizing fasciitis in 3 (3.9%), and pneumonia in 3 (3.9%). Pus culture was obtained in only 5 patients with skin and soft tissue infection, and all culture grew β-hemolytic GAS. Gram stain of synovial fluid showed positive cocci in all 3 patients with septic arthritis. Only 1 patient's synovial fluid culture grew GAS. Hip septic arthritis occurred in an 8-year-old girl, and hip arthrotomy with debridement was performed. Intravenous penicillin plus gentamicin for 4 weeks were prescribed in the other 2 cases. The other adult patient with septic arthritis received 2 weeks of intravenous penicillin treatment followed by sequential oral cefadroxil for 1 month. No permanent bone or joint sequelae was found in these 3 patients. Necrotizing fasciitis occurred in 2 adults aged 35 and 38 years with a trauma history. Both cases received hip disarticulation and leg amputation. One patient survived; the other had STSS and died of septic shock with multiorgan failure because of subsequent mixed nosocomial infections. An 85-year-old woman with necrotizing fasciitis was considered too old to receive surgical intervention, and she died soon after admission despite medical treatment. Three patients had pneumonia complicated with pleural effusion that did not grow any bacteria, but the culture showed gram-positive cocci in 1 patient.

Five patients with nosocomial infection were included in the group of patients with bacteremia without septic focus. The mean time of the diagnosis of GAS bacteremia was 9 days after hospitalization, and the predisposing factors included corticosteroid use (2 patients), chemotherapy (1), liver cirrhosis (1), and congenital heart disease (1).

High fever of more than 38.5°C (60 patients) and local painful, inflammatory lesions or wounds (52 patients) were the 2 most common symptoms prompting patients to seek medical treatment. These were, however, not specific symptoms of GAS infection. The

Table 1. Comparison of clinical characteristics of group A streptococcal bacteremia between children and adults

	Total n = 76 (%)	Children n = 12 (%)	Adults n = 64 (%)	*p*
Age (yr, mean ± SD)	47.6 ± 25.1	4.4 ± 4.1	55.7 ± 18.0	
Sex				
Male	43 (56.6)	8 (66.7)	35 (54.7)	NS
Female	33 (43.4)	4 (33.3)	29 (45.3)	NS
Underlying condition	44 (57.9)	2 (16.7)	42 (65.6)	0.005
Mean white blood cells (/μL)		15236	12980	
>10 000	59 (77.6)	5 (41.7)	54 (84.4)	0.004
<4000	6 (7.9)	3 (25.0)	3 (4.7)	0.047
Thrombocytopenia (/μL)				
<100 000	18 (23.7)	4 (33.3)	14 (21.9)	NS
Mean C-reactive protein (mg/L)	170.8	157.6	190.5	
>50	16/20 (80.0)	9/12 (75.0)	7/8 (87.5)	NS
Nosocomial infection	5 (6.6)	1 (8.3)	4 (6.3)	NS
High fever >38.5°C	60 (78.9)	10 (83.3)	50 (78.1)	NS
Portal of entry (cutaneous)	52 (68.4)	6 (50.0)	46 (71.9)	NS
Total mortality cases	24 (31.6)	4 (33.3)	20 (31.3)	NS
Related to GAS bacteremia	19 (25.0)	4 (33.3)	15 (23.4)	NS
STSS	12 (15.8)	6 (50.0)	6 (9.4)	0.002

Abbreviations: GAS = group A streptococcus; NS = not significant; STSS = streptococcal toxic shock syndrome

mean time between the onset of symptoms and a doctor visit was 2.8 days. Leukocytosis (>10 000/μL; 59 patients) and elevated C-reactive protein (>50 mg/L; 16/20 patients) were frequently found in GAS bacteremia patients (Table 1). Leukocytosis was more common in adults than in children. In contrast, leukopenia (white blood cell count <4000/μL) was more common in children ($p<0.05$). Eighteen patients had thrombocytopenia (<100 000/μL) and 10 of them met the criteria for STSS.

