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Group A streptococcal bacteremia: outcome and prognostic factors

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SUMMARY

In the last two decades, an increase in the incidence of invasive group A streptococcus (GAS) infections has been reported. The aim of this study was to determine the clinical and epidemiological characteristics and the natural history of GAS bacteremias at our hospital by performing a retrospective study of all cases of GAS bacteremia diagnosed at our University hospital from 1994 to 2003. We reported 42 cases of GAS bacteremia (27 men, mean age 42.3 ± 31.6 years). None had more than one episode and four cases were nosocomial. The mean annual incidence rate was 1.01 cases per 100,000 population. An increase in the incidence but not in severity of GAS bacteremia was observed in the last 5-year period (p<0.001). The rates were highest in young children and the elderly and those with underlying medical conditions; 73.8% of patients had some underlying chronic illness, and the most relevant conditions included peripheral vascular disease and diabetes mellitus. Mortality was high and the worst outcome corresponded to elderly patients with streptococcal toxic shock syndrome (STSS). Thirty patients (71.4%) had a disruption in the integrity of the skin barrier, 14 (33.3%) were immunocompromised patients and 6 patients (14.3%) were intravenous drug users. A source of the bacteremia was noted in 38 patients (90.5%), with skin and soft tissue infection being the major portals of entry. Twelve patients (28.6%) fulfilled the STSS criteria. All strains were susceptible to penicillin and vancomycin. Resistance to erythromycin was 21.4% and to ciprofloxacin was 17.5%. The global mortality rate was 28.6%. Only STSS was significantly associated with increased mortality in the multivariate analysis.

Key words: Group A streptococcus - Bacteremia - Streptococcal shock toxic syndrome - Blood cultures - Mortality

Bacteriemia por estreptococos del grupo A: resultados y factores pronóstico

RESUMEN

En las dos últimas décadas se ha descrito un aumento de la incidencia de infecciones por estreptococos del grupo A invasivos. El objetivo de este estudio fue determinar las características clínicas y epidemiológicas y la historia natural de las bacteriemias por estreptococos del grupo A en nuestro hospital. Se estudiaron retrospectivamente todos los casos diagnosticados en un solo hospital de nivel terciario entre 1994 y 2003, y describimos 42 (27 varones, edad media 42,3 ± 31,6 años). Ninguno presentó más de un episodio y cuatro fueron infecciones nosocomiales. La tasa media de incidencia anual fue de 1,01 casos por 100.000 habitantes. Se ha observado un aumento en la incidencia de bacteriemia por estreptococos del grupo A, pero no de su gravedad, durante los últimos 5 años (p <0.001). Las tasas de incidencia más altas se observaron en niños y ancianos. El 73,8% de los pacientes afectados presentaron una enfermedad crónica subyacente, siendo las más relevantes la enfermedad vascular periférica y la diabetes mellitus. *Treinta pacientes (71,4%) presentaban una herida u otra alteración de la integridad de la barrera cutánea, 14 (33%) estaban inmunodeprimidos y 6 (14,3%) eran drogadictos por vía intravenosa. En 38 casos (90,5%) se registró un foco de entrada de la bacteriemia, siendo los más habituales las infecciones cutáneas y de tejidos blandos. Doce pacientes (28,6%) cumplieron los criterios de síndrome de "shock" tóxico estreptocócico. Todas las cepas fueron sensibles a la penicilina y la vancomicina. La resistencia a la eritromicina fue del 21,4% y al ciprofloxacino del 17,5%. La tasa global de mortalidad fue del 28,6%. En el análisis multivariado, sólo el "shock" tóxico estreptocócico se asoció significativamente a una mayor mortalidad. Durante los últimos cinco años se ha observado un aumento en la incidencia de bacteriemia por estreptococos del grupo A en nuestro hospital. Los niños pequeños, los ancianos y los pacientes con enfermedades subyacentes son más susceptibles a adquirir esta infección. La mortalidad fue alta y los peores resultados se observaron en los pacientes ancianos con síndrome de "shock" tóxico estreptocócico.*

Palabras clave: Estreptococos grupo A - Bacteriemia - Síndrome de "shock" tóxico estreptocócico - Cultivos sanguíneos - Mortalidad

