

## Penicillin Resistant *Neisseria gonorrhoeae* Infection in Selected Clinic Populations

Investigators :                      John W. Crum, MAJ, MSC  
   Somnuk Vibulyasekha, COL, MC, RTA  
   Kalaya Suthisomboon, MD  
   Supath Suvanamalik, MD  
   Chiraphun Duangmani, MD

### OBJECTIVES :

1. To study patients having a bacteriologically confirmed infection with *N. gonorrhoeae*.
2. To identify gonococcal infections resistant to penicillin and to demonstrate evidence of penicillinase production by chemical and culture techniques.
3. To attempt to relate laboratory findings to chemotherapeutic success or failure.
4. To refine and make locally available a simple and rapid screening technique for penicillinase production.
5. To investigate various methods of specimen collection and techniques for future study, to include the immunological aspects of this disease.

**BACKGROUND :** Between 1972 and 1974 an increasing resistance to penicillin of *N. gonorrhoeae* infections was demonstrated in Bangkok (1). During 1976, world-wide reports of isolations of penicillinase producing strains of *N. gonorrhoeae*, suggested that a serious problem of great public health importance existed (3). The epidemiologic evidence shows an almost world-wide incidence of penicillinase producing strains and links many cases to travelers from residents of Australia, Belgium, Canada, Denmark, Hong Kong, Japan, Korea, Singapore, Sweden, Switzerland, the United Kingdom, and the United States. West Africa and the Far East also appear to be significant factors in the spread of infection (2). Determination of penicillin resistance and penicillinase production are not routinely performed by most venereal disease clinics or physicians.

This Laboratory, in collaboration with the Royal Thai Army Hospital's venereal disease clinic, demonstrated that penicillinase production occurred in 8% of 105 isolates over a 7 month period and that 55% of the isolates had penicillin minimum inhibitory concentrations, MIC, of between 0.4 and 1.2 units per milliliter. It was also demonstrated that 62% of patients reporting symptoms of gonorrhoeae were culture positive (3).

**METHODS :** Collaborative investigation efforts between our Laboratory, the Bangruk Hospital and the Royal Thai Army Hospital have provided a group of male and female patients for study. The Ban Chiwi Clinic, a subsidiary venereal disease unit of the Bangruk Hospital, is the source of female patients and the

Royal Thai Army Hospital's Venereal Disease Clinic is the source of male patients. Patients were selected as demonstrating clinical symptoms of *Neisseria gonorrhoeae* infection. Patients whose infections were resistant to treatment were followed (4).

*N. gonorrhoeae* (5) strains isolated from patients were collated with MIC testing data and with the production of penicillinase as demonstrated by the penicillin plate inhibition method (6), and by the iodometric and cephalosporin techniques (7). Experience with the iodometric and cephalosporin methods for penicillinase production as well as with the culture plate sensitivity technique allowed laboratory personnel to refine and make locally available the culture plate technique for rapid screening.

In addition to specimens for bacteriological identification, serum and vaginal washings were obtained for future investigation of the immunological aspects of the disease. Attempts will be made to correlate with case history files, penicillinase production, and penicillin MIC trends. Lyophilized isolates from all cases were retained.

RESULTS : Eighty two males and 100 females with a penicillin MIC greater than 0.2 Units per milliliter were studied from 13 March 1978 through 31 August 1978. Eight males and nine females demonstrated beta-lactamase production and very high penicillin MIC's (Table 1). Males had initial treatment as 5 megaunits of penicillin G sodium, intramuscular, and probenecid 1 gm, oral. Refractory patients in general were treated with Kanamycin, 2 gm., intramuscular. Initial standard treatment of females was Probenecid, 1 gm.(oral) and Ampicillin, 3.5 gm.(oral). Refractory patients were treated, in general, with more penicillin. Four representative case histories are presented in Table 2.

