Sensitivity of *Neisseria gonorrhoeae* to antibiotics in London (1976-78)

A. D. SETH, B. KOLATOR, AND A. E. WILKINSON

From the Venereal Diseases Reference Laboratory (PHLS), London Hospital Research Laboratories, London

SUMMARY Three surveys of the sensitivity of pretreatment isolates of gonococci to penicillin, ampicillin, tetracycline, spectinomycin, streptomycin, and co-trimoxazole were carried out during the period 1976-78. Compared with the results of previous surveys in the London area the decline in the proportion of strains of gonococci which are insensitive to penicillin appears to have halted. No changes were found in the levels of resistance to ampicillin, tetracycline, or spectinomycin during the period surveyed, although there was a slight increase in the proportion of strains requiring concentrations of 20 µg spectinomycin per ml for inhibition. Streptomycin resistance has decreased considerably and 91% of strains are now sensitive to 10 µg streptomycin per ml.

Introduction

The emergence of strains of *Neisseria gonorrhoeae* in the middle 1950s which were relatively insensitive to penicillin was rapidly followed by an increase in their prevalence; this trend was more marked in the United States than in the United Kingdom. Martin *et al.* (1970) found that only 0.6% of American strains isolated before 1955 had minimum inhibitory concentrations (MICs) greater than 0.03 µg/ml; in 1965 this figure had risen to 42% and between 1968 and 1969 to 65%. In a national survey carried out from 1972 to 1974 on 4405 isolates from 10 major American cities 70% of the strains had an MIC of ≥ 0.06 µg/ml, a figure almost identical with that of a previous survey carried out from 1970 to 1971 (Jaffe *et al.*, 1976). Marked differences were found in the proportion of the most resistant strains with an MIC of >0.5 µg/ml in different areas, from 7% in Des Moines to 26.6% in Denver; the overall figure for the whole survey was 17.4%.

More recently, penicillin resistance among gonococci appears to have shown a marked decline in the United States, from 53.2% of strains with an MIC of 0.25 µg/ml in 1972 to 29.2% in 1975 (Reynolds *et al.*, 1976). A similar rise and fall in the proportion of resistant strains has been found in Denmark but resistance is said to have increased during 1976 (World Health Organisation, 1978). The

appearance of β -lactamase-producing strains of gonococci early in 1976 (Ashford *et al.*, 1976) suggested that the favourable trend of decreasing resistance of gonococci to penicillin might be halted, but with the exception of the localised outbreak in Liverpool between 1976 and 1977, which was rapidly contained (Arya *et al.*, 1978), these strains do not appear to have been able to establish themselves in Europe or America.

Although sensitivity studies on nationally collected strains provide an overall picture of patterns of sensitivity, these may not reflect local situations because of geographical variations in sensitivity. This report presents the results of three annual surveys of strains isolated in the East End of London and compares them with previous reports from the London area.

Materials and methods

The strains studied were isolated from patients attending the Whitechapel Clinic at the London Hospital before any treatment was given. Cultures were made on Oxoid brain heart infusion agar with 10% horse blood containing 3.0 µg/ml vancomycin and 7.5 µg/ml colistin. Organisms were identified as *N. gonorrhoeae* on the basis of their colonial and microscopical morphology, a positive oxidase reaction, and the production of acid from glucose but not from maltose, lactose, or saccharose. Three surveys were made: June to December 1976 (454 strains), January to March 1977 (225 strains), and May to September 1978 (274 strains).

Address for reprints: Dr A. E. Wilkinson, VD Reference Laboratory, London Hospital, Ashfield Street, London E1 2BL

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SENSITIVITY TESTS

A plate-dilution method was used in which doubling dilutions of antibiotics were incorporated in brain heart infusion agar with 10% horse blood. Oxoid diagnostic sensitivity test agar with 5% lysed horse blood and 1% Kellogg's defined supplement was used in tests for sensitivity to co-trimoxazole.

Growth from an overnight culture was suspended by a vortex mixer in Oxoid nutrient broth to give an opacity corresponding to a McFarland No. 2 tube and transferred to the series of antibiotic-containing plates and an antibiotic-free control by a multipoint inoculator (Denley Instruments, Billingshurst, Sussex). This gave an inoculum of approximately 10^4 colony-forming units (cfu). Control strains of known sensitivity (IRC 3, IRC 5, obtained from the State Serum Institute, Copenhagen) and the Oxford staphylococcus were included in each set of tests. Plates were incubated for 48 hours in candle-extinction jars at 36°C and the MIC taken as the highest dilution of antibiotic which gave no growth or only a single colony.

