Journal of Infection (1997) **34**, 95–100

Group A Streptococcal Bacteraemia: Experience at a University Hospital in Riyadh

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Accepted for publication 13 August 1996

A recent increase in the frequency and severity of group A β-haemolytic streptococcal (GABHS) infections has been reported from several parts of the world. A retrospective analysis of bacteraemic GABHS infections encountered at a major teaching hospital in Riyadh, Saudi Arabia between 1982 and 1993 was performed. The epidemiologic, clinical and laboratory aspects of 29 episodes of GABHS bacteraemia were reviewed, and the differences between frequency and severity of these episodes were compared between the initial (1982–1989) and the late (1990–1993) periods of the study. The overall frequency of GABHS bacteraemia was 0.14 episodes per 1000 admissions with no difference between the initial and the late periods. Seventeen patients were adults and 12 were paediatrics. Adults were mostly females (82%) and paediatrics were predominantly males (75%). Seven episodes (24%) were nosocomial. Most patients (72%) had a predisposing factor for GABHS infections. Primary bacteraemia occurred in 13 patients (45%); and the skin and throat were the major sources of the bacteraemia in the rest of the patients. Shock complicated five episodes (17%) and acute renal failure developed in six (21%) patients. The overall case fatality rate was 21%. All five episodes complicated by shock were in the late period, and the rate of acute renal failure as well as the case fatality rate have doubled in the late vs. the early periods. Although no recent increase in frequency of GABHS bacteraemia was found, invasive GABH infections may have become more severe.

Introduction

Group A β-haemolytic streptococcus (GABHS) is a well known cause of several minor as well as major diseases. The commonest manifestations of GABHS infections are pharyngitis and impetigo.[1] Although invasive infections were common in the pre-antibiotic era, their incidence has decreased dramatically.[2] Recently, interest in GABHS infections emerged after a resurgence of invasive and serious infections caused by this organism. Many reports have appeared recording this phenomenon from several parts of the world over the last few years.[3–16] We are aware of only one report of GABHS bacteraemia from Middle East.[17] That study, however, reported GABHS bacteraemia up to the mid-1980s, before the recent observed resurgence of invasive GABHS infections. Our recent encounter of a patient with streptococcal toxic shock-like syndrome (STSLS),[18] a newly described serious invasive GABHS infection, prompted us to review all bacteraemic infections caused by this organism over the past 11.5 years to determine if there was a change in the frequency or severity of bacteraemic GABHS infections seen in our hospital over this period and to review clinical features and outcome of these episodes.

Methods

This study was conducted at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. KKUH is a 630 bed teaching hospital which provides primary and secondary care to the populations of Riyadh city and the surrounding areas; it is also a tertiary referral centre for the whole country with approximately 22 000 inpatient admissions per year. Patients with GABHS bacteraemia were identified by reviewing microbiology laboratory log books for patients whose blood culture was positive for GABHS between May 1982 and December 1993. All patients with one or more positive blood cultures were included. Hospital records were reviewed for demographic data, clinical features, underlying diseases, source of bacteraemia, laboratory data and course and outcome of each episode. The 4 year period from January 1, 1990 to December 31, 1993 was compared with the previous 8 years.

A patient was considered to have GABHS bacteraemia when GABHS was isolated from the blood on at least one occasion. Bacteraemia was considered nosocomial if the positive blood culture(s) was obtained more than 48 h after admission and there was no evidence of GABHS infection on admission.

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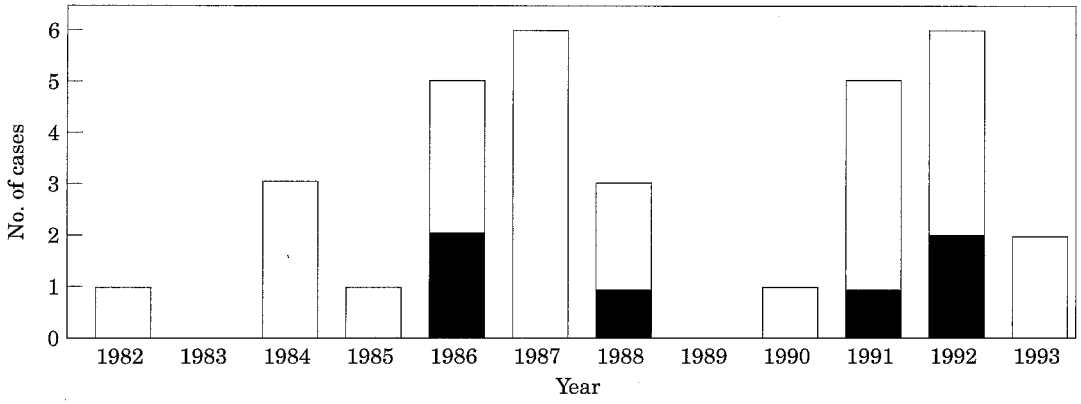

