

Increased Antibiotic Resistance of *Neisseria gonorrhoeae* in Korea

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There has been a marked increase in the resistance of *Neisseria gonorrhoeae* isolated in Korea to penicillin, ampicillin, and tetracycline. In contrast, there has been no increased resistance to spectinomycin.

Treatment failures of patients with gonorrhea in Korea have been reported for many years (2, 3, 10). Increased resistance of *Neisseria gonorrhoeae* has been correlated with treatment failures (4). To determine the extent of decreased susceptibility of strains recently isolated in Korea, the minimal inhibitory concentrations (MICs) of the commonly recommended antibiotics, penicillin, ampicillin, tetracycline, and spectinomycin, were determined and compared to strains isolated in 1958.

Bacterial isolates. *N. gonorrhoeae* was isolated from uncomplicated cases of gonorrhea in 1958 (17 cases) and 1974 (67 cases). Strains isolated in 1974 were obtained randomly over a 7-month period. No attempt was made to identify strains from patients in whom treatment had previously failed. Over 90% of the patients claimed that this was their first episode of gonorrhea. The identity of all gonococcal isolates was confirmed by a Gram stain, oxidase reaction, and fermentation of dextrose, but not maltose, sucrose, or lactose. Isolates were preserved by lyophilization in skim milk and stored in the Department of Bacterial Diseases, Walter Reed Army Institute of Research. Two strains of *N. gonorrhoeae* (4826, 4309) and a strain of *Staphylococcus lutea* of known antibiotic susceptibility obtained from the Center for Disease Control were used as controls.

Media. Agar dilution susceptibility tests were carried out on agar prepared from GC medium base plus defined supplement (7).

Antibiotics. Solutions of penicillin, ampicillin, tetracycline, and spectinomycin were prepared in distilled water from standard powders obtained from the National Reference Center for Antibiotic Analysis of the Food and Drug Administration and corrected to antibiotic base concentration.

Agar dilution technique. Antibiotic solutions were added to molten agar at 50 C to give

the desired concentrations and stored at 8 C for no longer than 10 days.

The bacterial inoculum was prepared by scraping the growth from a GC agar plate after 16 to 18 h of incubation at 37 C in a candle jar and preparing a suspension in GC broth to a concentration of approximately 10^7 organisms. A 100-fold dilution was made in GC broth.

Using a modified Lidwell phage replicator apparatus, 0.03 ml of each suspension was transferred to each antibiotic-containing plate, and incubated at 37 C in CO₂ for 48 h. The lowest antibiotic concentration to completely inhibit visible growth was taken as the MIC.

Statistical analysis. The mean, variance, and correlative coefficients were computed on a Hewlett-Packard 9810A calculator (Hewlett-Packard Calculator Products Division, Loveland, Col.). The unpaired Student's *t* test and analysis of variance were used to compare geometric MIC increases of tetracycline and penicillin.

Resistance of *N. gonorrhoeae* isolated in Korea to penicillin increased dramatically from 1958 to 1974 (Table 1), the mean MIC increasing 10-fold from 0.089 to 0.87 $\mu\text{g/ml}$.

A similar trend for ampicillin and tetracycline was also noted (Table 1). Also, there is a direct correlation of cross-resistance between penicillin and tetracycline (Fig. 1). On the other hand, the susceptibility to spectinomycin remained unchanged (Table 1).

The documentation of decreasing susceptibility of *N. gonorrhoeae* to penicillin was not unexpected (8, 11, 12). The association of treatment failures with isolates susceptible only at the higher ranges tested is well documented (4, 5), and this is certainly a plausible explanation for the difficulties in treatment experienced in Korea. Although there are risks in comparing data from various laboratories, the finding that 69% of strains had an MIC greater than 1 $\mu\text{g/ml}$

TABLE 1. MIC ($\mu\text{g/ml}$) of four antibiotics for *Neisseria gonorrhoeae*

Antibiotic and year	Antibiotic concn										Total no. of strains
	0.0039	0.0078	0.0156	0.0312	0.0625	0.125	0.25	0.5	1	2	
Penicillin											
1958		1 ^a	5	6		2	2	1			17
1974			1		1	7	4	8	40	6	67
	≤ 0.0025	0.05	0.1	0.2	0.4	0.8	1.6	≥ 3.2			
Ampicillin											
1958	7	5	1	4						17	
1974		1	2	12	46	6				67	
Tetracycline											
1958	1			4	11		1			17	
1974				2	1	8	19	37		67	
	1	2	4	8	10	12	14	16	32		
Spectinomycin											
1958			1	5	11					17	
1974			1	28	27	10	1			67	

^a Number of strains inhibited.

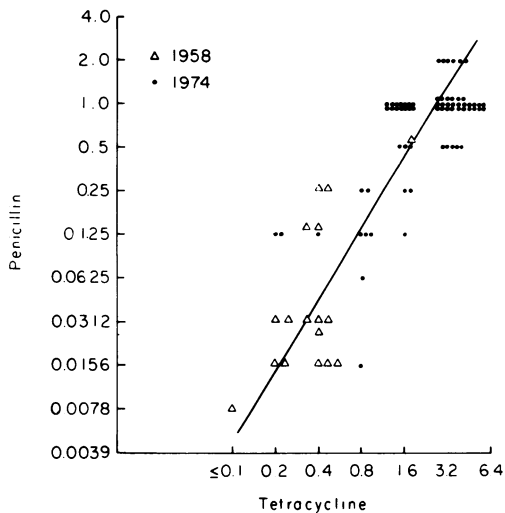


FIG. 1. Correlation of MICs of penicillin and tetracycline. Correlation coefficient = 0.5819, $P < 0.001$.

(1.6 IU/ml) and 9% at 2 $\mu\text{g/ml}$ suggests that a high degree of resistance existed (4, 6). Furthermore, the question as to how much longer the recommended dose of 4.8 million units of procaine penicillin plus probenidic will be adequate treatment for patients in Korea was raised.

The concomitant rise in resistance to ampicillin and tetracycline (Table 1) has been reported by others (1, 6). On the other hand, the susceptibility to spectinomycin was the same for

strains isolated in 1958 and 1974 (Table 1), which is probably a reflection of its relatively recent introduction as a therapeutic agent for gonorrhea. Also, in another study comparing current treatment regimen in the United States, the spectinomycin treatment results appeared to be independent of the isolate's susceptibility to other antibiotics (60). However, resistance to spectinomycin has been produced in the laboratory (9), and thus the search for other effective drugs must be maintained.

The reasons for such a marked increase in resistance of strains isolated in Korea is problematical, but the availability of "over the counter" antibiotics and their resultant indiscriminant use probably plays a major role.

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