INTRODUCTION

Group A streptococcus (GAS) is one of the most important bacterial pathogens in humans (1). This ubiquitous organism is the most frequent bacterial cause of acute pharyngitis, and it is also responsible for a variety of cutaneous and systemic infections with variable severity and prognosis. Its unique place in medical microbiology stems from its propensity to initiate two nonsuppurative sequelae: acute rheumatic fever and post-streptococcal acute glomerulonephritis (2). At the beginning of the 20th century, serious invasive infections caused by GAS were common, but a dramatic decline in their prevalence was observed throughout the second half of the century, probably as a result of improved socioeconomic conditions, changes in the virulence factors of GAS and the use of antibiotics (3, 4). However, in the last two decades, several reports have suggested that there has been an increase in the number and severity of streptococcal infections, including bacteremia (5-13). The reasons for this increase have not been clearly identified. Various factors have been suggested, including the spread of a more virulent clone, higher numbers of patients with conditions that interfere with the immune system and an increase in intravenous drug abuse.

The aim of our study was to determine the epidemiological and clinical characteristics of GAS bacteremia diagnosed in the last 10 years at our hospital and assess whether there have been any changes over this period.

PATIENTS AND METHODS

Patients

We conducted a retrospective study of GAS bacteremia occurring between January 1, 1994 and December 31, 2003 among patients treated at the University Hospital La Fe, which is a 1,360-bed teaching hospital in Valencia, Spain. The total number of admissions and the general population served by our hospital were used as the basis for calculating incidence rates. Our reference population was 530,000 subjects, until 1998 when it decreased to 317,000 because of the creation of a new hospital nearby. Patients with GAS bacteremia were detected using the microbiology laboratory database. Medical records were reviewed, and relevant demographic, epidemiologic and clinical data were recorded on standardized collection forms.

Definitions

A patient was considered to have GAS bacteremia when *Streptococcus pyogenes* was cultured from the blood on at least one occasion. If more than one organism was isolated from the blood, a patient was considered to have polymicrobial bacteremia. We used the definitions of sepsis and related conditions elaborated by the American College of Chest Physicians and Society of Critical Care Medicine (14). Streptococcal toxic shock syndrome (STSS) was defined according to The Working Group on Severe Streptococcal Infections criteria (15).

Immunosuppression was considered a potential predisposing factor for bacteremia and was defined as the presence of an underlying immunosuppressive disease or treatment with immunosuppressants or steroids at the time of blood extraction. The source of bacteremia was established by a compatible clinical picture or a culture of a body site specimen positive for *S. pyogenes.* If neither culture nor clinical evidence of obvious infection were present, the source was deemed unknown. Bacteremia was considered nosocomial if blood cultures obtained after 48 hours yielded GAS bacteremia and there was no evidence of GAS infection on admission. All patients were followed until death or discharge. Empirical antibiotherapy was considered effective if its activity was demonstrated with an antimicrobial susceptibility test. Recovery was defined as the absence of any sign or symptom at the end of treatment.

Those deaths produced during clinically active infection or because of any complications were considered as deaths related to bacteremia. A comparison between the first and the second 5-year period was made.

Microbiological procedures

Blood cultures were processed according to standard procedures. The microbiology laboratory uses the Bact/Alert (Organon Teknica, Boxtel, The Netherlands) or the Bactec 9240 (Becton Dickenson Diagnostic Instrument Systems, Sparks, Maryland) for culturing blood specimens. GAS was identified using standard microbiological techniques. Agglutination tests were performed with commercial antiserum (Slidex Strepto-Kit, bioMérieux, France). Antimicrobial susceptibility tests were done according to the standard disk diffusion method following the recommendations of the Committee for Clinical Laboratory Standards Institute.

Statistical analysis

Data were analyzed using a software program (SPSS version 10.0, Chicago). The distribution of quantitative