Figure 1. Annual variation of Group A streptococcal bacteraemia 1982–1993 (■) nosocomial cases.

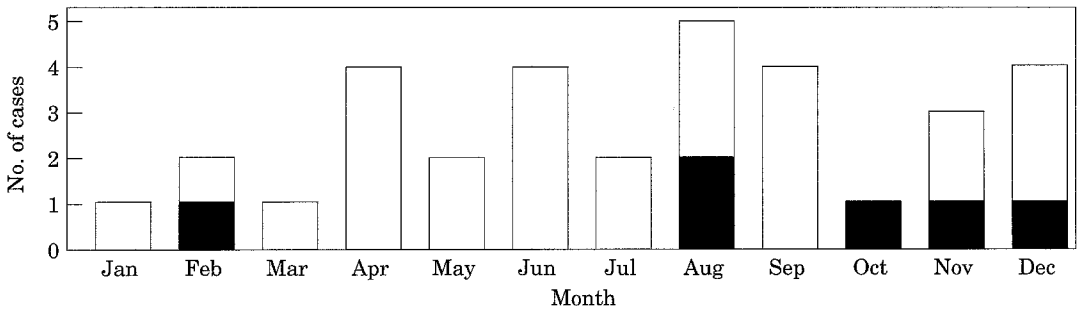

Figure 2. Monthly distribution of Group A streptococcal bacteraemia 1982–1993 (■) nosocomial cases.

The source of bacteraemia was established by a culture of a body site specimen positive for GABHS or a clinical picture compatible with a streptococcal infection such as erysipelas, wound infection, pharyngitis, etc. If neither was present, the source of bacteraemia was considered unknown.

All statistical analysis were performed with StatPac Gold Statistical package. Fisher's exact test was used for comparing proportions and *t*-test to compare means. A P value of <0.05 was used as the threshold at which results were considered to be statistically significant.

Results

Thirty-three patients had GABHS isolated from their blood during the period from May 1982 to December 1993. This gives an overall incidence of 0.14 episode per 1000 admissions. Nineteen episodes occurred from 1982 to 1989 (131 083 admissions), and 14 episodes occurred from 1990 to 1993 (109 171 admissions). This gives an average rate of GABHS bacteraemia of 0.15 and 0.13 episodes per 1000 admissions during the initial and the late periods respectively.

Annual variation was marked, with 0–6 cases diagnosed per year (Fig. 1). Monthly distribution of cases is shown in Fig. 2. Although, cases were encountered all year round, 15 (45%) of the 33 cases occurred between June and September. However, there was no statistically significant seasonal distribution.

Hospital records were available for 29 patients, 15 were seen in the initial period (1982–1989), and 14 in the late period (1990–1993). Further analysis is based on 29 patients. There were 12 (41%) males and 17 (59%) females. Ages ranged between 1 day and 75 years (median: 23 years) with a mean age of 26 years. Seventeen patients (59%) were adults and 12 (41%) were paediatrics. Adults were predominantly females (82%) whereas paediatric patients were mostly males (75%). The mean age of adult patients was (41.5 ± 18 years) with no significant difference between males (48.3 ± 18 years) and females (40 ± 18.4 years) or between those seen in the initial (39.3 ± 18 years) and the late (43 ± 19 years) periods. Seven episodes (24%) were nosocomial in origin.

Underlying conditions

Twenty-one patients (72%) had one or more concomitant underlying condition considered a risk factor for development of GABHS bacteraemia. Eleven patients (38%), however, had two or more risk factors. Malignancy, use

Table I. Underlying conditions in 29 patients with Group A streptococcal bacteraemia 1982–1993.

