Therapy of Gram Positive Bacteremias With Presentation of Four Cases


Improvement of therapeutic results in bacteremias due to the "resistant" organisms, staphylococci and enterococci, can best be achieved by a critical analysis of current concepts and adherence to certain fundamental principals. Experience with four successfully treated cases of this group of gram positive bacteremias is presented and specific therapeutic recommendations are set forth.

The BACTEREMIAS, despite more than a decade of experience with active therapeutic agents, remain a complicated and difficult problem. The results obtained during the sulfonamide era, with only 5 to 10 per cent cures, were disappointing. With the advent of penicillin the average cure rate of bacteremia rose to 70 per cent, where it has remained despite an increasing number of available antibiotics.2 During recent years a significant, and probably growing proportion of penicillin-resistant cases has been encountered. This aspect of the problem is largely attributable to the increased incidence of cases infected with enterococci and penicillin-resistant staphylococci. Dowling and co-workers3 have recently estimated that 300 new cases of staphylococcal endocarditis develop in the United States each year. Concurrently the ratio of Streptococcus viridans to staphylococcus endocarditis has been reported as 2.6 to 1,4 compared with the ratio of 7.4 to 1 reported by Thayer in 1926.4 In addition to this increasing incidence, both enterococcc and staphylococcal organisms have been shown to be more resistant to therapy than Streptococcus viridans. Widespread use of the newer antibiotics, such as chlortetracycline, oxytetracycline and chloramphenicol has not only failed to improve the situation, but has resulted in a high percentage of relapses and therapeutic failures.5 This failure of the broad spectrum antibiotics is primarily due to the fact that these agents, like the sulfonamides, are mainly bacteriostatic rather than bactericidal. Evolving from these considerations it might be postulated that an arbitrary line is being drawn between the bacteremias which can be cured with relative ease and those where treatment failures are common. Those due to Streptococcus viridans belong to the first group, while infections due to the staphylococci and enterococci constitute the most important members of the second group.

Case Reports

The following case reports constitute all cases of gram positive bacteremias treated on the Medical Service of this hospital over a two year period from August 1951 to August 1953.

Case 1. The patient, a 28 year old, white, male Sergeant, was initially hospitalized on Aug. 11, 1951, with a chief complaint of right lower quadrant pain. The significant findings on physical examination were an apical systolic murmur transmitted into the aortic area, moderate hepatomegaly, and clubbing of the fingers. Because of temperature elevation of 101 to 102 F., blood cultures were obtained. These cultures were positive for nonhemolytic streptococcus, subsequently identified as Streptococcus liquefaciens. By August 1951, the patient was noted to have splenomegaly and was manifesting embolic phenomena. Therapy was initiated on Aug. 25, 1951, consisting of streptomycin, 3 Gm. intramuscularly, daily, penicillin, 10,000,000 units daily by continuous intravenous drip, and sulfadiazine, 1 Gm. orally every four hours. This form of therapy was terminated on Aug. 31, 1951, in favor of chlortetracycline, 2 Gm. daily by the oral route, as the result of sensitivity studies by the disc method which revealed the organism to be sensitive to chlortetracycline, chloramphenicol, oxytetracycline, moderately sensitive to streptomycin, and resistant to penicillin. After two weeks of chlortetracycline therapy the patient had become afebrile and no longer manifested embolic

From the Medical and Pathology Services, Fitzsimons Army Hospital, Denver, Colo.
phenomena. The drug was continued for an additional two weeks, following which daily blood cultures were obtained. The patient was well until Oct. 15, 1951, when fever and embolic phenomena recurred. Blood cultures were again positive for Streptococcus liquefaciens, and antibiotic therapy was resumed, consisting of 25,000,000 units of penicillin and 2 Gm. of streptomycin daily. Sensitivity studies were again carried out, utilizing the disc method, and the organism reported as sensitive to 10 units per cubic centimeter of penicillin, and moderately sensitive to streptomycin. By Nov. 1, 1951, the patient's disease again manifested itself by fever and embolic phenomena, and the patient was transferred to Fitzsimons Army Hospital. On admission the positive physical findings included a systolic murmur over the entire precordium, splenomegaly, and generalized lymphadenopathy. The patient was placed on an antibiotic regimen consisting of chlor-tetracycline, 2 Gm. daily, and oxytetracycline, 4 Gm. daily, orally. This was continued until Dec. 23, 1951, during which time the patient's temperature became normal. He remained afebrile until Jan. 8, 1952, when the fever recurred and blood cultures were again positive for Streptococcus liquefaciens. On this occasion the freshly isolated organism was reported as sensitive to 8 units of penicillin per cubic centimeter and resistant to all other antibiotics by the disc method. Therapy was resumed on Jan. 12, 1952, consisting of 25,000,000 units of penicillin by continuous intravenous drip, 2 Gm. of streptomycin, intramuscularly, and 2 Gm. of probenecid, daily. On Jan. 22, 1952, penicillin dosage was increased to 40,000,000 units daily, and this combination was continued until March 9, 1952, when it was terminated. Bioassays revealed serum penicillin levels ranging from 50 to 75 units per cubic centimeter. The patient remained completely afebrile after Jan. 28, 1952, the last positive blood culture having been obtained on Jan. 11, 1952. He was followed for a period of two months after termination of antibiotic therapy and remained completely asymptomatic and afebrile during this period.

