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ELLIOT FRANK

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THE TREATMENT OF NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

By

Elliot Frank

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Medicine
1978

DEDICATION

To Dr. Vincent T. Andriole whose patient guidance made this endeavor possible and (almost) pleasant.

To Susan whose constant encouragement and stimulation (ideational, culinary and otherwise) were indispensible to me and this project.

To my Parents who have too often been taken for granted.

TABLE OF CONTENTS

INTRODUCTION

THE CHANGING PATTERN OF INFECTIVE ENDOCARDITIS

Infective Endocarditis (IE) is a disease which has fascinated clinicians for many years. The clinical picture of the patient with IE has undergone significant change over the years but the basic academic and clinical challenge remains. In recent years, several series have documented the changing pattern of this disease (4,7,13, 24,25,27,31). With the increasing life expectancy for the population at large, and, to an even greater extent, for those patients who are most vulnerable to cardiac infection, the average age of patients with IE and the number of patients in the oldest age groups have both increased. So too, there is now a significant likelihood that the patient with IE will have benefited from cardiac surgery, recovered from a previous episode of IE or have another, non-cardiac, underlying disease.

Several authors have noted a declining proportion of patients with Rheumatic Heart Disease (RHD) underlying IE and a concomitant rise in the incidence of non-specific cardiac murmurs and congenital heart disease (CHD) [with aortic stenosis (AS) as the congenital lesion most frequently identified] in this population. At the same time,

the anatomical distribution of cardiac infections has changed. There has been a steady rise in the percentage of patients with isolated aortic valve (AV) involvement and a decline in infection involving both aortic and mitral valves. Similarly, the increase in narcotic addiction has led to an increase in tricuspid valve infection.

The diagnosis of IE is now made more quickly and the overall duration of illness has, therefore, shortened significantly. As a result, the classical physical findings of IE are seen with decreasing frequency and the incidence of major embolization has also declined.

With the introduction of antibiotics, the advent of cardiac surgery, the increasing age of the patient population, and the rise in narcotic addiction, the microbiological spectrum of IE has been profoundly affected over the past half century. The incidence of staphylococcal endocarditis has been rising and these infections may account for 20-30 percent of all cases of IE at many medical centers. Pneumococcal and gonococcal endocarditis, on the other hand, have become extremely uncommon since the introduction of good antimicrobial therapy. Cardiac infections, due to fungi and gram-negative bacilli, although still seen relatively infrequently, are becoming more and more of a problem.

Streptococci, however, still account for more cases

of endocarditis than any other group of organisms. In most series through the late 1960's, streptococci were causitive in 70-80 percent of blood culture positive cases. More recently several authors have noted a decline in these figures. Pelletier and Petersdorf (31) reported 113 cases of endocarditis with positive blood cultures of which 47 (42%) were caused by streptococci. Similarly, Cherubin and Neu (7) noted a decline in the frequency of streptococcal endocarditis from nearly 70 percent of cases recorded prior to 1957 to approximately 60 percent of all subsequent cases. Enterococci account for a small, but growing, proportion of these infections with an incidence of around 10 percent of all culture-positive IE noted in large surveys. Thus non-enterococcal streptococci still cause at least 30 percent and probably as much as 40-50 percent of all IE in which an organism is isolated. If endocarditis in the addict and in those patients with prosthetic valves is not considered, these figures would be much higher, and, in fact, would probably have changed little from those reported in the 1950's and 1960's (24).

Clearly, though, the most dramatic change in the clinical picture of IE occurred in the 1940's with the introduction of penicillin. Once a hopelessly fatal illness, IE became approachable from a therapeutic standpoint. Now, some 35 years later, after much experience with penicillin and a host of other antimicrobial agents, the optimal

treatment regimen, particularly for non-enterococcal, penicillin-sensitive streptococcal endocarditis, remains a subject of controversy. In his recent monograph on IE, Kaye (25) advocated a combined regimen of four weeks of penicillin and two weeks of streptomycin but noted the ongoing disagreement among infectious disease experts regarding the need to use combination therapy.

The purpose of the present study centers around this controversy. We will attempt, first, to review the pertinent literature and outline the historical highlights that have fed this controversy. The second part of this investigation entails a review of the case records of all patients treated for non-enterococcal streptococcal infective endocarditis at the Yale University Hospitals over the past 13 years. It is hoped that within the limitations of a retrospective study, we shall be able to shed some light on the appropriate therapeutic approach to this important disease.

REVIEW OF THE LITERATURE: THE TREATMENT OF PENICILLIN-SENSITIVE STREPTOCOCCAL ENDOCARDITIS

Early in 1945, the Penicillin Trials Committee of the British Medical Research Council began to study the value of penicillin in the treatment of Subacute Bacterial Endocarditis (SBE). Between February of 1945 and March of 1946, 269 patients (90 percent of which had infection due to viridans streptococci) were treated at 14 British medical centers. In these early experiments, published by Christie in 1948 (8), several important observations were made, some of which still provide the rationale for current treatment regimens.

The first study demonstrated that duration of penicillin therapy was of greater importance than the total dose of such therapy. Each of 52 patients was treated with penicillin in a total dose of five million units administered over periods of five, 10, or 20 days. Eighty-three percent of those treated with the shortest regimen relapsed or died of uncontrolled infection, while 50 percent of those treated for 10 days and only 22 percent of those who were treated for 20 days, had a similarly poor outcome.

The second phase of these early trials was designed

to assess optimal penicillin dosage and involved 158 patients who received treatment for 28 days with varying amounts of penicillin. Seventeen patients received 100,000 units per day and seven of these patients (41%) relapsed or died of uncontrolled infection. Eighty-three additional patients were treated with a daily dose of 250,000 units and another 58 patients received 500,000 units per day. Thirteen of 83 or 16 percent and only four of 58 or 6.9 percent had recurrent infection or death with infection uncontrolled.

These two studies established the importance of sufficient duration and dosage of penicillin therapy to eradicate infection in Streptococcus viridans SBE.

Also in 1948, Spicer and Blitz (37) studied the in vitro response of bacterial populations to the actions of penicillin. These authors demonstrated that penicillin was, indeed, a bactericidal drug but also showed that, particularly with S. viridans, there were often residual organisms that were not killed despite varying concentrations of penicillin (up to 60 u/ml). These residual organisms were inhibited by small amounts of the same drug. They postulated that bacterial populations were heterogeneous and contained organisms capable of three different responses to penicillin: (1) organisms that were killed by lysis; (2) organisms that were killed but not lysed; and, (3) organisms that were not killed. In addition, these authors

demonstrated that, despite resistance of the parent culture to streptomycin, the residual organisms in five of six strains of S. viridans could be eradicated by the addition of that drug. Here, then, was the first suggestion that antibiotic synergy might be of clinical importance in the treatment of S. viridans, a fact already under study for enterococci (20,37).

The work of the Penicillin Trials Committee continued and, in October of 1949, Christie (9) published the results of treatment of an additional 89 new cases of culture-positive SBE. Seventy-one patients were treated for one month with 500,000 u of penicillin daily--the same regimen that had been reported earlier to have resulted in an unsuccessful outcome in less than seven percent of 58 patients. In this new series, however, 14 of 71 patients, or 20 percent, relapsed or died infected. No explanation was apparent for these poor results. Eighteen additional patients subsequently received 2,000,000 u/day for at least one month and, at the time of publication, none of these had relapsed or died of uncontrolled infection.

At about the same time, King et al. (26) attempted to obviate the need for prolonged therapy by markedly increasing the daily dosage of penicillin. In this experiment, eight patients with IE due to penicillin sensitive organisms (seven patients with S. viridans and one patient with a Staphylococcus) were treated with ten day courses of

penicillin in a daily dose of 14 million units. The results were dramatically poor. Bacteriological cure was achieved in only one of eight patients. Thus the need for prolonged penicillin therapy previously demonstrated by Christie was reaffirmed, and, in reviewing the status of treatment of SBE in December of 1950, Bloomfield (2) reemphasized the need to continue therapy for at least four weeks.

Between 1950 and 1952, based in part on the preliminary work of Spicer and Blitz (37), Hunter (21,22) undertook a series of in vitro experiments designed to compare the action of various antibiotics and antibiotic combinations on streptococci. Studies were carried out on enterococci and viridans streptococci in systems designed to approximate the characteristics of the infected site in SBE. Hunter noted the lack of reports of spontaneous cure in IE and the dismal results of therapy with sulfonamides, aureomycin and terramycin. While these bacteristatic agents often were capable of suppressing the infection, cure with these drugs was rare. Hunter attributed the difficulty encountered in treating IE to the nature of the vegetation, which was composed of fibrin and necrotic debris, and thus poorly vascularized. It provided a medium in which masses of bacteria were free to multiply, shielded from large numbers of leukocyles, and host defenses. In addition, metabolic exchange in such a setting would take place slowly

and so offer a slowly growing bacterial population to whatever small amount of antibiotic could penetrate the system.

In early studies, Hunter showed that, in cultures grown to maximum population density (where no further multiplication was possible), no antibiotic or combination of antibiotics, was capable of exerting a bactericidal effect. If an intermediate situation was achieved by removing half of the organisms each day (thus allowing limited growth at intervals), only the combination of penicillin and streptomycin was able to achieve a slow but progressive killing effect. It was postulated that this latter model was probably a close approximation of the real situation, in some vegetations, with respect to population density, and, that this might partly explain the need for intensive and prolonged therapy in SBE. It also gave support to the notion of combined penicillin-streptomycin therapy.

In another experiment, Hunter cultured two strains of S. viridans in standard broth and in clotted blood, for the purpose of comparing the action of penicillin in varying doses and combined with streptomycin. It was hoped that the infected blood clot would parallel the situation of the fibrin/debris vegetation present in IE. The first strain was eradicated from broth in a few days by either low dose (2u/ml) or high dose (20u/ml) penicillin. Sterilization

took longer, i.e., seven days, with infected blood clots, and required the higher dose of penicillin. The addition of streptomycin made no difference in either situation with this strain of S. viridans. The second strain, however, behaved quite differently, although both strains had minimum inhibitory concentrations (MIC's) of less than 0.1 u/ml. Killing was again achieved in broth with either dose of penicillin, however, this time, sterilization took more than a week. In infected clots this difference between the two strains was still apparent but less pronounced, with high dose penicillin achieving sterilization in twelve days. However, when streptomycin was added to either broth or clot infected with this second strain of S. viridans, the bactericidal effect was greatly enhanced. For example, in the infected clot, low dose penicillin (which used alone had no effect on either strain in blood clots) combined with 20 ug/ml of streptomycin (also totally ineffective by itself), resulted in complete eradication of this organism in ten days.

Based on these experiments, Hunter suggested that the addition of streptomycin might be worthwhile if it were to allow a decrease in the duration of therapy and thus reduce the danger of drug toxicity. Although no details are given, Hunter provided clinical correlation with six cases of endocarditis successfully treated with such a short-term regimen of combination therapy.

Further interest in a two week treatment schedule for S. viridans SBE was generated in 1952 by Hamburger and Stein (19) who reported 12 cases treated with 15 million units per day of pencillin. Two patients in this series died--one of congestive heart failure (CHF) and one of a pulmonary infarction--without evidence of ongoing infection. Two additional patients or 16.7 percent had bacteriologically proven relapses and required retreatment with a second two week course. These results would appear to conflict with those of King discussed earlier. It may be significant that the patients in the earlier series were treated for only ten days while in those reported by Hamburger and Stein, treatment was continued for fourteen days.

One year later, encouraged by the work of Hamburger and Stein and the preliminary data supplied by Hunter, Geraci and Martin (17) treated 23 patients with SBE due to penicillin-sensitive streptococci with a two week regimen of combined penicillin and streptomycin therapy. Five of twenty-three patients (22 percent) died. Three patients succumbed to CHF, one patient sustained a cerebral embolus and the fifth patient had a fatal myocardial infarction. None of the remaining eighteen relapsed or had persistent infection in a follow-up period that ranged from 3-24 months.

