Group A Streptococcal Bacteremia in Intravenous Drug Abusers

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The clinical and microbiologic features of group A streptococcal bacteremia are described in 40 patients, all of whom were seen between January 1982 and June 1983 and all of whom were intravenous drug abusers. Eleven patients had endocarditis (two with left-sided and nine with right-sided), and 29 patients had bacteremia without endocardial involvement. Twenty-seven of the 29 patients without endocarditis had soft tissue infections, primarily groin abscesses. Constitutional symptoms were more severe in patients with endocarditis. The two patients with left-sided endocarditis died despite antimicrobial therapy; all nine patients with right-sided endocarditis and all 29 patients without endocarditis were cured of their infection. A predominant strain of group A streptococcus was identified by serologic typing, suggesting a common source for these cases.

In the preantibiotic era, group A streptococci often caused bacteremia and endocarditis associated with cutaneous or deep tissue infections [1]. With the widespread use of penicillin, the frequency of group A streptococcal bacteremias decreased. Recently, we have observed a striking increase in the frequency of group A streptococcal bacteremias and endocarditis in intravenous drug abusers in southeastern Michigan. Except for six cases reported from Harlem Hospital, no large series of group A streptococcal bacteremias and endocarditis has been described in intravenous drug abusers [2]. This review documents our experience with 40 cases of group A streptococcal bacteremia identified over an 18-month interval.

PATIENTS AND METHODS

Case Review. Patients were identified as having group A streptococcal bacteremia by review of positive blood culture results. Charts were obtained for review, and the patients were interviewed by one of us, whenever possible. Patients with fever, positive blood culture results, a new or changing heart murmur, and autopsy evidence of valvular vegetations were considered to have definite endocarditis. Patients were considered to have probable endocarditis if there was fever, multiple positive blood culture results, a new or changing heart murmur, and roentgenographic evidence of septic pulmonary emboli.

Surveillance Studies. The carriage rate in this population was studied by prospectively performing cultures in intravenous drug abusers presenting to the Wayne County Emergency Department from March 1983 to May 1983. After informed consent was obtained, four cotton swabs premoistened in Todd-Hewitt broth (Difco Laboratories, Detroit, Michigan) were used to obtain culture specimens from the groin or perineum, the urethra or vagina, the anus, and the pharynx. Swabs were inoculated into Todd-Hewitt broth, and the

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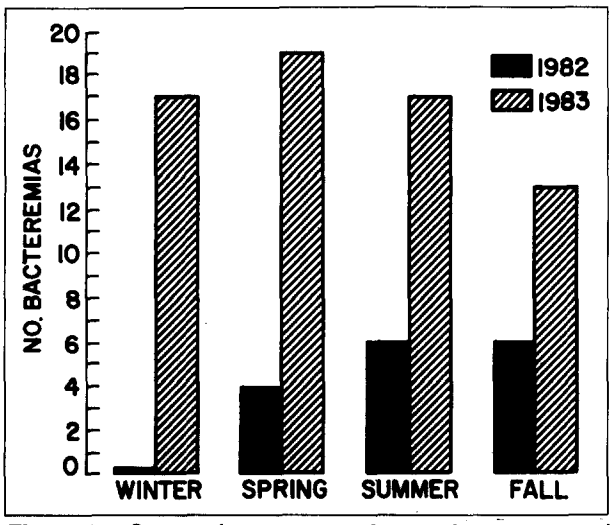

Figure 1. Seasonal occurrence of group A streptococcal bacteremia. No seasonal predominance was noted. Cases increased markedly in 1983 and persisted at a high rate throughout the entire year (the chemical study was concluded in June 1983).

specimens were incubated 12 to 18 hours at 37°C [3]. Subculturing was performed on Columbia colistin-nalidixic acid agar (BBL Laboratories, Cockeysville, Maryland). Colonies suspected to be streptococci were then subcultured to 5 percent sheep blood in trypticase-soy agar. Beta-hemolytic colonies were shown to belong to Lancefield group A using group A antiserum (BBL Laboratories) and the autoclave method [4].

Isolates Causing Bacteremia. During the same period of time as the surveillance study, all group A streptococci isolated from blood cultures were saved (12 isolates). The isolated organisms were tested for susceptibility to several antibiotics using the tube dilution technique and were sent to the Centers for Disease Control for serologic typing [5].

Drug Analysis. Three samples of "mixed jive" (a name for an opiate-containing street drug in common use in southeastern Michigan) were obtained for analysis of drug content and culture.