Comment. Two of the three relapses in this case demonstrate the fallacy inherent in the administration of bacteriostatic rather than bactericidal agents. The third relapse may be attributed to inadequate dosage of bactericidal agents resulting in failure to obtain bactericidal effect. Two highly significant defects thus become apparent in the disc method of estimating antibiotic sensitivity: (1) Only inhibition of organism growth is revealed. (2) It is impossible to relate zones of inhibition to the milliliter concentration of drug required. Although it is possible to subculture from the inhibition zone to determine whether viable organisms are present, this is an unreliable and impractical method for which the tube dilution-plate method is to be preferred. This method is performed in the following manner: a drop of 18 hour broth culture inoculum with a density equivalent to a number 3 nephelometer tube (900,000,000 organisms per milliliter) is added to appropriate concentrations of the antibiotic diluted in tryptose phosphate broth. This may be set up as a series of two-fold dilutions of the antibiotic through the desired range of concentrations to be evaluated. Tubes are incubated at 37 C. overnight and all turbid tubes are read as manifesting resistance to the respective concentration of the drug. Non-turbid tubes are re-incubated for an additional period to permit revitalizing the antibiotic sensitized organism. At the 24-hour level readings are made to determine if complete resistance was evidenced as previously manifested by turbidity. Lack of turbidity is not accepted as anything more than inhibition. At 48 hours all clear translucent tubes are plated to blood agar and any growth is considered as evidence of bacteriostasis, while the absence of growth is considered as evidence of complete inhibition, or, for practical purposes, bactericidal effect. The testing of a combination of antibiotics is performed in essentially the same manner.

Case 2. The patient, a 28 year old white woman, entered Fitzsimons Army Hospital for the second time on Nov. 20, 1952, for re-evaluation of a patent ductus arteriosus complicated by staphylococcus bacteremia. She was initially admitted to Fitzsimons Army Hospital in August 1952, for surgical treatment of a patent ductus arteriosus, which was ligated. The immediate postoperative course was uneventful. However, on the sixth postoperative day the patient was found to have a loud pulmonary systolic murmur, grade III–IV in intensity, accompanied by a systolic thrill. At that time it was considered that the ductus had been incompletely obliterated at surgery. The patient was subsequently discharged to return in two months for re-examination and re-evaluation. Three weeks following discharge the patient developed sudden onset of chills and fever and was hospitalized elsewhere. Blood cultures were found to be positive for Micrococcus pyogenes var aureus. In vitro bacterial antibiotic sensitivity studies revealed the organism to be resistant to penicillin, bacitracin, streptomycin, chlor-
amphenicil and moderately sensitive to chlortetracycline and oxytetracycline. The patient was therefore treated with three courses of oxytetracycline, given orally in the amount of 4 to 6 Gm. daily. She initially appeared to respond to the oxytetracycline, but symptoms recurred when the drug was discontinued. On Nov. 20, 1952, the patient was readmitted to Fitzsimons Army Hospital. On this admission she was feeling well and was afibrile, but had the classic findings of a patent ductus arteriosus and a palpably enlarged spleen. No therapy was initiated on this admission. By Nov. 23, 1952, the patient was acutely ill with chills and fever, and blood cultures were positive for *Micrococcus pyogenes var aureus*, which was found to be resistant to all concentrations of penicillin ranging from 1.5 units per cubic centimeter to 100 units per cubic centimeter by the tube dilution-plate method. On Nov. 25, 1952, prior to the reporting of the above sensitivity studies, the patient was started on penicillin, 25,000,000 units daily by continuous intravenous drip, combined with streptomycin, 2 Gm. intramuscularly daily, and probenecid, 2 Gm. orally in divided doses daily. By Nov. 25, 1952, the patient had shown no improvement so the daily dosage of penicillin was increased to 50,000,000 units. On the following day the patient's condition appeared even worse and the penicillin dosage was increased to 100,000,000 units daily by continuous intravenous drip. By the afternoon of Nov. 28, 1952, it was apparent that this antibiotic therapy was ineffective and the patient would have to be operated upon in spite of her critical condition in the hope of obtaining a surgical cure. Penicillin and streptomycin were discontinued and the patient was placed on oxytetracycline, 2 Gm. daily, in the hope that this would lower her temperature and improve her general condition.