In 1955, Geraci (15) reported 23 additional patients with similar findings. There were three deaths

resulting from CHF (one patient) and cerebral vascular accidents (two patients). Again no relapse or persistent infection was noted with the two week regimen of penicillin and streptomycin.

In that same year, Hall, Dowling and Kellow (18) treated 15 patients with penicillin-sensitive streptococcal endocarditis with penicillin and streptomycin in combination. The duration of therapy in this series ranged between ten and ten and seventeen days. Three patients were considered treatment failures, although not definite relapses. The first patient had persistent fever and a high white blood count (WBC) although blood cultures were sterile. He had significant mental status changes, developed pneumonia and died. Post-mortem examination was not obtained. The second patient also had persistent fever and died suddenly of autopsy-proven rupture of a mycotic aneurysm. The third patient had a relatively resistant organism (MIC=0.4u/ml) and remained febrile throughout 11 days of initial therapy. Drugs were stopped and the patient's condition worsened. Antibiotics were reinstituted and therapy was continued for six weeks with a good outcome. These authors concluded that, based on their experience and that of others cited above, a ten day treatment schedule with two drugs would suffice in SBE caused by sensitive streptococci.

In a review of bacterial endocarditis that appeared in 1956, Hunter and Patterson (23) recognized two success-

ful regimens for the treatment of disease due to penicillin-sensitive streptococci--single drug therapy with a four week course of penicillin in a daily dose of 2,000,000 units or more, or combination therapy with two weeks of penicillin and streptomycin. The latter regimen was recommended by Hunter and Patterson based on the work of Geraci and Martin (17), Geraci (15), and Hall, Dowling and Kellow (18) as described above. In addition, they gathered 146 unpublished cases treated at various medical centers with similar two-week--two drug schedules. Although no details were provided, they cited a relapse rate of six percent and concluded that these two protocols for treating non-enterococcal streptococcal endocarditis were comparable.

Shortly after this review appeared, Tompsett and his co-workers (41) reported more disappointing results in treating 35 endocarditis patients who had infections caused by streptococci inhibited by less than 0.4 u/ml of penicillin. All were treated with short-term combination therapy consisting of 6,000,000 units of penicillin and two grams of dihydrostreptomycin daily. Four cases (11.1%) had bacteriologically proven relapses (MIC's for the organisms isolated from these patients were less than 0.1 u/ml) and four additional patients had persistent fever or other clinical signs of possible continued infection which necessitated continued antibiotic therapy despite sterile blood cultures. These results suggested that a two week regimen was inadequate

for some patients. Because of the impossibility of predicting which patients might require prolonged therapy, these authors suggested the routine extension of treatment to 21-28 days.

Later in 1958, however, Geraci (16) reviewed the Mayo Clinic experience. In this large series, a proportion of which had been reported earlier (15,17), only three relapses (one definite, two probable) occurred, giving a bacteriological failure rate of four percent. The drug dosages employed at the Mayo Clinic--2,000,000 units of penicillin and one gram of streptomycin daily--were lower than those used by Tompsett et al.

No major developments occurred over the next several years and in 1964 the subject was again reviewed by Tompsett (39). He concluded that, while it seemed unlikely that even a four week regimen would be 100 percent effective, it would be unsatisfactory to accept bacteriological cure in 92-95 percent of patients without first establishing that these were the upper limits of any regimen. His recommendations, therefore, were to administer combination therapy with 4,000,000 units of penicillin and one gram of streptomycin daily for two weeks and to then continue penicillin alone for an additional two weeks. There were no relapses in 24 patients treated with this regimen although no specific details of these patients were provided.

In 1971, Tan et al. (38) described their experience

with 49 patients with S. viridans SBE. Thirteen patients received two week courses of 15-20 million units per day of penicillin and no other drug. Two of thirteen (15%) relapsed. Thirty-six patients were treated for two weeks with either penicillin-G (parenterally) or penicillin-V (orally) in combination with streptomycin. There were no relapses in this group and these authors concluded that two week combination therapy was adequate treatment in this disease.

Further support for prolonged (four week) therapy, combined with an aminoglycoside for the first two weeks, came in 1973 when Kaye (24) reported a series of 70 patients treated at the New York Hospital with four weeks of procaine penicillin (4,800,000 units/day) and two weeks of streptomycin (1.0g/d) without a single relapse. All organisms were inhibited by less than or equal to 0.16 u/ml of penicillin but no other details of these 70 cases were provided.

In 1974, Sande and Irvin (34) and Durack, Pelletier and Petersdorf (10) demonstrated that the combination of penicillin and streptomycin was more efficient in eradicating experimentally induced S. viridans endocarditis in the rabbit than either drug alone. The experiments carried out by Sande and Irvin revealed that bacteremia and fever persisted longer in rabbits treated with penicillin alone as compared with animals receiving a combination of the drugs. Furthermore, these authors observed that experimentally

induced vegetations could be sterilized in 3-4 days using a combination of penicillin and streptomycin while 7-10 days were required when only penicillin was employed. Similarly, Durack, Pelletier and Petersdorf were not able to sterilize vegetations in this same rabbit model by using either penicillin or streptomycin alone, for one to three days, but could completely eradicate the streptococci in eight of eight rabbits receiving both drugs for 12 hours.

Also in 1974, Wolfe and Johnson (46) observed the activity of penicillin, streptomycin and a combination of both agents in 48 strains of penicillin-sensitive streptococci (MIC's for penicillin $\leq$ 0.4 ug/ml). None was killed by streptomycin (10 ug/ml) alone and only one of 48 was killed by penicillin (1.6 ug/ml). Thirty-seven of the 48 strains, however, were eradicated by the combination of 0.8 ug/ml of penicillin with 5.0 ug/ml of streptomycin. In this same report, Wolfe and Johnson recounted their experience with thirty-five patients treated with two weeks of penicillin plus streptomycin followed by two weeks of penicillin alone. No relapses occurred.

Recently, Pelletier and Petersdorf (31) reviewed the University of Washington Hospital's experience with IE between 1963 and 1972. There were 28 patients with non-enterococcal streptococcal endocarditis and nineteen of the twenty-eight received single drug therapy whereas nine patients received combination therapy. There was no

significant difference in relapse rate between these two groups of patients (4/19=21% vs. 1/9=11%). This relapse rate, however, (5/28=18%), is higher than those previously reported. One patient in this study relapsed after two weeks of penicillin and streptomycin in combination. A second patient received seventeen days of penicillin and seven days of streptomycin and then died suddenly of ventricular fibrillation complicating an acute inferior wall myocardial infarction. Viable S. viridans were present in vegetations on the AV and the Sinus of Valsalva. Patient number three was treated for two months with 30 million units of penicillin per day plus probenicid, combined with chloramphenicol for three weeks. In this case, the combination of a bacteriostatic drug with penicillin may have resulted in inhibition of bactericidal activity. The fourth patient received penicillin for one month, underwent valve replacement (for CHF) and, one month after operation, had recurrent disease. Post-operative reinfection with a similar organism remained a possibility in this case. No information is available about the fifth probable relapse.

Finally, Phair and Tan (32) reported 85 patients treated for S. viridans endocarditis. Thirteen of 85 received penicillin alone for 11-17 days, eight patients received penicillin alone for more than 21 days, 39 patients received penicillin and streptomycin in combination for 11-17 days and 25 patients received penicillin for 21 days

or more plus streptomycin for at least twelve days. There were six relapses in this series (6/85=7%). Three of twenty-one patients treated with penicillin alone relapsed (14%) compared with three of 64 patients who had received combination therapy (5%). Phair and Tan also noted a relationship between relapse and duration of illness. Five cases of recurrent endocarditis occurred in 25 patients who had had symptoms for longer than three months while only one of 60 patients with IE of shorter duration suffered a relapse. These authors suggested that a 14 day course of therapy with penicillin and streptomycin in combination is appropriate for patients with penicillin-sensitive streptococcal endocarditis who have been ill for less than three months but that penicillin should be continued for an additional two to four weeks when disease has been present for a longer period of time.

Several important aspects of the treatment of IE due to non-enterococcal penicillin-sensitive streptococci are clearly illustrated in reviewing the literature:

1) Treatment with a single agent for less than three weeks may be associated with relapse rates of 17% or greater (19,26).

2) Cure in better than 90% of patients will be achieved with any of the following regimens:

    a) Four weeks of Penicillin at 2,000,000 units per day or more.

    No data is available on four week treatment with penicillin alone in doses conventionally employed today (5-6,000,000 units or more daily). Christie's early work (8,9), and subsequent reviews

of the subject of SBE (3,12,23,25,39) indicate that cure can be achieved in approximately 95% of cases.

b) Two week treatment with penicillin and streptomycin.

A large number of patients treated with this regimen are discussed in the literature with relapse rates ranging from 0 to 11% although the largest series observed a relapse rate of 4-6% (15,16,17,18,38,39,40,41).

c) Four weeks of penicillin combined with two weeks of streptomycin.

Although several authors have suggested that this treatment regimen is 100% effective, the results of their work are not detailed (24,25,39, 40,46). Moreover, instances of treatment failure with this regimen have been reported (32).

Since it is possible that the cure rate with this latter regimen may approach 100%, any other regimen must offer similarly good results and/or significantly less danger of drug toxicity to be considered as the treatment of non-enterococcal, penicillin-sensitive streptococcal endocarditis. Penicillin alone (regimen a above) may, in fact, achieve these goals. It is unfortunate that so little data is available on this four week treatment regimen.

Since the study of IE has been in progress for more than a decade at the Yale University Medical Center, it seemed reasonable that a sufficient number of cases would be available to serve as a basis for comparison of regimens involving three weeks or more of therapy with and without an aminoglycoside in the treatment of IE due to penicillin-sensitive streptococci.

METHODS

I. PATIENT POPULATION

At the two Yale University hospitals--the Yale-New Haven Hospital (YNHH) and the West Haven Veterans Administration Hospital (WHVAH) all available records bearing a discharge diagnosis of Bacterial Endocarditis between July 1, 1964 and June 30, 1977, were examined. Of 176 charts so coded at the YNHH during this interval, 121 records were available for review. At the WHVAH, where this discharge diagnosis appeared 41 times, there were 35 records that could be examined.

Of these 156 available records, only patients with non-enterococcal, streptococcal infective endocarditis (IE), who met the following criteria, were included in the present study:

1) Two or more blood cultures positive for a single non-enterococcal, streptococcal organism.
2) A clinical history compatible with IE.
3) A heart murmur.

Encocarditis caused by any other organism, as well as all culture-negative cases, and all cases of marantic endocarditis were excluded from consideration.

Of the 156 records available for review, 69 cases

[in 68 patients], fulfilled these criteria and form the basis of the present study. [The remaining 88 case records included 49 cases caused by other organisms, 16 miscoded charts, 16 culture-negative episodes, three cases of marantic endocarditis and four cases of possible streptococcal endocarditis whose clinical history and/or course of illness were not consistent with the diagnosis.]

II. DATA COLLECTION

Data on these 69 cases were collected by means of a careful review of the hospital record. The entire group was characterized as to sex, age, underlying cardiac conditions, pertinent past medical history, presenting symptoms and the duration of illness, physical findings and laboratory abnormalities. The identity of the causative organism and its antibiotic sensitivity was noted. Data was analyzed to assess the prognostic importance of these various factors for this population.

The parameters which we considered most significant in evaluating prognosis and outcome in this disease were:

1) the development of CHF
2) requirement of valve replacement
3) occurrence of major embolic phenomena
4) persistence of fever without other evidence of ongoing infection

5) recurrent disease, and

6) death.

