# Development Frequency of Penicillinase-producing Neisseria Gonorrhoeae (Jung-gu Community Health Center in Seoul, 1994-1998)

Tae Ho Rhee, M.D., Jae-Hong Kim, M.D.

*Department of Dermatology, Hanyang University College of Medicine, Seoul, Korea*

***Background*** **: Gonorrhea is one of the most common venereal diseases in the world. Antibiotic-resistance development has been an issue with the penicillinase-producing Neisseria gonorrhoeae (PPNG) development. It is possible for PPNG to be resistant to other medications. Therefore, it is significant to determine its frequency rate and its disposition.**

***Objective*** **: In this surveillance, we examined overall development frequency of PPNG from 1981 to 1998. Comparing current five years' frequency rate with that of previous five years, we predicted possible development rate and described the procedures the physicians must take into account in gonorrhea treatment.**

***Methods*** **: We examined the development frequency of PPNG in male patients of the venereal disease clinic of Jung-gu Community Health Center in Seoul from 1981 to 1998. Also, we analyzed the overall tendency with time series analysis using statistics package, SPSS 7.5. Grouping the years in five-year units, development frequency of PPNG of current five years (1994-1998) was compared with that of previous years.**

***Results*** **: For the result of monthly analysis of frequency rate of PPNG development from 1981 to 1998, the rate tendency came out with a slight rise (slope : 0.15). And for the result of comparison of grouped years, in current five years, its rate was 51.6%, marking a significant decline from that of the previous five years, which was 57.2 % (*p*-value : <0.0001).**

***Conclusion*** **: The rate of current five years was reported to have declined from the previous years. However, the rate is still over 50%. Therefore, the government should continue the PPNG surveillance with test of sensitivity of the medications in use. Moreover, to eliminate gonorrhea, the education on high risk groups should continue and physicians should use a dose of adequate antibiotics in treatment. (Ann Dermatol 14(2) 77-81, 2002).**

*Key Words :* Jung-gu community health center

Gonorrhea is one of the most common venereal diseases in the world, especially in developing countries. Neisseria gonorrhoeae was first identified from a urethral discharge by Neisser in 1879. The discovery of penicillin marked an epoch in gonorrhea treatment. However, when a group of strains that showed resistance to penicillin through $\beta$-lactamase formation was reported in Britain[1] and the United States[2] in 1976, the issue of antibiotic-resistance and the necessity of alternative therapy were raised. In Korea, PPNG was first recognized in an American soldier serving in Korea by Hernandez in 1978[3], and in 1979[4] the first Korean with PPNG was reported by Chong.

The sensitivity of N. gonorrhoeae to antibiotics and the frequency rate of PPNG vary within regions a great deal. Penicillin is only recommended in regions where resistance is found lower than 5% under surveillance[5]. Currently, the most commonly

Received June 1, 2001.
Accepted for publication August 10, 2002.
**Reprint request to** : Tae Ho Rhee, M.D., Department of Dermatology Hanyang University College of Medicine Haengdang-dong, Seongdong-ku, Seoul 133-792
Tel. (02)2290-8434, Fax. (02)2291-9619

used antibiotics are cephalosporin, spectinomycin, and newer fluoroquinolones[6-9]. Besides PPNG, tetracycline-resistant N. gonorrhoeae first appeared in 1985 in the United States[10,11]. Since then, it has become prevalent all over the world. Some state that tetracycline-resistant strain development may be promoted when used in other venereal diseases such as Chlamydia trachomatis infection[12,13].

We examined male gonorrhea patients in Jung-gu Community Health Center in Seoul. We looked at the overall frequency rate of PPNG development from 1981 to 1998 and compared the rate with that of previous years. We recognized the current tendency and predicted possible tendency that might come.

## MATERIALS & METHODS

### Patients and analysis

The subject of the analysis was 5133 male gonorrhea inpatients in the venereal disease clinic in Jung-gu Community Health Center from 1981 to 1998. Those who were under other treatments before and the ones who are allergic to medications were excluded. Patients were examined monthly on the development frequency of PPNG, and based on this surveillance, we did a time series analysis using statistics package, SPSS 7.5. From the analysis, we analyzed the overall tendency of its frequency rate from 1981 to 1998. Also to see the current tendency we grouped fifteen years from 1984 to 1998 in five-year units and examined its frequency rate. And using chi-square test, we perceived its importance.

### Isolation and identification of N. gonorrhoeae

Before treatment, we first extracted specimens from the patient's urethral meatus by inserting a sterilized cotton stick 1.0-1.5 Cm into the urethral meatus. Then, we smeared the specimens on the slide glass and using Gram stain, we examined diplococci that showed Gram negative in leukocyte. We rolled the objective in Z form on modified Thayer-Martin medium and cross-diluted using platinum loop. Then, we cultured it in a candle jar of 35-37 ℃ for 24 to 48 hours. If the growth of colonies showed a typical appearance of N. gonorrhoeae, we did an additional oxidase test and wat ched for its color change.

### Detection of β-lactamase

To detect β-lactamase formation in colonies, we did a modified chromogenic cephalosporin test. Test chemicals were made by diluting 10mg of nitrocefin (Nitrocefin, Glaxo, London) with 1ml of dimethyl sulfoxide and adding 19ml of phosphate buffer solution (pH 7.0). Chemicals were sterilized using millipore filter (pore size, 0.22μm) and kept in 4-10 ℃.

Using platinum loop, we smeared groups of colonies on the slide and poured a drop of chemicals in the next two minutes. If the test chemical turned orange in thirty seconds, then it was judged as β-lactamase positive. If the test chemical did not show any change in another fifteen minutes, then it was judged as β-lactamase negative.

