Acta Dermatovener (Stockholm) 51: 305–310, 1971

ORAL AMPICILLIN IN UNCOMPLICATED GONORRHOEA

III. *Results of Treatment in Women with Positive Rectal Culture*

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Abstract. The incidence of positive rectal cultures in a female gonorrhoeal material from the Outpatient Clinic for Venereal Diseases at Södersjukhuset in two consecutive years has been approximately 42%. In the first year 268 female patients had a positive rectal culture and were treated with an intramuscular injection of 2.2 MIU penicillin G. In the second year 370 women had a positive rectal culture and were treated with ampicillin orally, three groups being formed on a random basis, viz. patients given a single dose of 2 g ampicillin, a single dose of 2 g ampicillin combined with 1 g probenecid, and two doses of 1 g ampicillin with 5 hours' interval (1-day treatment). A comparison has been made of the results of treatment in the four groups. The percentage of treatment failures was throughout lowest in the group treated with ampicillin combined with probenecid in a single dose, and highest in the group given ampicillin in a high single dose. There was a statistically significant difference only between these two groups. Attention was paid to the in vitro sensitivity of the gonococcal strains during the 2 years covered by the study.

In recent years a positive culture has for many become equivalent to rectal gonorrhoea (11). This form of gonorrhoea is then not considered as a complication and standard treatment is given (9, 11, 13, 14). Other authors still consider rectal gonorrhoea more difficult to treat than urogenital gonorrhoea (18) and to require higher doses of penicillin (3, 19). Neither the route by which gonococci reach the rectum nor the significance of their occurrence there is completely clear. In a number of cases the infection is primary because of rectal intercourse. But the main reason for the rectal localization has been considered to be perineal spread into the rectum. Spread via the pelvic lymphatics from the urogenital region to the rectum has also been discussed as a possible route.

It has been considered that gram-negative penicillinase-forming bacteria in the rectum might destroy penicillin and thus leave a focus from which gonococci are able to reinfect the urethra and cervix (10). In view of the massive occurrence of such bacteria in the rectum it would hardly be possible to obtain such satisfactory results from standard treatment if the formation of penicillinase were of any significance (11).

Earlier, a male as well as a female gonorrhoea material collected during 2 successive years has been reported from Södersjukhuset (5, 6). A comparison was made between the results of one year's treatment with one intramuscular injection of penicillin G and one year's treatment with ampicillin orally in three different dosage forms. The treatment results of women showed no significant difference between any of the groups. As the result of treatment of patients with positive rectal culture was considered to be of special interest, this part of the female material is reported in this paper.

MATERIAL AND METHODS

The material consists of women presenting at the Outpatient Clinic for Venereal Diseases of Södersjukhuset for suspected gonorrhoea. Specimens for direct microscopy and culture are routinely taken from the urethra, cervix and rectum. This is also the procedure at the follow-up visits. This paper presents an analysis of cases with positive rectal culture, either alone or together with positive culture from urethra and/or cervix, treated with a single intramuscular injection of penicillin G during a one-year period 1967–68 and oral ampicillin during the following one-year period 1968–69. The total material of uncomplicated gonorrhoea in women during the 2 consecutive years was described in a previous paper as were methods of examination and analysis (6).

Table I. *Number of female patients followed up, totally and with positive rectal culture*

Patient group	Treatment	Total no. of women with gonorrhoea	No. of women with positive rectal culture
G	2.2 MIU penicillin G intramuscularly (1 MIU Na salt + 1.2 MIU procaine salt)	652	268
A	2 g ampicillin orally	300	125
B	2 g ampicillin + 1 g probenecid orally	262	115
C	1 g + 1g ampicillin orally with 5-hour interval	294	130

Grouping and dosage will be seen from Table I. The preparations used have been Doktacillin® (ampicillin), Probecid® (probenecid), Astra Läkemedel AB, Sweden, and Gonocillin® (combination of sodium and procaine penicillin G), AB Leo, Sweden.

The result of one year's treatment with oral ampicillin is compared for the three groups (groups A, B and C) as well as with the result of the previous year's penicillin G (group G) treatment.

In the evaluation at least two consecutive negative follow-up cultures have been required for patients to be denoted as *satisfactory*. Patients with positive culture at the first follow-up within 14 days have been denoted as *treatment failure* in one evaluation. In another evaluation patients with first or second follow-up culture positive within 21 days have also been denoted as treatment failure. In these contexts positive culture refers to a positive culture in any location(s). Only very probable reinfections (contact positive) have been excluded.