Persistent fever was considered significant when it was judged unrelated to hypersensitivity and necessitated a change in therapy. In all cases blood cultures and operative specimens were sterile.

Recurrent disease was defined as any case requiring retreatment for endocarditis with an identical organism occurring within six months of completion of initial therapy.

III. ASSESSMENT OF THERAPY

Patients were divided into two groups. Group I patients received penicillin, a cephalosporin, lincomycin or vancomycin and three days on less of an aminoglycoside. Group II patients were treated with either penicillin or a cephalosporin in combination with 5-28 days of aminoglycoside therapy.

Data was analyzed to detect any basic differences in the two groups with regard to both parameters demonstrated as having prognostic significance in our population, as well as those factors reported by other investigators to influence outcome in IE.

Finally outcome for patients in both groups was studied to determine whether the addition of an aminoglycoside for more than three days improved the prognosis in non-enterococcal streptococcal IE.

IV. DATA ANALYSIS

Frequencies and means as presented in Results are based on all patients for whom such data was available. The divisor, i.e., the number of patients on whom the particular observation was made, is given in all cases.

Data was analyzed using the t-test and X^2-test. Where appropriate the Yates correction for the latter test was applied (1,6).

RESULTS

A] SEX

Of the 69 patients reported here, 46 were male and 23 were female, so that the male:female ratio was 2:1 (Table 1). A male predominance still existed after correcting the ratio for eight male patients provided by the WHVAH. Thus a corrected sex ratio of 38:23 or 1.7:1 occurred. The higher incidence of IE in males has been previously noted (27,31,36).

Table 1 also shows the distribution of males and females by anatomical site of endocarditis. Twenty-one of 26 cases (81%) with aortic valve involvement and 6 of 7 cases (86%) of prosthetic valve endocarditis occurred in males, while 16 of 27 patients (59%) with mitral valve infection and only 3 of 9 patients (33%) with non-valvular congenital lesions were male. Male predominance, particularly in AV endocarditis, has also been observed before (31).

B] AGE

The average age for all patients included in the present study was 44.4 years and ranged between 8 months and 80 years (Table 2). This figure is similar to those reported by Pelletier and Petersdorf (31) and Cherubin and Neu (7) and supports recent observations by these authors

TABLE 1

RATIO OF MALES TO FEMALES IN 69 PATIENTS WITH NONENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

	YNHH and WHVAH			YNHH ONLY		
Site[a]	Male	Female	Ratio	Male	Female	Ratio
AV	21	5	4.2:1	17	5	3.4:1
MV	16	11	1.5:1	14	11	1.3:1
CONG	3	6	0.5:1	3	6	0.5:1
PROSTH	6	1	6.0:1	4	1	4.0:1
All	46	23	2:1	38	23	1.7:1

a) AV=Aortic Valve MV=mitral valve

CONG=Non-valvular congenital lesion

PROSTH=Prosthetic valve

TABLE 2

AGE--RANGE AND MEAN OF AGES FOR 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

	All Patients		Male Patients		Female Patients	
Site[a]	n	mean ± SE range	n	mean ± SE range	n	mean ± SE range
AV	26	47.7 ± 4.2 [10-80 yrs]	21	47.0 ± 4.4 [10-75]	5	50.0 ± 12.7 [15-80]
MV	27	51.7 ± 3.4 [7-76 yrs]	16	43.7 ± 4.0 [7-72]	11	55.5 ± 5.9 [13-76]
CONG	9	16.4 ± 4.3 [8 mos-31yrs]	6	22.3 ± 8.2 [6-31]	6	13.5 ± 5.0 [8 mos-31]
PROSTH	7	48.8 ± 6.8 [20-67 yrs]	3	53.3 ± 5.5 [32-67]	1	20.0 ------ -------
All Patients	69	44.4 ± 2.6	46	45.7 ± 2.7	23	41.8 ± 5.5

a) AV=aortic valve MV=mitral valve

CONG=non-valvular congenital lesion

PROSTH=prosthetic valve

of the increasing age of patients with IE. There was no significant age difference between males and females. Patients with infection of a prosthesis or of the mitral valve were slightly older, although this difference was not significant. The mean age of 16.4 years for patients with non-valvular congenital lesions was significantly lower than that for any other group of patients ($p < 0.001$).

C] UNDERLYING HEART DISEASE

There was evidence of some cardiac abnormality prior to presentation with IE in 83 percent of cases reviewed (Table 3). Twenty-four patients (35%) had congenital heart disease (CHD). Fifteen of these 24 had definite involvement of the aortic or mitral valve [10 AV patients including one with IHSS, 3 patients with congenital MR, and 2 patients with MR secondary to MV Prolapse Syndrome]. In two of these fifteen patients--one with AR and one with MR--there was a coexisting VSD. [For all other considerations, data for these fifteen patients have been analyzed with data for other patients with infection of the same heart valve.] Of the remaining nine patients with CHD, three had Fallot's tetralogy, two had VSD's, and one had a patent ductus arteriosus (PDA). The diagnosis was not specified in three patients.

Twenty-one of 69 patients (30%) had a heart murmur documented on at least two occasions prior to hospitalization for endocarditis but no specific diagnosis

TABLE 3

PRE-EXISTING HEART DISEASE IN 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Pre-existing heart disease	Number	%	Number	%	Number	%
	Male Patients		Female Patients		All Patients	
Congenital Heart Disease	15	(32.6)	9	(39.1)	24	(34.8)
Aortic Valve-AI/AS	7[a]		3[b]			
Mitral Valve-MI	4[b,c]		1			
Tetralogy of Fallot	2		1			
Not Specified	1		2			
Ventricular Septal Defect	1		1			
Patent Ductus Arteriosus	0		1			
Previous Heart Murmur--No Known Etiology	14	(30.4)	7	(30.4)	21	(30.4)
Site of Lesion NOT defined	10		6			
Site of Lesion Described	4[d]		1[e]			
No Previous Heart Disease Recognized	10	(21.7)	2	(8.7)	12	(17.4)
Prosthesis	6[f]	(13.0)	1	(4.3)	7	(10.1)
Rheumatic Heart Disease	1	(2.2)	4	(17.4)	5	(7.2)
Totals	46		23		69	

a) One patient with IHSS
b) One also had VSD
c) Two patients with MV prolapse
d) One-AI; One-AS/AI; One-MI,MS,AI; One-MI,MS,AI
e) One-MR
f) Two-Definite RHD

had been applied to these patients. In 16 of 21 the murmur was simply described as systolic, while in five patients the murmur had been characterized as to valvular site (AV vs. MV) and type of pathology (regurgitation vs. stenosis). It is probable that three patients in this latter group--(one patient with MR; one with MR,MS,AR; one with MR,AR,AS)--and, perhaps several members of the former group, had rheumatic heart disease (RHD).

Seven patients (10%) are considered to have had valvular prostheses underlying their infection. Six of these seven are men who had actually undergone valve replacement. Two of these had known RHD and four carried no etiologic diagnosis. The seventh patient is a woman who had an aortic valvuloplasty with residual suture material in her reconstructed valve.

Five additional patients (7%) actually carried the diagnosis of RHD. Although several authors (7,31) have recently pointed out the decreasing prevalence of RHD as an underlying problem in patients with IE, the percentage of patients who actually carried this diagnosis would seem to be much smaller in our series. Possibly, part of this discrepancy is due to a failure to apply an etiologic label to patients with cardiac murmurs who had true RHD but no clear-cut history of rheumatic fever.

In 12 of 69 patients (17%) no underlying cardiac abnormality had been previously recognized.

D] NON-CARDIAC UNDERLYING DISORDERS

Other factors which might have a significant impact on the course of IE are tabulated in Table 4 according to the frequency with which they occurred in our population. In seven cases there was a prior history of congestive heart failure (CHF) and in seven cases there had been a previous episode of IE. Coronary artery disease (CAD) was a factor in 6 patients, three of which had had a documented myocardial infarction in the past. Small numbers of patients had cancer, diabetes mellitus, renal failure or liver impairment secondary to excessive alcohol ingestion.

E] PRESENTING SYMPTOMS

Presenting symptoms for all patients are listed in Table 5. Fever occurred in 84 percent of patients. Non-specific complaints of fatigue, weakness and malaise were the next most common symptoms, occurring in 39 of 69 patients (57%). Ten patients or 15 percent of our group complained of new or increased symptoms of congestive heart failure. Neurological complaints including stroke, confusion, stupor and obtundation were obvious in eight patients (12%). One patient presented with both flank pain and hematuria. These figures parallel those reported in other large surveys (7,31,36).

F] DURATION OF SYMPTOMS

For 64 cases where data was available, the mean length of time between the onset of the first symptom related

TABLE 4

UNDERLYING PROBLEMS IN 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Underlying Problem	Number	%	Number	%	Number	%
	Male Patients		Female Patients		All Patients	
Pre-existing CHF	5	(10.9)	2	(8.7)	7	(10.1)
History of SBE	5	(10.9)	2	(8.7)	7	(10.1)
Coronary Artery Disease	5	(10.9)	1	(4.3)	6	(8.7)
Angina	3		0			
Documented Infarction	2		1			
Other	4	(8.7)	4	(17.4)	8	(11.6)
Liver Disease	2		1			
Cancer	1		1			
Diabetes Mellitus	1		1			
Renal Failure	0		1			
No Underlying Problem	28	(60.9)	15	(65.2)	43	(62.3)
Totals	47[a]		24[a]		71[a]	

a) Two Patients Had Two Underlying Problems.

TABLE 5

PRESENTING SYMPTOMS IN 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Symptom	Number	%
Fever	57	(84)
Fatigue, weakness, malaise	39	(57)
Chills	24	(41)
Anorexia, weight loss	20	(29)
Sweats	13	(19)
Arthralgias	12	(18)
Myalgias	10	(15)
CHF[a]	10	(15)
Headache	8	(12)
Stroke, confusion, stupor	8	(12)
Cough	7	(10)
Abdominal pain, nausea, diarrhea	6	(9)
Chest pain	5	(7)
Back pain	3	(4)
Flank pain	1	(1)
Hematuria	1	(1)

a) New or suddenly increased congestive heart failure.

to IE and presentation to the hospital was 51.2 days (Table 6). This is slightly lower than has been documented elsewhere (31). Patients with prosthetic valve infection had much shorter duration of symptoms (mean 12.6 days) prior to hospital admission ($p < 0.01$).

G] PHYSICAL FINDINGS

The classical signs of infective endocarditis were not commonly seen in the patients in the present study. Table 7 summarizes the physical findings noted within the first few days of hospitalization. All patients had a cardiac murmur and 66 of 69 patients had fever greater than 100.6°F. Splenomegaly was seen in 14 patients (20.3%), while petechiae and splinter hemorrhages occurred in 17.4% and 14.5% of cases respectively. Clubbing was noted in only four patients (5.8%) as a new finding and Roth spots were described in three patients. Two patients had at least one Janeway's lesion each. No Osler's nodes were described.