She was re-operated on Dec. 1, 1952, at which time an abscess was found in the upper mediastinum, which was incised and drained of pus positive for *Micrococcus pyogenes var aureus*. The mediastinal abscess connected directly with the patent ductus. No attempt was made to divide the ductus in view of the septic field, but it was ligated with several chronic sutures. The patient tolerated the surgical procedure fairly well, but continued to be acutely ill. Further bacterial sensitivity studies revealed that a combination of oxytetracycline, erythromycin, and bacitracin were bactericidal in the amount of 8 micrograms of oxytetracycline, 1.6 micrograms of erythromycin and 8 micrograms of bacitracin combined. On Dec. 4, 1952, the patient was placed on erythromycin, 0.5 Gm. every six hours and bacitracin, 10,000 units every four hours intramuscularly, in addition to the oxytetracycline, 2 Gm. intravenously daily. On December 5, the patient showed evidence of congestive heart failure and was therefore digitalized. After one week of the above antibiotic therapy the oxytetracycline was reduced to 1 Gm. intravenously daily. By December 18 the patient refused more intravenous therapy. At that time her temperature was falling but had not returned to normal. Consequently oxytetracycline was changed to the oral route, the patient receiving 1 Gm. every four hours. A few days later her temperature returned to normal. By December 27 the urinary sediment revealed abnormal findings so the bacitracin was discontinued, the oxytetracycline and erythromycin being maintained. On Jan. 1, 1953, the patient relapsed with chills and fever. Blood cultures were again positive. On that date oxytetracycline and erythromycin were discontinued and she was placed on neomycin, 0.5 Gm. intramuscularly every 12 hours, which had been shown to be bactericidal at a level of 0.5 micrograms per cubic centimeter in vitro by the tube dilution-plate method. This therapy was continued until January 21 when it was terminated because of nephrotoxicity manifested by abnormal urinary sediment.

No therapy was administered after January 21 and the patient remained afibrile; she felt well, and blood cultures were negative. She manifested gradual clearing of the moderately abnormal urinary sediment. However, urinary function studies continued to show inability to concentrate the urine above 1.010 after 24 hours of dehydration. On March 12, 1953, a follow-up evaluation was performed, at which time blood cultures were found to be negative and the blood urea nitrogen normal. However, she was still unable to concentrate urine above a specific gravity of 1.010. On August 29, 1953, the patient returned for further follow-up evaluation, at which time she complained of loss of hearing, which had been progressive since first noted one month following the termination of neomycin. Otologic evaluation revealed a primary acoustic neuritis with inner ear deafness, bilateral and severe, which the consultant considered to be permanent but not progressive. The remainder of the examination revealed the patient to be in excellent general condition, tolerating full activity without restriction. The previous impairment of renal function had returned to normal.

Comment. This case presented the problem of a subacute bacterial endarteritis due to *Micrococcus pyogenes var aureus*, which manifested resistance to the common forms of therapy. Therapy was delayed until after positive blood cultures had been obtained and the organism identified. Because of her precarious condition it was necessary to begin the most logical form of treatment before the in vitro sensitivity studies were completed. As it became apparent that the bacteremia was not controlled, the penicillin dosage was elevated rapidly to 100,000,000 units daily.
along with 2 Gm. of streptomycin and 2 Gm. probenecid. As a result of continued deterioration in the patient’s condition, it soon became evident that this antibiotic regimen would not suffice. Completion of the antibiotic sensitivity studies revealed that the organism was resistant to penicillin in concentrations ranging from 1.5 Oxford units per cubic centimeter to 100 Oxford units per cubic centimeter, but sensitive to 100 micrograms of dihydrostreptomycin. Several in vitro combinations were tried with the following results:

