

Epidemiology of Beta-haemolytic Group G Streptococcal Bacteraemia in Singapore (1996 to 1998)

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Abstract

Introduction: Group G streptococcus (GGS) accounted for 8% to 44% of all bacteraemias due to beta-haemolytic streptococci according to various reports. The aims of this study were 1) to describe the epidemiology of GGS bacteraemia in Singapore for which local data are lacking and 2) to compare its frequency of isolation to the other Lancefield groups. **Patients and Methods:** The study period was from 1 January 1996 to 30 June 1998. The laboratory records of 2 large acute care hospitals were examined. There was a total of 85 patients. The medical records of 52 patients were available for analysis. In addition, laboratory microbiological data from 1993 to 1999 were reviewed and the number of blood cultures that were positive for beta-haemolytic streptococci groups A, B, C and G was collated. **Results:** The majority involved the elderly. The mean age was 67 years. The skin was the major portal of entry. Local conditions predisposing the skin to infection occurred in 40.4%. Co-morbidity included malignancies in 28.8% of patients, diabetes mellitus in 11.5% and liver disease in 9.6%. Mortality was 15.4% including fatal septic shock. Recurrent bacteraemia occurred in 5.8% of the patients. The majority (90.4%) were community-acquired infections. GGS, along with group B streptococcus (GBS), was the most common streptococcus among the beta-haemolytic streptococci causing bacteraemia in these 2 hospitals.

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Introduction

Human isolates of group G streptococci (GGS) that form large colonies are similar to group A streptococci (GAS) in terms of virulence and cause a range of serious infections. These included infective endocarditis which had been emphasised in older reports¹ but was found to be uncommon in later studies.²⁻⁴ Of interest were the rates of underlying malignancy which was reported to range from 21% to 65%.^{2,3,5-7}

There has been increasing interest in GGS as an emerging opportunistic or nosocomial pathogen⁷ and the organism had been reported to account for 8% to 44% of all bacteraemias due to beta-haemolytic streptococci.^{2,5,8} Reports on beta-haemolytic streptococcal bacteraemia had often shown that either group B streptococcal (GBS) or GAS bacteraemia was the most frequent.^{2,4,8-10}

Therefore, the aims of this study were 1) to describe the epidemiology of GGS bacteraemia in Singapore for which local data are lacking and 2) to record its frequency of occurrence compared to the other beta-haemolytic streptococci.

Patients and Methods

The study period was from 1 January 1996 to 30 June 1998. The laboratory records of two large acute care hospitals were examined.

The Singapore General Hospital (SGH) has 1600 beds with an annual admission rate of approximately 78,000 patients. The Tan Tock Seng Hospital (TTSH) has 1032 beds with an annual admission rate close to 51,000 patients. In addition to the usual Medical and Surgical Departments, SGH has Oncology and Haematology, Obstetrics and Gynaecology, Neonatal, Burns and Renal Units. TTSH has a Geriatric Unit which receives referrals from two community hospitals. Both hospitals had closed their paediatric service from May 1997.

Laboratory records of patients with streptococcal group G bacteraemia were retrieved from the laboratory computer system. There was a total of 85 patients from the two hospitals (44 patients from SGH and 41 patients from TTSH). An average of 18 and 16 patients per year was noted for SGH and TTSH, respectively. The medical records of 52 of these 85 patients were available for

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analysis. Since the patient demography was similar for the 2 hospitals, all available data were analysed together.

In addition, microbiological data from 1993 to 1999 (SGH) and from 1994 to 1997 (TTSH) were reviewed and the number of blood cultures that were positive for beta-haemolytic streptococci groups A, B, C and G was collated.

Laboratory Method

The organism was identified by its typical colony morphology, Gram stain appearance of Gram-positive cocci in chains and a negative catalase reaction. The Lancefield grouping of the beta-haemolytic streptococci was determined using a commercial latex agglutination kit (Streptex, Wellcogen, England). Antibiotic susceptibility was performed using the Kirby Bauer disc diffusion method on Mueller-Hinton agar supplemented with 5% sheep blood and referring to the National Committee for Clinical Laboratory Standards (NCCLS) criteria.¹¹ Minimum inhibitory concentration (MIC) values were available for some strains and this was done using the E test (AB Biodisk, Solna, Sweden).

Results

Age and Sex Distribution

Of the study population, 71% (37/52) were more than 60 years old. The mean age was 67 years, with an age range of 23 to 96 years. There were 25 male patients and 27 female patients.

