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Research Article

CLINICAL EXPERIENCE WITH AUREOMYCIN [1, 2]

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During the past nine months a study has been made by members of the medical service at the Johns Hopkins Hospital concerning some of the possible therapeutic uses of aureomycin. Forty-eight patients with a variety of infectious processes were selected for treatment. In many cases the patients had been treated unsuccessfully with one or more chemotherapeutic agents before aureomycin was given but in each instance an effort was made to curtail other drugs during the period that aureomycin was used. Whenever possible the infectious agent was recovered before treatment with aureomycin was started, and other cultures were made during and following this therapy. The sensitivity to aureomycin of the bacteria recovered was tested *in vitro* in each instance.

Certain studies were made to evaluate the possible toxicity of the drug. The patients were examined daily for evidence of rashes or untoward symptoms. The blood and urine were examined before, during, and after treatment. The liver function of 37 cases was tested before and after treatment, by the thymol turbidity, cephalin flocculation, and BSP excretion tests and serial electrocardiograms were obtained from 39 cases. No patient developed drug fever or dermatitis, and no signs of toxicity to the bone marrow, kidneys, liver, or myocardium were noted. Twenty-six of the 48 patients complained of nausea or epigastric distress. Diarrhea was noted in addition in nine cases. The gastrointestinal symptoms seemed to depend on idiosyncrasy and some patients could take large doses without discomfort. In general, the same dose caused less discomfort when divided into small amounts given frequently rather than large amounts at wider intervals. Aureomycin was better tolerated when given with food or with a buffer like Alugel but its effectiveness might be decreased by this procedure since it is known to deteriorate in alkaline environments. Many patients developed tolerance to aureomycin as treatment progressed. In only five cases was therapy stopped because of uncontrollable vomiting. It is of interest that four of these five were ambulant patients with sinusitis.

The patients have been divided into separate groups according to the diagnosis. The therapeutic results in each group will be considered separately.

Fifteen cases of urinary tract infection were treated. Six had chronic pyelonephritis, four had acute cystitis, three had post-operative infection with associated bacteremia, one had hydronephrosis, and one had a horse-shoe kidney. In 11 cases the infecting bacterium was *E. coli,* in two cases enterococcus, and in one, *Pseudomonas aeruginosa.* Each of the infecting strains of *E. coli* was inhibited *in vitro* by aureomycin in concentrations between 0.7 and 15 μg./cc. of medium. The strain of pseudomonas was resistant to 50 μg./cc. Fourteen of the 15 cases had not responded to other types of chemotherapy. The patients each received a total dosage of 4 to 32 gm. with an average of 13.2 gm. The results obtained were uniformly satisfactory except in the case of infection due to pseudomonas. All symptoms subsided within one to four days (average three and two-tenths days). In every instance the urine was sterilized. The follow-up periods are not yet very long but so far only the one patient with pseudomonas infection has had recurrence of the disease. Two other patients, following cystitis due to *E. coli,* developed stubborn infections due to proteus. This led us to avoid catheterization of other patients.

Six patients with primary atypical pneumonia were treated. The results are summarized in Table I. All of the cases developed agglutinins against streptococcus MG, and cold hemagglutinins were also detected in one. The average total dosage of aureomycin 13.3 gm. was given over an average period of eight and one-half days. All

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[2] Aureomycin supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

TABLE I

Primary atypical pneumonia treated with aureomycin

Case	No. of lobes	Agglutination		Day temperature reached normal			Aureomycin	
		Strept. MG	Cold	Disease	Hospital	Treatment	Grams	Days
JG	1	+	0	17	6	5	12.5	8
SK	1	+	0	6	4	4	16.0	7
ES	1	+	0	11	7	5	12.5	7
MF	1	+	0	11	5	4	7.0	4
FG	2	+	0	14	6	2	21.5	12
MF	2	+	+	7	5	4	12.5	7
Average				11.0	5.5	4.0	13.3	8.5

these patients recovered. The temperature reached normal on the second to fifth day of treatment (average four days). This corresponded with the 11th day of disease, or five and one-half days after hospitalization commenced. Nine additional patients with primary atypical pneumonia, admitted to the hospital during the study period, received no chemotherapy. The results are summarized in Table II. The first five listed were alternate admissions to the six treated cases. In this untreated series the results observed were just as satisfactory as in the treated cases. The temperature reached normal on the average after 10.1 days of disease and four and seven-tenths days of hospitalization. The results observed in these small groups of patients fail to indicate that aureomycin in the dosage employed affected the course of this disease. It seems obvious that larger groups of patients with adequate controls are necessary to settle this point.