Bactericidal effect with combination of... 10 mcg. oxytetracycline 2 mcg. erythromycin

Bactericidal effect with combination of... 16 Oxford units penicillin 8 mcg. oxytetracycline 8 mcg. bacitracin

Bactericidal effect with combination of... 8 mcg. oxytetracycline 8 mcg. bacitracin 1.6 mcg. erythromycin

It was hoped that surgical intervention might result in a cure, and immediately following surgery the oxytetracycline, erythromycin, bacitracin combination, which appeared to be most efficacious in vitro, was instituted. Subsequently the bacitracin was stopped because of the signs of nephrotoxicity. After the patient refused further intravenous therapy it became impossible to maintain an adequate blood level of oxytetracycline because the oral preparation caused nausea and vomiting to the point of inanition. At this point in vitro sensitivity studies were carried out with neomycin revealing the organism to be sensitive to a concentration of 0.5 micrograms per cubic centimeter. Since the patient had recovered from the previous nephrotoxic effect of bacitracin, and with close check for signs of toxicity, Neomycin was instituted and continued for a period of 21 days, at which time evidence of nephrotoxicity was again manifest and all drug therapy was discontinued, with the hope that an adequate period of clinical and laboratory “cure” had been effected. It seemed justifiable to state that without (1) adequate bacteriologic studies, (2) surgical drainage of the mediastinal abscess, and (3) the discovery of the efficacy of newer antibi­otics, both singularly and in combination, this case would have terminated fatally. Neomycin contains both nephrotoxic and ototoxic factors which appear to be due partly to impurities and partly to the active drug itself. Although the drug was discontinued in this case because of the appearance of nephrotoxicity, the most prominent toxic effect subsequently proved to be the ototoxicity. This patient received 20 mg. per kilogram of neomycin daily for a period of 21 days, thus confirming the experience of others that doses in the range of 15 to 20 mg. per kilogram cannot be administered for relatively long periods of time without adverse effects.

Case 3. The patient, a 36 year old woman, was admitted to Fitzsimons Army Hospital on Dec. 19, 1952, with chief complaint of fatigue, fever, and painful nodules in the skin of the right foot and left chest, of six weeks duration. There was no past history of acute rheumatic fever, although she had scarlet fever at the age of 8 years, and was known to have had a heart murmur since the age of 12 years. In August 1952, the patient experienced an episode of right costovertebral angle pain attended by fever and genito-urinary symptoms. She was treated with chlortetracycline by a local physician and had a complete genitourinary workup, including cystoscopy. Two weeks later the patient noted the onset of what she described as “flu,” characterized by low-grade fever, generalized muscular aches, headaches, lethargy and weakness. From the time of onset of this illness until Dec. 9, 1952, the patient was treated intermittently with chlortetracycline by her local physician. She had at least five exacerbations of her symptoms, all of which responded to chlortetracycline, but with recurrence of symptoms following termination of this form of therapy. Physical examination at the time of admission revealed the presence of embolic nodules in the skin of the left chest and the lateral aspect of the right foot. There were no other skin lesions or further evidence of petechiae. Examination of the heart revealed a rough systolic murmur heard in the mitral area, grade III in intensity, radiating toward the axilla and left sternal border. A palpable spleen was present.

Blood cultures were obtained and were positive for Streptococcus faecalis, subsequently shown on the basis of gelatin liquefaction to be Streptococcus liquefaciens. This same organism was likewise cultured from the urine on several occasions during the first week of hospitalization. Sensitivity studies were performed and a bactericidal effect was found in vitro with 25 micrograms of streptomycin, and 100 units of penicillin per cubic centimeter in com-
THERAPY OF GRAM POSITIVE BACTEREMIAS

The organism was also demonstrated to be sensitive to 15 units of bacitracin, but resistant to all other antibiotics, both alone and in combination. On Dec. 27, 1952, she was started on crystalline penicillin, 50,000,000 units daily by continuous intravenous drip, streptomycin, 2 Gm. intramuscularly daily, and oral probenecid, 2 Gm. daily. Weekly blood cultures were obtained throughout the hospital course but remained negative subsequent to the fifth day following admission. Serum antibiotic assays were performed periodically revealing a combined antibiotic activity equal to 150 Oxford units of penicillin and streptomycin, with penicillin activity equalling 125 units per cubic centimeter and streptomycin activity equaling 25 micrograms per cubic centimeter. The patient did well on therapy and remained afebrile throughout the remainder of her hospitalization. By Feb. 6, 1953, the patient had completed six weeks of antibiotic therapy and she complained considerably of dizziness, which was attributed to the streptomycin therapy. Prior to discharge on Feb. 18, 1953, weekly blood cultures remained negative and the patient remained afebrile. Four month follow-up revealed that the patient had resumed normal activity without restriction and had had gradual but complete regression of the vertigo. Blood cultures obtained at bimonthly intervals following discharge for a period of two months remained negative.