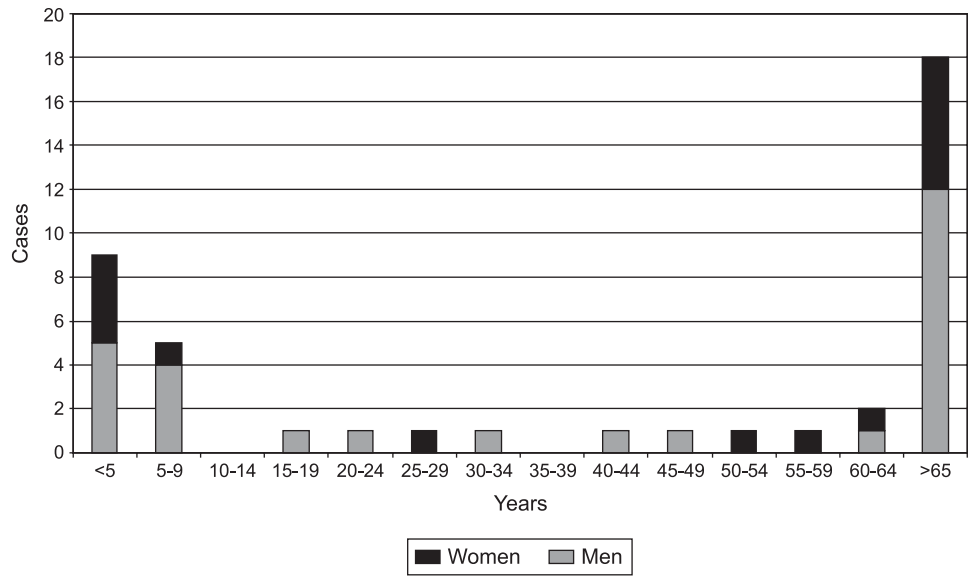

Figure 1. Age and sex of patients with GAS bacteremia.

variables was characterized by reporting the mean ± SD, whereas the distribution of qualitative variables was expressed as frequencies. Comparisons of qualitative variables were performed by using two-tailed χ^2 tests with Yates' correction for continuity and Fisher's exact test, as appropriate. Quantitative variable analysis was performed with the Mann-Whitney U test. Multivariate analysis using stepwise logistic regression was undertaken to identify the variables independently associated with mortality from GAS bacteremia, using those that had been retained after univariate analysis. A $p < 0.05$ was considered significant.

RESULTS

Epidemiology

GAS was cultured from the blood of 42 patients, 27 of whom were men (64.3%). None of the patients had more than one episode of GAS bacteremia. Corresponding medical records were available for all 42 episodes. All patients except one were hospitalized; one patient who was an intravenous drug user (IVDU) was treated as an outpatient and could not be followed adequately. The mean age was 42.3 ± 31.6 years (range, 13 days to 86 years); GAS bacteremia was more frequent in children younger than 10 years and adults older than 65 years (Fig. 1).

Table 1. Incidence of GAS bacteremia, 1994-2003.

Year	Episodes (number)	Incidence (per 10,000 admissions)	Incidence (per 100,000 persons)
1994	3	0.47	0.57
1995	4	0.66	0.75
1996	1	0.16	0.19
1997	2	0.32	0.38
1998	3	0.47	0.57
1999	2	0.36	0.67
2000	5	0.94	1.67
2001	6	1.16	2
2002	9	1.73	3
2003	7	1.36	2.21
Total	42	0.73	1.01

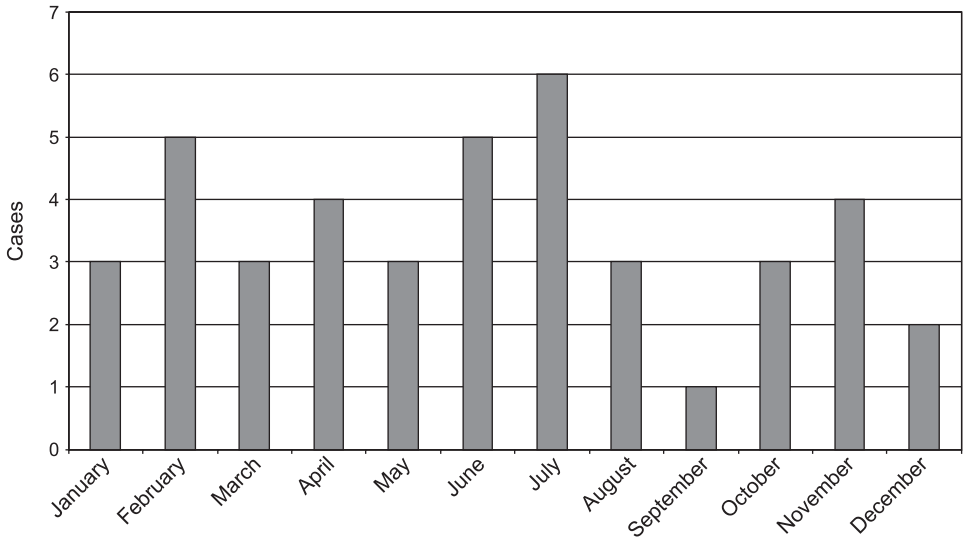

Figure 2. Monthly incidence of GAS bacteremia.