Table 1

Male (n=8)		Female (n=9)	
Case	MIC(U/ml)	Case	MIC(U/ml)
A2	40	BC30	10
A5/A19	40	BC43	40
A47	40	BC53	40
A49	10	BC94	10
A61	40	BC189	40
A78/A83	40	BC192	40
A131	40	BC194	40
A132	40	BC209	5
		BC211	40

Table 2. Selected case historys

Case A2 : 21 yrs., male, single, symptomatic 3 days after contact exposure.  
culture positive *N. gonorrhoea*

1st treatment : Pen. G sodium 5 MU(IM), Probenecid 1 gm.(oral)  
3 days after, pus occurred, no contact exposure  
culture positive *N. gonorrhoea*

2nd treatment : Kanamycin 2 gm.(IM) 1 dose  
1 day after, asymptomatic  
culture negative *N. gonorrhoea*

Case A5/A19 : 32 yrs., male, chronic urethritis for 2-3 weeks,  
last contact exposure over one month  
culture positive *N. gonorrhoea*

1st treatment : Pen. G sodium 5 MU(IM), Probenecid 1 gm.(oral)  
1 week later, discharge and dysurea  
culture positive *N. gonorrhoea*

2nd treatment : Kanamycin 2 gm.(IM) 1 dose  
1 month later, asymptomatic  
culture negative *N. gonorrhoea*

Case BC192 : 20 yrs., bar girl, leukorrhoea and itching, 2-3 days  
smear positive *N. gonorrhoea*

1st treatment : Probenecid 1 gm.(oral), Ampicillin 3.5 gm.(oral)  
1 day later, leukorrhoea  
smear and culture positive *N. gonorrhoea*

2nd treatment : Probenecid 1 gm.(oral), Ampicillin 3.5 gm.(oral)  
1 day later, no signs, symptoms present  
smear negative *N. gonorrhoea*, no culture taken

3rd treatment : Probenecid 1 gm.(oral), Ampicillin 3.5 gm.(oral)  
20 days later, lower abdominal bilateral pain, 2 days  
smear negative *N. gonorrhoea*, no culture taken

4th treatment : Trobicin (Sepectinomycin dihydrochloride) 2 gm.(IM)  
1 day later, symptoms diminishing  
smear negative *N. gonorrhoea*

5th treatment : Trobicin 2 gm.(IM)  
no patient follow-up

Case BC209 : 21 yrs., bar girl, leukorrhea, 1 day  
smear and culture positive N. gonorrhoea

1st treatment : Probenecid 1 gm.(oral), Ampicillin 3.5 gm.(oral)  
 1 day later, leukorrhea  
smear negative N. gonorrhoea

2nd treatment : Probenecid 1 gm.(oral), Ampicillin 3.5 gm.(oral)  
 18 days later, leukorrhea  
smear negative N. gonorrhoea  
culture positive N. gonorrhoea

