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DETECTION OF REPEATED GONORRHEA BY A MODIFIED FOLLOW-UP METHOD

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Abstract. The rate of reinfection after treatment was studied in four groups of patients. The first group of 100 patients were evaluated retrospectively after treatment with 1.0 g ampicillin twice followed by two re-examinations over a 2-week period during which time intercourse was prohibited. The second and third prospective groups consisted of 100 and 200 patients respectively, treated with 1 g ampicillin twice and 1.4 g pivampicillin + probenecid respectively, with re-examinations at intervals of 1 week and 4 weeks after treatment. In these two groups sexual intercourse was allowed during the last 10 days of the follow-up period. The fourth study group consisted of all patients infected with gonococci having MIC ≥0.3 μg/ml for ampicillin and/or benzylpenicillin, who were treated with 1 g ampicillin twice during the period of 1973–76. In the first group no positive cultures were obtained at re-examination. In groups two and three, 35 out of 300 (12%) were found to have positive cultures at re-examination. Some of these were probably treatment failures. The failure rate in group four was found to be 20%, indicating that the treatment regimen used left a narrow therapeutic margin. However, the risk of re-infection, in this urban clinic, seems to be higher than the risk of treatment failure which would have remained undetected had sexual intercourse been forbidden.

Key words: Neisseria gonorrhoeae; Treatment; Ampicillin; Treatment failures; Reinfection

Oral ampicillin given in one dose with probenecid, or in two divided doses separated by a 5-hour interval has been shown to be a very effective treatment for uncomplicated gonorrhea (5, 8, 11, 14). A negative culture is usually obtained at the first re-examination after treatment. Although the National Board of Health in Sweden recommends two re-examinations within 2 weeks after treatment of gonorrhea, few additional recurrent infections are detected by the second re-examination culture (1, 3)—provided the patient complies with the instructions not to have sexual intercourse during the interim.

It is often difficult, particularly in larger cities, to find the source of infection, as the patient will often decline to name a traceable contact regardless of the efforts of clinic social work personnel (12, 13). Gonococcal infections will then persist in the social group in which the patient is sexually active; s/he will be at risk of re-infection when sexual intercourse is resumed, and may thus appear as a 'repeated' (2, 17). Re-infection is often more common than treatment failure in controlled clinical trials with effective treatment regimens (9, 14, 18).

To assess the influence of earlier resumption of intercourse on the yield of positive second re-examination cultures, we advised patients to abstain from sexual intercourse only until the first re-examination culture had been found negative, and allowed sexual activity about 10 days before the second re-examination. With this modification, the proportion of patients found to have positive post-treatment cultures was higher than previously observed with the conventional method of follow-up The relative contribution of treatment failure to this high rate of relapse will be discussed.

MATERIAL AND METHODS

Patients

Four groups of patients were studied (Table I). All patients were treated for uncomplicated urogenital gonorrhea at the outpatient clinic for venereal diseases at Sodersjukhuset, Stockholm.

Group 1. Fifty consecutive male and 50 consecutive female patients were treated during October and November 1975, with two doses of 1.0 g ampicillin (Doktacillin, Astra Pharmaceutical) separated by a 5-hour interval (5). The first post-treatment culture was obtained one week after treatment and the patients were requested to return for one further reexamination and culture 2 weeks after treatment and refrain from sexual intercourse until the second control culture was reported negative. The results of re-examinations were analysed retrospectively.

Group 2. During November and December 1976, 50 consecutive males and 50 consecutive females were studied prospectively. Treatment was the same as in Group 1. The patients were asked to return for two re-

Table I. *Treatment regimens, re-examinations schedule and constraints on sexual activity following treatment for study groups*

Study group	Females	Males	Treatment	No. of weeks Post-treatment Re-exam 1	Re-exam 2	Comment
2	50	50	Ampicillin 1 g, twice	1	4	Sexual intercourse allowed 10 days after re-examination 2. Retrospective
2	50	50	Ampicillin 1 g, twice	1	4	Sexual intercourse allowed 10 days after re-examination 1
3	100	100	Pivampicillin 1.4 g + probenecid 1 g	1	4	Sexual intercourse allowed 10 days after re-examination 1
4	19	36	Ampicillin 1 g, twice	1	2	Sexual intercourse proscribed until 10 days after re-examination 2. MIC ≥0.3 for penicillin G and/or ampicillin. Retrospective

examinations, one and 4 weeks after treatment. They were asked to refrain from sexual intercourse only until 10 days after the first re-examination, allowing time to contact them if their first post-treatment cultures were positive.