The annual incidence rate was not stable (Table 1); during the second period we detected a statistically significant increase (0.49 cases per 100,000 during the period between 1993 and 1998 *versus* 1.91 cases per 100,000 between 1999 and 2003, p <0.001). Monthly distribution of cases is illustrated in Figure 2; there was no seasonal pattern of episodes.

Four infections were hospital acquired, all of them in the second period. Three patients were diagnosed with a hematological malignant disease and the fourth one was a 13-month-old child with a diagnosis of chickenpox.

A comparison of GAS bacteremia between children and adults is shown in Table 2.

Underlying chronic diseases and risk factors

Thirty-six patients (85.7%) had one or more concomitant underlying condition that may have predisposed them to GAS infection. An underlying chronic disease was present in 31 patients (73.8%). The major chronic underlying

Table 2. Comparison of GAS bacteremia between children and adults.

	Children (n=14)	Adults (n= 28)	p
Age (yr, mean ± SD)	3.43 ± 2.77	61.71 ± 18.4	
Sex (female/male)	5/9	10/18	1*
Cases 1994-98/1999-2003	4/10	9/19	1**
Community	11	27	0.1***
Underlying chronic disease	4	27	<0.001***
Predisposing factor: immunosuppression and/or ruptured skin barrier	8	25	0.046**
Underlying chronic disease and/or predisposing factor	9	27	0.011***
HIV infection	0	6	0.083***
Ruptured skin barrier	7	23	0.07**
Pharyngitis	2	0	0.106***
Malignant cancer	3	1	0.1***
Fever (>38 ºC)	13	27	1***
Chickenpox	5	0	0.002***
STSS	1	11	0.036***
Total mortality cases	1	11	0.036***

*χ^2; **Yates' correction for continuity; ***Fisher's exact test.

Table 3. Underlying diseases in patients with GAS bacteremia.

Disease	Cases (%)
Vascular disease (arterial or venous)	12 (28.6%)
Diabetes mellitus	9 (21.4%)
Chronic cardiomyopathy	9 (21.4%)
Chronic liver disease	9 (21.4%)
Immunosuppressant therapy	8 (19.0%)
HIV infection-IVDU	6 (14.3%)
Chronic renal failure (creatinine > 1.3 mg/dl)	5 (11.9%)
Chickenpox	5 (11.9%)
Chronic pulmonary disease	4 (9.5%)
Malignant cancer	4 (9.5%)
Rheumatoid arthritis	1 (2.4%)
Liver transplant	1 (2.4%)
Kidney transplant	1 (2.4%)
None	11 (26.2%)

conditions were peripheral vascular disease, diabetes mellitus, heart disease, chronic liver disease and immunosuppressant therapy (Table 3). Thirty patients had preexisting conditions that altered the integrity of the skin barrier and 14 had some type of immunosuppression. Thirteen adult patients (13/28, 46.4%) had chronic ulcers located on the legs and five previously healthy children (5/14, 35.7%) had had recent varicella infections. All six adult patients (6/28, 21.4%) who were known to be HIV positive were IVDU and all of our patients with GAS bacteremia and who were 15-50 years of age were also IVDU.

Source of bacteremia

A source of bacteremia could be identified in 38 patients (90.5%). The skin (29 patients) was the major identifiable portal of entry. Seven patients had pneumonia; the portal of entry in five of these patients was the lungs and in the other two, it was the skin via a hematogenous route to the lungs. Two patients had a sore throat and a throat swab culture from them yielded GAS. Two patients had bone and joint infections: one neonate patient with septic arthritis involving the left hip and one IVDU patient with chronic fistulizated osteomyelitis of the proximal tibia with septic arthritis of the right knee. The source of bacteremia was unknown in 4 patients (9.5%).

Skin and soft tissue infections: Clinical manifestations

Twenty-nine patients (69%) had skin and/or soft tissue infections and all of them had preexisting conditions that altered the integrity of the skin barrier. Nineteen of these patients had cellulitis and five patients had gangrene or necrosis of the skin or subcutaneous tissues. Other types of infections included streptococcal pyoderma (n=2), central venous related catheter infection associated with skin suppuration (n=1), psoas abscess (n=1) and chronic toe ulcer without cellulitis (n=1).