Bacteriological method. The specimens were cultured on Thayer-Martin medium. In vitro antibiotic susceptibility tests were made on all positive cultures.

Determination of the in vitro sensitivity of the gonococci to penicillin G, chloramphenicol and tetracycline was routinely done by the diffusion method reported by Ericsson et al. (4). Furthermore tests were carried out against streptomycin during the first and against ampicillin during the second year of the trial.

The patients were also divided into two groups according to the sensitivity of the gonococcal strains to penicillin G and ampicillin, namely fully and less sensitive. Strains with MIC ≥ 0.1 IU penicillin G and ≥ 0.1 µg ampicillin per ml have been denoted as less sensitive. The bacteriological aspects will be further discussed in a subsequent paper (8).

The statistical analysis was made in cooperation with the Statistical Research Group at the University of Stockholm. The χ^2 test was used. Significance limits for the χ^2 values are:

–	$\chi^2 < 3.841$	for	$P > 0.05$
*	$3.841 < \chi^2 < 6.635$	for	$0.01 < P < 0.05$
**	$6.635 < \chi^2 \leq 10.827$	for	$0.001 < P < 0.01$
***	$\chi^2 > 10.827$	for	$P < 0.001$

Yates' correction has been used, and for small groups Fisher-Yates' test.

RESULTS

During the first year of investigation (1967–68) a total of 846 patients showed positive culture in one or more locations compared with 936 patients during the second year (1968–69) (6). The criteria of positive culture in any location, sensitivity test performed and treatment with the stipulated drug and dose, were fulfilled in 652 patients during the first year and in 856 during the second. The proportions of positive *rectal* culture in these patients were 41.1% (268) and 43.2% (370) respectively (Table I). During the first year of the trial 17 (6.4%) and during the second year 16 (4.3%) of these patients had positive rectal cultures exclusively.

According to the random allocation during the second year 125 patients (group A) were given a high single dose of ampicillin, 115 patients (group B) a high single dose of ampicillin combined with probenecid, and 130 patients (group C) the same dose as group A but on a divided basis (Table I).

The incidence of all gonococcal strains with reduced sensitivity to penicillin G isolated at the

Table II. *Results of treatment in women with positive rectal culture*

Treatment group	Results of treatment				
	No. of negative follow-up cultures		Positive culture at follow-up number		
	I	2–4	I	I or II	III
G	12	226	17	27	3
A	3	110	10	12	–
B	2	106	3	6	1
C	3	116	5	7	4

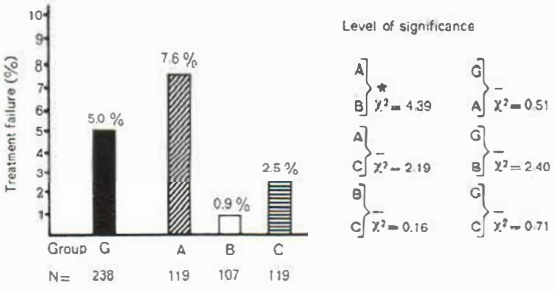

Fig. 1. Result of treatment (all patients). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

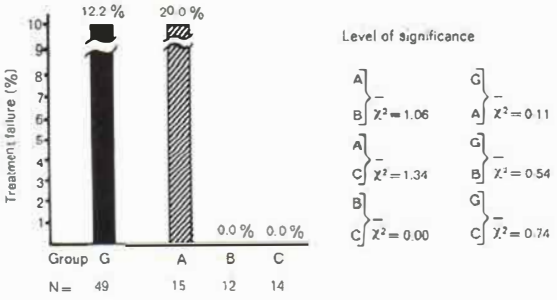

Fig. 3. Result of treatment in patients harbouring less sensitive strains (MIC ≥ 0.1 IU penicillin G/ml and ≥ 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

Bacteriological Laboratory at Södersjukhuset in 1967–68 was 23.3% and, in 1968–69, 26.5%. The frequency of strains with reduced sensitivity to penicillin G in the statistically evaluated material in this paper was the same, approximately 21%, in each of the 2 years.

The results of treatment are summarized in Table II and Figs. 1–7. In one respect a statistically significant difference is obtained between the results of the various treatment groups. In group A the result is significantly less favourable than in group B ($0.01 < P < 0.05$) when all patients are included (irrespective of the degree of sensitivity of the gonococci) and when a positive first follow-up culture within 14 days is counted as treatment failure (Fig. 1).