Comment. This case presents the problem of an enterococci subacute bacterial endocarditis developing subsequent to urologic instrumentation in a patient with mitral insufficiency. Unfortunately the patient was subjected to repeated courses of a bacteriostatic agent in the treatment of a "urinary tract infection" without attempt to recover the causative organism and without consideration of the possibility of a blood stream infection. Fortunately she was spared the development of major complications frequently resulting from delay in adequate therapy. Serum bioassay performed following the initiation of the combined therapy revealed that we were able to obtain in vivo blood levels in excess of those shown to be bactericidal in vitro. The method for determining levels for the combined drugs was performed as follows: a specimen of the patient's serum was divided into two parts; to one aliquot enough penicillinase was added to inactivate the serum penicillin and several paper discs were impregnated with this material. The discs were then placed on a culture of Bacillus subtilis spores and the resultant zones of inhibition compared with zones of known strength on the same plate. In this manner it was possible to deduce streptomycin activity only. The untreated portion of serum was similarly titrated against the subtilis spores and by comparison with zones of known strength it was possible to infer the summative action of the two drugs. Subtraction of the streptomycin level from the combined serum activity level resulted in the approximate penicillin content of the serum.

Case 4. The patient, a 22 year old white female, was initially admitted on Dec. 19, 1952, to the Gynecology Service, Fitzsimons Army Hospital, in a state of shock, delirium tremens with temperature of 103 F. Onset of the illness was Dec. 15, 1952, with severe cramping abdominal pain and profuse vaginal bleeding, which terminated on Dec. 16, 1952, with passage of an 8 to 10 week fetus. On December 18, the patient had a temperature elevation and by December 19 had become delirious so she was hospitalized. Past history revealed some question of rheumatic fever at age 6 years, but she had never known of the presence of a heart murmur. Physical examination at the time of admission revealed the patient to be in a state of shock, irrational, and in a semicomatose condition. Blood pressure was 90/30, pulse 120, respirations 22. The significant physical findings included a tense abdomen, minimal vaginal bleeding and a systolic murmur along the left sternal border. Neurologic examination revealed the presence of aphasia, slight nuchal rigidity, sluggish reaction to light of the right pupil. She had some difficulty in turning her eyes conjugately to the right. There was weakness of the right facial muscles and hypalgesia over the entire right side of the body with the tongue protruding to the right. The deep tendon reflexes were hypoactive on the right. Pelvic examination revealed the uterus to be three times normal in size, moveable and tender, with purulent discharge exuding from the external os, which appeared to be widely patent. Laboratory studies revealed a red blood cell count of 1,460,000 and hemoglobin of 4 Gm. per 100 cc.; hematocrit of 20.