Group 3. From September to December 1977, 100 consecutive males and 100 consecutive females were treated once with 1.4 g pivampicillin (Pondocillin, Lovens Pharmaceutical), and 1.0 g probenecid (Probecid, Astra Pharmaceutical) (11). The re-examination schedule and recommendation to avoid intercourse during the follow-up period was identical with the instructions given to patients in Group 2.

Group 4. The medical records were reviewed of all 55 patients seen during 1973–76 from whom gonoccal strains were isolated requiring ≥0.3 μg/ml of penicillin G and/or ampicillin for inhibition, as calculated from the results of the disc diffusion method. All 55 received the same treatment as Groups 1 and 2 and had returned for at least one post-treatment culture.

Laboratory methods

At all visits, samples for microscopy and culture were taken from the urethra of all patients, from the cervix and rectum of females, and from other sites when indicated. The smears were stained with methylene blue and microscopy was immediately performed by the physician in the clinic. The samples for culture were collected on charcoaled swabs and transferred into modified Stuart's transport medium (15), and within a few hours inoculated onto selective and non-selective media (4). In 1977 the samples from females were inoculated directly onto the same media, placed in a candle jar at 37°C, and after a few hours transported to the laboratory for further incubation in a CO_2 incubator. Suspected gonococcal colonies were identified by means of microscopy, oxidase test and sugar utilization tests. Sensitivity to penicillin G and ampicillin was determined by the single-disc diffusion technique, from which the MIC was calculated (5). (Strains with a MIC of ≥0.1 μg/ml of benzylpenicillin G or ampicillin were considered as less sensitive.)

Table II. *Results of follow-up in patient Group 2, in relation to penicillin sensitivity of initial strain and resumption of intercourse showing relationship of recurrent infection at second re-examination vs. re-exposure*

F = females, M = males, MIC = minimal inhibitory concentration of ampicillin in μg/ml

Re-examination	Patient sex	Number	Penicillin sensitivity of initial isolates from patients with positive cultures: Admitted intercourse MIC <0.1	Admitted intercourse MIC ≥0.1	Denied intercourse MIC <0.1	Denied intercourse MIC ≥0.1	Patients with negative cultures: Admitted intercourse	Denied intercourse	Not re-examined
1	F	50	–	–	2	1	3	42	2
	M	50	–	–	1	1	2	45	1
	Total	100	–	–	3	2	5	87	3
2	F	45	2	–	–	–	15	23	5
	M	47	2	–	–	–	11	24	10
	Total	92	4	–	–	–	26	47	15

Table III. *Results of follow-up in patient Group 3, with regard to sensitivity of initial strains and resumption of intercourse*

F = females, M = males, MiC = minimal inhibitory concentration of ampicillin in μg/ml

Re-examination	Patient sex	Number	Penicillin sensitivity of initial isolates from patients with postive cultures				Patients with negative cul-tures		
			Admitted intercourse		Denied intercourse				
			MIC <0.1	MIC ≥0.1	MIC <0.1	MIC ≥0.1	Admitted intercourse	Denied intercourse	Not re-examined
1	F	100	3	–	–	–	10	85	2
	M	100	4	1	4	5	6	77	3
	Total	200	7	1	4	5	16	162	5
2	F	95	4	–	–	–	43	37	11
	M	83	3	1	1	–	38	32	8
	Total	178	7	1	1	–	81	69	19

[a] Showing relationship of recurrent infection at second re-examination vs. re-exposure.

Epidemiological methods

All patients were interviewed at the time of treatment by a social worker and asked to identify and refer sex partners for examination. They were also informed about the need to return for a check-up and how long they had to refrain from sexual intercourse. The same social workers (A.J. and M.H.), interviewed all the patients. Efforts were made to display the same attitude and epidemiological routine in the two prospective studies (patient Groups 2 and 3) as in the retrospective group (patient Group 1). Fisher's exact test was used for statistical evaluation of the data.