The course of GAS bacteremia was rapid and the mean time of evolution before diagnosis was made was 2.07 ± 1.67 days. Most patients presented with fever (97%) and clinical features reflecting the focus of infection, but four patients presented with fever alone. At the time blood was drawn for cultures, 10 patients (23.8%) had altered conscience level, 9 patients (21.4%) had acute renal failure (creatinine >1.3 mg/dl), 8 patients (19%) had acute respiratory insufficiency (PaO_2 <60 mmHg) and 6 patients (14.3%) had coagulopathy.

The majority of patients (54.8 %) presented clinical criteria of sepsis. Severe sepsis was present in 16.6% and clinical criteria corresponding to septic shock or STSS was present in 28.6%. Percentage of cases of sepsis, severe sepsis and septic shock related to GAS bacteremia did not show statistically significant differences in the two periods studied (p=0.936, p=0.405 and p=0.342 respectively). Thirteen cases of STSS were diagnosed at our center from 1994 to 2003; all of the patients had at least one underlying disease, none was IVDU and all patients but one had positive blood cultures (16).

Microbiological data

Three patients (7.1%) had polymicrobial bacteremia. In all of them, the microorganism isolated concomitantly with GAS was *Staphylococcus aureus*.

All GAS strains were susceptible to penicillin and vancomycin. Nine (9/41, 21.4%) were resistant to erythromycin and seven (7/40, 17.5%) were resistant to ciprofloxacin. Of the 16 strains tested, 14 (87.5%) were susceptible to clindamycin.

Treatment and outcome

Except for three, all patients received effective antibiotic therapy on the day that positive blood cultures were taken. Two patients survived although the effective antibiotic therapy was not given until 2 days after the positive blood culture was obtained. Most of the patients were initially treated with empirical broad-spectrum antibiotics

Table 4. Prognosis factors associated with mortality by univariate analysis.

	Exitus (n=12)	No exitus (n=30)	p
Age (yr, mean ± SD)	62.17 (19.45)	34,33 (32.25)	0.03*
Mean days of hospital stay (SD)	5.83 (6.91)	12.3 (7.67)	0.006*
Sex (female/male)	5/7	10/20	0.879**
Cases 1994-98/1999-2003	4/8	9/21	1**
Age >60 years	9	11	0.025+
Age <15 years	1	13	0.07**
Intensive care unit admission	8	5	0.005**
Underlying chronic disease	12	19	0.018++
Predisposing factor: immunosuppression and/or ruptured skin barrier	10	23	1++
Chickenpox	0	5	0.298++
HIV infection	0	6	0.159++
Ruptured skin barrier	10	20	0.453++
Immunosuppression (except AIDS)	5	3	0.54**
Community	10	28	0.565++
STSS	10	2	<0.001++
Unknown portal of entry	1	3	1++
Altered conscience level	6	4	0.034**
Monotherapy	9	25	0.852**
Need of mechanical ventilation	9	3	<0.001**
Acute renal failure	7	2	0.001**
Hemoglobin >12 g/dl	6	16	0.845+
Leukocytes >12000 cells/ml)	5	22	0.114**
Leukocytes (SD)	9282 (6160)	15456 (7040)	0.01*
Leukopenia (<4000/ml)	2	0	0.077++
Thrombocytopenia (<100,000/ml)	9	3	<0.001**

*Mann Witney U test; **Yates' correction for continuity; +χ^2 test; ++Fisher's exact test.

which were usually changed after the microbiologic results were known. The most frequent empirical antimicrobials used were beta-lactam antibiotics (88.1%), fluoroquinolones (9.5%) and macrolides (2.4%). Eight patients were initially treated with two antibiotics: beta-lactam antibiotic and aminoglycoside (n=3), beta-lactam antibiotic and vancomycin (n=2), beta-lactam antibiotic and clindamycin (n=1), beta-lactam antibiotic and metronidazole (n=1) and two beta-lactam antibiotics (n=1). The mean duration of antibiotherapy was 16.08 ± 11.89 days. Other therapeutic interventions were performed in 9 patients including debridement of necrotic tissue or amputation (n=5), repeated arthrocentesis (n=2), percutaneous abscess drainage (n=1) and chest tube drainage (n=1).