TABLE II

Primary atypical pneumonia with no antimicrobial therapy

Case	No. of lobes	Agglutinations		Day temperature reached normal	
		Strept. MG	Cold	Disease	Hospital
AM	1	+	0	14	1
SR	1	+	0	12	1
MC	1	+	0	9	4
SM	1	+	0	5	3
JP	1	−	−	4	2
AC	1	+	0	7	3
ES	1	0	0	15	9
FL	1	−	−	8	6
WK	1	−	−	17	3
Average				10.1	4.7

Three patients with lung abscess were treated. Two had chronic infections for six and nine months, respectively. The third was acutely infected. The abscess in one patient was secondary to a pulmonary adenocarcinoma. From this case a pure culture of *E. coli* sensitive to 0.75 μg./cc. of aureomycin was obtained from the pus. No improvement had been noted following treatment with penicillin and sulfadiazine. After treatment with aureomycin, 4 gm. daily for 20 days, subjective improvement was noticeable and the temperature returned to normal. Subsequently, however, both fever and symptoms recurred and surgical drainage was necessary. It is of interest that the pus then contained no *E. coli* but instead a pure culture of proteus.

The second chronic case with a mixed infection resistant to penicillin and streptomycin was markedly improved after receiving aureomycin 4 gm. daily for six weeks. Fever and sputum disappeared and roentgenographic examination revealed a normal lung. The third patient had multiple acute abscesses due to staphylococcus and improved dramatically when treated with aureomycin although penicillin had seemed ineffective. Six patients with sinusitis were treated with satisfactory results.

An additional group of nine patients with different types of infections was treated with good results. These included two cases of lymphopathia venereum, and one case each of Rocky Mountain Spotted Fever, rat bite fever, tonsillitis due to *Streptococcus pyogenes,* meningitis due to *E. coli,* meningitis due to pneumococcus Type XIX, rodent ulcer, lobar pneumonia, and chronic brucellosis. One case of chronic ulcerative colitis showed marked symptomatic improvement on treatment.

Unsatisfactory results were observed in five additional patients comprising one case each of thyroiditis, pemphigus, sarcoid, osteomyelitis, and typhoid fever.

Four patients with bacterial endocarditis were treated. In two the infections, due to *Streptococcus fecalis,* developed following the Blalock-Taussig operation. The other two patients developed spontaneous infections due to microaerophilic streptococci. The courses of these four patients are summarized in Figures 1–4. In the case of K. S. (Figure 1) the *Streptococcus fecalis* was

