

SENSITIVITY OF GONOCOCCAL STRAINS TO PENICILLIN G, AMPICILLIN AND DOXYCYCLINE IN A FINNISH METROPOLITAN MATERIAL IN 1971

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Abstract. Gonococcal strains isolated at the Out-patient Department for Venereal Diseases, University Central Hospital, Helsinki in 1971 were tested for their sensitivity to penicillin G, ampicillin and doxycycline. The minimal inhibitory concentration (MIC) value for penicillin G was ≥ 0.2 IU/ml in 24.6%, for ampicillin ≥ 0.1 μ g/ml in 34.7%, and for doxycycline ≥ 1.0 μ g/ml in 18.8%. Strains with markedly decreased sensitivity to penicillin (≥ 1.0 IU/ml) are on the increase although the overall incidence of strains with decreased sensitivity has not increased since 1969. Strains with decreased sensitivity to penicillin G were, in most cases, also equally resistant to ampicillin. There was also a definite correlation between sensitivities to penicillin G and doxycycline.

The routine treatment of gonorrhoea in Finland is a single shot of 2.4-3.0 mega units of procaine penicillin. Alternatively, ampicillin is used in oral doses of 2-3 g with or without probenecide. Patients with confirmed or suspected hypersensitivity to penicillin are usually treated with doxycycline in one or two doses of 300 mg. It therefore seemed desirable to study a large series of gonococcal strains for their sensitivity to the above-mentioned antibiotics.

MATERIAL AND METHODS

The present series comprises 1 699 gonococcal strains isolated in 1971 at the Out-patient Department of Venereology, University Central Hospital, Helsinki. In 1 595 cases the strain had been contracted in Finland (93.9%). The remaining 104 strains were in most cases isolated from seamen and tourists and had in 93 cases been contracted in other parts of Europe and in 11 cases outside Europe. The series represents about one-eighth of the total number of reported cases of gonorrhoea in Finland 1971.

The specimens for culture and sensitivity determinations were obtained from the urethra (males) and urethra, cervix and rectum (females). The samples were brought

to the laboratory in Stuart's medium within 24 hours of being taken. Gonococci were classified under the usual morphological, cultural and biochemical groups. The antibiotic sensitivity tests were performed using the plate dilution method described by Reyn et al. (12) and the inoculation was carried out according to Juhlin (9). All the 1 699 strains were tested for sensitivity to penicillin G, 1 446 strains for sensitivity to ampicillin, and 1 413 strains for sensitivity to doxycycline.

RESULTS

Table I shows that 418 (24.6%) of all the 1 699 strains tested had a minimal inhibitory concentration (MIC) value for penicillin G ≥ 0.2 IU/ml and were regarded as having a decreased sensitivity. Of these 418 strains 378 had been contracted in Finland (23.7% of the total 1 595) and 40 abroad (38.5% of all 104). Strains from the other Scandinavian countries showed about the same degree of decreased sensitivity to penicillin G as those contracted in Finland, but almost half of the strains from other parts of Europe and outside Europe had a MIC value to penicillin G ≥ 0.2 IU/ml. In 103 cases (6.1% of all 1 699) the MIC value for penicillin G was ≥ 0.5 IU/ml and 41 of these (2.4% of all) had a MIC value ≥ 1.0 IU/ml. In 12 of these 103 cases (11.7%) the strain had been contracted abroad.

Altogether, 1 446 strains had been tested for their sensitivity to ampicillin (Table II). In 502 cases (34.7%) the MIC value was ≥ 0.1 μ g/ml. These were classified as having a decreased sensitivity to ampicillin. According to the classification, 465 (34.2%) of the 1 359 strains contracted in Finland and 37 (42.5%) of the 87 strains contracted abroad showed decreased sensitivity to

Table I. Sensitivity of 1699 gonococcal strains to penicillin G

Infection contracted in	Minimal inhibitory concentration (IU/ml)							Total
	0.01-0.1	0.2	0.3	0.4	0.5	0.7	≥ 1.0	
Finland	1 217	124	92	71	30	24	37	1 595
Scandinavia	26	1	3	3	1		1	35
Western and Central Europe	14	3	2	1	1	2	2	25
Eastern Europe	10	1	2	1	1	2	1	18
Southern Europe	8	2	1	4				15
Outside Europe	6	1	3		1			11
Total	1 281	132	103	80	34	28	41	1 699

Table II. Sensitivity of 1446 gonococcal strains to ampicillin

Infection contracted in	Minimal inhibitory concentration (μg/ml)					Total
	0.01-0.05	0.1	0.2	0.5	≥ 0.7	
Finland	894	181	191	75	18	1 359
Scandinavia	18	3	3	2	1	27
Western and Central Europe	9	3	4	6		22
Eastern Europe	8	2	2	5		17
Southern Europe	8	1	2			11
Outside Europe	7		2	1		10
Total	944	190	204	89	19	1 446

Table III. Sensitivity of 1413 gonococcal strains to doxycycline

Infection contracted in	Minimal inhibitory concentration (μg/ml)					Total
	0.3	0.5	1.0	2.0	≥ 3.0	
Finland	894	193	80	134	19	1 320
Scandinavia	18	3	3	7		31
Western and Central Europe	11	3	2	2	3	21
Eastern Europe	6	3	3	2	3	17
Southern Europe	6	3	1	2	1	13
Outside Europe	6	1	2	1	1	11
Total	941	206	91	148	27	1 413