The mortality of GAS bacteremia was 28.6%. All deaths were directly attributable to infection. The mean time from admission to death was 4.83 ± 6.64 days. Table 4 lists potential risk factors for mortality due to GAS bacteremia by univariate analysis. Multivariate analysis showed that the only factor significantly associated with a higher mortality was the diagnosis of STSS (HR 15.73, CI 95% 3.2-77.2).

DISCUSSION

The incidence of invasive streptococcal disease is similar in Europe and the United States, although variations in incidence can be expected from year to year and from country to country (17). GAS bacteremia is uncommon and persons of all ages may be afflicted. Its annual incidence ranges from 0.7 to 4.16 cases per 100,000 population in published reports (8, 9, 18-24) and *S. pyogenes* was responsible for 0.5-1.2% of all significant bacteremias in Spain (18-20). Several studies have reported an increase in the incidence of GAS bacteremia in all age groups, but the highest increase has been found in young adults in association with intravenous drug abuse (10, 20, 25). In our series, we report a significant increase in the incidence but not in severity and mortality of GAS bacteremia during the second 5-year period of the study. The reasons for this increase are unknown. Progressive aging of population and higher number of underlying chronic diseases and other predisposing factors for GAS infection have been suggested. Our prevalence of IVDU was lower than in previous reported studies of GAS bacteremia in our country (20). We

do not know if it may be explained by differences between our reference populations or by the period studied.

In contrast to other series that have reported a seasonal variation in the prevalence of GAS bacteremia, with fewer cases occurring in the summer months (8, 26), we did not observe a seasonal pattern of episodes. GAS is an uncommon cause of nosocomial bacteremia; it accounted for only 9.5% of the episodes in our study, although its prevalence ranged from 3-66% in published reports (27) and it seems to be more frequent in patients with cancer and in series with a high percentage of bacteremia with an unknown source of infection (7).

Underlying chronic diseases and predisposing factors for GAS infections were common in patients with GAS bacteremia. Their percentage ranges from 35-93% of the episodes in published reports and the highest percentage is in elderly patients (5-9, 28). Among children, predisposing factors, other than scarlet fever, include burns, chickenpox, malignancy, immunosuppression and age <2 years (1, 29-31). In elderly patients, GAS bacteremia has been associated with diabetes mellitus, peripheral vascular disease, malignancy and use of immunosuppressant therapy (1, 2). In our study, it is important to note the association between GAS bacteremia and peripheral vascular disease with chronic leg ulcers among the adult population and chickenpox among children. In contrast to previous series (26), none of our patients presented with solid tumors or recent surgical wounds. Although underlying chronic diseases were common in patients who died, none of them was associated with a fatal outcome in the statistical analysis. The lack of statistical significance may be due to an insufficient sample size.

Our study confirms previous reports that GAS bacteremia causes a spectrum of diseases that varies from uncomplicated bacteremia, metastatic suppurative focal disease to severe local infection and overwhelming infection with shock and multiorgan failure syndrome that can cause a patient to die within a few hours (5). The clinical features of our patients are quite similar to those described in other series. Cellulitis and soft tissue infection are common presentations of GAS bacteremia; these infections represent 18-74% of cases (26). Five patients in our study had gangrene and skin and soft tissue necrosis, which are known to be associated with GAS infection and to carry an especially bad prognosis. Pneumonia was the second most common focal infection. Only 9% of our patients had primary bacteremia with an unknown source of infection. This percentage is smaller than that reported in other studies of unselected patients (26, 28, 32, 33), although the rate of primary bacteremia without a source of infection reported in the literature has ranged from 0-41%. Studies from selected patient populations, such as intravenous drug users, often report much lower percentages (<10%) of primary bacteremia and the highest rates have been reported for patients with malignant diseases. In contrast to previous studies, we did not observe that bacteremia without an obvious portal of entry was associated with STSS or with a higher mortality (8). Although GAS is the most frequent bacterial cause of acute pharyngitis, the upper respiratory tract is a relatively uncommon focus of GAS bacteremia, as observed also by others (1, 20, 21). Postpartum GAS infection, a well recognized feature of severe GAS infections in the past, was not seen in any patients of our series and it may be as a result of the screening and prevention of streptococcal infections in pregnant women.