On the other hand no significant differences can be shown in the results, if patients with fully sensitive and less sensitive gonococci, respectively, are assessed separately or if a positive first or second follow-up culture within 21 days is counted as treatment failure. In all comparisons group A shows the highest proportion of treatment failure. The result in group G is percentually always better than in A but less favourable than in B and C (Figs. 1–6).

A comparison of treatment results in patients with and without positive rectal culture shows that penicillin G is significantly less effective in cases with positive rectal culture ($0.01 < P < 0.05$). Such a difference cannot be seen in groups B and C (Fig. 7).

DISCUSSION

The great importance of direct microscopy for diagnosing rectal gonorrhoea has been emphasized owing to the risk of overgrowth of the gonococcal colonies by intestinal organisms (21). The disadvantage of direct microscopy is that the gonococci are easily overlooked, especially in large and busy venereal departments. Besides, other gram-negative intracellular organisms such as Mimae may occasionally be mistaken for gono-

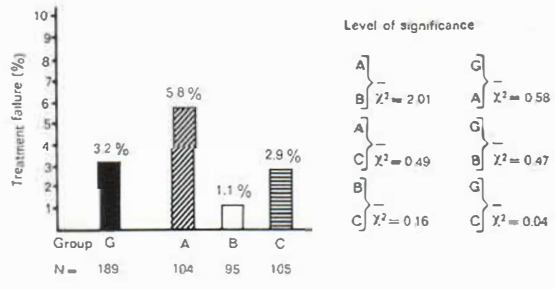

Fig. 2. Result of treatment in patients harbouring sensitive strains (MIC < 0.1 IU penicillin G/ml and < 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

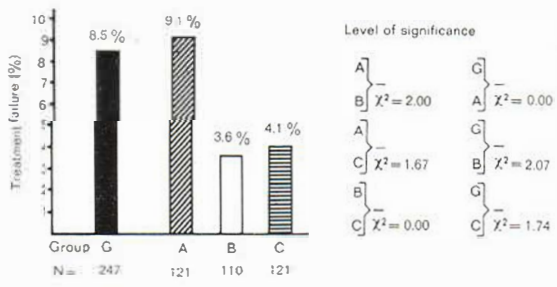

Fig. 4. Result of treatment (all patients). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

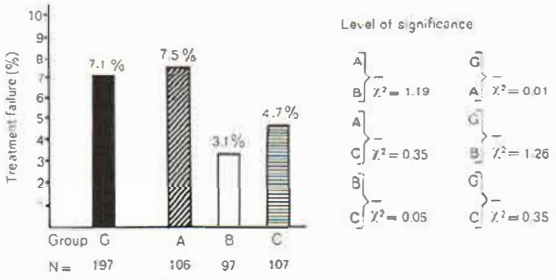

Fig. 5. Result of treatment in patients harbouring sensitive strains (MIC < 0.1 IU penicillin G/ml and < 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

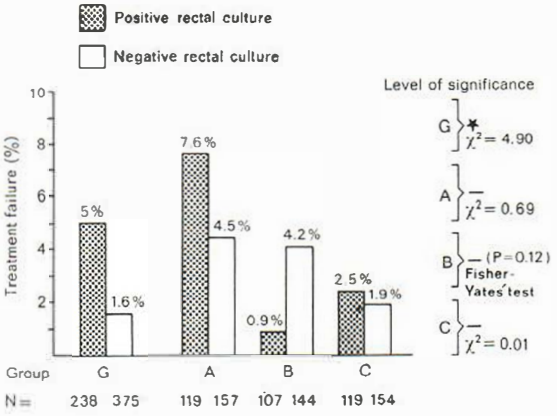

Fig. 7. Comparison of result of treatment in patients with and without positive rectal culture (all patients). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

cocci. Through the incorporation of two antibiotics in the medium (Thayer & Martin, 1964) the culturing has allowed growth of gonococci but suppressed the growth of intestinal organisms (20). The great advantage of this medium compared with the routine medium, especially in rectal gonorrhoea, has been reported by, e.g. Wilkinson (22) and Roepstorff & Hammarström (18). Through the improved culturing procedure the incidence of positive rectal cultures from female patients with gonorrhoea has risen, a figure of 32% being reported by Roepstorff & Hammarström (18), 42% by Scott & Stone (19), 50% by Molin (15), and 26% by Groth & Hallqvist (9), and in this material during the 2 years 41.1% and 43.2% respectively.