H] LABORATORY STUDIES

(Table 8) An elevated erythrocyte sedimentation rate (ESR) was the most constant laboratory finding and occurred in 49 of 54 patients (90.7%) with a mean value of 40.9. Fifty-three of 63 patients or 84.1% of our group were anemic; the mean hematocrit was 33.1%. Reversal of the albumin:globulin ratio occurred 21 of 43 patients (48.8%) in whom measurement of serum proteins was performed. The mean white blood count (WBC) was 9400 with 28 of 67 patients

TABLE 6

DURATION OF ILLNESS PRIOR TO TREATMENT[a] IN 64[b] PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Site[c]	Number of Patients	Duration (Days) Median	Duration (Days) (Mean ± SE)
AV	24	42	52.5 ± 11.8
MV	25	30	58.9 ± 12.2
CONG	9	14	53.2 ± 35.5
PROSTH	6	7	12.6 ± 6.2
All Patients	64	30	51.2 ± 8.4

a) Period beginning with first symptom attributed to IE.

b) Data unavailable for 5 patients.

c) AV = aortic valve MV = mitral valve
CONG = non-valvular congenital lesion
PROSTH = prosthetic valve

TABLE 7

PHYSICAL FINDINGS ON PRESENTATION IN 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Sign	Number	(%)
Murmur	69	(100)
Fever	66	(96)
Splenomegaly	14	(20)
Petechiae	12	(17)
Splinter Hemorrhages	10	(15)
Clubbing	4	(6)
Roth Spots	3	(4)
Janeway's Lesions	2	(3)
Osler's Nodes	0	(0)

TABLE 8

LABORATORY DATA ON ADMISSION FOR 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

	Measurement	No. pts with Abnormality/No. Tested	(%)
a)	ESR [Mean-40.9] ≤25: 6 pts 26-45:24 pts 46-65:24 pts	49/54	(91)
b)	Hematocrit [Mean=33.1]	53/63	(84)
c)	Albumin/globulin ratio	21/43	(49)
d)	WBC [Mean 9,400] ≤5,000: 8 pts 5-10,000: 31 pts 10-15,000: 24 pts >15,000: 4 pts	28/67	(42)
e)	RF	16/49	(33)
f)	Hematuria	15/68	(22)
g)	Proteinuria	9/68	(13)

a)	↑ESR= >15♂ , >20♀	13 pts - Data Unavailable	2 pts-Had Polycythemia
b)	Anemia= <40♂ , <37♀	4 pts - Data Unavailable	2 pts-Had Polycythemia
c)	Reversal of Ratio=Abnormality	26 pts - Data Unavailable	
d)	WBC >10,000=Abnormality	2 pts - Data Unavailable	
e)	Titer ≥ 1:40, where given	20 pts - Data Unavailable	
f)	≥3 RBC/hpf on adm & 1 other exam	1 pt - Data Unavailable	
g)	≥1+ on dipstick on adm & 1 other exam	1 pt - Data Unavailable	

having a WBC in excess of 10,000. Rheumatoid Factor was present in titers of at least 1:40 in 32.7% of patients (16/49). Hematuria and proteinuria were detected less frequently (15/68 or 22.2% and 9/68 or 13.2% respectively).

I] FOLLOW-UP

Six patients died within or just after the treatment period. Of the remaining 63 patients, all were followed for at least six months with a mean duration of follow-up of 53.9 months. Thirty-eight of 63 were followed for more than one year.

J] INFECTING ORGANISMS

The streptococci isolated from blood cultures in these 69 patients are listed in Table 9. Minimum Inhibitory Concentrations (MIC's) for penicillin were done on approximately half of the organisms isolated and were less than 0.19 u/ml in all cases.

K] MORBIDITY

Table 10 describes major complications (including death) of endocarditis seen in these 69 patients during the period beginning with the onset of disease-related symptoms and ending six months after completion of therapy. Thirty-three of 69 patients (49.3%) developed one or more major complication; 36 patients (50.7%) had an uneventful course. Twenty-three patients (33%) developed CHF or had a sudden worsening of a previously stable pattern of CHF. Fifteen of 23 patients had AV endocarditis, three patients each had

TABLE 9

STREPTOCOCCI ISOLATED FROM 69 PATIENTS WITH

NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Organism	Number	(%)	Number Tested	(%)	MIC-Penicillin (Range in units/ml)
S. viridans	55	(80)	26	(47)	0.02-0.19
S. bovis	4	(6)	1	(25)	< 0.19
Non-enterococcal Gamma-Streptococcus	3	(4)	2	(67)	0.10-0.19
[a]Beta-streptococcus	3	(4)	2	(67)	0.19
Anaerobic streptococcus	2	(3)	1	(50)	0.02
S. equinus	1	(1)	0		--
Untyped	1	(1)	0		--
Total	69		32[b]		

a) Non-Group A,D
b) Remaining 37 organisms sensitive by disc method.

TABLE 10

MAJOR COMPLICATIONS[a] IN 69 PATIENTS WITH NON-ENTEROCOCCAL STREPTOCOCCAL ENDOCARDITIS

Site	n	NO COMP (%)	CHF(%)[b]	EMBOLI (%)	FEVER (%)[b]	RECURRENCE (%)	DEATH(%)	ANY COMP (%)
AV	26	8 (31)	15 (58)	2 (8)	2 (8)	1 (4)	3 (12)	18 (69)
MV	27	20 (74)	3 (11)	3 (11)	0	1 (4)	1 (4)	7 (26)
CONG	9	6 (67)	2 (22)	1 (11)	0	0	0	3 (33)
PROSTH	7	1 (14)	3 (43)	2 (29)	1 (14)	0	2 (29)	6 (86)
All Patients	69	36 (52)	23 (33)	8 (12)	3 (4)	2 (3)	6 (9)	33 (48)

a) Period of Observation - Onset of Symptoms to six months after completion of therapy.

b) AVR:9 patients - 7 for CHF, 1 for fever, 1 for fever in a patient who also had CHF.
MVR:1 patient for CHF
AVR/MVR:1 patient for CHF
MVR/TVR:1 patient who died p op.
Aortic Prosthesis Re-replacement:4 patients - 3 for CHF, 1 for fever.

prostheses or mitral valve disease and two had non-valvular CHD. Thus, 58 percent (15/26) of patients with IE involving the AV and 43 percent (3/7) of those with prostheses developed CHF compared with 11 percent of MV patients (3/27) and 22 percent of those with non-valvular CHD (2/9). The AV and prosthetic valve predominances in the development of CHF were highly significant ($p < 0.001$) and are consistent with the findings of other investigators (33,35). Eight patients had definite, major embolic episodes including stroke (6 patients) and major peripheral arterial occlusion (ophthalmic a.-1, femoral artery -1). Three patients had persistent fever, felt to be unrelated to hypersensitivity, despite repeatedly sterile blood cultures. All three patients came to operation. In one a mycotic aneurysm near the aortic valve ring was identified, while in the other two patients there was no obvious source of fever. Fever abated following valve replacement in these three patients, although operative specimens in all cases were sterile on culture, including culture for L-phase variants. There were two recurrences in our group, both occurring within one month of completion of a course of therapy (3%). Six of the 69 patients died (a mortality rate of 8.7%).

Of the 33 patients developing major complications, 26 developed a single complication, five developed two complications and two patients suffered three complications.

Two patients with persistent fever had another complication of IE--one developed CHF and one sustained a sterile femoral artery embolus after undergoing valve replacement. The other five patients with multiple complications all died. One presented with CHF, relapsed and died suddenly shortly after readmission. Two additional patients had developed CHF, and subsequently died, another presented with a stroke and died and, finally, one presented with a stroke and CHF succumbing only two days after admission.

What is clearly evident from Table 10 is that patients with prosthetic valve endocarditis did extremely poorly. Two patients died (29%) and four patients required re-replacement of their valve. The course in two of these six was further complicated by major emboli resulting in a stroke in one patient and occlusion of a femoral artery in the other. Only one patient had an uneventful course. Thus six of seven patients (86%) developed seven major complications of IE. This complication rate was significantly higher than that in the remainder of patients (86% vs. 45%, $p < 0.05$).

L] INFLUENCE OF UNDERLYING FACTORS, AGE AND MODE OF PRESENTATION ON OUTCOME IN IE

Table 11 describes major complications of endocarditis as they occurred in individuals with various underlying conditions which have been implicated in worsening the prognosis in this disease (30). Patients with prosthetic

TABLE 11

RELATIONSHIP OF POSSIBLE DETERMINANTS OF PROGNOSIS TO MAJOR COMPLICATIONS IN 62 PATIENTS WITH NON-PROSTHETIC VALVE ENDOCARDITIS

Underlying Condition	n	NO COMP.	CHF	EMBOLI	FEVER	RECURRENCE	DEATH	ANY COMP.
H/O CHF	5	2	1	2				3
No H/O CHF	57	33	19	4	2	2	4	24
No Underlying Disorder	39	22	12	4	2	1	3	17
H/O SBE	5	4	1					1
No H/O SBE	57	31	19	6	2	2	4	26
No Underlying Disorder	39	22	12	4	2	1	3	17
CAD	5	3	2			1	1	2
No CAD	57	32	18	6	2	1	3	25
No Underlying Problems	39	22	12	4	2	1	3	17
Ca, D.M., etc.	8	4	4				1	4
None of these	54	31	16	6	2	2	3	23
No Underlying Problems	39	22	12	4	2	1	3	17
Totals	62	35	20	6	2	2	4	27

TABLE 11 - Cont.

Underlying Disorder	n	NO COMP	CHF	EMBOLI	FEVER	RECURRENCE	DEATH	ANY COMP
Presentation with CHF	9	3	4/9[a]	0	1	1	2	6
Presentation without CHF	53	32	6/11[a]	6	1	2	2	21
Presentation with CNS S_x	8	6	2	-	0	0	2	2
Presentation without CNS S_x	54	29	18	-	2	2	2	25
Age 60	20	9	7	1	0	2	4	10
Age 60	42	26	13	5	2	0	0	17
Duration 3 mos.	13	3	7	1	0	2	1	10
Duration 3 mos.	49	32	13	5	2	0	3	17
Totals	62	35	20	6	2	2	4	27

a) Valve replacement

valve endocarditis were not included in this analysis because of their already grave prognosis as discussed above. Although the numbers are small, there does not appear to be any definite relationship between these factors (H/O CHF, H/O SBE, CAD, Cancer, D.M., Renal Failure, EtOH Excess) and outcome for this group of patients.

Similarly, the data was analyzed to determine whether, as in several other series (5,8,31), there was a relationship between presentation with CHF or symptoms referable to the central nervous system (CNS) and outcome in IE. Eight patients presented with CHF. Five of eight had AV endocarditis, one had MV endocarditis and two had endocarditis associated with non-valvular congenital lesions. Four of eight (all AV patients) required placement of a prosthetic valve. In three of these, CHF was the sole indication for surgery while in the fourth patient the primary factor leading to operation was persistent fever. One patient in this group--who also presented with a CVA--died within 48 hours of admission. The incidence of complications (valve replacement, fever, death) was not significantly greater in this group than for all patients or for patients who developed CHF later in the course of illness ($p > 0.20$, $p > 0.20$).

Eight patients presented with either a stroke or significant neurological impairment (stupor, obtundation) felt to be related to IE. Six of these patients had

no complications. Two of the eight patients (25%), however, died. This death rate was not significantly greater than that for all other non-prosthetic patients ($p > 0.10$).

Patients at the extremes of age have reportedly faired poorly in IE (5,8,30,31). Only four patients reported here were less than ten years old and none of these developed a major complication. On the other hand, twenty patients were in the seventh decade of life and these patients accounted for all four deaths (20%) and both episodes of recurrent disease (10%) in non-prosthetic IE. Both the relapse rate and the mortality rate were significantly greater than for patients under 60 years old ($p < 0.05$, $p < 0.01$ respectively).

Patients who were to develop a major complication of IE had a significantly longer symptomatic period prior to presentation than those who had an uncomplicated course (69 vs. 35 days, $p < 0.01$).