Results

The results of three surveys from 1976 to 1978 of the sensitivity of gonococci to the six antibiotics tested are shown in Tables 1-3 and are compared with earlier surveys from the London area in Table 4. The patterns of sensitivity to tetracycline and streptomycin among the strains which were found to be insensitive to penicillin are shown in Table 5.

Discussion

PENICILLIN

In the surveys reported by Rodin and Seth (1972) and Taylor and Seth (1975) the method used was the same as in the present study except that a multipoint inoculator was not used, so that the results are comparable. Differences in the medium, technique, and inoculum size used in the other series (Table 4) allow only a general comparison of results. These show a similar trend to that found in the United States and in Denmark, a rise in the proportion of the most resistant strains (MIC 0.125 µg/ml) from 1958 to a peak between 1968 and 1970, followed by a decline until 1976, and a slight increase from this year to 1978. The proportion of strains with an intermediate level of sensitivity (0.03-0.06 µg/ml) also increased from 19.1% in 1976 to 25.3% and 25.6% in 1977 and 1978 respectively. These may be chance variations and further surveys will be necessary to determine whether the proportion of resistant strains is again increasing.

The appearance of β -lactamase-producing strains has not significantly affected the position in the area

Table 1 Sensitivity of gonococci to penicillin, ampicillin, tetracycline, and spectinomycin

MIC (µg/ml)	% of strains		
	1976	1977	1978
Penicillin			
≤0.004	30.6	18.2	18.3
0.008	25.6	27.1	27.0
0.015	6.4	9.8	7.3
0.03	7.9	8.4	8.4
0.06	11.2	16.9	17.2
0.125	8.6	10.2	8.0
0.25	5.7	7.1	7.3
≥0.5	4.0	2.2	6.6
No. of strains tested	454	225	274
Ampicillin			
≤0.004	0.4	0.4	
0.008	19.2	12.4	
0.015	25.0	27.1	
0.03	11.6	14.7	
0.06	12.5	13.3	
0.125	20.1	20.0	
0.25	8.9	11.1	
≥0.5	2.2	0.9	
No. of strains tested	224	225	
Tetracycline			
≤0.06	1.1	1.8	3.3
0.125	24.7	22.2	38.0
0.25	40.1	40.0	24.1
0.5	21.6	23.1	22.0
1.0	11.5	12.0	12.0
≥2.0	1.1	0.9	0.7
No. of strains tested	454	225	274
Spectinomycin			
≤5	13.7	13.3	16.1
10	80.4	83.1	71.9
20	5.9	3.6	12.0
40	0	0	0
No. of strains tested	454	225	274

Table 2 Sensitivity of gonococci to streptomycin

MIC (µg/ml)		% of strains		
10	500	1976	1977	1978
S	S	76.7	83.1	90.9
R	S	5.5	1.8	0.7
R	R	17.8	15.1	8.4
No. of strains tested		454	225	274

S = sensitive; R = resistant

Table 3 Sensitivity of gonococci to trimethoprim-sulphamethoxazole (1978)

MIC (µg/ml)		% of strains
TMP	SMX	
0.06	1.87	2.8
0.125	2.375	7.9
0.25	4.75	23.3
0.5	9.5	36.0
1.0	19	23.7
2.0	38	5.9
4.0	76	0.4
No. of strains tested		253

TMP = trimethoprim; SMX = sulphamethoxazole

Table 4 Sensitivity of gonococci to penicillin in the London area (1958-78)

Authors	Year	No. of strains tested	% resistant*
Curtis and Wilkinson	1958	302	14.2
Cradock-Watson <i>et al.</i>	1958	200	10.5
Nicol <i>et al.</i>	1968	91	37.4
Leigh <i>et al.</i>	1969	189	20.0
Phillips <i>et al.</i>	1970	96	35.0
Rodin and Seth	1972	228	32.9
Taylor and Seth	1975	277	30.0
Phillips <i>et al.</i>	1976	264	30.0
Platt	1976	95	25.3
Present series	1976	454	18.3
	1977	225	19.5
	1978	274	21.9

*MIC ≥ 0.125 μ g/ml or ≥ 0.2 units/ml.