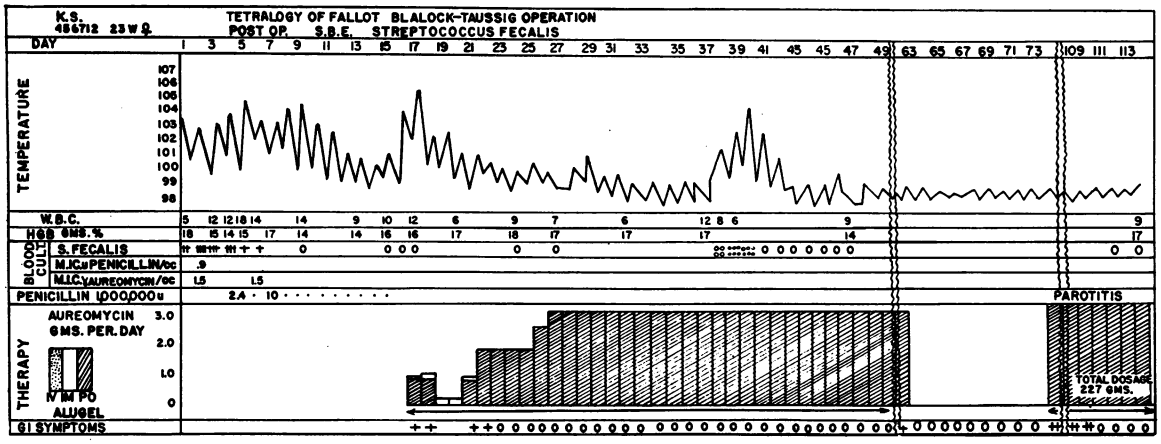

FIG. 1. SUBACUTE BACTERIAL ENDOCARDITIS, TREATED WITH AUREOMYCIN

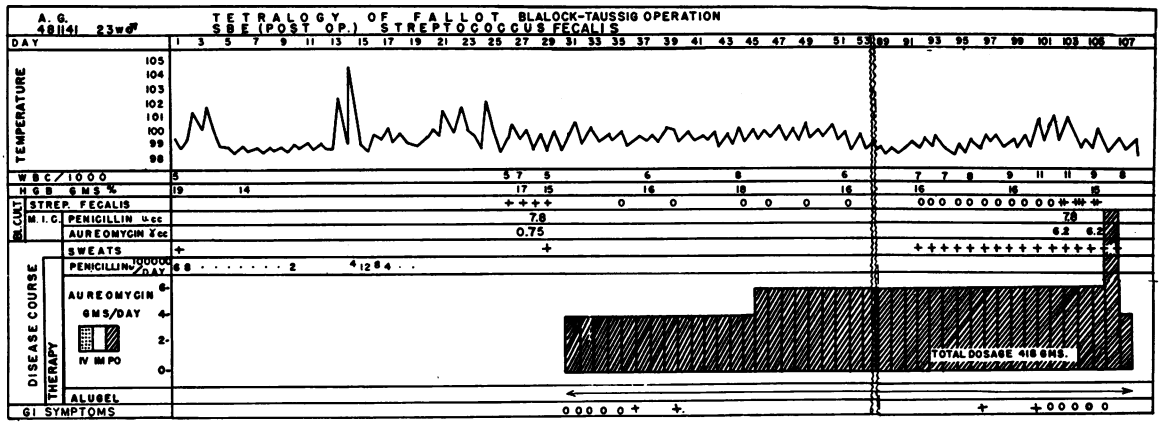

FIG. 2. SUBACUTE BACTERIAL ENDOCARDITIS, TREATED WITH AUREOMYCIN

sensitive *in vitro* to .9 u. of penicillin/cc. and 1.5 μg. of aureomycin/cc. The patient was given 92 million u. of penicillin for 12 days when this was stopped because of the development of sensitivity to this drug. During penicillin therapy the blood cultures had become sterile, and the patient showed definite clinical improvement although low grade fever continued. Following aureomycin therapy