Analyzing the data from 58 non-prosthetic endocarditis patients (as was noted in section F, PV patients had a much shorter duration of illness), it can be shown that patients who developed CHF were, on the average, symptomatic for 79 days prior to hospitalization and, furthermore, that those who ultimately required valve replacement because of CHF, presented after a mean of 99 days of symptoms (Table 12). Both of these values contrasted sharply with the duration of illness in non-prosthetic endocarditis

TABLE 12

RELATIONSHIP OF DURATION OF ILLNESS TO SPECIFIC COMPLICATIONS IN 58[a] PATIENTS WITH NON-PROSTHETIC ENDOCARDITIS

	NO COMP	CHF	CHF → VALVE	EMBOLI	FEVER	RECURRENCE	DEATH
n	34	18	9	6	4	2	2
Duration (Mean in Days)	35.6	78.8	99.4	56.3	17.5	120.0	63.1
± SE	±8.1	±15.8	±21.0	±26.7	±3.5	--	±8.4

a) Data unavailable in four patients

patients who had no complications (mean 35 days; $p < 0.001$, $p < 0.001$). The relationship between duration of illness and development of CHF has been previously observed (3,8,30).

The mean duration of illness in patients who developed major emboli (56 days) and those who died (63 days) was also longer than in those patients who had no complications although these differences were not significant ($p > 0.05$). Patients who developed persistent fever had a very short pre-treatment duration (18 days), but again this was not significantly different from the mean duration of illness in patients with uncomplicated IE ($p > 0.05$). Both of the patients who relapsed had four month histories prior to hospital admission. This was significantly longer than the duration of illness in patients who had uneventful courses ($p < 0.001$).

In addition, patients with illness prior to therapy of three months or greater had a higher incidence of relapse than those with illness less than three months prior to therapy (Table 11). The relapse rate for patients with longstanding illness was 15.4 percent (2/13) and was significantly higher than the rate for the remainder of patients on whom data was available (0/51, $p < 0.05$). This observation has been made by others (32). It was also noted that patients with illness greater than or equal to three months in duration developed CHF with greater

frequency than all other patients, but this difference was not significant (7/13 or 54% versus 13/51 or 26%, $p > 0.05$).

M] TREATMENT

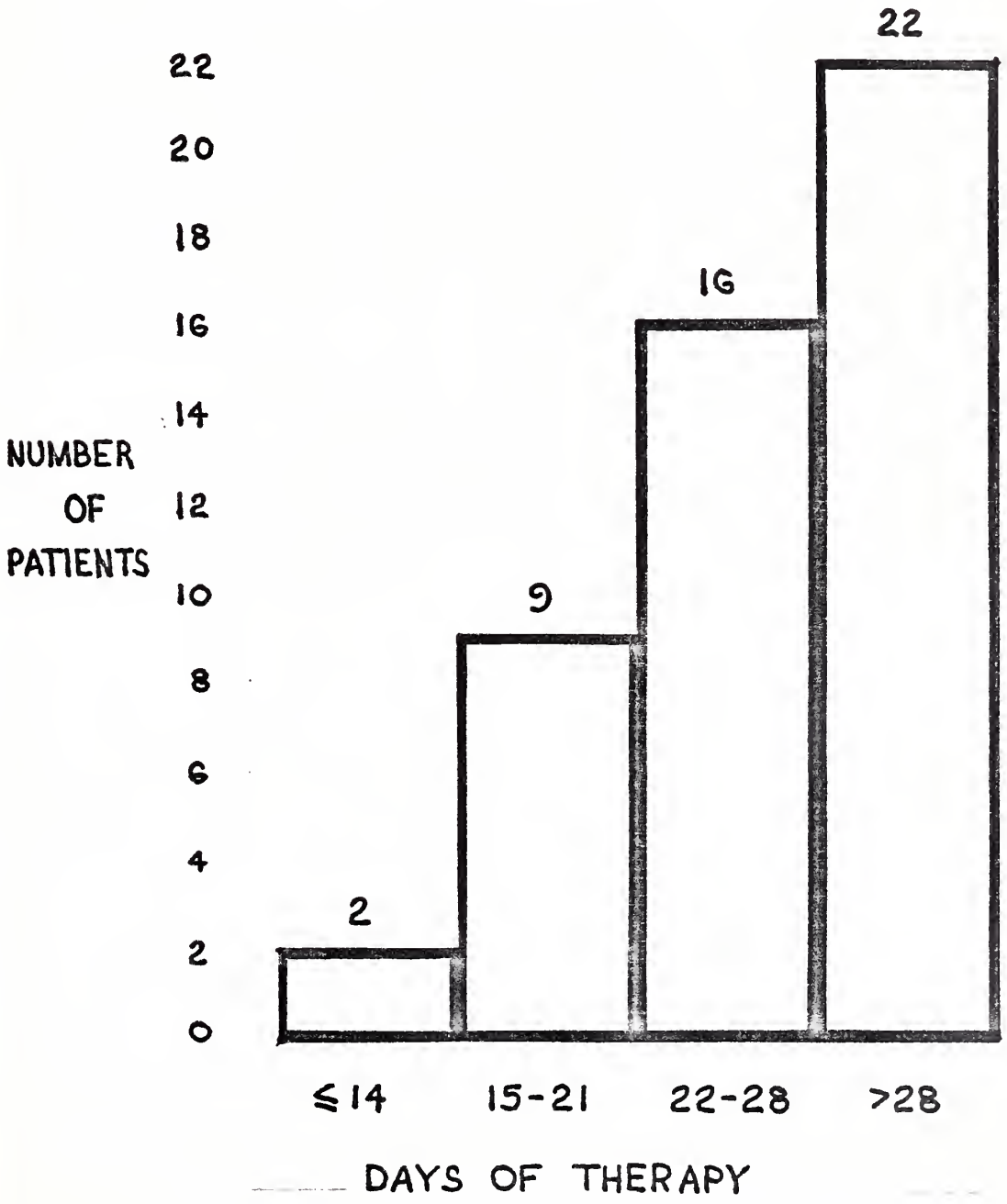
Of the 69 patients discussed above, 68 patients survived for at least one week and are included in the analysis of efficacy of antimicrobial therapy. One patient died within 48 hours of admission so that therapy could not be evaluated.

GROUP I: Forty-nine of 68 patients were treated with a bactericidal antibiotic and three days or less of an aminoglycoside. Of these, 41 patients received penicillin and eight patients received a cephalosporin, lincomycin or vancomycin singly or in sequence. Eleven of these 49 patients received an aminoglycoside for three days, five additional patients received two days of aminoglycoside therapy and three other patients received streptomycin for one day. The remaining thirty patients received single drug therapy.

Figure 1 illustrates the duration of antibiotic therapy for all Group I patients which ranged from 7-50 days with a mean of 30.2 days. Eleven patients (22%) were treated for 21 days or less. Two of these died within the first two weeks of therapy; the remaining nine received 15-21 days of antibiotic. Sixteen patients (33%) were treated for a period of 22-28 days and 22 patients (45%) received more than 28 days of therapy.

Parenteral penicillin was given intravenously for

FIGURE 1. DURATION OF THERAPY IN 49 GROUP I PATIENTS.
(mean: 30.2 ± 1.2 days)



at least one week in 39 of 41 penicillin treated patients. Dosage ranged from 2,000,000 units per day in a three kilogram infant, to 24 million units per day. One adult patient received 4,000,000 units daily and four patients were treated with 8,000,000-9,000,000 units per day. The remaining 33 patients received 10 million units or more each day. Six of these 39 patients received the latter part of their therapy intramuscularly in dosages of 2.4-4.8 million units daily and ten patients received some oral penicillin in dosages that ranged between 2-4 grams daily.

Intramuscular penicillin was the primary form of therapy in the remaining two of 41 patients. One patient received 4.8 million units per day for 21 days while the other patient began his 28 day course with two days of intravenous penicillin (24 million units/day) and continued with intramuscular penicillin in doses of 4.8 million units per day for one week, 3.6 million units per day for one week and 2.4 million units per day for the last twelve days.

The remaining eight of 49 Group I patients received the following agents, employed singly or sequentially, during the course of treatment: cephalothin (6-9g/d, IV or IM), cephaloridine (4g/d, IM), lincomycin (1-6g/d, IM), vancomycin (2g/d, IV) and chloramphenicol (4g/d, IM).

Details of treatment for each patient in Group I may be found in Table 13.

GROUP II: The 19 remaining patients (49 + 19 = 68)

TABLE 13

DETAILS OF TREATMENT REGIMENS EMPLOYED IN 49 GROUP I (SINGLE AGENT) PATIENTS

No.	Intravenous Pcn Dose & Duration	Intramuscular Pcn Dose & Duration	Oral PCN Dose & Duration	Aminoglycoside Duration	Total Duration
1.	12MU x21d	-	-	2	21d
2.	6MU x15d	-	4.8MU x26d	0	41d
3.	10MU x28d	-	2.4MU x30d	0	58d
4.	20MU x14d	-	4g x14d	0	28d
5.	20MU x21d	-	-	0	21d
6.	10MU x6d/2.4MU x8d	2.4MU x5d	2g x10d	2	29d
7.	24MU x28d	-	3.2MU x17d	2	45d
8.	24MU x41d	-	-	0	41d
9.	-	4.8MU x21d	-	0	21d
10.	20MU x28d	-	-	0	28d
11.	10MU x21d	-	-	2	21d
12.	20MU x 21d	-	24MU x14d	0	35d
13.[a]	2MU x21d	-	1.6MU x2d	0	23d
14.	20MU x9d	4.0MU x14d	-	0	23d
15.	15MU x35d	-	-	3	35d
16.	9MU x28d	-	-	0	28d
17.	15MU x28d	-	-	0	28d
18.	9MU x25d	-	-	0	25d
19.	4MU x25d	-	-	1	25d
20.	12MU x8d	2.4MU x21d	-	3	29d
21.	20MU x26d	-	-	0	26d
22.	10MU x17d	4.8MU x12d	-	3	29d
23.	12MU x17d	2.4MU x18d	-	3	35d
24.	24MU x2d	4.8/3.6/2.4 x7d/7d/12d	-	2	28d
25.	12MU x27d	-	2g x12d	0	39d
26.	15MU x42d	-	-	3	42d
27.	20MU/10MU x18d/11d	-	-	0	29d

TABLE 13 - Cont.

No.	Intravenous Pcn Dose & Duration	Intramuscular Pcn Dose & Duration	Oral Pcn Dose & Duration	Aminoglycoside Duration	Total Duration
28.	21MU x24d	-	2g x5d	0	29d
29.	18MU x21d	-	-	0	21d
30.	20MU x42d	-	-	0	42d
31.	12MU x28d	-	-	0	28d
32.	12MU x28d	-	-	3	28d
33.	6MU x28d	-	-	0	28d
34.	10MU x28d	-	-	0	28d
35.[b]	12MU x21d	-	-		29d
36.	10MU x25d	-	4g x18d	1	43d
37.	10 MU x ?	2.4MU x ?	-	0	28d
38.	10MU x21d	-	-	0	21d
39.	12MU x9d	2.4MU x12d	-	0	21d
40.	12MU/3MU x10d/18d	-	-	3	28d
41.	8MU/3.6MU x10d/31d	2.4MU x9d	-	0	50d

a) 3 kg infant

b) also received cephalothin x3d, lincomycin x5d

TABLE 13 - Cont.

No.	Drug(s)	Route, Dose & Duration	Aminoglycoside Duration	Total Duration
42.	Ampicillin ? Dose	4d	3	35d
	Penicillin 6MU	3d		
	Keflin ? Dose	10d		
	Lincomycin 6g	28d		
43.	Penicillin 20MU	5d	3	21d
	Keflin 6g	9d		
	Chloramphenicol 4g(1M)	7d		
44.	Penicillin 6MU	5d	0	43d
	Keflin 6g	3d		
	Loriden 4g-1M	15d		
	Lincomycin 1g-1M	20d		
45.	Penicillin 20MU	21d	0	46d
	Keflin 9g	4d		
	Lincomycin 1.8g	21d		
46.	Keflin bg	35d	0	35d
47.	Keflin 6g IV	10d		21d
	Keflin 6g 1M	11d		
48.	Vancomycin 2g	3d	3	7d
	Keflin 8g	4d		
49.	Penicillin 24MU	7d	3	14d
	Keflin 6g	7d		

formed the second treatment group where each patient had received parenteral penicillin (17 cases) or a cephalosporin (2 cases) in addition to at least five days of an aminoglycoside.