Table IV. Sensitivity of 1446 gonococcal strains to penicillin G and ampicillin

Minimal inhibitory concentration (of ampicillin μg/ml)	Minimal inhibitory concentration of penicillin G (IU/ml)											Total
	0.01	0.03	0.05	0.07	0.1	0.2	0.3	0.4	0.5	0.7	≥ 1.0	
0.01	99	13	5	2	2	2	1					124
0.03	350	265	13	8	4	1	6	1	2	1		651
0.05	46	77	24	2	5	6	6	1		1	1	169
0.1	13	19	17	18	26	52	32	11	1		1	190
0.2	2	5	4	4	12	43	47	50	20	13	4	204
0.5	3	2	6	2	1	7	7	11	9	12	29	89
≥ 0.7			1	1	4	2	4	1	2		4	19
Total	513	381	70	37	54	113	103	75	34	27	39	1 446

Table V. Sensitivity of 1413 gonococcal strains to penicillin G and doxycycline

Minimal inhibitory concentration of doxycycline ($\mu\text{g/ml}$)	Minimal inhibitory concentration of penicillin G (IU/ml)							Total
	0.01-0.1	0.2	0.3	0.4	0.5	0.7	≥ 1.0	
0.3	872	36	24	6	2		1	941
0.5	165	20	10	9			2	206
1.0	32	10	19	12	9	2	7	91
2.0	27	23	15	35	16	18	14	148
≥ 3.0	3	5	3	6	2	3	5	27
Total	1 099	94	71	68	29	23	29	1 413

ampicillin. Strains from Central and Western Europe as well as strains from Eastern Europe seemed especially frequently to have a decreased sensitivity to ampicillin.

Table III illustrates the sensitivity to doxycycline of the 1413 strains tested. Altogether, 266 strains required at least 1.0 $\mu\text{g/ml}$ of doxycycline for inhibition of the growth (18.8%). This level of decreased sensitivity was found in 233 of 1320 strains contracted in Finland (17.7%) and 22 of the 93 strains contracted abroad (35.5%).

The correlation between sensitivity to penicillin and ampicillin was studied in 1446 strains (Table IV). In 915 cases the MIC value for penicillin G was <0.2 IU/ml and the MIC value for ampicillin <0.1 $\mu\text{g/ml}$ (63.3%) and 362 strains (25.0%) had a MIC value for penicillin G ≥ 0.2 IU/ml and for ampicillin ≥ 0.1 $\mu\text{g/ml}$. In the remaining 169 cases there was a discrepancy between the sensitivity to penicillin G and to ampicillin, respectively. In 29 cases (2.0% of all 1446) the MIC value for penicillin G was ≥ 0.2 IU/ml and for ampicillin <0.1 $\mu\text{g/ml}$. In 140 cases (9.7%) the strains were inhibited by 0.1 IU/ml of penicillin G or less but required 0.1 $\mu\text{g/ml}$ or more of ampicillin.

In 1413 cases the strains had been tested for their sensitivity to both penicillin G and doxycycline (Table V). The MIC value for penicillin G was <0.2 IU/ml and for doxycycline <1.0 $\mu\text{g/ml}$ in 1037 cases (73.4%) while 204 strains were resistant to both antibiotics in such concentrations (14.4%). Sixty-two strains (4.4%) showed a MIC ≥ 1.0 $\mu\text{g/ml}$ of doxycycline while the MIC value for penicillin G was <0.2 IU/ml. The remaining 110 strains (7.8%) had a MIC value ≥ 0.2 IU/ml of penicillin and a MIC value <1.0 $\mu\text{g/ml}$ of doxycycline.

DISCUSSION

The present series is not representative for Finland and not even for the Helsinki area, since it included only a little over 40% of the cases reported in Helsinki in 1971. However, it is comparable with the series collected by us in 1967 to 1969 from the same clinic (11). The series includes probably slightly more strains contracted abroad than in other areas of the country. On the other hand, the annual percentage of strains contracted abroad in the whole country is about 5% (7), which does not differ significantly from the 6% in this series.

The overall incidence of strains with decreased sensitivity to penicillin G has not changed since 1967-1969 (11). On the other hand, strains with a MIC value for penicillin G ≥ 0.5 IU/ml seem to be on the increase. In the present series, 6.1% of all strains showed such a level of decreased sensitivity as compared with 2.1% in 1968 and 4.5% in 1969. In addition, formerly rare strains with a MIC value for penicillin G ≥ 1.0 IU/ml were found in 2.4% of the present cases. Furthermore, almost 90% of them had been contracted in Finland.

Ampicillin is now a widely used drug in the treatment of gonorrhoea in many countries (2, 3, 4, 5, 6, 10). In the present series there was an obvious cross-resistance of the gonococcal strains to penicillin G and ampicillin; both sensitive and resistant strains seemed to be more sensitive to penicillin G than to ampicillin which is in contrast to earlier studies (11, 13) in which resistant strains have been found more sensitive to ampicillin than to penicillin.

The incidence of strains with decreased sensitivity to doxycycline was higher in this series than in the series of Jokipii & Renkonen (8). *Neis-*

seria gonorrhoea is known to develop resistance to tetracyclines easily (1). There was a certain cross-resistance of the strains to penicillin and doxycycline, which was also found by Jokipii & Renkonen (8). This might be because these strains have been selectively developed through unsuccessful treatments. A minority of the strains showed decreased sensitivity to doxycycline although they were sensitive to penicillin, but the opposite pattern was found almost twice as often.

The present series shows that in Finland penicillin is still the drug of choice in the routine treatment of gonorrhoea, but the increase of highly resistant strains demands that the sensitivity to penicillin must be kept under continuous observation.

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