

**PENICILLIN TREATMENT OF SULFONAMIDE-RESISTANT
GONOCOCCAL INFECTIONS IN THE FEMALE***

ALFRED COHN, M.D., HOWARD C. TAYLOR, JR., M.D., AND
ISAAC GRUNSTEIN, M.D., NEW YORK, N. Y.

(From the Venereal Disease Research Unit, Department of Health, City of New York, and the Obstetrical and Gynecological Service [Third Surgical Division], Bellevue Hospital, and from the Department of Obstetrics and Gynecology, New York University College of Medicine)

THE use of penicillin therapy in the control of gonococcal infections in the female has already been reported by several investigators.¹

A preliminary report on the successful penicillin treatment of sulfonamide-resistant gonococcal infections in 44 female patients under our care appeared in the *Journal of the American Medical Association* of April 8, 1944.² The present paper deals with the analysis of the ad-

*The laboratory work was aided by a grant from the United States Public Health Service.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

ditional results obtained in 108 hospitalized female patients suffering from gonococcal infections, who were treated with varying amounts of penicillin.

Clinical Material

A total of 108 adult female patients was diagnosed as gonococcus positive by cultures and/or smears during a 9-month period, from September, 1943, to June, 1944.

The urethra alone was found to be infected in 3 cases; the cervix alone in 39. A concurrent urethral and cervical infection was present in 66 women. Adnexal involvement was observed in 34 patients, although it was of a severe character only in exceptional cases. This paucity of acute adnexal disease may have been due to the long duration of the infection which averaged 70 days, and to the fact that the majority of the patients had already received two or more courses of sulfonamide in addition to other supportive therapy. One patient suffered from a diffuse peritonitis. Another developed arthritis of the right elbow during the course of penicillin treatment. Pregnancy ranging from 3 to 9 months was present in 6 patients.

Prior to penicillin treatment, 101 of these patients had failed to respond to at least two courses of 20 Gm. each of various chemotherapeutic agents of the sulfonamide group. The remaining 7 patients received penicillin treatment because they had shown a marked sensitivity to the sulfonamides.

Schedule of Treatment and Dosage

In order to determine a simple yet adequate schedule of penicillin treatment for sulfonamide-resistant gonococcal infections, the following plan was adopted: Two constant factors were maintained throughout the study: (1) A 3-hour interval between successive injections of penicillin, and (2) The intramuscular injection in the gluteal region.

The variable factors were: (1) the administration of varying amounts of penicillin, i.e., from 25,000 to 100,000 Oxford Units, as total dosage, and (2) the variation of the total period of time during which the total amount of penicillin was administered.

Three different brands of penicillin were investigated: Reichel Laboratories, Pennsylvania; E. R. Squibb & Sons, New York; Charles Pfizer, New York, but no essential differences of reactions or efficacy were observed. Each 5,000 Oxford Units of penicillin was dissolved in 1 c.c. of sterile normal saline.

The following table shows the number of hospitalized patients treated, the time required for each treatment, the amounts of single doses and the total dosages of penicillin, and finally the therapeutic results obtained.

Results of Therapy

All 108 patients treated with penicillin became bacteriologically negative with regard to cervical and urethral cultures. As may be seen in Table I, 99 patients who received varying amounts of penicillin over different periods of time, responded to a single course of therapy. The remaining 9 patients, who did not respond to the initial treatment, were cured by a second course of 100,000 O.U. given in divided doses of 25,000 O.U. each at 3-hour intervals.

TABLE I

SCHEDULE NO.	NO. OF PATIENTS TREATED	NO. OF INTRA-MUSCULAR INJECTIONS	HOURS REQUIRED FOR TREATMENT	OX-FORD UNITS PER DOSE	TOTAL DOSAGE OF PENICILLIN O. U.	NO. OF PATIENTS	
						CURES	FAILURES
I	12	5	12	20,000	100,000	12	—
II	11	4	9	25,000	100,000	11	—
III	21	3	6	25,000	75,000	20	1
IV	15	2	3	25,000	50,000	12	3
V	29	2	3	50,000	100,000	28	1
VI	10	1	6	50,000	100,000	10	—
		2		25,000			
VII	1	1	3	50,000	75,000	1	—
		1		25,000			
VIII	1	3	6	20,000	60,000	1	—
IX	4	1	—	25,000	25,000	2	2
X	2	1	—	50,000	50,000	1	1
XI	2	1	—	75,000	75,000	1	1

Following penicillin treatment daily clinical and bacteriologic examinations of the hospitalized patients were performed. The patients were followed up for an average period of 7.8 days, during which an average of 5.7 examinations were carried out.

