

Minimum Inhibitory Concentrations (MIC) of Penicillin G and
Ampicillin for *Neisseria gonorrhoeae*

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OBJECTIVE: To determine the minimum inhibitory concentrations (MIC) of penicillin G and ampicillin for *Neisseria gonorrhoeae* in Thai males and to determine serum levels of ampicillin and ampicillin combined with probenecid in the single oral dose used to treat uncomplicated gonorrhea.

BACKGROUND: Despite the spread of resistant strains of *Neisseria gonorrhoeae* throughout the world, penicillin remains the drug of choice for the disease because of its minimal cost and low toxicity. The resistant strains are not absolutely resistant and the majority will respond provided a suitably high serum level of penicillin can be reached and maintained for a long enough period of time.

A single oral dose of ampicillin appears to be the most convenient and effective treatment for uncomplicated gonorrhea. Oral ampicillin combined with oral probenecid produces a higher serum ampicillin level of longer duration than ampicillin alone. To test the efficacy of this treatment regimen the following study was conducted. The study is divided into two parts:

PART I:

DESCRIPTION: This part of the study was carried out at the V.D. Clinic, Royal Thai Army Hospital, Bangkok, from November 1972 to January 1974. A total of 280 male patients presented with purulent urethral discharge of uncomplicated gonorrhea.

Specimens were obtained with cotton swabs from the urethra and streaked directly on Thayer—Martin agar with hemoglobin, isovitalax and V.C.N. added (TM Media) and on blood agar plates for culture of *N. gonorrhoeae* and other possible causative organisms. The TM plates were incubated at 35—37°C in candle jars and observed at 48 hrs. Typical oxidase positive colonies of gram negative diplococci were tested for dextrose, maltose and sucrose fermentation. Blood agar plates were incubated anaerobically at 37°C. Organisms were identified after 24 hrs incubation.

The MIC's of penicillin and ampicillin were determined with initial isolates of *N. gonorrhoeae* by the agar plate dilution technique. The concentrations of ampicillin used were 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.4 µg/ml. Concentrations of penicillin G were 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 IU/ml.

RESULTS: A total of 280 patients were studied. Pure gonococcus isolates were obtained from 33 cases (11.7%). The other 247 cases (88.3%) were mixed infections. The bacteria other than *N. gonorrhoeae* isolated from mixed infections are listed in Table 1. Penicillin G MIC's for ampicillin were determined on 158 isolates. The definition of sensitivity is that proposed by Amies (1) and is based on the average peak blood level after a therapeutic dose of a particular drug has been administered. The term "less

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Table 1. Bacteria other than *N. gonorrhoeae*
Isolated from Mixed Infections

Organisms	Number of Isolates	Percentage
Staph. epidermidis	113	46.1
Staph. aureus	9	3.7
Alpha streptococcus	33	13.5
Beta streptococcus	1	0.4
Gamma streptococcus	11	4.5
Streptococcus fecalis	6	2.5
Diphtheroids	18	7.3
Micrococcus spp.	52	21.2
Enterobacter cloacae	1	0.4
Pseudomonas spp.	1	0.4
TOTAL	245	100.0

sensitive" refers to those organisms which will continue to multiply in the presence of > 0.05 IU/ml of penicillin or 0.8 μ g/ml of ampicillin. In this study 98% of the isolates were shown to be less sensitive to penicillin and 3.2% less sensitive to ampicillin.

DISCUSSION: This report indicates that the frequency of recovery of strains of *N. gonorrhoeae* less sensitive to penicillin has increased 10.6% since our report on the year 1971-1972 in which 87.2% of the strains studied in this laboratory were less sensitive to penicillin G (2). Most of the patients in the present study had medicated themselves with antibiotics purchased from drug stores without the prescription of a physician. This antibiotic pressure may be responsible for the increase of less sensitive strains.

The MIC's of ampicillin to gonococcal strains showed fewer isolates with reduced sensitivity (3.2%). Ampicillin given orally is still effective against *N. gonorrhoeae*.