The course of severe invasive GAS infections is often rapid, requiring prompt diagnosis and quick initiation of appropriate therapy. Supportive measures typically used in the management of sepsis and shock are indicated, and antibiotic therapy should be instituted early. GAS continues to be extremely susceptible to beta-lactam antibiotics, and numerous studies have demonstrated the clinical efficacy of penicillin in treating most GAS infections because all strains are susceptible. In more severe infections, such as necrotizing fascitis and STSS, clinical failures of penicillin therapy have been documented. The failure of penicillin to eradicate GAS may be explained by the slow replication rate of GAS when a large inoculum is present, a situation commonly seen with severe invasive GAS infections (1). This reduced replication rate of GAS results in diminished expression of the target sites for penicillin activity (penicillin-binding proteins). Then, it is necessary to use antibiotics since their efficacy is not affected by inoculum size or stage of growth. Clindamycin inhibits protein synthesis, its efficacy is not affected by inoculum size or stage of growth and it has demonstrated a greater efficacy than penicillin in experimental models of fulminant streptococcal infection (2, 3). In addition, clindamycin inhibits the synthesis of both M protein and streptococcal pyrogenic exotoxins, and its action on bacteria persists longer than that of penicillin. As there is a small portion of strains of GAS which are clindamycin-resistant, we recommend combined therapy with penicillin and clindamycin. Resistance of strains of GAS to macrolides (erythromycin) was unusual (20, 34), but in the last 15 years it has progressively increased in different countries like Spain (35, 36). Fluoroquinolones have a higher spectrum of activity against Gram-positive microorganisms and although GAS strains resistant to fluoroquinolones have been described, they are

still uncommon in this species and there are few published cases with a high level of resistance (37). Our rate of resistance to fluoroquinolones has been higher than the one shown in previous literature, but due to the limitations of the antimicrobial susceptibility test used, we are unaware of the MIC_{50} and $MIC_{90,}$ which would have been of great utility for comparing in a more precise way our results with the ones shown in other series. No conclusions about optimal antibiotic therapy can be drawn from this small group, but, due to the high resistance rate of *S. pyogenes* to macrolides and ciprofloxacin which have been found at our center, it is not advisable to use them as monotherapy for the empirical treatment of serious invasive infections caused by this microorganism. The use of new antibiotics must be evaluated.

When a GAS deep-seated infection associated with necrosis is suspected, prompt and aggressive surgical drainage, debridement, fasciotomy or amputation is necessary and mandatory; intravenous immunoglobulin given in addition to appropriate antimicrobial and surgical therapy may be beneficial, although further studies are needed (38).

The overall mortality of GAS bacteremia found in this study is comparable to that found by other authors which ranges from 5-48% (8, 9, 20, 21, 26, 31, 39, 40). The outcome of GAS bacteremia appears to be dependent on host factors. Whereas there is a low mortality rate in patients with IVDU and the pediatric population, it increases in elderly patients with underlying chronic diseases. The rapidly fatal course of GAS bacteremia is noteworthy and in spite of the fact that there are diverse clinical and laboratory variables related to a high severity and mortality, the only variable significantly associated with mortality in the multivariate analysis was the presence of STSS. But, in a recent and more extensive study of 98 cases of GAS bacteremia (41) occurring during another 10-year period (1993-2002), parameters associated with mortality ($p < 0.05$) were older age, lower temperature, hypotension, a need for surgical intervention, STSS, disseminated intravascular coagulation, thrombocytopenia, lymphopenia, hypocalcemia, renal failure and acidosis. In this series, the overall mortality rate was 12% (41), which was lower than that previously reported.

Several limitations of the current study need to be considered. The first and major 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. Second, the present data represent a referral center series rather than a population-based study. Additional information is needed from other medical centers to determine whether the increased incidence in GAS bacteremia has occurred elsewhere. Third, none of the isolates were typed, streptococcal pyrogenic exotoxins were not studied and we do not know if variations in the expression of virulence factors and in the production of pyrogenic exotoxins by the pathogen have taken place. Other reports have documented an increase in the isolation of more virulent strains of GAS (M1, M3 serotypes) in outbreaks of rheumatic fever, bacteremia and STSS and the production of pyrogenic exotoxins has frequently been demonstrated in isolates from serious GAS infections (1, 5, 8).

In summary, there has been an increase in the incidence but not in the severity of GAS bacteremia in the last 5-year period at our medical center; bacteremia mainly affected very young individuals and the elderly. Elderly patients with major underlying chronic diseases are the most common patients seen with high mortality rates. Supportive measures and the use of effective therapy are necessary to reduce mortality. New therapies should be evaluated in prospective clinical trials.

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