Source of Infection

Thirty-six patients (36/52 or 69.2%) had signs and symptoms referable to the skin as the portal of entry for infection. Twenty-two of these 36 patients presented with acute cellulitis, often involving the lower limbs. The other 14 patients had infected ulcers, pressure sores, abscesses or gangrene, and 1 of the 14 had burns. Six patients (11.5%) had signs and symptoms suggestive of chest infection. However, none of these patients had sputum cultures that were positive for the organism. Three patients (5.8%) had other sources of infection; they were epididymo-orchitis, perforated empyema of the gallbladder and pharyngitis. For 7 patients (13.5%), the source of infection could not be determined.

Underlying Clinical Disease or Co-morbidity (Table I)

Fifteen patients (15/52 or 28.8%) had underlying malignancies. All had solid tumours. Six patients were diabetic (11.5%) and of these, 2 had concomitant malignancies. There were 5 patients (9.6%) with liver cirrhosis. Alcoholism was noted for 2 of the 5 patients with liver cirrhosis. Twenty-one patients (40.4%) had underlying conditions affecting the integrity of the skin. These included pressure sores, various forms of dermatitis, chronic

TABLE I: NUMBER OF PATIENTS WITH UNDERLYING DISEASES OR CO-MORBIDITY

	No.	(%)
Underlying conditions affecting the skin	21	(40.4)
Malignancy	15	(28.8)
Diabetes mellitus	6	(11.5)
Liver cirrhosis	5	(9.6)
Neurological disorders/bedridden	10	(19.2)
Anaemia	6	(11.5)
Renal impairment	5	(9.6)
Others	6	(11.5)
No significant co-morbidity	4	(7.7)

lymphoedema and peripheral vascular disease.

Six patients were suffering from neurological disorders such as cerebrovascular accidents or Parkinson's disease. Four patients were bed-bound, but the cause was not defined. Six patients had anaemia and 5 had renal impairment. Six patients had various co-morbidity including hypoalbuminaemia, chronic joint pain, osteoarthritis, congestive cardiac failure, congenital heart disease and bronchiectasis. Four patients (7.7%) had no significant co-morbidity.

The Clinical Course and Response to Antimicrobial Therapy.

For the majority (39/52 or 75%), the clinical course was uncomplicated. Defervescence often occurred within 48 hours upon administration of appropriate antimicrobial therapy, similar to previous reports.^{2,6,12}

Mortality

There were 9 deaths in this study. Six died within a week of admission, 2 within 10 days of illness and 1 patient died 5 weeks later from nosocomial methicillin-resistant *Staphylococcus aureus* bacteraemia. Therefore, the mortality due to GGS bacteraemia in this study was 8/52 or 15.4%.

Complications

There were 6 patients (11.5%) who were hypotensive at presentation. Five (83%) of these patients died. Of the 5 patients, 2 were on chemotherapy for neoplastic disease and 2 were more than 80 years old. There were 2 cases (3.8%) with a prolonged coagulation time.

Recurrent Infections

There were 3 patients (3/52 or 5.8%) with recurrent infections. One was a 32-year-old female patient with carcinoma of the breast with skin and spinal metastases. She presented with fever of acute onset. Clinical examination showed nodular lesions on the chest wall at the mastectomy site. Blood cultures were positive for GGS. She was treated with intravenous crystalline penicillin followed by oral

penicillin for almost 2 weeks. She became afebrile and was well enough to receive chemotherapy after completing the antibiotics. One week after the chemotherapy, she developed fever with a knee effusion. There was no culture result for the knee effusion. This time, blood cultures were positive for both GGS and *S. aureus*. In both instances, the streptococci remained sensitive to penicillin.

The second case was a 44-year-old male patient with alcoholic liver cirrhosis. He presented with cellulitis of the legs. He received intravenous ceftriaxone and cloxacillin for 1 day followed by oral cefuroxime and cloxacillin for 1 week. He was afebrile after 4 days of antibiotics. Two weeks later, the patient was readmitted for fever and cellulitis of the legs. Blood cultures were again positive for the same organism. The organism was sensitive to penicillin in both episodes.