PART II:

DESCRIPTION: Ten male patients with uncomplicated gonorrhea were studied. All were hospitalized throughout the course of infection at the Royal Thai Army Hospital, Bangkok. Two sets of blood specimens were obtained from each subject. A control specimen of 3 ml of blood was taken from each patient when admitted. Ampicillin (2 gm) was administered orally in a single dose and blood specimens were taken 30 minutes, 1, 2, 4, 6, 8, 10 and 12 hours afterward.

The following day 1 gm of probenecid and 2 gm of ampicillin were given to the same patients and the same sampling schedule was followed.

RESULTS: Ampicillin serum levels after an oral dose of 2 gm with and without 1 gm of probenecid are presented in Table 4. The mean maximum concentration was observed at 2 hours (9.2 μ g/ml) and the

Table 2. Minimum Inhibitory Concentration of penicillin G for *N. gonorrhoeae**

MIC of Penicillin G IU/ml	No. of Strains	Percentage
< 0.05	2	1.1
0.05	2	1.1
0.1	3	1.6
0.2	15	8.2
0.4	18	9.8
0.6	38	20.8
0.8	31	17.0
1.0	31	17.0
1.2	14	7.6
1.4	10	5.5
1.6	6	3.3
1.8	9	4.9
2.0	1	0.5
> 2.0	3	1.6
TOTAL	183	100

* Less sensitive strains = 97.8% (Definition of less sensitive strain = MIC > 0.05 IU/ml).

drug was detectable until 8 hours after administration. When 1 gm of probenecid was administered with the ampicillin, the highest mean serum level observed was 18.7 $\mu\text{g/ml}$ at the 4th hour. Serum levels remained high until 6 hours after administration, then decreased rapidly to 0.05 $\mu\text{g/ml}$ in the samples obtained at 12 hours (Fig. 1).

DISCUSSION: The data presented in Table 4 illustrate that there was a variation in serum ampicillin levels among the ten patients. Many factors such as protein binding of the antibiotic, the status of the gastric mucosa during treatment, presence or absence of food, and the enzyme penicillinase produced by some organisms in the body may play a role in this variation. A single oral dose of ampicillin combined with probenecid produced higher serum levels than ampicillin alone. The drug was detectable in serum at one-half hour and increased to a maximum concentration at 4 hours after ampicillin and probenecid were administered. The serum level remained high until 6 hours and decreased to minimum levels after 12 hours.

Table 3. Minimum Inhibitory Concentrations of Ampicillin for *N. gonorrhoeae**

MIC of Ampicillin $\mu\text{g/ml}$	No. of Strains	Percentage
0.1	5	3.2
0.2	34	21.5
0.4	55	34.8
0.6	35	22.2
0.8	24	15.2
1.0	4	2.5
1.4	1	0.6
TOTAL	158	100

* Less sensitive strains = 3.2 % (Definition of less sensitive strains = MIC > 0.8 $\mu\text{g/ml}$).

REFERENCES :

1. Amies, C.R.: Sensitivity of *Neisseria gonorrhoeae* to penicillin and other antibiotics. Studies carried out in Toronto during the period 1961-1968. *Brit. J. Vener. Dis.* 45: 216, 1969.
2. McMinn, M.T.: The SEATO Medical Research Laboratory Annual Report, April 1972.

Table 4. Serum Concentration ($\mu\text{g/ml}$) after Oral Dose of 1 gm Ampicillin with and without 1 gm Probenecid