The initial empiric antibiotics treatment varied, but a combination of cefazolin or penicillin plus gentamicin was most commonly used (46 patients). Group A streptococcal was uniformly sensitive to penicillin by disc diffusion test if sensitivity test had been done. After the blood culture report was obtained, antibiotics were shifted to Aq-penicillin in 16 patients who had not initially been given Aq-penicillin for empiric antibiotics. The disease progression of 15 patients was too rapid and they died before any change of the initial antibiotic regimen could been done. Initial antibiotics of vancomycin plus second- or third-generation cephalosporins were maintained in another 9 patients. Clindamycin had been added in 7 adult patients. Excluding 19 patients with a cause of death related to GAS bacteremia, the mean duration of antibiotic treatment was 21 days. Two

Table 2. Clinical characteristics of streptococcal toxic shock syndrome in 12 patients

Case no.	Age (yr)/sex	Focus of infection	Underlying condition	Features of STSS	Outcome
1	13/M	None	None	H, LPLT	Died
2	4.0/M	Cellulitis, necrosis	Chickenpox	H, LPLT, N	Died
3	54/M	Cellulitis	DM	R, H, DIC	Died
4	25/F	Cellulitis, necrosis	None	R, H, LPLT, N	Survived
5	35/M	Necrotizing fasciitis	None	R, H, DIC	Survived
6	76/M	Pneumonia	None	R, H	Died
7	0.6/F	None	None	R, H, DIC	Died
8	6.5/M	None	None	R, LPLT, rash	Survived
9	10/M	Cellulitis, necrosis	None	R, H, DIC, N	Died
10	0.7/M	Pneumonia	None	R, LPLT	Survived
11	34/M	Cellulitis	Alcoholism	R, H, DIC	Died
12	53/M	Cellulitis	Gouty arthritis	R, H	Died

Abbreviations: DIC = disseminated intravascular coagulopathy; DM = diabetes mellitus; H = hepatic impairment; LPLT = low platelet count <100 000/μL; N = soft tissue necrosis; R = renal impairment; STSS = streptococcal toxic shock syndrome

Table 3. Comparison of streptococcal toxic shock syndrome between children and adults with group A streptococcal bacteremia

	Children (n = 6)	Adults (n = 6)
STSS cases in GAS bacteremia[a]	6/12 (50%)	6/64 (9.4%)
Sex		
Male	5	5
Female	1	1
Underlying condition	1	3
Mortality related to STSS	4	4

Abbreviations: GAS = group A streptococcus; STSS = streptococcal toxic shock syndrome
[a] $p = 0.002$.

children with STSS also received intravenous immunoglobulin therapy (1 gm/kg/d for 2 days and single dose of 2 gm/kg, respectively) and had a good prognosis.

Streptococcal toxic shock syndrome most often happened within 1 day of hospitalization. The syndrome occurred in 6 (50%) of the 12 children and in 6 (9.4%) of the 64 adults. Broad-spectrum antibiotics were initially prescribed in all STSS cases. Eight (66.7%) of 12 patients with STSS died, of whom 6 died within 2 days of the onset of STSS. The clinical features of the cases of STSS are described in Table 2. The percentage of children and adults with STSS, the sex distribution, underlying conditions, and mortality are shown in Table 3. Death related to GAS bacteremia, defined as death within 5 days of GAS isolation and without other contributing factors, was noted in 19 patients (mixed infection in 3 cases). The mortality rate was 25% (33.3% in children, 23.4% in adults).

Discussion

Since mid-1980s, several studies have reported an increase in the frequency of GAS bacteremia [6-12]. In this retrospective study, the incidence of GAS bacteremia did not increase significantly from year to year within the 5-year period. Due to the lack of available data before October 1995, we could not determine whether there was an increasing trend in frequency during the past decade at the Linko Chang Gung Memorial Hospital. The higher prevalence of GAS bacteremia among children younger than 10 years and adults older than 50 years is consistent with results of the population-based surveillance conducted in Toronto [10]. In the Toronto study, the rate of invasive GAS infection among children younger than 10 years was about 2 cases per 100 000 persons annually and slightly exceeded the overall rate of 1.5 cases per 100 000; the lowest rates were identified among individuals aged 10 to 29 years, whereas higher rates were more marked among the elderly [10].

Reported patient groups at increased risk of GAS infection include persons with chronic pulmonary disease, cardiovascular disease, diabetes, alcohol abusers, malignant cancer, and use of corticosteroid or other immunosuppressive agents [3,10]. In this study, 65.6% of the adult patients had underlying conditions, with malignant cancer and diabetes being the 2 most common conditions. In contrast, most children were previously healthy, as had been reported by other studies [9,11]. Chickenpox has been shown to be a major predisposing factor for GAS cellulitis and invasive infection among children [10,12,14,15], which is consistent with the results of this study. Reports of surveillance in Toronto indicated that risk among young children who had chickenpox increased 39-fold within 2 weeks of illness onset compared with those who did not have chickenpox [10]. Widespread use of varicella vaccine is thus encouraged to decrease the incidence of childhood varicella and the resultant complication of invasive GAS infection [14].