The third patient was a 28-year-old man who presented with acute onset of right testicular pain and fever of short duration. Clinical examination revealed a tender and thickened right epididymis and a swollen and tender right testis. He had fever between 38°C and 40°C. He received intravenous ceftriaxone for 3 days followed by oral amoxycillin for 1 week. The fever settled rapidly after 1 day of intravenous ceftriaxone. A little over a month later, he was again admitted for similar complaints. Clinical examination this time revealed that he was febrile with a swollen and tender left testis. He was given oral ciprofloxacin but this was changed to oral amoxycillin after the blood culture results were known. He responded within 3 days after taking amoxycillin. Urine microscopy was normal and the urine culture was negative. He later complained of abdominal pain radiating to the back. Magnetic resonance imaging showed degenerative disc changes or early discitis at L5, S1 and possible sacroilitis. Bone scan revealed intense tracer uptake at S1 and both sacroiliac joints, revealing possible infection. The patient was given amoxycillin for 12 days and was well on discharge. It was possible that the patient had a genital nidus of infection which persisted and subsequently led to haematogenous seeding of the sacroiliac joints.

There were no endocarditis or meningitis in this study.

Community-acquired or Nosocomial Infection

Forty-seven out of the 52 patients (90.4%) had positive blood cultures within 48 hours of admission in addition to signs and symptoms of infection and were thus considered to be community-acquired infections. Five patients (9.6%) had nosocomial infections. Of these, 3 patients had primary complaints related to the presence of malignancy. One complained of leg swelling due to a fungating tumour growth at the groin, another complained of abdominal distension and was subsequently diagnosed to be suffering

from lymphoma of the stomach. This patient had leg ulcers and pedal oedema. Infection occurred 7 and 10 days post admission respectively. The third patient, a case of laryngeal carcinoma, had symptoms of aspiration pneumonia post-operatively after stomaplasty for tracheostomal stenosis. Both GGS and *S. aureus* were isolated from blood cultures and the sputum culture grew *S. aureus*. The last 2 patients included a burns patient and a comatose trauma patient requiring assisted ventilation. Both developed signs and symptoms of infection whilst in the ward.

Treatment

The majority was treated with either penicillin, ceftriaxone, ampicillin or amoxycillin. The most common mode of treatment was intravenous penicillin or ceftriaxone followed by an oral beta-lactam after the fever had settled. Cloxacillin was often included in the empiric treatment of patients reflecting the commonly occurring skin and soft tissue infections. The most common duration of treatment was 2 weeks.

Laboratory Findings

All the isolates were susceptible to penicillin by disc diffusion method, according to the NCCLS criteria,¹¹ except for one isolate with intermediate susceptibility. This isolate came from a 76-year-old patient with necrotic sacral sores. The patient responded to standard doses of amoxycillin.

MIC data were available for 26 isolates. The MIC₅₀ was 0.016 ug/mL and the MIC₉₀ was 0.023 ug/mL. The isolate with intermediate sensitivity to penicillin had a MIC of 1.0 ug/mL. All the isolates were susceptible to vancomycin.

Three of the 52 cases (5.8%) were polymicrobial infections. In 2 cases, GGS was isolated with *S. aureus*. In another, it was isolated with *Klebsiella* species.

Microbiology laboratory data¹³⁻¹⁹ from SGH and TTSH, for the years 1993 to 1999 and 1994 to 1997, respectively, showed that GGS accounted for a significant proportion of beta-haemolytic streptococcal bacteraemias (Table II). This proportion ranged from 27.6% to 47.8% annually. For SGH, GGS accounted for 34.2% of beta-haemolytic streptococcal bacteraemia from 1993 to 1999 compared to 36.5% for GBS. As for the trend of isolation (Fig. 1), group G was the most common Lancefield group from 1993 to 1995. However, in the following years, GBS bacteraemia was more common. In 1999, both GGS and GBS were isolated almost as frequently. For TTSH, group G was generally the most common Lancefield group (Fig. 2). Group A was the third most commonly isolated group and group C the least common for both hospitals. The proportion accounted by group C streptococci (GCS) was less than 10% for these years.

TABLE II: NUMBER OF BLOOD CULTURES POSITIVE* PER YEAR FOR BETA-HAEMOLYTIC STREPTOCOCCI IN SGH AND TTSH

Singapore General Hospital (SGH)

	Group G streptococci	Group A streptococci	Group B streptococci	Group C streptococci	Total
Year	No. (%)	No. (%)	No. (%)	No. (%)	
1993	45 (36.6)	38 (30.9)	36 (29.3)	4 (3.2)	123
1994	59 (37.6)	41 (26.1)	45 (28.7)	12 (7.6)	157
1995	66 (47.8)	40 (29)	28 (20.3)	4 (2.9)	138
1996	47 (30.9)	45 (29.6)	54 (35.5)	6 (4)	152
1997	42 (27.6)	38 (25)	68 (44.7)	4 (2.6)	152
1998	49 (28.5)	19 (11)	97 (56.4)	7 (4.1)	172
1999	58 (32.8)	44 (24.8)	63 (35.6)	12 (6.8)	177
Total	366 (34.2)	265 (24.7)	391 (36.5)	49 (4.6)	1071