Reversal from positive to negative of the initial bacteriologic findings took place within 24 hours after termination of penicillin therapy in all but one case. In the one exception, reversal occurred after 48 hours. Among seven cases in which cultures were taken at hourly intervals after treatment had been initiated, three became negative within 2 hours.

The following factors seem to determine the therapeutic efficacy of penicillin in the treatment of sulfonamide-resistant gonococcal infections. (1) The administration of an optimal amount of penicillin: In this study, this amount proved to be a total dosage of 100,000 O.U. (2) The total period of time during which the total amount of penicillin was administered: 6, 9 and 12 hours were all found to be satisfactory. The intramuscular route of injection was used in all of these cases.

Some bacteriologic cures were obtained with amounts of penicillin smaller than 100,000 O.U. and administered in less than six hours. Single doses of 75,000 O.U., 50,000 O.U. or even 25,000 O.U. were likewise found to be adequate in some cases. However, this type of therapy is not to be recommended since the percentage of failures was high. The observation, that such subtherapeutic doses can cure individual patients, is consistent with laboratory findings that different gonococcus strains vary markedly in their susceptibility to penicillin.³

Clinical Changes

The following clinical changes were observed after penicillin therapy. The urethral discharge diminished in amount, or disappeared completely within a week or less in practically all of the cases studied. The cervical discharge, however, persisted in most cases throughout the entire follow-up period. In a very limited number of patients, the cervical discharge disappeared for a few days, but soon recurred. In general, it may be stated that the amount and character of the discharge observed in the urethra and cervix before and after penicillin treatment did not differ essentially from that observed in women receiving sulfonamide therapy.⁴

Adnexal Involvement

In 20 of the 34 patients in whom adnexal involvement was present, tenderness and thickening of the tubes or ovaries subsided within a few days after penicillin treatment. In 10 other patients suffering from acute exacerbation of chronic pelvic inflammatory disease, the acute symptoms and signs appeared to be improved by penicillin therapy. However, in these patients no essential changes were observed in the size or character of the adnexal masses which were present before therapy. In the remaining 3 cases, an exacerbation of the adnexal involvement was observed following the use of penicillin. One of the patients, without any adnexal disease prior to penicillin treatment, developed salpingitis following therapy. Within 1 to 2 weeks after penicillin treatment, the acute symptoms and signs of adnexal involvement disappeared in all 34 patients.

Gonococcal peritonitis, in the one patient reported, responded strikingly to 100,000 O.U. of penicillin; the same amount which was found necessary in less complicated cases. The patient who developed acute arthritis of the right elbow during the course of penicillin therapy recovered within a few days without any further treatment. The course of pregnancy in 6 patients was unaffected by penicillin.

There were 14 women who suffered from a concurrent infection of *Trichomonas vaginalis* which remained unchanged by penicillin therapy.

Clinical Follow-up

After their discharge from Bellevue Hospital, 81 of the total of 108 women were followed up at the Research Clinic of the Department of Health, City of New York, for an average period of 43.6 days during which an average of 3.5 examinations were performed. During the course of this follow-up, there were 15 women who were found to be gonococcus positive again after an average of 51.7 days and 3.4 examinations. Nine of these had originally suffered from adnexal involvement. The question arose as to whether these cases represented a relapse of their previous infection or new infections. Thirteen of the patients admitted new exposures, while 2 persistently denied the possibility of a new infection. Of these 15 women, 6 who were originally sulfonamide-resistant responded to one course of sulfathiazole therapy for their reinfection. Four, including the 2 who denied exposure, were cured by a second course of penicillin. The remaining 5 cases were delinquent.

It is difficult to decide whether these 15 cases represent instances of relapse or of reinfection. Among the hospitalized patients it was observed, that relapses after inadequate therapy always occurred within 24 hours after the administration of the penicillin. In the 15 women who became gonococcus positive during follow-up, reversals to positive occurred after an average of 51 days' observation. Thirteen of these admitted new exposures, the remaining two women were completely unreliable. Another fact which points to reinfection was that 6 patients in this group responded to one course of sulfonamides although they had previously been sulfonamide-resistant cases. In view of these facts, it is our impression that practically all 15 of these cases represent reinfections rather than recurrences.

Toxicity

One of the greatest advantages of penicillin therapy is the absence of any serious toxic symptoms in patients thus treated. The only complaint of the majority of these patients was a transitory numbness or pain following injection radiating from the site of injection in the gluteal region down to the thigh or ankle. Chills of a mild degree, rising temperature, a macular rash and generalized lymphadenopathy were observed in one patient, who suffered from a concurrent early syphilitic infection (Herxheimer reaction).