Initial therapy consisted of whole blood replacement transfusions with antibiotic therapy consisting of penicillin 200,000 units every two hours and streptomycin 0.5 Gm. twice daily. The patient responded clinically to the whole blood replacement; however, the motor aphasia and meningismus persisted. A spinal tap was performed which was normal except for the presence of 18 lymphocytes and subsequent growth on culture of Micrococcus pyogenes var aureus. Culture of the purulent discharge from the external os of the cervix was also positive for Micrococcus pyogenes var aureus. The neurologic consultant's impression was thrombosis, probably
venous, of the cortical vein in the left cerebral region, secondary to infection with *Micrococcus pyogenes var aureus*. On December 22, the patient had a temperature elevation to 104.8 F. Streptomycin and penicillin were discontinued and blood cultures were obtained. The patient was started on intravenous oxytetracycline, 500 mg. in 1000 cc. of 5 per cent glucose and distilled water, every 12 hours. On Dec. 25, 1952, the original cultures were reported as positive for *Micrococcus pyogenes var aureus* with sensitivity studies reflecting bacteriostatic effect with chlorotetracycline, oxytetracycline and chloramphenicol. The organism was reported as resistant to penicillin and streptomycin. On Dec. 27, 1952, the intravenous oxytetracycline was discontinued, and on December 31 the patient again had a temperature elevation to 104 F. Blood cultures were again obtained and intravenous oxytetracycline was resumed. Five days later the oxytetracycline was again discontinued and the patient started on 20,000,000 units of penicillin daily by continuous intravenous drip, streptomycin, 2 Gm., intramuscularly daily, and probenecid, 2 Gm. daily by the oral route in divided doses. This antibiotic regimen was initiated following report of sensitivity studies which revealed a bactericidal effect at a level of 200 Oxford units of penicillin and 25 micrograms streptomycin per cubic centimeter combined. Other antibiotics tested included neomycin and oxytetracycline singly and in combination with bacitracin, penicillin and streptomycin. These sensitivity studies revealed the organism to be most sensitive to bacitracin, with no growth in a concentration of 1 microgram per cubic centimeter by the tube dilution-plate method. However, in view of the tendency toward nephrotoxicity associated with the use of bacitracin, and the apparent need for rather protracted therapy, the decision was made to treat the patient with the regimen of combined penicillin and streptomycin. On Dec. 28, 1952, the dosage of penicillin was increased to 50,000,000 units daily with dosage of streptomycin and probenecid remaining the same. On Jan. 4, 1953, serum assays were performed revealing 35 micrograms per cubic centimeter of streptomycin and 165 Oxford units of penicillin per cubic centimeter. Subsequent serum assays performed on Feb. 16, 1953, revealed a penicillin level between 150 and 200 units per cubic centimeter and streptomycin level between 10 and 25 micrograms per cubic centimeter. Levels obtained using 50,000,000 units of penicillin, 2 Gm. of streptomycin, and 2 Gm. of probenecid daily did not significantly exceed the concentration in which the organism had been revealed to be sensitive in vitro. However, the effectiveness in vivo was apparently adequate insomuch as the patient's clinical course continued to improve and the blood cultures subsequent to January 12 remained consistently negative. By March 1 the patient had completed six weeks of antibiotic therapy subsequent to her last positive blood culture and all therapy was discontinued. By March 6 there was no residual neuromuscular involvement. She was discharged from the hospital on March 10, 1953, and was subsequently followed at bimonthly intervals for a period of four months, during which time she remained completely asymptomatic, progressively resuming full activity. Blood cultures obtained during this period were consistently negative.

Comment. In this case of bacteremia due to *Micrococcus pyogenes var aureus*, the antibiotic sensitivity studies revealed that bactericidal levels could be obtained only with massive doses of penicillin combined with streptomycin and with bacitracin. Previous experience (case II) with bacitracin indicated that we could probably not prolong bacitracin therapy beyond three weeks without obtaining nephrotoxicity. Because of the clinical severity of the infectious process it was thought that this would not be an adequate period of treatment. For this reason it was believed that by elevating the penicillin dosage it would be possible to achieve the blood level which had been shown to be bactericidal in vitro. It was further believed that massive dosage of penicillin combined with streptomycin could be continued for an adequate period of time without any danger of toxicity. Moreover, the drug bacitracin constituted a strong weapon to be held in reserve. Unfortunately the in vitro sensitivity levels were not sharply enough delineated between the penicillin level of 125 and 200 units to verify that the in vivo level of 165 units was bactericidal. However, the patient's clinical course demonstrated that this must have been the case. The clinical cure achieved in this case may be attributed to an adequate correlation of in vitro and in vivo data leading to the use of a combination of bactericidal agents in amounts, which in the past would have been considered heroic doses.

Discussion

It would seem appropriate to reiterate for the sake of emphasis certain fundamental concepts and principals which must be considered prerequisite to the improvement of therapeutic results in bacteremias.