Statistical Analysis. Results from the patients with endocarditis were compared with those from the patients without endocarditis and were analyzed for significant differences using chi-square and Student t tests.

TABLE I Symptoms in Patients with Group A Streptococcal Bacteremia

Symptom	Patients with Endocarditis (N = 11) (percent)	Patients without Endocarditis (N = 29) (percent)
Constitutional		
Fever	10 (90.9)	27 (93.1)
Chills	8 (72.7)	25 (86.2)
Sweats	6 (54.5)	12 (41.4)
Headache	4 (36.4)	8 (27.6)
Rigor	3 (27.3)	10 (34.5)
Respiratory		
Productive cough	6 (54.5)	7 (24.1)
Pleuritic pain	6 (54.5)	4 (13.8)
Gastrointestinal		
Nausea/vomiting	8 (72.7)	14 (48.3)
Diarrhea	7 (63.6)	20 (69.0)
Abdominal pain	3 (27.3)	8 (27.6)

RESULTS

Forty-two patients were identified as having group A streptococcal bacteremia from January 1982 through June 1983 at Wayne County General Hospital. Charts were available for 41 of these patients. One patient who was not an intravenous drug abuser was excluded from analysis. There were 26 men and 14 women (male to female ratio = 2:1); 37 patients were black and three were white. The mean age of the group was 32.5 years (range 23 to 46 years). No seasonal predominance of group A streptococcal infection was noted, although the occurrence of group A streptococcal bacteremia increased sharply in 1983 (**Figure 1**).

Seventy-eight percent of the patients injected into the femoral vein at the location of the femoral triangle. The other patients injected into subclavian, internal jugular, or peripheral veins. A variety of substances were injected, "mixed jive" being the most common (18 of 40, 45 percent), with heroin the next most frequently injected (10 of 40, 25 percent), and Dilaudid (hydromorphone hydrochloride), Demerol (meperidine), Talwin (pentazocine) and Pyribenzamine (tripelennamine) ("T's and B's"), and cocaine each used by one patient. In five instances, the drug of abuse was not noted. Only six patients had self-administered oral antibiotics, usually a cephalosporin, before their hospital admission.

In addition to intravenous drug abuse, other underlying diseases seen were osteomyelitis (one patient), congestive heart failure (one patient), and alcohol abuse (one patient). Eight patients, including two of the patients with group A streptococcal endocarditis, had a history of a previous episode of endocarditis.

Clinical Findings. Definite endocarditis was present in two patients with fever, positive blood culture results, a heart murmur, and valvular vegetations at autopsy; nine patients had probable endocarditis on the basis of fever, positive blood culture results, a heart murmur, and roentgenographic evidence of septic pulmonary embolization.

Most patients had symptoms for less than one week before admission and complained of fever, chills, and sweats (**Table I**). No patient complained of a sore throat. Pleuritic pain and cough were prominent complaints in

those patients with endocarditis. Twenty-seven of the 40 patients (67.5 percent) complained of loose stools at the time of admission, and 23 patients had other gastrointestinal symptoms. Patients with endocarditis appeared more ill than those without endocarditis; the average number of symptoms recorded for the patients with endocarditis was 7.3, and 4.4 for the patients without endocarditis ($p < 0.004$).

The mean peak oral temperature for the first 24 hours was 103.9°F (range 97.4°F to 106°F) for the patients with endocarditis and 102.3°F (range 100°F to 106°F) in the patients without endocarditis ($p < 0.002$). Murmurs were heard on admission in 26 patients (65 percent) (**Table II**). Eight patients with endocarditis had systolic murmurs on initial examination. Four of these eight patients also had diastolic murmurs. For three other patients with endocarditis, murmurs were heard at the left lower sternal border later during the hospitalization. Eighteen patients, all without endocarditis, had soft (grade I or II/VI) left lower sternal border systolic ejection murmurs. Two of the patients with endocarditis had a third heart sound and cardiomegaly on chest roentgenography, consistent with congestive heart failure. Rales or dullness was noted on pulmonary examination in 10 patients. Peripheral embolic manifestations of endocarditis and hepatosplenomegaly were unusual.

A variety of extracardiac infections were noted, primarily in those patients without endocarditis. Twenty-seven of 29 patients without endocarditis were documented to have soft tissue infections. Sixteen patients had a groin abscess or an open groin wound. Deep venous thrombosis was documented on venography or Doppler studies in four patients. One patient had lower extremity cellulitis, another had pyoderma, and a third required surgery for myonecrosis of a lower extremity. Both pneumonia and an infected pilonidal cyst were noted in one patient. Upper extremity infections were seen in only three patients. For two remaining patients without endocarditis, the site of infection was not determined. Five patients with endocarditis had extracardiac infections, two with pulmonary infiltrates, two with groin abscesses, and one with septic arthritis of the knee.