Tan Tock Seng Hospital (TTSH)

	Group G streptococci	Group A streptococci	Group B streptococci	Group C streptococci	Total
Year	No. (%)	No. (%)	No. (%)	No. (%)	
1994	20 (36.4)	15 (27.3)	15 (27.3)	5 (9)	55
1995	45 (35.1)	33 (25.8)	48 (37.5)	2 (1.6)	128
1996	34 (40)	24 (28.2)	26 (30.6)	1 (1.2)	85
1997	25 (41)	17 (27.9)	19 (31.1)	0 (0)	61
Total	124 (37.7)	89 (27.1)	108 (32.8)	8 (2.4)	329

* Multiple or repeat positive cultures were not excluded.

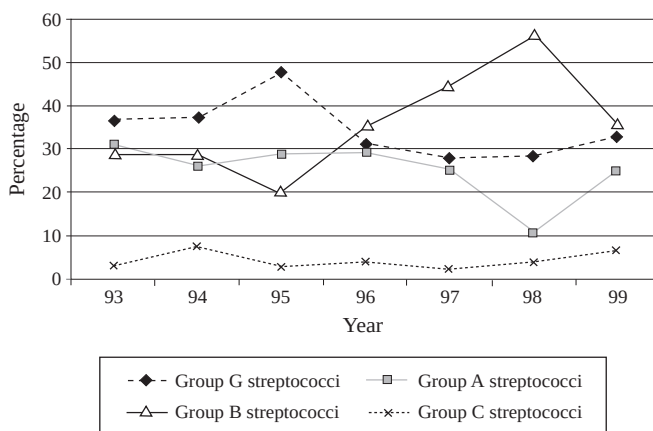


Fig. 1. Distribution of Lancefield groups among blood cultures positive for beta-haemolytic streptococci in SGH from 1993 to 1999.

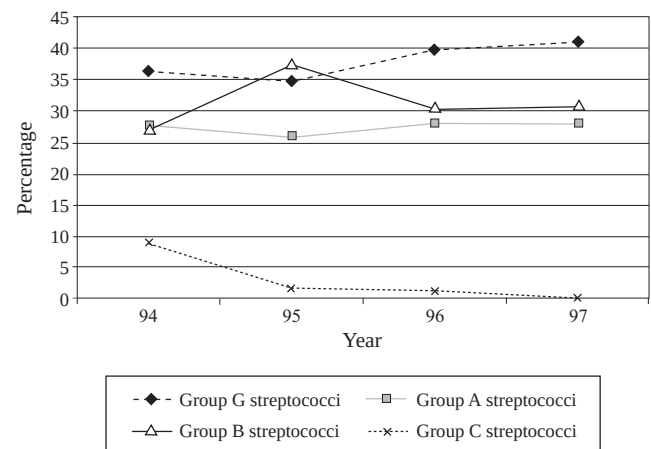


Fig. 2. Distribution of Lancefield groups among blood cultures positive for beta-haemolytic streptococci in TTSH from 1994 to 1997.

Discussion

The incidences of GGS bacteraemia were 2.3 per 10,000 admissions for SGH and 3.1 per 10,000 admissions for TTSH during the study period and are close to the rate reported by Watsky et al² (2.6 per 10,000 admissions). GGS bacteraemia was common in the older age groups similar to previous reports.^{2,4}

Previous reports have noted high rates of underlying neoplasms associated with GGS bacteraemia at 21% to

65%.^{2,3,5-7} In our study, 28.8% had underlying malignancies. The commonest malignancy was carcinoma of the breast in female patients (4 of 9 female patients), reflecting the leading cancer for females in Singapore.²⁰ There were 6 male patients with malignancies; 2 with carcinoma of the stomach, 1 each with lung, larynx, tongue and skin carcinoma. There were no haematologic malignancies. Since this was not a case control study, we could not determine if underlying malignancy was truly associated

with group G bacteraemia. However, there was a report which found that the proportion of patients with solid tumours to be significantly higher only when compared to GAS bacteraemia.⁹