Underlying conditions	No. of patients (%)
None	8 (28)
Any*	21 (72)
Cytotoxic medications	6
Malignancy	5
Post-operative	5
Heart diseases	4
Steroid therapy	4
Diabetes mellitus	3
Lymphoedema	3
Post-partum	2
Collagen diseases (SLE; Rheumatoid arthritis)	2
Chronic liver disease	1
Eczema	1
Recent varicella	1

*Eleven patients had ≥2 underlying conditions.
SLE = systemic lupus erythromatosis.

Table II. Clinical features in 29 patients with Group A streptococcal bacteraemia 1982–1993.

Findings	No. of patients (%)
Fever	27 (93)
Chills	6 (21)
Hypotension	10 (34)
Shock	5 (17)
Gastrointestinal manifestations	
Any	16 (55)
Vomiting	12 (41)
Diarrhoea	7 (24)
Abdominal pain	6 (21)
Respiratory manifestations	
Any	11 (38)
Pharyngitis	5 (17)
Cough	4 (14)
Shortness of breath	2 (7)
Skin/soft tissue manifestations	
Any	9 (31)
Cellulitis	7 (24)
Wound infection	2 (7)
Rash	2 (7)
Osteoarticular manifestations	
Septic arthritis	2 (7)
Osteomyelitis	1
Others (one each with endocarditis, meningitis and thrombophlebitis)	3

of immunosuppressive therapy, and surgery were the major underlying conditions in this series. Other conditions are shown in Table I. Eight patients (28%) were previously healthy with no known underlying risk factors for GABHS bacteraemia. Five were seen in the initial period and three in the late period. There was no significant difference in the proportions of previously healthy patients seen in the early and the late periods (33% vs. 21%; $P=0.38$).

Source of bacteraemia

A probable source of bacteraemia could be identified clinically in 16 (55%) patients. This was bacteriologically confirmed in the nine patients from whom a culture of the suspected site was obtained. The skin and the throat were the major identifiable portals of entry. They were implicated in nine (31%) and five (17%) patients respectively. The vagina and a site of a peripheral intravenous line were the portal of entry in another two patients. Of the 13 patients without an identifiable source of bacteraemia (primary bacteraemia), six were seen in the initial period and seven in the late period.

Clinical manifestations and course

Table II shows the clinical manifestations of patients with GABHS bacteraemia. Fever was the most common feature encountered. It was present in 27 (93%) patients. Sixteen (55%) of 29 patients had one or more gastrointestinal complaints. Ten (34%) patients had hypotension (systolic blood pressure ≤90 mmHg) and half of these went into shock. Seven of the 10 patients who were hypotensive and all five patients who developed established shock were in the late period ($P=0.017$). Nine patients (31%) had skin and/or soft tissue infections. In all instances there were antecedent insult or abnormality of the involved skin or soft tissue. These include skin trauma (3), surgical wound (2), abnormal lymphatic drainage (2), diabetic foot (1) and infantile eczema (1). A maculopapular rash was noted in one patient and bullous skin lesions in another, however, no patient had typical scarletiniform rash or desquamation. Three patients had osteoarticular involvement: two with septic arthritis involving the hip in one, and proximal interphalangeal joint in another; and one with osteomyelitis of the distal femur. Endocarditis developed in a child with a congenital heart disease, and meningitis occurred in a newborn baby. The patient with thrombophlebitis was a 2-year-old girl who was receiving intravenous hydration therapy for gastroenteritis via a peripheral vein; GABHS was grown from the blood as well as the pus from the involved vein.

All but one of the patients received one or more antibiotics appropriate for treatment of GABHS infections. The most commonly used antibiotics were penicillins or cephalosporin derivatives. The patient who did not receive any antibiotic arrived in the Emergency Department in shock and died before antibiotic therapy could be initiated.

Nosocomial cases

Seven cases (24%) were acquired nosocomially, four (27%) in the initial period, and three (21%) in the late period. No link between any two was found. The underlying conditions in these patients were malignancy (3), surgery (2), steroid therapy (1), and gastroenteritis with intravenous hydration (1). Three (43%) patients died, two were patients with malignancy and one was after post-cardiac surgery.