The mean duration of therapy for Group II patients was 27.0 days (range: 14-42 days) (Figure 2). Six Group II patients (32%) were treated for 21 days or less. One of six died after two weeks of therapy; the other five patients received 21 days of antibiotics. Eight patients (42%) received antibiotics for 22-28 days and the remainder received longer courses.

The pattern of administration of the aminoglycoside is illustrated in Figure 3. Duration of aminoglycoside therapy ranged from 5 to 28 days with a mean of 13.3 days. Three patients received an aminoglycoside for less than a week, five additional patients were treated with an aminoglycoside for 7-10 days, six patients received an aminoglycoside for 11-14 days and the remaining 5 patients received at least three weeks of such therapy. Six patients received gentamicin; 13 patients received streptomycin.

Penicillin was the only drug given in addition to the aminoglycoside in 17 of 19 patients and in all but one of these patients, it was administered intravenously in doses of at least 10 million units daily. The seventeenth patient received 4.8 million units per day intramuscularly for 18 days and then intravenous penicillin (10 million units/

FIGURE 2. DURATION OF THERAPY IN 19 GROUP II PATIENTS.
(mean: 27.0 ± 1.8 days)

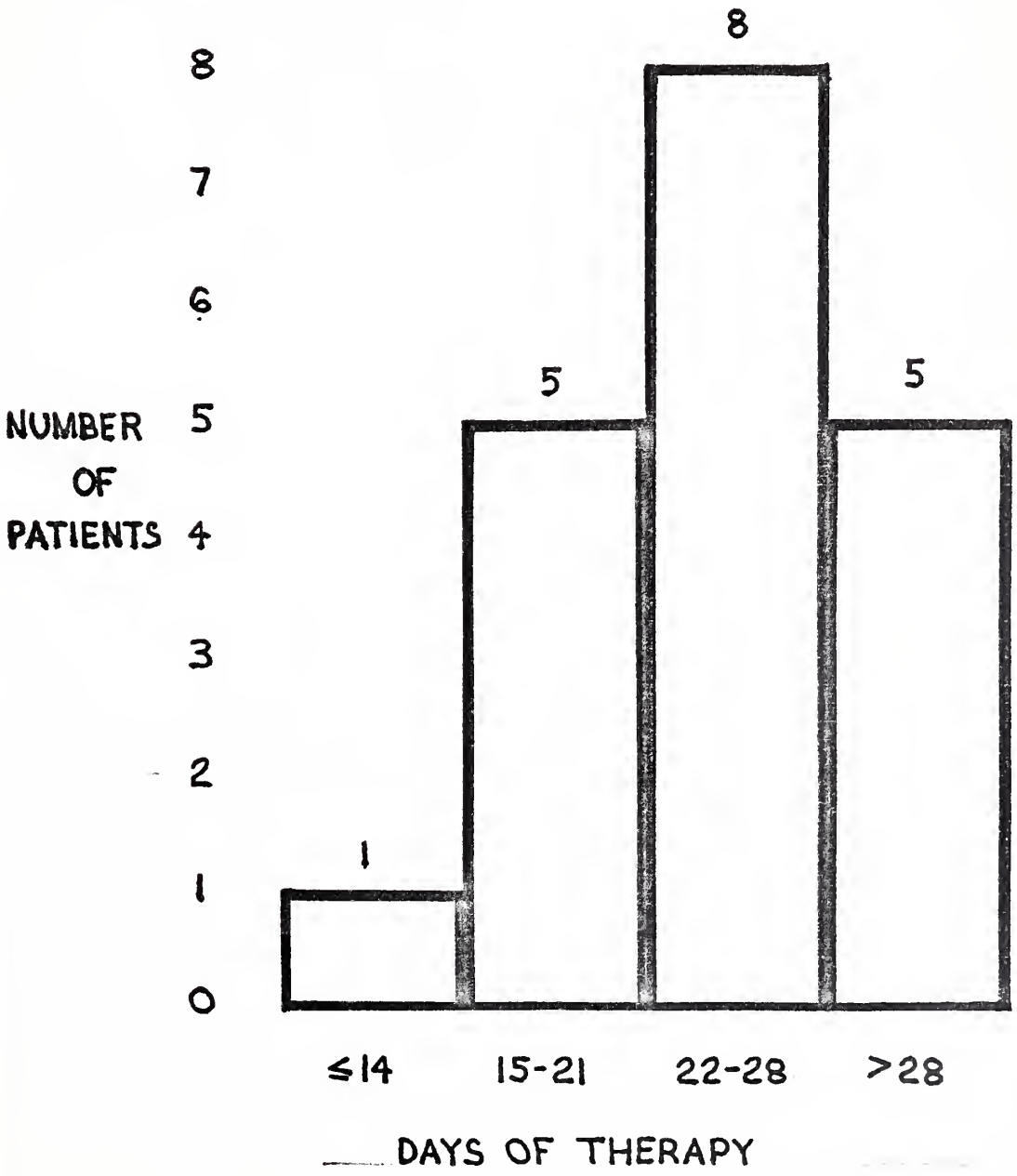
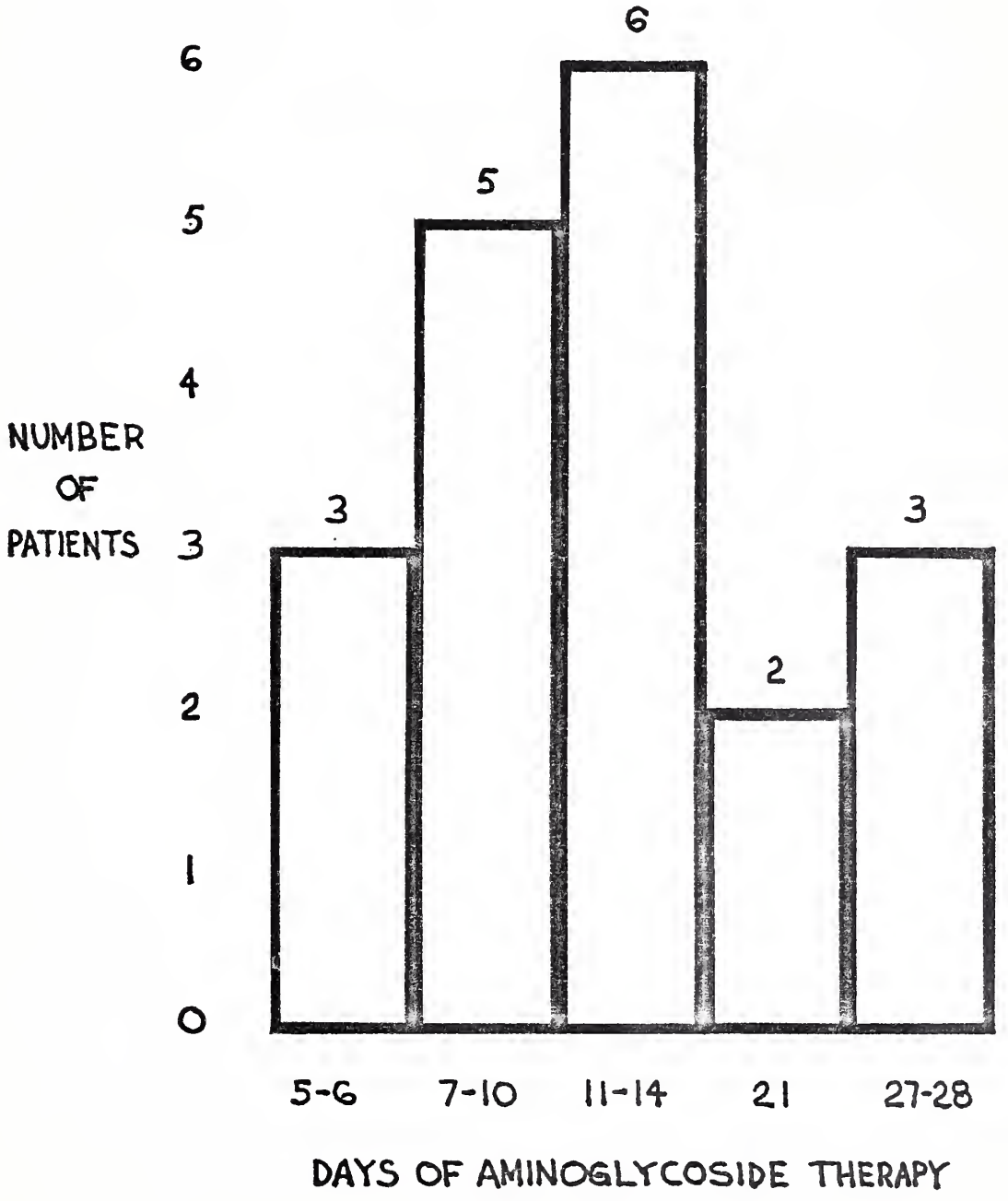


FIGURE 3. DURATION OF AMINOGLYCOSIDE THERAPY IN 19 GROUP II PATIENTS. (mean: 13.3 ± 1.8 days)



day) for an additional nine days.

Two of 19 patients received a cephalosporin. One patient received cephazolin in a dose of 2.0 grams per day intravenously for 21 days. The other patient was begun on penicillin for two weeks and, when a question of drug allergy arose, was changed to cephalothin, 8.0 grams per day, for an additional 20 days.

Details of treatment for Group II patients are outlined in Table 14.

N] MONITORING THERAPY

Efficacy of antibiotic therapy was assessed with serum bactericidal levels in 48 of these 68 patients. Thirty-four of 49 (69%) had titers of 1:16 or greater, 11 had a titer of 1:8 while only three patients had titers of less than 1:8. None of the three patients in the latter group suffered any major complication of endocarditis.

The erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) were repeated in so few patients that no statement can be made about these parameters as monitors of therapy.

O] COMPLICATIONS OF THERAPY

A rash occurred in five Group I patients treated with penicillin and resulted in a change in medication to cephalothin in all cases. Four of these five patients, however, showed continued signs of hypersensitivity to the second drug, requiring a further alteration in therapy.

TABLE 14

DETAILS OF TREATMENT REGIMENS EMPLOYED IN 19 GROUP II (COMBINATION) PATIENTS

No.	Route, Drug(s) Dose & Duration		Route, Drug(s) Dose & Duration	Oral Pcn Dose & Duration	Aminoglycoside Duration	Total Duration
50.	IV-Penicillin 12MU	x14d	IV-Cephalcthin	-	Strep x28 days	34d
51.	IV-Penicillin 24MU	x35d	IV 8g x20d	-	Strep x 7 days	35d
53.	IV-Penicillin 10MU	x28d	-	-	Genta x 5 days	28d
54.	IV Cephazolin 2g	x21d	-	-	Genta x14 days	21d
55.	IN-Penicillin 4.8MU	x18d	IV-Penicillin 10MU x9d	-	Strep x27 days	27d
56.	IV-Penicillin 12MU	x42d	-	-	Strep x11 days	42d
57.	IV-Penicillin 10MU	x24d	-	-	Strep x12 days	24d
58.	IV-Penicillin 20MU	x21d	-	-	Strep x11 days	21d
59.	IV-Penicillin 18MU	x14d	-	2g x14d	Strep x14 days	28d
60.	IV-Penicillin 12MU	x28d	-	-	Strep x21 days	28d
61.	IV-Penicillin 10MU	x21d	-	-	Genta x 9 days	21d
62.	IV-Penicillin 12-24MU	x38d	-	-	Strep x21 days	38d
63.	IV-Penicillin 24MU	x24d	-	-	Genta x 5 days	24d
64.	IV-Penicillin 20MU	x35d	-	-	Genta x28 days	35d
65.	IV-Penicillin 15MU	x28d	-	-	Strep x 8 days	28d
66.	IV-Penicillin 6MU	x28d	-	-	Strep x14 days	28d
67.	IV-Penicillin 10MU	x21d	-	-	Strep x 5 days	21d
68.	IV-Penicillin 12MU	x21d	-	-	Genta x 7 days	21d
69.	IV-Penicillin 24MU	x14d	-	-	Strep x 7 days	14d

One additional patient in Group I developed hives while on penicillin and, again, on cephalothin. Superficial phlebitis at the site of penicillin infusion posed some difficulty for a patient in Group II.