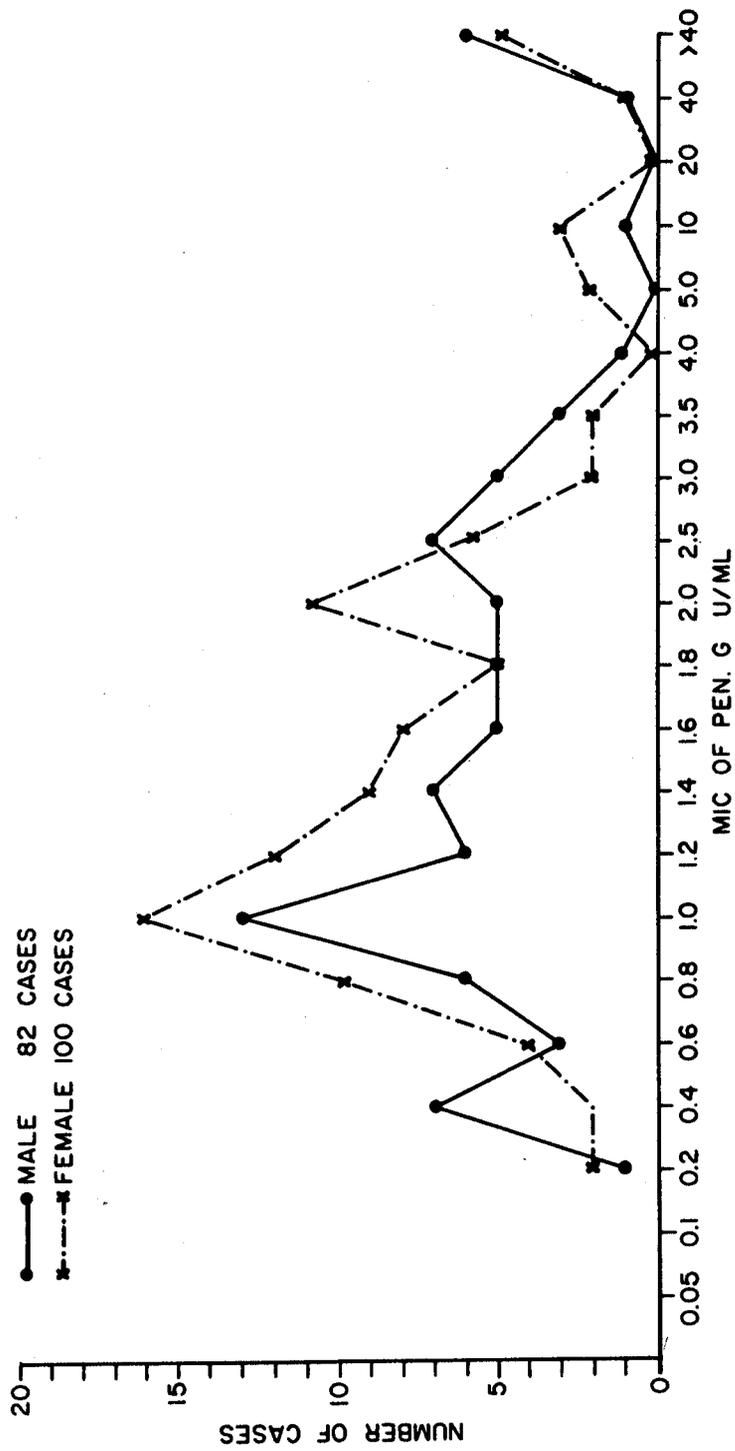
3rd treatment : Trobicin 2 gm.(IM)  
 1 day later, leukorrhea  
smear and culture negative N. gonorrhoea

Ten percent of the male patients and nine percent of the female patients (nine percent of all patients) with MIC's greater than 0.2 Units per milliliter were infected with penicillinase producing *N. gonorrhoea*. Seventy six percent of the PPNG positive patients had MIC's of 40 U/ml. or greater (Table 3). The male and female pattern of MIC activity is summarized in Table 4.

Table 3. Pattern of pen. G MIC (U/ml) activity

MIC Pen. G U/ml.	Male (n=82) Cases	Female (n=100) Cases
0.05	0	0
0.1	0	0
0.2	1	2
0.4	7	2
0.6	3	4
0.8	6	10
1.0	13	16
1.2	6	12
1.4	7	9
1.6	5	8
1.8	5	5
2.0	5	11
2.5	7	6
3.0	5	2
3.5	3	2
4.0	1	0
5.0	0	2
10.0	1	3
20.0	0	0
40.0	1	1
40.0	6	5

TABLE IV  
 MINIMUM INHIBITORY CONCENTRATION (MIC) PATTERN



REFERENCES :

1. Spence, M.R., *et al.* : Changing Penicillin Resistance of the Gonococcus in Thailand, 32-34, J. Am. Vener. Dis. Assn., 3(1), 1976.
2. Scatliff, J.N.R. : Editorial-Penicillinase-Producing Gonococci and the Public Health, 11-12, Can. J. of Pub. Health, 68, 1977.
3. Duangmani, Chiraphun, *et al.* : A Laboratory Study of Venereal Disease as *Neisseria gonorrhoea* in Male Patients over a 7 Month Period, Annual Report-1978 USAMC AFRIMS, Bangkok (1977).
4. Warren, R.M. : Symposium-Differential Diagnosis of Gonorrhoea, 729-733, The Practitioner, 217, 1976.
5. Lennette, E.H., *et al.* : Manual of Clinical Microbiology, 70, 124, Am. Soc. for Micro. Wash. D.C., 1974.
6. Tramont, E.C. : Personal Communication, Culture Plate Method-Penicillin Inhibition Testing, Walter Reed Army Institute of Research, Wash. D.C., 1977.
7. Thornsberry, C. : Rapid Laboratory Tests for Beta-Lactamase Production by Bacteria, U.S. Dept. Health, Ed., and Welfare Center for Disease Control, Atlanta, Ga.