Laboratory Findings. The white blood cell count ranged from 4,800/mm^3 to 28,000/mm^3 and was greater than 10,000/mm^3 in 30 of the 40 patients. Twenty-six patients were anemic on admission, with a hematocrit less than 40 percent (range 20 to 39.3 percent). The hepatic transaminase levels were elevated (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase greater than 40 IU/dl) in 37.5 percent (15 of 40) of the patients, and the alkaline phosphatase level was elevated (120 IU/dl or greater) in eight of 15 patients. The Westergren sedimentation rate was over 25 mm per hour in 15 patients, and in 5 patients this value surpassed 100 mm per hour. No significant differences in these laboratory values were noted between patients with and patients without endocarditis.

TABLE II Signs Observed in Patients with Group A Streptococcal Bacteremia

Sign	Patients with Endocarditis (N = 11) (percent)	Patients without Endocarditis (N = 29) (percent)
Systolic murmur		
Left-sided	2 (18.2)	1 (3.4)
Right-sided	9 (81.8)	17 (58.6)
Congestive heart failure	2 (18.2)	0
Rales/dullness	5 (45.4)	5 (17.2)
Splinter hemorrhages	1 (9.1)	0
Conjunctival hemorrhages	0	1 (3.4)
Hepatomegaly	2 (18.2)	0
Splenomegaly	2 (18.2)	1 (3.4)

Seven patients had hematuria and five had pyuria. Culture results were available in five of these patients, three of whom had endocarditis, and all showed gram-positive cocci in chains. One culture specimen was identified as group A streptococci; the other cocci were not identified.

Eleven patients had other sites of infection cultured, and 10 yielded organisms. Nine cultures grew group A streptococci, four of which also yielded other organisms (Staphylococcus aureus in three, and group G streptococcus in one). Escherichia coli, S. aureus, and group B streptococcus were isolated from the remaining culture. Blood cultures yielded group A streptococci in both bottles of a paired set of cultures in all but two patients, both of whom had only one culture bottle that showed a positive finding. Twenty-seven patients had group A streptococci in four or more blood culture bottles. Four patients without endocarditis had polymicrobial bacteremia, three with S. aureus plus group A streptococci and one with Flavobacterium plus group A streptococci. In patients that self-administered antibiotics, 18 of 20 (90 percent) blood culture bottles showed positive results.

In 11 patients, chest roentgenography showed an abnormality, nine with either an infiltrate or a pleural effusion and two with cardiomegaly. Seven of the patients with abnormalities on chest roentgenography had endocarditis. Twenty-six patients underwent echocardiography: results in seven were abnormal, showing dilated ventricles (five patients, two of whom had endocarditis), aortic insufficiency (one patient with endocarditis), and a thickened aortic valve (one patient

with endocarditis). No abnormalities of the tricuspid valve were noted.

Treatment and Outcome. On admission, the two patients with definite endocarditis had congestive heart failure and showed echocardiographic evidence of aortic valve abnormalities. Initial therapy consisted of vancomycin (1 g intravenously every 12 hours) plus gentamicin (80 mg intravenously every eight hours) in one patient, and nafcillin (2 g intravenously every four hours) plus gentamicin (80 mg intravenously every eight hours) in the other patient. Once group A streptococcus was identified as the infecting organism, therapy was changed to intravenous aqueous penicillin G (10 to 12 million units per day). Despite excellent anti-streptococcal therapy and attempts to replace the damaged cardiac valves, both patients died within the first week of hospitalization.

Nine patients classified as having probable endocarditis did significantly better than the two patients with definite endocarditis. None of the nine patients had valvular vegetations noted on echocardiography. Initial therapy consisted of nafcillin or vancomycin plus an aminoglycoside and was subsequently switched to intravenous aqueous penicillin G (10 to 12 million units per day) once group A streptococcus was identified as the infecting organism. There were no deaths among the patients with probable endocarditis. For all 11 patients with endocarditis, the mean time until defervescence was 3.4 days and the mean duration of antimicrobial treatment was 19 days (range two to 35 days).