A history of penicillin allergy was obtained from four patients (Group I-3; Group II-1). Three of these received alternative agents while the fourth patient was desensitized to penicillin and underwent uncomplicated treatment with that drug.

A transient ataxic tremor developed in one Group II patient and resulted in discontinuation of streptomycin therapy.

P] COMPARISON OF GROUPS: I-SINGLE DRUG II-COMBINATION THERAPY

The data was analyzed to detect any underlying differences between the two treatment groups which might have had an effect on the course of the disease (Table 15). The mean age of Group I patients was higher than that of Group II patients but this difference was not significant (49.9 years vs. 40.9 years, $p > 0.05$). The percentage of patients in their seventh decade of life, however, was significantly higher than in Group II, i.e., 18 of 49 or 36.7% of Group I patients were over 60 years old as opposed to only two of 19 Group II patients (10.5%) ($p < 0.05$). Moreover, the proportion of patients in Group I having IE for a period of three months or more prior to treatment was 22.4%

TABLE 15

COMPARISON OF TREATMENT GROUPS

Item	Group I	Group II	Significant Difference
Number of Patients	49	19	-
Age (Years): Mean(Median)	49.9(51)	40.9(32)	NS
No. & % 10 years old	2(4.1)	2(10.5)	NS
No. & % 60 years old	18(36.7)	2(10.5)	$p < 0.05$
No. & % with AV involvement	19(38.3)	6(31.6)	NS
No. & % with MV involvement	21(42.9)	6(31.6)	NS
No. & % with Non-Valv Cong	6(12.2)	3(15.8)	NS
No. & % with Prostheses	3(6.1)	4(21.1)	NS
*H/O CHF	3(6.5)	2(13.3)	NS
H/O CAD	5(10.9)	0	NS
H/O SBE	4(8.7)	0	NS
Cancer, DM, Renal Failure, etc.	6(13.0)	2(13.3)	NS
*Presented with CHF	3(6.5)	4(26.7)	NS
Presented with CNS Sx	5(10.9)	1(6.7)	NS
Duration of Symptoms (days)	52.6(1-240)	55.2(3-365)	NS
> 3 mos	11(22.4)	2(10.5%)	$p < 0.05$
Duration of Therapy (days)	30.2(7-50)	26.9(14.42)	NS
$\leq$ 21 days	11(22%)	6(32%)	NS

*Prosthetic Valve Cases not included in Analysis

(11/49) and was significantly larger than the percentage with a greater than three month pre-treatment duration in Group II (2/19=11%, $p < 0.05$) even though the mean duration of illness in Groups I and II (52.6 vs. 55.2 days) did not differ significantly. No significant differences between the two groups were noted when other factors were analyzed. The distribution of anatomical sites of involvement was roughly equivalent and, while there were slight differences in the percentages of patients having various underlying conditions or presenting with CHF or CNS symptomatology, none of these was significant. Similarly, the duration of therapy did not differ between Groups I and II with means of 30.2 and 26.9, respectively.

Q] COMPARISON OF OUTCOME: GROUP I vs. GROUP II

The incidence of major complications of IE, occurring in each of the two treatment groups, during the period beginning one week after initiation of therapy and ending six months after therapy, is summarized in Table 16. For the purposes of these analyses, complications whose onset antedated the initiation of a therapeutic regimen, were not considered.

Of 68 patients assigned to either treatment group, 49 were in Group I and 19 in Group II. Thirty-eight and eight tenths percent of patients in Group I (19 of 49) developed one or more major complication. The comparable figure for Group II was 26.3% (5/19). This difference, however, was not significant ($p > 0.30$).

TABLE 16

COMPARISON OF RATE OF COMPLICATIONS IN GROUPS I AND II

(GROUP I: SINGLE AGENT THERAPY
GROUP II: COMBINATION THERAPY)[a]

	n	CHF(%)	Emboli(%)	Fever(%)	Death(%)	Recurrence(%)	Any Comp(%)
I	49	10(20)[b]	4(8)	1(2)	4(8)	2(4)	19(39)
II	19	3(16)[c]	0	2(11)	1(5)	0	5(26)
Significance		$p > 0.50$	$p > 0.30$	$p > 0.20$	$p > 0.50$	$p > 0.50$	$p > 0.30$
Totals	68	13	4	3	5	2	24

a) Period of Observation: One week after initiation of therapy to 6 mos. after termination of therapy

b) 6 Valve replacements - 6/10=60%

c) 2 Valve replacements - 2/3=67%

A total of thirteen patients (13/68=19%) developed CHF during this period. Ten of thirteen were Group I patients and six of these ten required valve replacement (AVR-4; MVR-1; Prosth Re-replacement-1). Three patients in Group II developed CHF, two of them requiring operation (AVR-1, Prosthesis Re-replacement-1). The differences in the incidence of CHF--10/49 (20%) in Group I versus 3/19 (16%) in Group II--and in the rate of valve replacement were not significant ($p > 0.50$, $p > 0.50$).

Although major emboli occurred in four patients, all of whom had received single drug therapy (Group I) as compared to none in Group II, this difference was not significant ($p > 0.50$). Persistent fever occurred in three patients--one from Group I (2%) and two from Group II (11%) and this was not significantly different ($p > 0.50$).

> CASE 36-PERSISTENT FEVER: This patient was a ten year old white male who presented with a three week history of anorexia, a mild cough, and several days of flank pain and hematuria. Physical examination revealed palatine petechiae and splenomegaly in addition to a harsh grade IV/VI systolic ejection murmur. The hematocrit was 30%, WBC was 7800 and the ESR was elevated to 28. The urine showed ++ protein and 20-25 RBC/hpf. Reversal of the albumin:globulin ratio (3.5/3.8) was noted. Five of five initial cultures (10 bottles) grew alpha-hemolytic streptococcus equivocally sensitive to kanamycin and streptomycin and sensitive to all other antibiotics tested. Therapy was begun with Penicillin-G in a daily dose of 10 million units and this was continued for 26 days with the patient intermittently febrile during therapy. Pen-V-K (4g/d) was given for an additional 20 days but the patient continued to have fever and new petechiae were noted. Multiple blood cultures showed no growth. The

patient underwent surgery where findings included large vegetations and a small mycotic aneurysm near the aortic valve ring. AV replacement and resection of the aneurysm were carried out. Cultures of blood and operative specimens were sterile. The patient became afebrile post-operatively and has been followed for eight years in good health.

CASE 58-PERSISTENT FEVER: A 31 year old white female was admitted to the hospital because of chest pain and CHF. She was pregnant at 33 weeks gestation. There was no history of cardiac disease, although an apical systolic murmur had been noted intermittently during pregnancy and on one occasion previously. She was afebrile on admission. The hematocrit was 25, the WBC 10,250 and ESR 30. The urine showed 0-4 RBC/hpf in several specimens. The RF was negative (Titer 1:20) and there was reversal of the albumin:globulin ratio (1.9:3.1). Two of eight sets of blood cultures grew alpha hemolytic streptococcus. The MIC of penicillin for this organism was 0.045 ug/ml. The patient was treated for two weeks with penicillin (20 million units per day) and streptomycin (1.0 gram per day) and for one week more with penicillin alone. Fever persisted during treatment despite the achievement of adequate serum bactericidal levels (1:512) and sterile blood cultures. It was decided to undertake operation and a cage ball prosthesis was placed. Significant tissue destruction in the region of the AV was noted but, again, operative specimens yielded no growth on culture. The patient became afebrile and was doing well until, some four years later, she died suddenly (presumed secondary to a myocardial infarction).

CASE 50-PERSISTENT FEVER: This patient was a 20 year old white female who presented to the hospital after six weeks of illness with fever, chills, sweats, weight loss, and weakness and malaise. Her past history was remarkable for an aortic valvuloplasty with a suture remaining in the reconstructed valve. In addition to a systolic murmur, there was a question of splenomegaly on physical exam. The hematocrit was 27, the WBC 2700 and the ESR was 40 but corrected to 12. RF was present only in a titer of 1:20; the albumin:globulin ratio was reversed 3.1:3.7. Cultures grew microaerophilic alpha-hemolytic

streptococcus inhibited by 0.18 ug/ml of penicillin. Therapy was initiated with penicillin alone (12 million units/day) but after six days there was no clinical improvement and streptomycin was added (1.0 gram/day). Two weeks into therapy, still febrile, she was changed to Keflin (8.0g/d). Streptomycin was continued. Many cultures were performed and all were sterile. Serum cidal levels were consistently adequate (up to 1:1028). After a total of 34 days of therapy AV replacement was performed and the patient became afebrile. At operation large vegetations and significant tissue destruction were observed. Cultures were sterile. She has been in good health for nine years and is still followed regularly.

There were five deaths among the 68 patients in this series, four in Group I and one in Group II. This difference was not significant ($p > 0.50$). One patient in Group I died shortly after sustaining a relapse and will be discussed later. Case summaries for the other four patients who died appear below.

CASE 37-DEATH: Only a discharge summary and autopsy report is available on this 67 year old white male treated at the WHVAH. He had a history of ethanol abuse with slight hepatic impairment. The duration of illness is not known, but he was obtunded and febrile on presentation. Physical examination revealed a cachectic man with a grade II/VI systolic murmur and the stigmata of liver disease. The hematocrit was 30 and the WBC 13,050. The urine showed + protein. Blood cultures grew S. viridans which was very sensitive by tube dilutions. He was treated with 10 million units per day of IV penicillin initially and then continued on 1.2 million units of procaine penicillin every 12 hours. He improved neurologically but developed aortic insufficiency and CHF. He died suddenly just after completion of a four week course of therapy. Post mortem examination revealed vegetations about the AV with non-viable gram-positive cocci apparant on smear. There was

"acute suppurative pancarditis" in addition to a sterile coronary artery embolus, an acute splenic infarct and hepatic cirrhosis.

CASE 49-DEATH: A 76 year old white female with RHD and mitral regurgitation was admitted to the hospital because of fever, weakness and malaise, and weight loss of six weeks duration. The temperature was 102°F. Physical examination was remarkable for a grade III/VI holosystolic murmur and splenomegaly. The hematocrit was 29, WBC 4700, and ESR 58. There was ++ protein and several RBC/hpf on examination of the urine. The albumin:globulin ratio was reversed (2.9:4.0). Four of four initial blood cultures grew alpha-hemolytic streptococcus with an MIC of 0.19u/ml of penicillin. Treatment was begun with penicillin-G (24 million units/day) and streptomycin (2.0 grams/day), the latter being discontinued after three days. A rash developed and the temperature, which had normalized, rose on the sixth hospital day. Penicillin was stopped, and Keflin (6g/d) was begun. The patient defervesced and appeared to be doing well but was found comatose on the thirteenth day of hospitalization and died that same day. Autopsy demonstrated a cerebral hemorrhage although no definite mycotic aneurysm was discerned. All cultures were negative.