In contrast to the existing 70 per cent cure rate in bacteremias, Friedberg has proposed a
90 to 95 per cent cure rate as theoretically possible with the available antibiotics. The discrepancy may be largely attributed to the development of complications, such as heart failure and major embolic accidents resulting from delayed diagnosis, inadequate treatment, or both. Full cognizance must be taken of the fact that a successful outcome depends upon early diagnosis, followed by prompt identification of the infecting agent and administration of appropriate and adequate therapy. It must be emphasized that a complete diagnosis requires accurate identification of the organism and determination of its sensitivity to antibiotics. Hunter4 has stated, "The central principal of antibiotic therapy of bacterial endocarditis should be the administration of a drug, or combination of drugs, which is the most rapidly and completely bactericidal." Jawetz5 has likewise stressed that only the in vitro bactericidal action of the antibiotics should be considered, not its bacteriostatic effect. A laboratory method permitting completely accurate and reliable determinations of this in vitro bactericidal action has not as yet been devised. Moreover, it must be recognized that there is not an infrequent lack of correlation between the results of a test for sensitivity to an antibiotic and the effect in vivo. The paper disc method of estimating bacterial susceptibility is satisfactory for most routine screening purposes but it fails to distinguish bactericidal and bacteriostatic effect and moreover is valueless for testing combinations of antibiotics.6 Foremost emphasis must be placed on one fact: when determination of bactericidal effect is an important factor, as is true in bacteremia, the tube dilution-plate method is indispensable. In spite of its limitations8 no other method presently available provides the clinician with a more accurate guide to adequate therapy. This is particularly true when dealing with organisms such as the enterococci and staphylococci, different strains of which tend to show considerable variation in their susceptibility to antibiotics.9 With the assistance of an adequate bacteriologic laboratory, the appropriate antibiotic or combination of antibiotics can be chosen and administered, with due regard to toxic potentialities, in quantities sufficient to attain in vivo the bactericidal effect as delineated in vitro. A valuable corollary guide to the attainment of these in vivo bactericidal levels is also provided by the bacteriological laboratory in the form of serum antibiotic assays, which should be carried out at intervals during the patient's therapeutic course.

In selecting the appropriate antibiotic agent or agents, sensitivity tests may be first carried out on penicillin, streptomycin, chlorotetracycline, chloramphenicol and oxytetracycline. The first two drugs belong to Jawetz10 group I bactericidal category, the last three drugs belong to the group II bacteriostatic category and are to be avoided as the sole agents of therapy because of the high relapse rate which follows their use.11 The remaining group I bactericidal drugs, neomycin, bacitracin, and polymyxin may be tested alone or in combination if the organisms prove resistant. Sweet11 recommends holding these drugs in reserve because of their tendency toward nephro- and neurotoxicity. In general penicillin remains as the most effective and innocuous of the available antibiotic agents. Recent years have witnessed a gradual increase in the empirical criteria for penicillin resistance. The current concept appears to be on the order of a concentration of 10 units per cubic centimeter above which organisms are considered resistant to penicillin. Our experience, and that of others,12, 13 indicate that massive doses of penicillin combined with an agent such as probenecid permit the attainment of extremely high blood levels of penicillin with relative safety.14 It is, therefore, recommended that sensitivity studies be carried to high levels, at least 200 units per cubic centimeter, before penicillin is rejected as an effective therapeutic agent in any specific bacteremia, particularly since it is possible to obtain serum levels of at least 2000 units per cubic centimeter. Moreover it is important to bear in mind that sterilization of the blood stream constitutes the ultimate test and should constantly serve as the guide to adjustment in the therapeutic regimen.

In the treatment of staphylococccie bacteremia penicillin is the antibiotic of choice provided an in vivo bactericidal level can be readily attained. Minimum initial dosage should be 20,000,000 units of penicillin daily.
for penicillin-resistant staphylococci. Increased serum penicillin levels may be readily attained by giving probenecid 2 to 4 Gm. daily in divided doses. The addition of streptomycin, 2 to 3 Gm. daily, may frequently produce a valuable synergistic effect. In our opinion therapy should be continued for a period of four to six weeks following the last positive blood culture and the patient observed for an additional two months. Weekly blood cultures should be obtained throughout the patient’s hospitalization. Reed and Wellman have recently reported a case of staphylococcic endocarditis successfully treated with neomycin. The tendency of this drug to produce nephro- and neurotoxicity was manifest in case II, the latter particularly in the form of ototoxicity. The suggested dosage for neomycin is 10 to 14 mg. per kilogram of body weight for chronic administration, but doses of 15 to 20 mg. per kilogram of body weight may be used for only a few days without risk of toxic effect. Bacitracin should also be considered in staphylococcic endocarditis since it is also effective on gram positive cocci. The usual dosage is 50,000 units intramuscularly every 24 hours in divided doses. This drug may be nephrotoxic and the patient should be observed for impairment of renal function or abnormal urinary sediment. With regard to erythromycin, Herrell and associates caution against its routine use in staphylococcic bacteremia because of a tendency toward the development of resistance and the difficulty in obtaining bactericidal levels.