The remaining 29 patients were considered not to have endocarditis. Both the initial and the subsequent therapy in this group was identical to that in the patients with endocarditis. The time until defervescence (mean three days) was not significantly different from that in patients with endocarditis. The patients were treated for a mean of 15 days without any deaths. One patient with myonecrosis of the right leg remained febrile, despite appropriate antibiotics, until the limb was amputated.

Antimicrobial Susceptibility Testing. Twelve blood isolates obtained from patients with bacteremia were uniformly sensitive to beta-lactam antibiotics and vancomycin, with minimal inhibitory concentrations less than 1 μg/ml. All patients were treated with antimicrobial agents to which the group A streptococcal isolates were susceptible (penicillin, nafcillin, and vancomycin). One isolate had a high minimal inhibitory concentration for clindamycin (6.25 μg/ml). Neither gentamicin nor tetracycline resistance was found, although relatively high minimal inhibitory concentrations of 1.6 μg/ml for gentamicin and 3.1 μg/ml for tetracycline were found in two isolates.

Surveillance Studies. Thirty-eight patients underwent cultures at the four sites described in Patients and Methods. All 152 culture specimens grew one or more organisms. Of the gram-positive organisms recovered on the colistin-nalidixic acid agar plates, only one isolate obtained from the urethra of one patient was typed as a group A streptococcus, giving an overall carriage rate of 2.6 percent. Of the 38 patients in whom cultures were performed in the emergency department, six patients were admitted and later found to have group A streptococcal bacteremia. The patient with the urethral isolate was one of these six patients.

During the period of the surveillance study, the 12 blood isolates that were obtained and tested for antimicrobial susceptibilities were sent to the Centers for Disease Control for antigen typing. All isolates were nontypable by M antigens, but were typed using T antigens. Six (50 percent) of the isolates were T type 11. Three were 8/25/IMP 19 and one each was 5/27, IMP 19, and 3/B3264.

Drug Analysis. Several samples of "mixed jive" were obtained from a patient. Cultures of the samples did not yield any organisms. Analysis indicated that the major components in this street drug were morphine and lactose.

COMMENTS

Recently, we have noted an increase in the occurrence of group A streptococcal bacteremia in intravenous drug abusers. Except for a series of six patients from New York City who had group A streptococcal endocarditis, this is an uncommon cause of bacteremia and endocarditis in intravenous drug abusers [2]. S. aureus bacteremia and endocarditis are far more common in this population [6]. Before 1930, group A streptococci accounted for 20 percent of bacteremias, and endocarditis developed in 4 percent of these patients [1]. Although currently it is unusual to see endocarditis in patients with group A streptococcal bacteremia, 27.5 percent of the patients in our study had probable or definite endocarditis. In this population of intravenous drug abusers, many similarities to previously reported clinical findings of group A streptococcal bacteremia were observed. However, there were important differences in microbiologic and epidemiologic findings when compared with group A streptococcal bacteremias in the preantibiotic era.

We thought that sampling the common colonization sites in this population of intravenous drug abusers with frequent group A streptococcal bacteremias would yield recovery of the organism at higher than normal rates. Yet, the rate of carriage in this population was 2.6 percent, only slightly higher than normal anal and vaginal colonization [3]. In contrast, Tuazon and Sheagren [7] showed that staphylococcal endocarditis in intravenous drug abusers was associated with an increased

rate of nasal, pharyngeal, and skin carriage of S. aureus.

Our data are consistent with the observation that, in adults, group A streptococcal infections and bacteremia are often acquired from exogenous sources [8,9]. Exogenous sources of infection may include foodstuffs, such as milk and potato salad [10], or nasopharyngeal, rectal, and vaginal carriers who transfer the organism via contact or airborne transmission [3,11]. Most of the addicts obtained their drugs from a few persons regarded as selling better quality material, and most frequented "shooting galleries," where a skilled person was paid to inject into the large caliber veins. A drug dealer or drug injector may have been a group A streptococcal carrier.

A common origin is possible for many of the group A streptococcal bacteremias seen in our population, since 50 percent of our isolates were T type 11. This serotype was isolated in a previously reported outbreak associated with a vaginal carrier [3]. None of the isolates was M typable. Although the presence of the M protein correlates with virulence, more recent outbreaks have had fewer M-typable organisms [12]. The small sample size or the inability of currently available antiserum to detect the M protein in these isolates may explain the lack of M-typable antigen in our isolates.

Previous studies of clusters of group A streptococcal bacteremia and other streptococcal infections found certain patterns of occurrence [13,14]. In the preantibiotic era, Keefer et al [1] noted a peak incidence of bacteremias in the winter months when nasopharyngeal colonization and streptococcal pharyngitis were highest. Certain studies have shown more streptococcal cellulitis in the summer months when skin colonization is highest [15], and others have found no seasonal increase in streptococcal bacteremias [8]. We found no seasonal predominance over the 18 months our cases were collected.