The importance of having smear and culture taken as standard practice from rectum is emphasized by the number of patients with exclusively positive rectal cultures, namely 7.3% reported by Roepstorff & Hammarström (18), 3% by Scott & Stone (19) and 7% by Barr & Danielsson (2). If culture specimens from rectum had not been taken 2.6% of the patients with gonorrhoea during the first year covered by the investigation and 1.9% during the second year might have remained undiagnosed. They would thus have constituted a source of infection. Besides, the majority of patients with rectal gonorrhoea complain of no symptoms (16, 17).

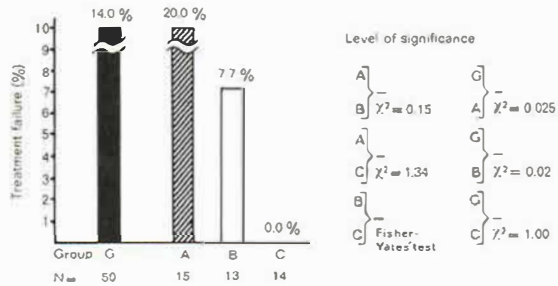

Fig. 6. Result of treatment in patients harbouring less sensitive strains (MIC ≥ 0.1 IU penicillin G/ml and ≥ 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

In view of the improved culturing procedure and the shortage of time at the large Outpatient Clinic for Venereal Diseases we considered that direct microscopy with too low a frequency of positive specimens involved too great an uncertainty, for which reason, in this and the earlier reported studies, the assessment has been based on the result of the cultures.

During the first year of the trial the patients were given one intramuscular injection of penicillin G. During the second year the patients were assigned at random to treatment groups A, B or C. This has been done without respect to the location in which the gonococci were found and without respect to whether treatment was given after diagnosis by direct microscopy or whether the result of the sensitivity determination was known at that time. Thus patients harbouring less sensitive gonococci are randomly distributed in the different treatment groups.

The proportion of strains with reduced sensitivity to penicillin G was approximately 21% during the 2 years in the statistically evaluated

material consisting of patients with positive rectal culture. A detailed comparison between the clinical result and in vitro sensitivity of the gonococci will be presented in a subsequent paper (8). A comparison between clinical results and pharmacology will also be reported (7).

In accordance with the recommendations of the Swedish Board of Social Welfare and with the methodology presented in the earlier reports (5, 6) only cases with at least two negative follow-up cultures have been regarded as *satisfactory*. The patients with a first negative follow-up who did not come to more than one check-up have not been included in the statistical analysis. They might have been positive at a second follow-up (Table II).

Also in accordance with the methodology in the paper on the total female material, patients either with positive culture at first follow-up within 14 days or with positive first or second follow-up culture within 21 days have been counted as *treatment failures*. This implies a positive culture from one or more sites irrespective of whether the site was the same as in the diagnostic test or not. Excluded are very probable reinfections, i.e. patients with a positive contact. In both the penicillin G and ampicillin groups 5 among the patients with positive culture at follow-up no. I were excluded from the evaluation because of probable reinfection or positive follow-up culture after more than 14 days. When the time limit was 21 days 1 further patient had to be excluded from group G. None of the 8 patients who had a positive culture at the third follow-up were included in the evaluation. These patients would have been assigned to the satisfactory group if they had not appeared at this examination. Besides, only one of these patients appeared for the third check-up within the time limit of 21 days (Table II).

In this material groups B and C show the lowest percentages of failures in all comparisons (Figs. 1–6). Group A is percentually least favourable. This is in accordance with both the total female and male materials (5, 6).

The result of treatment of the rectal cases of gonorrhoea in women showed that both ampicillin in divided dose (1-day treatment) and ampicillin combined with probenecid in a single dose are equivalent therapeutically to a single injection of 2.2 MIU penicillin G. This agrees with the report by Groth & Hallqvist (9), the only one dealing with oral ampicillin in the treatment of women with gonorrhoea, including cases with positive rectal culture, found in the literature by the author. They successfully treated 27 cases harbouring sensitive gonococci with the same regimen as in group C in this material.

In the course of the years there has been much discussion as to whether there are more relapses in rectal than in urogenital gonorrhoea. Opinions on this point have differed (1, 3, 10, 12, 18). In this material there is a statistically higher proportion of treatment failures in group G than in the total female material (Fig. 7). This is in agreement with recommendations of a higher dosage of penicillin G in rectal cases (3, 19).