The initial clinical presentations and laboratory findings of GAS bacteremia are often nonspecific. In this study, skin rash was rarely documented in the medical charts. Skin rash is much less common than STSS [4], but this may be caused by clinical doctors ignoring and not recording the symptom. Skin and soft tissue infection was the most common manifestation reported in previous studies [3,4,9-11,16], and was present in 60.5% of patients in this study. The reported main portal of entry for GAS was skin with local trauma or mucous membrane [4,17], but patients with symptomatic pharyngitis rarely developed STSS [17]. In this study, pneumonia was less common (3.9%) than in the Toronto surveillance study (11%) [10].

In 1987, Cone *et al* [1] reported 2 cases of non-bacteremic streptococcal cellulitis with toxic shock-like syndrome. Stevens *et al* [2] subsequently published a report on a series of 20 patients with invasive GAS infections associated with STSS. Thereafter, invasive GAS infection and STSS received greater attention, and more cases were reported in previously healthy and young people. In this study, the incidence of STSS in all cases of GAS bacteremia was 15.8%, and is extremely high in children (50%). A male predominance with 83.3% was found, but the reasons for this were not clear from the known pathogenesis of STSS [17-19]. The mortality of STSS was 66.7% in both children and adults. There were few studies to compare the incidence and mortality of STSS between children and adults. Davies *et al* [12] reviewed 4 series that reported both pediatric and adult cases concurrently using the same inclusion criteria and concluded that children

(n = 51) had a lower incidence (4%) of STSS and a lower mortality (7.8%) in invasive GAS infections, compared with a 43% incidence and 43% mortality in 209 adults. There were too few (only 2) cases of childhood STSS to make a valid comparison of the mortality between children and adults. In the Toronto surveillance study, the incidence of STSS in invasive GAS infection was 5% (4 cases) in 79 children and 15.6% (38 cases) in 244 adults. Among the 42 STSS cases, 25 aged more than 60 years [10]. In this study, the discrepancy of high STSS incidence and high mortality in children is intriguing, but the sample size was too small to make a conclusion about its possible cause. Further studies are needed to characterize the virulence of GAS strains, and more cases should be included to delineate the conditions.

In this study, the usage of antibiotics varied, even after the blood culture was reported. The clinicians did not seem to be aware of, or were unfamiliar with, the resurgence and treatment of invasive GAS infection. Penicillin is uniformly active against GAS in *in vitro* susceptibility test, but invasive GAS infections such as overwhelming sepsis, necrotizing fasciitis, myositis, and empyema respond less well to monotherapy with penicillin, and morbidity and mortality rates can be high [17,20]. Stevens *et al* [17] recommended antibiotic treatment for serious GAS infections using a combination of a β-lactam and a protein synthesis inhibitor (clindamycin or erythromycin) [18]. The decreased potency of erythromycin against GAS isolates was first reported by Lowburry and Hurst [21] in 1959. Hsueh *et al* [22] collected 78 clinical GAS isolates from southern Taiwan during 1992 and 1993 and found a high resistant rate to macrolides of 77.8%. Macrolides should therefore no longer be considered as an option for the treatment of GAS infection in Taiwan. Compared with β-lactam antibiotics, the minimal inhibitory concentration of clindamycin for GAS was high [22]. β-hemolytic streptococci showed a high resistance rate (36.1%) to clindamycin in a study of 8 medical centers of Taiwan in 1996 [23]. These data indicate that clindamycin should not be used as monotherapy for severe GAS infections. However, clindamycin has an important role in suppressing streptococcal toxins production and M protein synthesis in combination therapy with a β-lactam [17-19]. In addition to antibiotics, intravenous immunoglobulin as a successful adjunctive therapy for STSS was first reported in 1992 [24]. Several subsequent reports also indicated the clinical effectiveness of intravenous immunoglobulin in serious GAS infections [25-27]. Among the 4 surviving patients (2 children, 2 adults) with STSS in this study, 1 child received penicillin plus intravenous immunoglobulin therapy (1 gm/kg/d for 2 days) and another received penicillin, clindamycin, and intravenous immunoglobulin therapy (2 gm/kg). Intravenous immunoglobulin as an adjunctive therapy should be considered in STSS, but the effectiveness and the optimal dosage should be further defined [27].

In summary, most GAS bacteremia occurred in young children, elderly, and persons with decreased host defenses. Skin and soft tissue infection was the most common manifestation. Chickenpox, though preventable, was a predisposing factor to invasive GAS infection in children. The development of necrotizing fasciitis, gangrene, and STSS was life-threatening and required prompt and aggressive management. The initial clinical presentations and laboratory data were nonspecific and early diagnosis could only be made based on a high level of suspicion. A β-lactam plus clindamycin and/or adjuvant therapy with intravenous immunoglobulin, and surgical intervention if indicated, may lead to a favorable outcome.

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