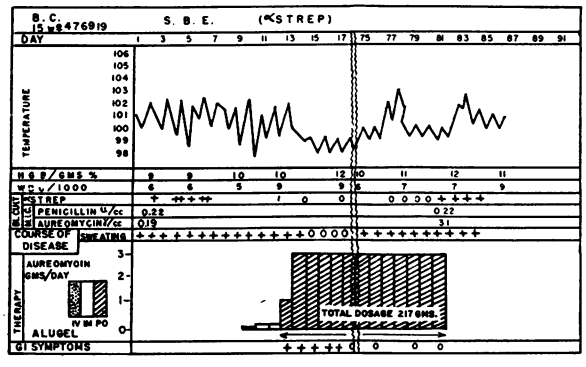

FIG. 3. SUBACUTE BACTERIAL ENDOCARDITIS, TREATED WITH AUREOMYCIN

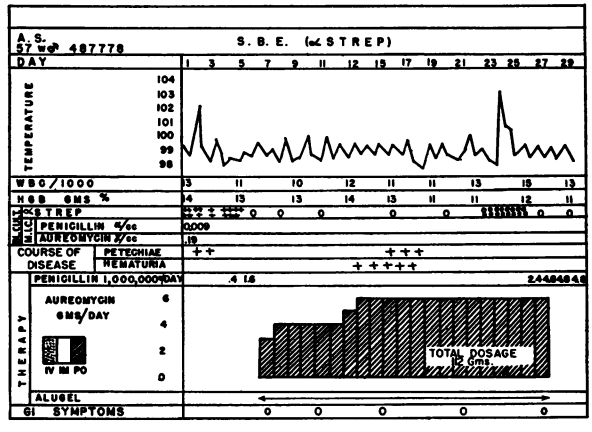

FIG. 4. SUBACUTE BACTERIAL ENDOCARDITIS, TREATED WITH AUREOMYCIN

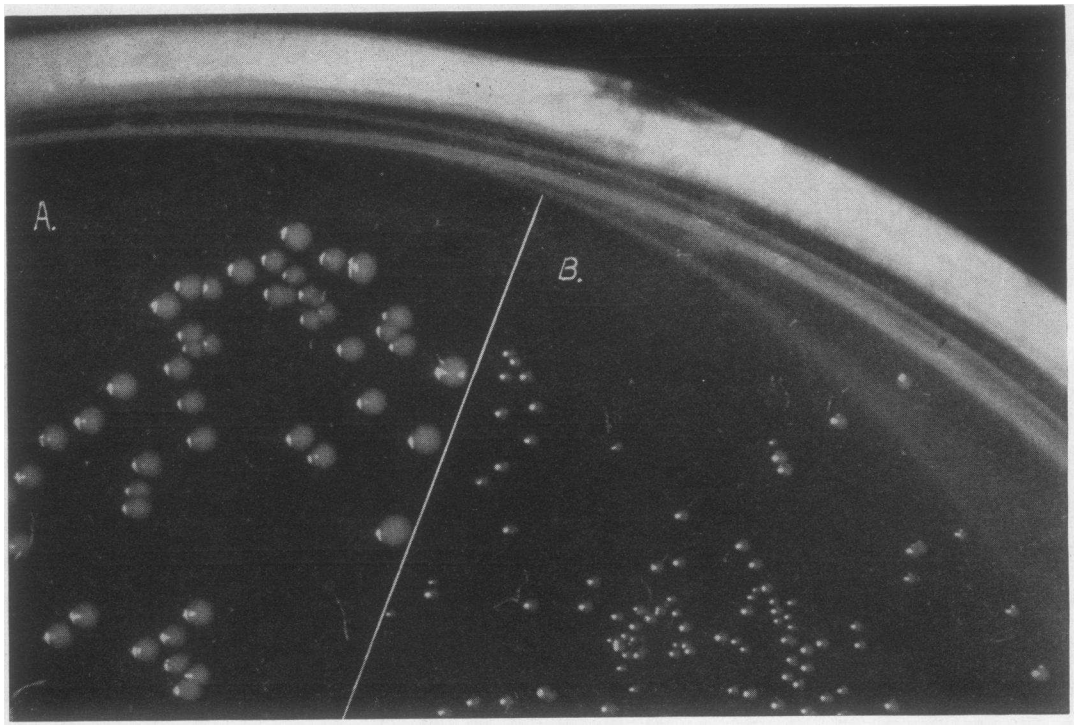

FIG. 5. COLONIAL FORMS OF *Streptococcus fecalis* GROWN ON AGAR PLATE CONTAINING BLOOD

A represents the large colonies formed by the strain recovered before treatment, inhibited by 0.75 μg./cc. of aureomycin, but not less. B represents smaller colonies formed by the strain recovered after treatment with aureomycin, inhibited by 6.2 μg./cc. of aureomycin, but not less.

TABLE III

Characteristics of Streptococcus fecalis—*Strain AG*

Characteristics	Strain No. 1 before therapy	Strain No. 2 after therapy
Sensitivity Aureomycin	0.75 μg./cc.	6.2 μg./cc.
Sensitivity Penicillin	7.8 u./cc.	7.8 u./cc.
Colonies Blood agar	large, translucent	small, more opaque
Growth—T.S. broth	6 hr.—500,000,000/cc. 24 hr.—1,500,000,000/cc.	6 hr.—50,000,000/cc. 24 hr.—50,000,000/cc.
Morphology	Large, elongated G+ cocci in pairs, groups, and short chains	Same
Growth in broth	Smooth	Smooth
Heat resistance 62° C.—30 min.	+	+
Litmus milk	Reduced, coagulated, peptonized	Same
Loeffler's serum slants	Liquefied	Liquefied
Lactose, salicin, mannite, trehalose, sorbitol	+	+
Dextrose final pH	6.5	7.0
Sodium hippurate	Hydrolyzed	Hydrolyzed

the temperature became normal, clinical improvement was progressive, and the patient remains well five months since discharge from the hospital. In the other three cases, evidence of infection persisted during or subsequent to the aureomycin treatment.

It is of interest to note that the strains of streptococci recovered from the blood stream of cases B. C. and A. G. after aureomycin treatment showed greater resistance to the bacteriostatic effect of aureomycin *in vitro* than the original strain obtained before treatment. The increases noted were 16 fold and eight fold, respectively. Detailed studies were made of the strain obtained from A. G. It was noted that the resistant strain grew more slowly in broth and the colonies on agar plates containing blood were smaller than those of the original sensitive strain. All the other characteristics tested were identical. These observations are shown in Table III and Figure 5. The changes in growth rate and colonial form are

suggestive of those described by Eriksen (1) for staphylococci resistant to penicillin. The small resistant variants of this streptococcus were unstable and reverted quickly to the fast growing aureomycin sensitive type.

It is quite obvious that in each case the drug has some therapeutic effect in that the temperature became normal and blood cultures became sterile. The reasons for the subsequent reappearance of the bacteremia in two of the cases infected with organisms quite sensitive *in vitro* are not now obvious. The development of increased resistance as illustrated in the two cases B. C. and A. G. may have played a part in the ultimate failure in therapy but there may be other equally important factors such as the inability of aureomycin to penetrate the vegetations.

In summary, aureomycin is a non-toxic drug which may be useful in a variety of infectious diseases. In our experience the results in urinary tract infections were particularly good. The relatively slow deterioration of aureomycin in acid environments may contribute to its effectiveness in this type of infection. The use of aureomycin in combination with other antimicrobial agents was not tested.

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