During the antibiotic era, most reports of group A streptococcal bacteremia have emphasized that patients usually are elderly, have severe underlying diseases such as alcoholism, diabetes mellitus, solid tumors, and connective tissue diseases, or have received treatment with cytotoxic drugs, corticosteroids, or irradiation [16–18]. These predisposing factors were not found in our patients, most of whom were healthy except for intravenous drug abuse.

The clinical findings in the 29 patients without endocarditis were those of septicemia, with fever, rigors, and systemic toxicity. Gastrointestinal symptoms were present in most of the patients. The illness was usually less than a week in duration. This description is similar to that noted in other groups of patients with group A streptococcal bacteremia [8,13,17].

Thayer [19], in 1931, described acute left-sided streptococcal endocarditis in patients who had a rapid onset of "symptoms of intense septicemia and high continued fever" and died quickly of their infection. These patients were usually in the second to fifth decades of life and had as their initial site of infection infected wounds, pleural empyema, genitourinary tract infection, and puerperal sepsis. Since the introduction of antibiotics, the incidence of left-sided endocarditis in patients with group A streptococcal bacteremia (0 to 6 percent) has been little changed from that noted in the preantibiotic era [1]. However, our experience and that of Savage and Brown [2], emphasizes a marked increase in right-sided endocarditis in patients with group A streptococcal bacteremia who are also intravenous drug abusers. Six of seven patients described by Savage and Brown had right-sided endocarditis, and five had roentgenographic evidence of pulmonary emboli. All six recovered with antimicrobial therapy. Nine of 11 of our patients followed this clinical pattern. The remaining two patients had left-sided endocarditis, and both patients died with fulminant infection as did patients in the preantibiotic era.

Group A streptococcal endocarditis shares certain features with staphylococcal endocarditis, a far more common infection in intravenous drug abusers (**Table III**). The major symptoms of fever, chills, and cough were present in both groups, and the incidence of congestive heart failure was similar [20]. However, other constitutional symptoms, such as headache, sweats, and gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), were more common in patients with streptococcal bacteremia. Pe-

TABLE III Comparison of Symptoms and Signs in Intravenous Drug Abusers with Staphylococcal and Streptococcal Endocarditis

Symptoms/Signs	Staphylococcal* (N = 41) (percent)	Streptococcal (N = 11) (percent)
Fever	37 (90.2)	10 (90.9)
Chills	16 (39.0)	8 (72.7)
Chest pain	13 (31.7)	6 (54.5)
Cough	10 (24.4)	6 (54.5)
Nausea and vomiting	10 (24.4)	8 (72.7)
Headache	10 (24.4)	4 (36.4)
Sweats	5 (12.2)	6 (54.5)
Abdominal pain	4 (9.8)	3 (27.3)
Diarrhea	Rare	7 (63.6)
Murmur	37 (90.2)	11 (100)
Skin lesions	5 (12.2)	1 (9.1)
Pulmonary findings	4 (9.8)	5 (45.4)
Neurologic findings	4 (9.8)	0
Hepatomegaly	4 (9.8)	2 (18.2)
Splenomegaly	Not stated	2 (18.2)

* Reprinted with permission from [20].

ripheral embolic findings were uncommon in patients with staphylococcal endocarditis (12.2 percent) or streptococcal endocarditis (9.1 percent), presumably because most had right-sided infection. Neurologic manifestations were more often seen in staphylococcal endocarditis [20]. Patients with staphylococcal endocarditis have been noted to remain blood culture-positive for a mean of four days and febrile for a mean of six days after therapy is begun [21]. None of the patients with streptococcal endocarditis had positive blood culture results after antibiotic therapy was begun, and most were afebrile within 72 hours, reflecting the more rapid response of streptococci to antimicrobial agents.

In the preantibiotic era, the mortality rate was 72 percent from group A streptococcal bacteremia and 100 percent from group A streptococcal endocarditis [1]. Since the introduction of antibiotics, mortality rates for group A streptococcal bacteremia have ranged from 6 to 35 percent [13,17,18]. The higher mortality rates reflect those patients who were elderly and had severe underlying illnesses. The patients in the present series were similar to intravenous drug abusers with staphylococcal endocarditis in that they were young and otherwise healthy. The mortality rate was only 5 percent, and few sequelae were seen.

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