rate than did a similar group treated with penicillin alone. These observations were not immediately confirmed, and the lack of demonstration of antibiotic interference in other infections of humans suggested to some that the study of Lepper and Dowling (11) represented an exception and that combination therapy was not detrimental (2).

Multiple-drug therapy is often recommended in bacterial meningitis, even when the etiology is known, despite the repeated demonstration that this entity can be treated satisfactorily with a single drug. The demonstration that ampicillin alone is effective against the three major etiological agents of bacterial meningitis allowed a comparison of a single drug with a combination of drugs in the treatment of bacterial meningitis (3, 8, 15, 20, 22).

MATERIALS AND METHODS

The patients studied included all persons 2 months of age or older admitted to the Communicable Disease Service, Los Angeles County General Hospital, for the treatment of acute bacterial meningitis during the period 1 July 1965 through 4 July 1966. All age groups, both sexes, and diverse socioeconomic groups were represented. Each patient was assigned to a treatment group on the basis of an odd or even chart number. The hospital numbers were assigned by an office in a separate building. Thus, the physicians caring for the patients had no means of influencing allotment of chart numbers, and a random assignment of patients to the two treatment groups was assured. All patients received an initial rapid intravenous infusion of ampicillin at a dose of 50 mg/kg followed by 150 mg/kg daily divided into six equal intravenous doses. Patients with odd hospital numbers received the same dosage schedule of ampicillin plus two other antibiotics. They received a rapid intravenous infusion of 33 mg of chloramphenicol per kg 30 min after the initial dose of ampicillin. Subsequently, chloramphencol, 100 mg/kg daily to a maximal dosage of 4.0 g/day, was given by rapid intravenous infusion in six equal divided doses. Streptomycin, 20 mg/kg, was given intramuscularly every 12 hr for four doses. No patient received more than 2.0 g of streptomycin per 24-hr period. The administration of each dose of chloramphencol was delayed until 30 min after the ampicillin had been given in an effort to avoid antibiotic interference. Treatment was continued until the patient was afebrile for 5 days and the cerebrospinal fluid had returned to normal.

RESULTS

Patients studied. During the period of study, 308 patients 2 months of age or older were admitted to the service—44 of these were excluded from the analysis for the following reasons: unusual organisms, 15; error in treatment assignment or penicillin allergy, 21; endocarditis, mechanical defect, etc., 6; inadequate records, 2. There were 9 deaths among the 44 excluded patients. The two treatment groups were comparable with respect to age distribution, severity of illness on admission, and distribution of etiological categories. A preliminary analysis of these patients stressing the outcome of therapy has been reported previously (22).

Frequency of case fatality and neurological sequelae. The results of therapy, as measured by frequency of death or neurological residua, are presented in Table 1. The disadvantage of triple therapy is apparent from increased rates both of case fatalities and of residua. All deaths, except one, occurred in patients categorized as severe on admission. The statistical significance of the difference in case fatality rates hovered about 5%, depending upon the method of analysis. Perhaps more important is an analysis of the combined case fatality and residual rates. The residua included such serious disabilities as hemiparesis, 6 patients; cranial nerve paresis, 6; deafness, 4; seizures, 1; ataxia, 5; hyrdocephalus, 1; and mental retardation, 2. By the X^2 technique correcting for continuity, the difference between single and triple therapy with respect to the combined residual and fatality rates was significant at the 4% level.

Other clinical variables. Factors other than death or disability which might have illustrated the advantages of either treatment regimen are listed in Table 2. The duration of fever did not differ significantly by treatment group. Within 7 days after admission, 80% of the patients became afebrile. Fever was more prolonged, in both treatment groups, in patients with pneumococcal and *Haemophilus influenzae* meningitis than in the meningococcal and "purulent unkown" groups.