It seems that treatments B and C can safely be used also for patients with positive rectal culture although certain problems remain concerning the choice between these two modes of treatment. Admittedly, treatment with a single dose is an advantage, but treatment B implies that the patient is given two drugs with allergenic properties. In treatment C a single drug is given but in two doses, even if on the same day (1-day treatment). On the basis of the results the routine administration of 1-day treatment might be well recommended as first alternative, but patients who for any reason may be suspected of not taking the second dose (e.g. owing to a misunderstanding arising from language difficulties) had better be treated with a single combined dose of ampicillin and probenecid.

ACKNOWLEDGEMENTS

I am grateful to Gösta Wallmark, M.D., for the bacteriological work in connection with this study, to Lars Hedström, Fil. lic., Statistical Research Group, University of Stockholm, for statistical evaluation, and to Astra Läkemedel AB for the oral preparations used in this trial.

REFERENCES

1. Bang, J.: Demonstration of gonococci in rectal cultures. Acta Dermatovener (Stockholm) *34:* 4, 1954.
2. Barr, J. & Danielsson, D.: Personal communication, 1970.
3. Enfors, W.: A survey of female patients with gonorrhoea at St. Görans sjukhus, 1954–1958. Acta Dermatovener (Stockholm) *40:* 393, 1960.
4. Eriksson, H., Högman, C. & Wickman, Kristina: A paper disc method for determination of bacterial sensitivity to chemotherapeutic and antibiotic agents. Scand J Clin Lab Invest *6:* Suppl. 11, 1954.

5. Eriksson, G.: Oral ampicillin in uncomplicated gonorrhoea. I. Treatment of gonococcal urethritis in men. Acta Dermatovener (Stockholm) *50:* 451, 1970.
6. — Oral ampicillin in uncomplicated gonorrhoea. II. Results of treatment in women. Acta Dermatovener (Stockholm) *50:* 461, 1970.
7. Eriksson, G., Magni, L. & Wessman, J.: Oral ampicillin in uncomplicated gonorrhoea. IV. Comparison of pharmacological and clinical results. Acta Dermatovener (Stockholm). In press.
8. Eriksson, G. & Wallmark, G.: Oral ampicillin in uncomplicated gonorrhoea. V. Comparison of bacteriological and clinical results. To be published.
9. Groth, O. & Hallqvist, L.: Oral ampicillin in gonorrhoea. Clinical evaluation. Brit J Vener Dis *46:* 21, 1970.
10. Hagerman, G.: On the factors causing recurrence after penicillin treatment of gonorrhoea. Acta Dermatovener (Stockholm) *28:* 362, 1948.
11. Hanson, H. & Juhlin, I.: Terapeutiska synpunkter på behandling av rektalgonorré. National Medical Annual Congress, Stockholm, 1969.
12. Jensen, T.: Rectal gonorrhoea in women. Brit J Vener Dis *29:* 222, 1953.
13. Juhlin, I.: Principer för behandling av gonorré. Sv Läk-Tidn *66:* 2078, 1969.
14. Molin, L.: Principer för behandling av gonorré. Sv Läk-Tidn *66:* 1008, 1969.
15. — Gonorrhoea in 1968. Acta Dermatovener (Stockholm) *50:* 157, 1970.
16. Nicol, C. S.: Some aspects of gonorrhoea in the female, with special reference to infection of the rectum. Brit J Vener Dis *24:* 26, 1948.
17. Pariser, H. & Marino, A. F.: Gonorrhoea: Frequently unrecognized reservoirs. Southern Med J *63:* 198, 1970.
18. Roepstorff, S. O. & Hammarström, E.: Experience with a selective medium in the routine diagnosis of gonorrhoea with special regard to rectal gonorrhoea in women. Acta Path Microbiol Scand *67:* 563, 1966.
19. Scott, Jane & Stone, A. H.: Some observations on the diagnosis of rectal gonorrhoea in both sexes using a selective culture medium. Brit J Vener Dis *42:* 103, 1966.
20. Thayer, J. D. & Martin, J. E.: A selective medium for the cultivation of N. gonorrhoeae and N. meningitidis. Publ Health Rep *79:* 49, 1964.
21. Wilkinson, A. E.: The use of vaginal and rectal cultures in the management of gonorrhoea in the female. Brit J Vener Dis *25:* 9, 1949.
22. — A note on the use of Thayer and Martin's selective medium for *N. gonorrhoeae*. Brit J Vener Dis *41:* 60, 1965.

Received December 23, 1970

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