Diabetes mellitus occurred in 11.5% of patients. This is higher than a recent report from Denmark (6.9%)⁴ but much lower than a recent report on invasive streptococcal group G infections from Taiwan (24.3%).¹² In contrast, diabetes occurred in a fairly large proportion of patients with GBS bacteraemia (27.5% and 19%).^{4,9} Liver disease (only 2 of 5 patients were associated with alcoholism) occurred in 9.6% whilst alcoholism was featured more prominently in 2 reports (3 of 24 patients and 21% of patients).^{2,7}

Skin and soft tissue infections (69.2%) were predominant sources of infection in bacteraemias due to this organism similar to previous reports.^{2,4,5} There were local predisposing factors for skin infection in a large proportion of our patients (40.4%) as previously reported.^{2,3} The occurrence of polymicrobial infection with *S. aureus* as a frequent co-isolate is similar to other reports.^{6,7,21} The occurrence of GGS bacteraemia with *S. aureus* further emphasises its association with skin and soft tissue infections.

Later and larger studies have shown that infective endocarditis was not common with streptococcal group G bacteraemia²⁻⁴ and this was emphasised here as there was no endocarditis detected in this study. Joint infections and bacteraemia have been alluded to in previous reports.^{1,2} In our series, there was 1 patient with unconfirmed sacroilitis. This case was unusual because he had initially presented with GGS bacteraemia associated with epididymo-orchitis 1 month earlier. A second patient may possibly have had arthritis of the knee although there was no culture result of the knee fluid. This was the 32-year-old female patient with carcinoma of the breast and recurrent infection mentioned earlier. Because this study only considered GGS bacteraemias, the occurrence of arthritis due to this organism without a blood-stream infection was not captured here. Six patients (6/52 or 11.5%) in this study were considered to have had possible pulmonary infection because the presenting signs and symptoms were from the lung. However, none of the patients in this group had positive cultures for GGS from the lower respiratory tract. GGS is generally not associated with primary invasion of the lung unlike GAS. However, the organism was isolated from the pleural fluid and endotracheal aspirate of patients with GGS bacteraemia⁷ and 2 studies have found GGS bacteraemia associated with pneumonia in 3 of 24 and 2 of 36 patients.^{2,4}

There was a preponderance of age-related conditions such as neurological disorders, immobility, renal impairment and anaemia due to the large proportion of elderly patients in the study. These conditions are also

often associated with pressure sores and eczema which provide a portal of entry for the organism.

Hypotension occurred in 6 patients (11.5%) and of these, 5 died. Patients who were hypotensive had high mortality (83%). Debilitated and immunocompromised patients appeared at risk for developing shock.

In this study, response to antimicrobial therapy was rapid. However, recurrent infection occurred in 5.8% (3/52 patients). The likely reasons for this were a persistent nidus of infection or reinfection from an endogenous source in the susceptible host or inadequate initial antibiotic therapy. The mortality rate was 15.4% which is comparable to those reported elsewhere (8% to 19%).^{2,4,5} Nosocomial infection (9.6%) was much lower than the range of 24% to one third of cases from previous reports.^{2,4,10}

The majority of GGS have MICs less than 0.1 µg/mL.^{1,22} Therefore, the strain with an MIC of 1.0 µg/mL was uncommon. Unfortunately, the strain could not be retested as all the bacterial strains were not stored. Tolerance, defined as a minimum bactericidal concentration (MBC) 32 times or more than the MIC, has been reported for penicillin and vancomycin. A recent study in the United States revealed that tolerance to vancomycin was more common than tolerance to penicillin which was not detected in that study.²² However, the clinical significance of tolerance is unclear and the majority of infections due to this organism respond well to penicillin⁶ as seen in this study.

GGS was more frequently isolated when compared to the other Lancefield groups causing bacteraemia from 1994 to 1997 for TTSH. This was further reflected by TTSH's higher incidence rate per admission for GGS bacteraemia and may be due to a larger proportion of geriatric patients admitted to the hospital. For SGH, both group G and GBS were the leading causes of beta-haemolytic streptococcal bacteraemia.

Conclusion

The incidences of GGS bacteraemia per year were 2.3 per 10,000 admissions for SGH and 3.1 per 10,000 admissions for TTSH during the study period and are similar to a previous report by Watsky et al² (2.6 per 10,000 admissions).

Of the 52 patients seen over 2½ years, bacteraemia caused by GGS predominantly affected the older person, the average age was 67 years. The skin was the major portal of entry and cellulitis of the lower limbs was common. Factors predisposing the skin to infection occurred in large proportion of patients. The proportion of patients with malignancies was relatively high. GGS along with GBS was the most common streptococcus among the beta-haemolytic streptococci causing bacteraemia, and should not be regarded as possible blood culture contaminants.

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