Cases	Hours after Administration								
	0	1/2	1	2	4	6	8	10	12
1. Without	0	0	1.8	13.8	7.9	2.1	0	0	0
With	0	4.6	10.6	ND	12.5	7.9	6.8	3.2	0
2. Without	0	1.6	1.6	6.1	6.1	2.8	1.6	0	0
With	0	5.3	9.3	4.0	23	5.3	1.7	1.6	0
3. Without	0	1.6	2.0	7.3	2.3	1.6	0	0	0
With	0	1.6	3.3	6.5	9.2	9.2	4.9	2.4	1.6
4. Without	0	1.5	8.8	18.5	3.3	0	0	0	0
With	0	12.5	12.3	42	20	7.8	3.5	1.5	1.5
5. Without	0	0	2.5	9.3	6.1	3.2	1.5	1.5	0
With	0	0	4.8	13.8	26.8	13.8	6.7	4.6	2.1
6. Without	0	0	5.7	7.5	0	6.7	3.3	1.4	0
With	0	2.7	6.5	11.5	14.5	6.2	2.5	1.5	0
7. Without	0	1.5	1.5	2.9	1.5	1.5	0	0	0
With	0	0	11.2	24.2	7.2	2.1	1.5	0	0
8. Without	0	0	0	19.0	5.4	2.1	1.3	0	0
With	0	0	1.5	10.0	6.0	> 100	6.5	1.5	0
9. Without	0	8.8	13.2	3.0	6.0	0	0	0	0
With	0	0	4.0	25.5	29	11.5	3.5	1.4	0
10. Without	0	0	0	4.3	6.6	2.3	0	0	0
With	0	0	1.6	5.7	38.5	14.5	6.6	2.2	0

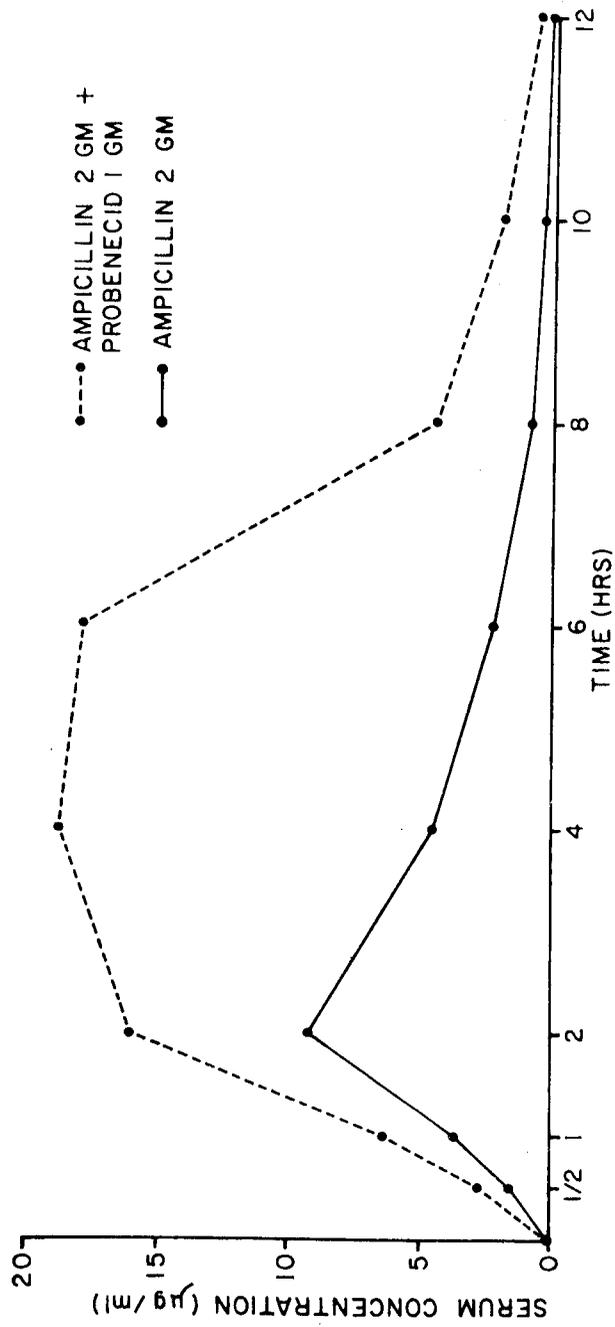


FIGURE 1. MEAN SERUM AMPICILLIN LEVELS AFTER ORAL DOSES ADMINISTRATION (10 CASES)