Table 5 Percentage of resistance to tetracycline or streptomycin or both among gonococci with diminished sensitivity to penicillin (1976-78)

Antibiotic		% of strains		
		1976	1977	1978
Penicillin	R	16.9	36.4	48.3
Tetracycline	S			
Streptomycin	S			
Penicillin	R	9.6	6.8	23.3
Tetracycline	R			
Streptomycin	S			
Penicillin	R	44.6	38.6	10.0
Tetracycline	S			
Streptomycin	R			
Penicillin	R	28.9	18.2	18.3
Tetracycline	R			
Streptomycin	R			
No. of strains		83	44	60

Penicillin R = MIC ≥ 0.125 μ g/ml; tetracycline R = MIC ≥ 1 μ g/ml; streptomycin R = MIC ≥ 10 μ g/ml

served by the Whitechapel Clinic. Three such strains were found in 1976, two in 1977, and two in 1978; they formed less than 0.2% of the gonococci isolated from clinic patients over the period and were traceable to importations from outside the London area.

AMPICILLIN

The distribution of sensitivity of gonococci to ampicillin was similar in 1976 and 1977; 31.2% and 32% of the strains had MICs of ≥ 0.125 μ g/ml respectively.

TETRACYCLINE

No changes in the proportion of insensitive strains (MIC ≥ 1.0 μ g/ml) were detected during the three surveys: 12.6% in 1976, 12.9% in 1977, and 12.7% in 1978. These insensitive strains tended to show decreased sensitivity to penicillin. In 1978 25 of 35 strains with an MIC to tetracycline of ≥ 1.0 μ g/ml had MICs of ≥ 0.125 μ g penicillin/ml. The

proportion of strains with decreased sensitivity to tetracycline is considerably less than the figure of 30% reported by Phillips *et al.* (1970).

SPECTINOMYCIN

No strains resistant to spectinomycin were found during the period surveyed, but the proportion of strains requiring a concentration of 20 μ g/ml for inhibition rose slightly to 12% in 1978. Two of these 33 strains were also insensitive to penicillin, four to tetracycline, and one to streptomycin. Because of the value of spectinomycin for the treatment of infections with β -lactamase-producing strains of gonococci, restriction in its use has been recommended to lessen the risk of emergence of spectinomycin-resistant strains. These show high-level resistance which has been observed to develop during treatment (Reyn *et al.*, 1973). This is evidently a very rare event; Karney *et al.* (1977) found no evidence of increased resistance when this antibiotic was used as a routine form of treatment for 2938 patients over a period of two years. However, while there are equally effective and cheaper alternatives available for routine treatment, restriction of the use of spectinomycin seems a wise precaution.

STREPTOMYCIN

The rapid development of high-level resistance to streptomycin led to its abandonment for the treatment of gonorrhoea. Resistance was usually linked to diminished sensitivity to penicillin. In 1970 about a third of the strains had an MIC of ≥ 12.5 μ g/ml (Phillips *et al.* 1970). The results of the present surveys (Table 2) show that the proportion of streptomycin-resistant strains fell progressively, and in 1978 90.9% of the strains were sensitive to a concentration of 10 μ g/ml. In this period 43 of 60 strains with an MIC of ≥ 1.125 μ g penicillin/ml were sensitive to 10 μ g/ml of streptomycin. A similar fall in resistance to streptomycin has been reported in surveys in Denmark (WHO, 1978).

CO-TRIMOXAZOLE

Co-trimoxazole was tested only in 1978 (Table 3). There was some correlation between the sensitivity to penicillin and to the trimethoprim-sulphamethoxazole mixture. Thirty-four (60.7%) of 56 strains with an MIC of ≥ 0.125 μ g penicillin/ml required ≥ 1.0 μ g/ml trimethoprim plus 19 μ g/ml sulphamethoxazole for inhibition compared with 21.3% of 197 strains which were sensitive to ≤ 0.06 μ g penicillin/ml.

MULTIPLE RESISTANCE AMONG PENICILLIN-INSENSITIVE STRAINS

Gonococci with diminished sensitivity to penicillin often show resistance to other antibiotics such as the

tetracyclines and streptomycin (Table 5). During the three years covered by the surveys there was a progressive decrease in the proportion of strains which had a multiple resistance, and in 1978 almost half the strains which were insensitive to penicillin were sensitive to both tetracycline and streptomycin.

Gonorrhoea is usually treated on the finding of presumptive gonococci in Gram-stained smears before the results of cultures and sensitivity tests are available. This presupposes a knowledge of the usual patterns of sensitivity of the gonococcal strains in local circulation. The results of these surveys show that, with the exception of the rare β -lactamase-producing strains, treatment with penicillin or ampicillin plus probenecid should still give high cure rates in this area. Tetracycline resistance is not common and does not seem to be increasing. Spectinomycin should also be very effective, but its general use is thought to be inadvisable. Further surveys will be needed to see whether the present favourable trend continues.

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