Enterococcal endocarditis constitutes 4 to 10 per cent of cases of bacterial endocarditis in hospital practice. The enterococcus organism is known to be moderately to highly resistant to penicillin. The in vitro effect of penicillin on the enterococcus is primarily one of inhibition. This is paralleled clinically by the fact that enterococccic bacteremia is not cured by penicillin alone. Streptomycin alone is likewise ineffective. However, it has been shown repeatedly, both in vivo and in vitro, that there is an effective synergistic action produced by these agents in combination. The enhanced bactericidal effect has been attributed to the elimination by streptomycin of bacteria partially inhibited but not killed by penicillin.

Clinical results have clearly indicated that enterococcic bacteremia can usually be cured by high doses of penicillin plus streptomycin. We would recommend an initial minimum dose of 20,000,000 units of penicillin daily by continuous intravenous drip, 2 Gm. of streptomycin intramuscularly, and 2 Gm. of probenecid daily in divided doses by the oral route. Dosage should be varied as indicated by sensitivity tests, serum levels and clinical response. Therapy should be continued for a period of at least four weeks following the last positive blood culture. Use of the broad spectrum antibiotics, chlorotetracycline, oxytetracycline and chloramphenicol has been disappointing with clinical results far inferior to those obtained with penicillin plus streptomycin.

**Summary**

1. The cure rate of bacteremias has failed to show significant improvement despite an increasing number of available antibiotics. This may be largely attributed to the so-called “resistant” organisms of which staphylococci and enterococci constitute the majority.

2. Experience with four successfully treated cases of this group of gram positive bacteremias is presented and briefly analyzed. Two cases of enterococcic and one of staphylococcic bacteremia responded satisfactorily to massive doses of penicillin combined with streptomycin and probenecid. A case of staphylococcic endocarditis is of particular interest in that the patient was cured with neomycin after all other antibiotics had failed.

3. Certain fundamental principles considered essential to the improvement of therapeutic results are emphasized. The primary aim of therapy should be the administration of a bactericidal agent or agents in sufficient quantity to attain a bactericidal level in vivo and to maintain that level for an adequate period. Thus, the importance of adequate bacteriological control of therapy is evident. Although no completely reliable method of testing antibiotic sensitivity is presently available, the tube dilution-plate method provides the clinician with the most accurate guide to adequate therapy.

4. Specific recommendations regarding the
treatment of both enterococcal and staphylococcal bacteremia are set forth.

**SUMARIO ESPAÑOL**

1. El promedio de bacteremias curadas ha dejado de mostrar un aumento significativo no obstante el número aumentado de antibióticos disponibles. Esto se puede atribuir grandemente a los llamados organismos "resistentes", de los cuales estafilococos y enterococos constituyen la mayoría.

2. La experiencia en cuatro casos tratados con éxito con bacteremias Gram positivas de este grupo se presenta y brevemente se analiza. Dos casos de bacteremia estafilocónica y uno de estafilococcal respondieron satisfactoriamente a dosis masiva de penicilina combinada con estreptomicina y probenecid. Un caso de endocarditis estafilococca es de particular interés en que el paciente fue curado con neomicina luego que todos los demás antibióticos fallaron.

3. Algunos de los principios fundamentales considerados esenciales en mejorar los resultados terapéuticos se enfatizan. El objetivo principal en la terapia debe de ser la administración de un agente o agentes bactericidas en cantidades suficientes para obtener un nivel bactericida en vivo y mantener ese nivel por un período adecuado. La importancia de control adecuado bacteriológico en la terapia es evidente. Aunque en el presente no hay ningún método completamente seguro de probar la sensibilidad del antibiótico, el método de tubo y dilución de platicultivo provee al clínico con una guía bastante exacta para la terapia adecuada.

4. Recomendaciones específicas sobre el tratamiento de las bacteremias entéricas y estafilocócicas se exponen.

**REFERENCES**


15. LOGUE, R. B.: Personal communication.


Therapy of Gram Positive Bacteremias With Presentation of Four Cases
RICHARD R. BECKWITH, CAPT., EDWIN M. GOYETTE, COL., WM. S. SPICER, CAPT. and CHAS. D. GRABER, MAJ.

_Circulation_. 1954;10:56-64
doi: 10.1161/01.CIR.10.1.56
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1954 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/10/1/56

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/