Mortality

Six (21%) of the 29 patients died, three within 24 h and two within 5 days of obtaining the positive blood cultures. One patient presented in shock and died 3 weeks after the onset of the bacteraemia as a result of progressive multiorgan failure. All six patients had underlying disorders. These include malignancies (3), chronic liver disease (1), cardiac surgery (1), and the last patient was a boy with congenital lymphoedema who had recovered recently from varicella. He died with STSLS and his details have been described in a previous report.[18]

Four of the deaths occurred in the late period and two in the initial period ($P=0.29$).

Laboratory values

Fifteen (52%) patients had elevated leukocyte counts with a mean of 18 600 cells/mm^3 (range: 13 800–28 000/mm^3). Four (14%) patients had leukopenia (<5000 cells/mm^3), secondary to overwhelming sepsis in at least three; the fourth patient was on cytotoxic therapy for malignancy. Three of these four patients developed shock and two died. Among the 10 patients who had normal leukocyte counts, differential counts were available for eight. All had a predominance of neutrophils and six (75%) had shift to the left (bands >5%). Five (17%) patients had platelet counts <100 000/mm^3 and three had a haemoglobin value <10 g/dl. The prothrombin and/or partial thromboplastin times, determined in eight patients, were prolonged in five. Twelve (75%) of 16 patients for whom erythrocyte sedimentation rate was done had a value >20 mm after 1 h (mean = 60; range: 26–125 mm).

Acute renal failure (serum creatinine value twice the upper limit of normal) developed in six (21%) patients, two in the initial and four in the late periods. However, none of them required dialysis and the four patients who survived their acute illness recovered completely.

Discussion

GABHS is an infrequent cause of bacteraemia. In our hospital, the overall rate of 0.14 episodes per 1000 admissions is, at least, 10-fold less than that caused by *Brucella species* (1.46/1000 admissions), and even less in relation to *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* species.[19] However, it is similar to the incidence rate of 0.18 episodes per 1000 admissions reported by Burkett and Watanakunakorn from a general hospital in Ohio, U.S.A. (1980–1989),[20] and to the rate found in two paediatric series from children's hospitals in the U.S.[10] and in Canada.[14] Other series have reported much higher rates, however, these had originated from hospitals which serve a large population of intravenous drug abusers, a group known to be at increased risk of GABHS bacteraemia.[12,13,21] This was substantiated by Navarro *et al.* who reported an increase in cases of GABHS bacteraemia in an inner city hospital (with high intravenous drug users), but not in a suburban hospital in close geographic proximity over the same period.[13]

Since the late 1980s, an apparent increase in the incidence and/or severity of GABHS infections has been reported in several hospital series as well as population based studies worldwide.[3–16] In this study, along with others,[14,15,20] no recent increase in frequency of GABHS bacteraemia was observed. However, the frequency of severe and complicated bacteraemia have increased. Shock complicated five (36%) episodes of GABHS bacteraemia in the late period (1990–1993), but none of the episodes in the earlier period ($P=0.017$). Furthermore, both the frequency of acute renal failure, and the case fatality rate have doubled in the late period (28% vs. 13%); however, the difference lacked statistical significance ($P=0.29$). We observed no increase in the involvement of previously healthy hosts, or a shift towards a younger age group in the most recent period, features frequently described with the recent resurgence of severe GABHS infections.[3,4,7,20,22] Hoge *et al.*, in a population-based study of invasive GABHS infections, found that patients with streptococcal toxic shock-like syndrome (STSLS) were significantly younger than patients with other GABHS invasive infections and were more likely to be previously healthy.[4] In this series, only one patient was diagnosed to have STSLS in the late period.

The reasons for the resurgence of severe GABHS infections are not fully known. However, a few observations are noteworthy. First, there has been a documented increase in the isolation of M_1, M_3, and M_{18} serotypes (previously known virulent strains of GABHS) in outbreaks of rheumatic fever, bacteraemia, and TSLS from different parts of the world.[3,5–11,22] Second, production

of pyrogenic exotoxins A, B, and/or C has frequently been demonstrated in isolates from serious GABHS cases.[3,6–8,15,22] Third, lack of specific antibodies to the M proteins of the recently circulating serotypes, and to the relevant pyrogenic exotoxins were demonstrated in patients developing invasive and fatal GABHS infections.[22] It seems likely that return of virulent streptococcal strains with the capacity to produce high levels of exotoxins in populations with low levels of protective antibodies to the M antigens and to the produced exotoxins at least partially explains the observed resurgence of severe and invasive GABHS infections. We cannot comment on the serotypes or toxin-production profiles of our isolates as these were not tested in either period of the study.