RESULTS

Persistent and recurrent infections in Group 1

In patient Group 1, for which intercourse was proscribed during the entire follow-up period after initial treatment, no positive cultures were obtained from any of 94 patients at the first exam or from the 83 patients who returned for the second examination. This was in agreement with earlier studies from the same clinic (5).

Persistent and recurrent infection in Group 2

The rate of persistent or recurrent infection in study Group 2 (Table II) was higher than in Group 1 ($p<0.001$). Group 2 was studied one year later, and again differed in that the interval between the first and second re-examination was 3 weeks and that intercourse was allowed during the last 10 days before the second re-examination. Five of 97 (5%) patients in Group 2 had positive cultures at the first re-examination one week after treatment and were again treated. Four of 77 (5%) had a positive culture at the second re-examination. The MIC of ampicillin was ≥0.1 μg/μl for the initial isolate in 2 of 5 patients with positive cultures at the first re-examination, and none of 4 at the second re-examination. Sexual re-exposure was not admitted by any of those with positive cultures at the first re-examination, but by all of those with positive cultures at the second re-examination.

Persistent and recurrent infections in Group 3

Patients were treated with 1.4 g pivampicillin and 1.0 g probenecid in an alternative regimen recommended by the National Board of Health in Sweden (Table III). At the first re-examination, positive cultures were obtained from 3 (3%) of 98 women and 14 (14%) of 97 men ($p=0.005$), including 8 (33%) of 24 who admitted intercourse and 9 (5%) of 171 who denied intercourse during the interim period ($p=0.002$). At the second re-examination, positive cultures were obtained from 9 (6%) of 159 patients, including 8 (9%) of 89 who admitted intercourse, and one (1%) of 70 who denied intercourse ($p=0.04$, one-tail test).

In summary, of the 22 patients in patient Groups 2 and 3 who had positive cultures at the first re-examination, 10 were deemed to be possible reinfections: 8 of 22 (36%) admitted sexual intercourse, compared with 21 of 270 (8%) patients with negative cultures at the first visit, and 2 patients had a ten-fold difference in MIC for two antibiotics between the initial cultures and the relapse. The remaining 12 patients denied sexual intercourse and 6 (50%) had initial cultures with MIC ≥0.1 μg/ml to

ampicillin, compared with 15%, 18%, and 16% respectively in patient Groups 1, 2, and 3.

Thirteen patients had positve cultures at the second follow-up in patient Groups 2 and 3 (Tables 2 and 3). That the positive cultures were due to re-infection is supported by the finding that 12 of 119 patients who had admitted sexual intercourse had a positive culture, compared with 1 of 107 of those who denied sexual intercourse ($p<0.001$).

In the total material (patient Groups 1, 2, and 3) 21 of 200 women (10.5%) and 45 of 200 men (22.5%) had initial cultures with reduced sensitivity to ampicillin (MIC$\geq$0.1 μg/ml). Positive post-treatment culture was obtained from one of these women and 9 (20%) of the men. The MIC was $\geq$0.1 μg/ml for pretreatment isolates from 5 of 10 who denied reexposure, vs. 2 of 16 who admitted re-exposure during follow-up ($p=0.05$, one-tail test).

Thus, the re-isolation of gonococci was more common from men than from women at the first visit; was related to sexual re-exposure at both visits; and among those not re-exposed, was related to increased resistance to ampicillin in the pretreatment isolate.

No difference in age could be found between patients with and without positive control cultures. When the patients with positive post-treatment cultures were matched with regard to sex and age with earlier patients with negative control cultures, no difference was observed in the number of earlier gonococcal infections, interval from treatment to time of post-treatment culture, or efforts of the clinic personnel to persuade the patient to return for re-examinations. No overrepresentation of homosexual men was observed in any group.

Twenty-one of 92 (23%) and 60 of 178 (34%) patients from Groups 2 and 3 respectively failed to return for their scheduled re-examination appointments, compared with 8 of 94 (9%) in Group 1. Despite repeated efforts on the part of the clinic staff and County Medical Officers to recontact those who missed their scheduled re-examination, 15 of 92 (16%) and 18 of 178 (10%) in Groups 2 and 3 respectively missed their second follow-up appointment, compared with 7 of 94 (7%) in Group 1.