CASE 48-DEATH: A 67 year old white male who had undergone AV replacement seven years earlier, was admitted to the WHVAH with a two week history of fever, chills, weakness and malaise. His temperature was 101°F, a grade II/VI systolic ejection murmur was heard and a question of splenomegaly was raised. The hematocrit was 39.5, the WBC 10,900 and the ESR was 34. RF was present in a titer of 1:80 and subsequently rose to 1:160. The urine was benign and the ratio of albumin:globulin was normal. Three of three sets of blood cultures grew S. bovis. Because there was a history of penicillin allergy, the patient was treated with vancomycin (500mg IV every 6 hours) for three days and Keflin (8.0g/d) for another four days. During this week, the patient also received three days of an aminoglycoside. Tube dilution sensitivities for this organism were carried out with vancomycin revealing both MIC and MBC to be 0.39ug/ml. Serum cidal levels on Keflin were 1:8 and on vancomycin, 1:16. The patient appeared to be doing well but was found dead on the eighth hospital day.

Autopsy failed to reveal a specific cause of death but this was presumed to be CHF. Findings included large vegetations and acute fibrinous pericarditis. There was generalized atherosclerosis and four chamber cardiac enlargement. Focal myocardial fibrosis, both old and recent, was noted. All cultures, once again, were sterile.

CASE 69-DEATH: A 49 year old black male with RHD and a history of AV replacement and mitral commisurotomy, experiences spiking temperatures to 104°F and was admitted to another hospital. Six blood cultures grew S. viridans inhibited by penicillin at 0.012 u/ml. There was a loud diastolic rumble and a loud holosystolic murmur as well. Penicillin was administered beginning on the third hospital day in a dose of 20-24 million units per day achieving serum inhibitory titers of 1:64 but cidal levels of only 1:2. CHF and prerenal azotemia complicated the course. On the eleventh hospital day, penicillin dosage was increased, probenecid was added and streptomycin-1.0g/d-was begun. This therapy was maintained for the next eight days and serum cidal levels rose to 1:128. Cardiac failure worsened. Chest pain and a pleural rub required heparin administration. Hypotension developed and the patient became intermittently dependent on pressors. The patient was transferred to YNHH three weeks after his original admission. Emergency MV and TV replacement was undertaken but the patient became increasingly hypotensive and acidotic post-operatively. He died on the first post-operative day.

Post-mortem examination was remarkable for massive hypertrophy and dilatation of the heart (weight:980g), a possible recent anteroseptal myocardial infarction, a recent, large pulmonary infarction and prominent pulmonary arteriosclerosis. No growth was produced in multiple cultures of blood and tissue.

The final and most important category to consider in the evaluation of the antimicrobial treatment of IE is recurrent disease. There were two bacteriologically proven

relapses in this patient population (rate: 2/68=3%). Both patients were readmitted within one month of their original discharge. (The only other patient who received two courses of therapy in our group was judged to have had a reinfection based on the fact that a disease-free interval of more than one year had passed from the time he originally completed therapy until new symptoms were noted.) Both patients who relapsed were treated with penicillin only but the rate of relapse for Group I (2/49 or 40%) was not significantly greater than for Group II (0/19, $p > 0.50$).

CASE 38-RELAPSE LEADING TO DEATH: A 63 year old white male was admitted to another hospital because of anemia, fever, cardiomegaly and a heart murmur. He had been in excellent health until four months earlier when he developed symptoms of CAD with a question of inferior wall myocardial infarction and very mild CHF. He was treated with nitrates. For some years he had been aware of the presence of a murmur. On admission there was a low grade fever and a grade III/VI holosystolic murmur that radiated from the apex to the left axilla. Six blood cultures were positive for S. viridans. The patient was treated with 10 million units of penicillin-G daily, for 21 days. He improved and was discharged. Two weeks after discharge he re-presented to the same hospital with symptoms of CHF. He was transferred to YNHH for evaluation. On admission, a grade III/VI murmur of MR was again noted. There were scattered petechiae on the right leg. The hematocrit was 34.1, WBC 5000 and ESR 53. Three of three sets of blood cultures were positive for S. viridans. Treatment with penicillin-G (20 million units/day) was begun on the third hospital day. Streptomycin was added to the regimen on day four. Two days later the patient sustained a cardiorespiratory arrest and could not be resuscitated. Permission for autopsy was denied.

CASE 39-RELAPSE: A 63 year old white male was admitted to the hospital complaining of lethargy, fatigue and weight loss. There was no known cardiac history. Physical examination revealed a low grade fever, palatine petechiae, splinter hemorrhages and the murmurs of aortic stenosis and insufficiency. The patient was anemic with an hematocrit of 31.1; the WBC was 8100 and the ESR was 60. The titer of RF was 1:80; albumin was 2.9, globulin was 3.2. Nine blood cultures grew alpha-hemolytic streptococcus with an MIC of 0.098 ug/ml of penicillin. Penicillin was given at a dose of 12 million units daily by intermittent intravenous infusion for the first seven days and, subsequently, procaine penicillin 2.4 million units per day was given for an additional 14 days. Serum cidal levels were determined on the day that the route of administration of antibiotic was changed and showed adequate bactericidal activity (titer 1:16). The patient improved and was discharged only to be readmitted three weeks later with a recurrence of fever, weakness and anorexia. The ESR was still 60 and the RF was positive at 1:320. Again, seven of seven blood cultures grew alpha-hemolytic streptococcus with an MIC of 0.078 ug/ml of penicillin. Treatment was undertaken with intravenous penicillin. Twenty million units were administered each day for the first three days and then 6,000,000 units were given daily for an additional 38 days. The patient was discharged in good condition and did very well over the next year. He remained completely asymptomatic.

Unfortunately he suffered a third bout of streptococcal endocarditis some 13 months after completing the above therapeutic course. This third infection, alluded to earlier in this section, was judged a reinfection and was treated successfully with penicillin. He has since been followed for five years during which time he has been in good health.

In conclusion, it should be noted that these data were extensively analyzed to ascertain whether any statistically significant difference in outcome between Group I and

Group II could be demonstrated by grouping various combinations of complications together. Accordingly Groups I and II were compared with respect to the percentage of patients in each who developed:

a) CHF or emboli

b) CHF, emboli, or death

c) CHF, emboli, relapse, persistent fever or death

d) CHF, relapse, fever or death

e) Relapse, fever, or death

f) Relapse or fever

g) Relapse or death

h) Relapse, death or emboli.

No significant difference between the two groups was observed (p:0.20-0.50).

Moreover, the data was studied by anatomical site of endocarditis with separate analysis of AV patients, MV patients, patients with prostheses, patients with non-valvular congenital heart lesions, patients with either AV or MV endocarditis, and, finally, all non-prosthetic patients. In carrying out these analyses Groups I and II were compared with respect to the percentage of patients in each who developed:

a) any one of the five major complications previously defined

b) each of the five major complications, and

c) any of the combinations (a-h) listed above.

In the literally scores of comparisons thus performed, no difference was significant and all "p" values were greater than 0.20.

DISCUSSION

In the present study 68 courses of therapy were administered. It would appear that sterilization of endocardial vegetations was achieved in 66 of 68 cases, regardless of the treatment regimen employed. Operative or post-mortem specimens were cultured and were sterile in all 3 instances of persistent fever and in all patients who died without relapse. Follow up for at least six months was available for all other patients.

Two of 68 patients, however, did sustain bacteriologic relapse; both of these episodes of recurrent disease occurred in patients treated with a single drug regimen (Group I).

Comparison of Groups I and II reveals no statistical differences in site of involvement of endocardial infection, duration of therapy, underlying disorders or rates of complications. However, the prevalence of patients who were greater than 60 years of age, as well as the prevalence of patients in whom the duration of illness was greater than, or equal to, three months, were significantly greater in Group I. Both of these factors have been demonstrated here and elsewhere (32,42), to adversely affect outcome, and specifically, to predispose to recurrent endocarditis. Thus, a significantly greater proportion of patients in Group I were at "risk" for relapse than in Group II.

Indeed both patients who relapsed had both risk factors.

Moreover, relapse may have occurred in the two patients because of inadequate therapy. It should be noted that controversy exists over both dosage and duration of therapy for the treatment of this disease (45), and, therefore standards for treatment have been derived empirically. Although some investigators do not feel that the fibrin layer prevents diffusion of antibiotics into the endocardial vegetation, the central necrotic portion of the lesion is where bacteria reside and it appears that penetration into this space, at least of leukocyles is retarded until the outer fibrin layer has been vascularized (29). Clearly, duration of therapy must be critical under these conditions.

In addition, it would appear that plasma peak levels of penicillin are the major factor in determining the degree of antibiotic penetration and activity (12,43). Therefore, intravenous therapy, with a larger instantaneous pulse of antibiotic, would offer significant advantage over intramuscular procaine penicillin in this disease.

In the present series both patients who relapsed were treated for only three weeks and while one of these patients received high doses of intravenous penicillin (10 MU/d), the other received relatively low doses by intramuscular injection (2-4 MU procaine penicillin). It may be argued therefore that in one patient therapy was

inadequate because of duration and in the other because of both dose and duration.

In light of the evidence that combination of an aminoglycoside with penicillin results in more efficient eradication of streptococci, in vitro and in vivo (as discussed above), it is possible that the addition of streptomycin to the treatment regimen of the two patients who relapsed after three weeks of therapy, may have prevented these treatment failures. The findings of Phair and Tan (32) however, cited above would indicate that combination therapy surely does not guarantee bacteriologic cure, especially with longstanding endocarditis, even when the total duration of such therapy is four week or more.

It would appear, from the data presented here, and the findings of Phair and Tan, that when patients with penicillin-sensitive streptococcal IE who do not have longstanding illness receive appropriate dosage and duration of penicillin therapy, they fare as well as cohorts receiving combination therapy.

The importance of this last observation is obvious. Protracted aminoglycoside therapy is not without hazard, especially in the presence of pre-existent renal compromise. The opportunity to spare patients exposure to aminoglycoside toxicity is thus suggested by the results of the present study.

It should be noted, however, that the issue is

less clear for patients at high risk for recurrent disease, especially those in whom the duration of illness is greater than three months. In the present study, two of eleven patients (18%) with a three month history relapsed after single agent therapy as compared with zero of two patients treated with combination therapy. Phair and Tan observed that one of three single agent recipients (33%) relapsed as compared with two of seven patients (29%) treated with two drugs. Pooling these results yields relapse rates of 21% and 22% for single and combination therapy, respectively. This difference is obviously insignificant and would suggest that, in fact, the addition of an aminoglycoside makes little difference in treating these patients, provided that total duration of therapy is sufficient. It should be kept in mind, however, that these comparisons are based on very small samples and thus need to be interpreted with caution.

In dealing with a treatment failure rate of less than 5% regardless of therapy, an extremely large number of patients would be required to definitively settle this question. Although a prospective, multi-center trial would be appropriate, a careful analysis of retrospective data from this study and a review of the literature, strongly suggest that the treatment of choice for patients with non-enterococcal penicillin-sensitive streptococcal IE, who do not have longstanding illness (i.e., $\geq$3 months), is

intravenous penicillin in a dosage that is at least 6 million units per day and that is sufficient to ensure serum bactericidal levels of at least 1:8 (36), for a duration of not less than four weeks. Although there is good evidence that this same regimen may be comparable to combined penicillin-streptomycin regimens of equal duration in the treatment of longstanding illness, more careful judgment of the relative risks of aminoglycoside toxicity and relapse from IE is warranted in these patients.

Finally, it should be noted that patients with prosthetic valves may have a different clinical course with a much shorter symptomatic period prior to diagnosis. Their prognosis, despite a short duration of illness, is extremely poor and this factor (i.e., duration of illness) may not be relevant in this subgroup of IE patients. Therefore, all patients with prostheses should be regarded as high risk patients and the addition of an aminoglycoside to their treatment regimen considered.

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