Although our findings are generally in keeping with those of previous reports, a few differences exist. Significant seasonal variation in the distribution of GABHS bacteraemia was reported, and the same studies observed more cases of GABHS bacteraemia during the colder months of the year.[9,17,20] We, and others,[23–25] found no such association. However, our findings of relatively more cases during the warmer months of the year (June–September) has not been reported before and for which we have no explanation. It was not related to nosocomial clustering as only two nosocomial cases occurred during this period, and they had occurred in two different years.

More than two-thirds of our patients had one or more underlying condition known to predispose to GABHS infections. This is in accordance with other series reporting rates ranging from 38 to 93%.[8,17,20,23,25–27] The spectrum of the identified underlying conditions is similar to previously reported experience with malignancies, immunosuppressive therapy and surgery being the major factors. Of the five patients with malignancies in this series, three had solid tumours, a finding in agreement with the report of Henkel *et al.* from a cancer hospital which observed that 63% of the patients with GABHS bacteraemia had solid tumours.[24] Alcohol and intravenous drug abuse were not among the predisposing factors in this series but they have previously been identified as important factors in other series.[3,7,9,12,21] Similarly, recent varicella was identified in only one (8%) of 12 paediatric patients with GABHS bacteraemia in this series which is less than the rate of 22–24% reported in two paediatric studies.[15,25]

In this series, many patients (45%) with GABHS bacteraemia had no obvious source. This is in agreement with other reports of unselected patients.[8,11,17,20,25,26] Studies from selected patients' populations, such as injecting drug users, often report much lower percentages (<10%) of primary bacteraemia.[13,21] We have confirmed previous reports of skin as the most common portal of entry in patients with GABHS bacteraemia.[12,17,23,27]

Clinical manifestations of patients with GABHS bacteraemia observed in this series differ little from those of previous publications. However, our group had no patients with scarlatiniform rash or desquamation, which were occasionally noted by others.[7,8] Similarly, pneumonia and necrotizing fasciitis, well recognized features of severe GABHS infections, were not seen in any patients of our series.[3,6,7,9,27]

In general, GABHS is an infrequent cause of nosocomial bacteraemia. In published reports of GABHS bacteraemia, contributions of nosocomial cases ranged between 3 and 66%.[7,11–14,17,20,23,24,26–28] Studies on patients with malignancies had higher rates of nosocomial cases (44–66%).[24,28] In this study, nosocomial acquisition accounted for 24% of the cases which is comparable to previous studies,[7,11,14] but higher than other series reporting rates <10%.[12,17,23]

In the present study, the overall mortality rate of patients with GABHS bacteraemia was 21%, similar to that reported in most studies in the antibiotic era[9,13,17,20,23,27,28] and less than other studies reporting a case fatality rate of >40%.[11,24,26] The rapidly fatal course of GABHS sepsis is noteworthy. Half of the deaths in our series occurred within 24 h of obtaining the positive blood cultures. Most alarming, was the observation reported by Henkel *et al.* from a cancer hospital where the diagnosis of GABHS bacteraemia was made from post-mortem data in 15 (31%) of 49 patients.[24] The rapidly fatal course, however, was also observed in patients with no underlying chronic diseases. In a report of GABHS bacteraemia from England, 15% of the patients died at home or en route to hospital; and 50% of them had no known chronic underlying illness.[26] It is plausible that the difference in the published mortality rates is contributed, at least in part, by the variation of the inclusion of such rapidly fatal cases from series to series.

In conclusion GABHS bacteraemia, although a rare event, is associated with a high morbidity and mortality. The observed increase in severity of GABHS infections in other countries may also be occurring in this country. However, a nationwide surveillance system needs to be instituted in order to properly monitor the frequency and severity of all forms of invasive GABHS infections in this part of the world.

Acknowledgement

The author wishes to thank Gemma S. Gemaol for her secretarial assistance.

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