Outcome of treatment in Group 4

Among the 55 patients (19 women and 36 men) in Group 4 with gonococci with MIC $\geq$0.3 μg/ml for penicillin and/or ampicillin who were treated with ampicillin 1.0 g twice with a 5-hour interval, 11 cases (20%) were deemed to be treatment failures on the basis of denial of sexual re-exposure and similar MICs of penicillin, ampicillin, tetracycline, and streptomycin for the pre- and post-treatment isolates. Four were deemed to have a probable reinfection due to isolation of gonocci fully sensitive to penicillin and ampicillin at the post-treatment visits. Another 3 patients (one woman and 2 men) had positive methylene blue smears at the first re-examination, but negative cultures.

DISCUSSION

When prolonging the interval between the first and second test-of-cure culture from one to 3 weeks and allowing sexual intercourse during the latter half of this period, 12% of the patients were found to have positive cultures at the follow-up. This is substantially more than in treatment studies using the same regimens but with intercourse prohibited (6, 7, 11).

Treatment failures contributed to this high rate of positive follow-up cultures. For example, at the first re-examination, 8 of 22 culture-positive patients had pretreatment cultures with MIC $\geq$0.1 μg/ml to ampicillin, compared with one of 13 at the second re-examination. Furthermore, 6 of these 9 strains with reduced sensitivity had MICs $\geq$0.2 μg/ml. This level of sensitivity was associated with 20% treatment failures in the retrospecitve study Group 4 comprising patients treated with ampicillin 1 g twice and pretreatment strains with MIC $\geq$0.3 μg/ml to ampicillin. That such a high failure rate has not previously been observed in Scandinavian treatment studies is probably due to the small number of patients with such strains in these studies. Strains with reduced sensitivity were found more often in men both in the retrospective and prospective study groups, and were associated with the higher rate of treatment failure in men.

In treatment studies, admission of sexual intercourse before re-examination is often taken as an indication of possible re-infection. In this study 8 of 22 (36%) of the patients with positive cultures at the first re-examination admitted intercourse and 12 of 13 (92%) of the patients with positive cultures at the second.

At the time of their first re-examination, 21 of 270 (8%) patients with negative follow-up cultures, reported having had intercourse, while 107 of 213 (50%) reported sexual activity by the time of their second visit. Part of the reporting of a higher rate of

intercourse in patients with positive cultures is related to the more intensive questioning of these patients, though the data suggest that a reservoir of undetected gonorrhea exists in the social groups in which the patient is sexually active (2).

The patients were not randomized with regard to follow-up instructions in order to avoid the resulting confusion in patient-to-patient interactions. The failure rates are well documented (5), a retrospective study (Group 1) did not indicate any deterioration of treatment results, and the overall frequency of strains with reduced sensitivity had not changed over the period studied nationally (I. Moberg, National Bacteriological Laboratory, personal communication) or locally (G. Wallmark, unpublished data). The same social workers dealt with all patients throughout the study.

The time between the first and second re-examination was extended in order to permit treatment of patients with positive cultures at the first re-examination before the recommended resumption of sexual activity. However, it appears that sexual intercourse rather than the extended time period influenced the rate of positivity. Eight of 29 patients who reported having had intercourse between the treatment and the re-examinations one week later, had positive cultures.

The change in treatment schedule, from ampicillin 1 g twice to the equimolar dose of pivampicillin (1.4 g) with probenecid, coincided with a larger number of positive cultures at the first visit, mainly in patients with strains with MIC ≥ 0.2 μg/ml to ampicillin among those who denied intercourse. Both regimens seem to leave a narrow therapeutic margin to strains with moderately higher MIC (10). At the second examination, the results were the same, with about 5% reinfections.

Minimal inhibitory concentration, MIC, was estimated by the disc diffusion method (5), since this test had been in continuous use since the previous treatment studies (6, 7), and retrospecive comparisons were thus possible. With the variability of this test in mind, it was sufficiently sensitive to show that the majority, seven of eight, recurrences with strains with MIC ≥ 0.1 μg/ml, occurred at the first visit and that strains with MIC ≥ 0.2 μg/ml had a high (20%) risk of failure with the indicated treatment regimens.

It can be concluded that in an urban enviroments, re-infection is at least as common as treatment failure, even with the relatively low antibiotic dosages used. By allowing intercourse before the final re-examination, an estimate of this frequency can be obtained and the 'repeaters' rapidly treated.

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