Comment

The total dosage of penicillin and the time-dose ratio are apparently the basic factors which determine a successful schedule of penicillin therapy. Our investigation was directed at evaluating the minimum effective dosage of penicillin due to the fact that the amount of penicillin available during the course of the study was very limited. Furthermore, we wanted to establish an effective time-dose ratio which could be used for the treatment of ambulatory patients. From our results thus far, it appears that a minimum total dosage of 100,000 O.U. of penicillin administered in 3 intramuscular injections at 3-hour intervals—an initial injection of 50,000 O.U. followed by 2 injections of 25,000 O.U. each—is a satisfactory treatment schedule which is completed within a period of 6 hours.

Although we have not yet encountered any instances of penicillin failure in our series, it is a possibility which cannot be eliminated at our present state of knowledge. Failure of penicillin might be due to two main factors: (1) A true resistance on part of the gonococcus strain to the bactericidal action of penicillin itself, the occurrence of which has not yet been proved; (2) the inability of penicillin to reach and act upon organisms which may be walled off in inaccessible foci of the genital tract.

It may be pointed out that a second course of penicillin treatment consisting of 4 single doses of 25,000 O.U. each, administered at 3-hour intervals has proved to be therapeutically effective in 9 patients who failed to respond to a first course of penicillin therapy.

The most difficult problem involved in this study of female gonorrhea is the establishment of definite cure. Clinical signs are of no appreciable value in its determination. Repeated bacteriologic examination, extended over a period of 2 to 3 months if possible, is the only means of establishing cure with any degree of certainty. The differentiation between relapse or reinfection after apparent cure is frequently impossible. History of new exposure, time of follow-up after treatment, number of examinations performed and final response or failure to a repetition of the original therapeutic schedule are factors which may aid in the clarification of this problem.

Summary and Conclusions

1. Various amounts of penicillin were used in the treatment of 108 adult female patients suffering from gonococcal infections. Of these, 101 had failed to respond to at least two courses of various sulfonamides; the remaining 7 patients showed a definite sensitivity to sulfonamide compounds.

2. Of the total of 108 patients, 99 promptly became bacteriologically negative after one course of penicillin treatment, and 9 by the administration of a second course of penicillin.

3. The results obtained by the administration of various amounts of penicillin point to the fact that a minimum total dosage of 100,000 O.U., injected intramuscularly in divided doses, is both necessary and sufficient for bacteriologic cure. The minimum total period of time required for successful therapy was found to be six hours.

4. Smaller doses of penicillin and shorter total time of treatment were adequate in individual cases, but this type of therapy cannot be recommended.

5. Urethral discharge following penicillin therapy disappeared within a week; cervical discharge was not appreciably affected in the majority of cases.

6. Acute symptoms and signs of adnexal involvement subsided within 1 to 2 weeks after penicillin treatment. There were 3 cases which had an exacerbation of the adnexal involvement immediately following the use of penicillin, and 1 patient who developed salpingitis following therapy.

7. After their discharge from the hospital, 81 of the total of 108 women were followed up for an average period of 43.6 days, during which an average of 3.5 examinations were performed.

8. Fifteen patients were found gonococcus positive after an average follow-up of 51.7 days. It may be assumed for various reasons that all these patients represent reinfections rather than recurrences.

9. No serious toxic symptoms appeared in this group of patients treated with penicillin.

References

1. Cook, E. N., Pool, T. L., and Herrell, W. E.: Further Observations on Penicillin in Sulfonamide-Resistant Gonorrhea, *Proc. Staff Meet. Mayo Clin.* 18: 433, 1943.
Strauss, Hyman: Cure by Penicillin Following Repeatedly Unsuccessful Sulfonamide Therapy in a Pregnant Woman With Gonorrhea, *AM. J. OBST. & GYNEC.* 47: 271, 1944.
Bloomfield, A. L., Bantz, L. A., and Kirby, W. M. M.: The Clinical Use of Penicillin, *J. A. M. A.* 124: 627, 1944.
Barringer, Emily Dunning, Strauss, Hyman, and Horowitz, E. A.: Penicillin Treatment in Sulfa-Resistant Cases of Gonorrhea in the Female, *Ann. Meeting of the Medical Society of the State of New York*, May 10, 1944.
2. Cohn, Alfred, Studdiford, William E., and Grunstein, Isaak: Penicillin Treatment of Sulfonamide-Resistant Gonococci Infections in Female Patients; Preliminary Report, *J. A. M. A.* 124: 1124, 1944.
3. Cohn, Alfred, and Seijo, Irma: The in Vitro Effect of Penicillin, *J. A. M. A.* 124: 1125, 1944.
4. Cohn, Alfred, and Grunstein, Isaak: Gonorrhea in the Female. Bacteriologic and Clinical Aspects, *AM. J. OBST. & GYNEC.* 48: 339, 1944.