Table 1. Prevalence of PPNG strains isolated at the venereal disease clinic of Jung-gu Community Health Center in Seoul, Korea from 1981 to 1998.

| year | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 |
|---|---|---|---|---|---|---|---|---|---|
| NG | 899 | 916 | 679 | 791 | 993 | 848 | 646 | 461 | 231 |
| PPNG | 197 | 283 | 178 | 214 | 429 | 378 | 339 | 258 | 130 |
| % of PPNG | 21.9 | 30.9 | 26.2 | 27.1 | 43.2 | 44.6 | 52.5 | 56.0 | 56.3 |
| year | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 |
| NG | 162 | 123 | 98 | 187 | 168 | 97 | 136 | 99 | 93 |
| PPNG | 80 | 58 | 51 | 139 | 109 | 41 | 53 | 44 | 60 |
| % of PPNG | 49.4 | 47.2 | 52.0 | 74.3 | 64.9 | 42.3 | 39.0 | 44.4 | 64.5 |

NG (*Neisseria gonorrhoeae*), PPNG (*penicillinase-producing Neisseria gonorrhoeae*)

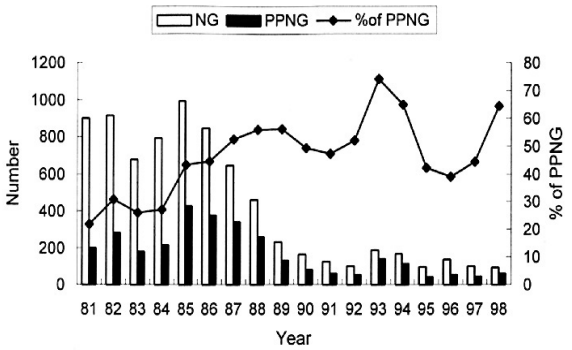


Fig. 1. Number of PPNG isolates, prevalence of PPNG as proportion of reported gonococcal isolates at the venereal disease clinic of Jung-gu Community Health Center in Seoul, Korea, 1981-1998.

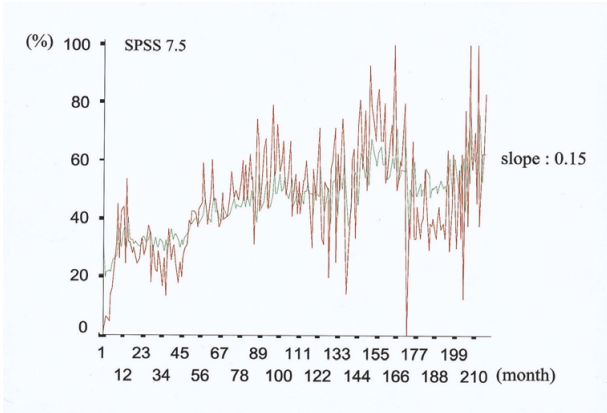


Fig. 2. Time series analysis : The red colored units are examined results whereas the blue colored units are expected results that came out from the autoregressive process. The blue shows a bit of a variation, but the analyzed slope is 0.15 (statistics package : SPSS 7.5)

## RESULTS

Yearly frequency rate of PPNG development in eighteen years from 1981 to 1998 is shown in table 1. From the table, we can see that the absolute number of gonorrhea and PPNG patients have decreased. However, the frequency rate of PPNG in general has raised (figure 1).

In figure 2, to have a closer examination of its tendency, we made a time series analysis using statistics package, SPSS 7.5 with monthly development rate as its unit. The red colored units are examined results whereas the blue colored units are expected results that came out from the autoregressive process. The blue shows a bit of a variation, but the analyzed slope is 0.15, which stands for a slight increase.

To see the frequency rate of PPNG development and its tendency along with its current tendency, we compared its rate within fifteen years from 1984 to 1998 in groups of three in five-year units (figure 3). Frequency rate of PPNG development from 1984 to 1998 was 43.3% (NG : 3739, PPNG : 1618) whereas from 1989 to 1993, it was 57.2% (NG : 801, PPNG : 458). The rate has increased from the previous five years. From 1994 to 1998, the rate was 51.6% (NG : 593, PPNG : 307), which shows a decline from the previous five years. And in chi-square test, *p*-value came out under 0.0001, showing a significant rise and decline.

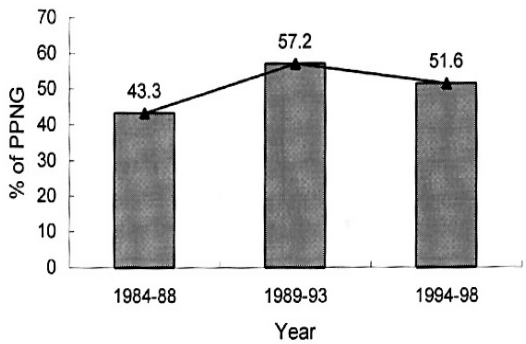


Fig. 3. Comparison between the frequency rate of PPNG in the recent five years and the past ten years based on a 5-year-unit study.

## DISCUSSION

Gonorrhea is one of the most common sexually transmitted diseases in the world, especially in developing countries and its sequelae include pelvic inflammatory disease which may lead to infertility and ectopic pregnancy. However, in many countries, it is reported that its rate is abruptly declining. The decrease is the result of control programs carried out since 1970 and the behavioral change due to the appearance of AIDS[14]. Control of sexually transmitted diseases including gonorrhea is important to prevent these sequelae and because treatment

has been shown to reduce the incidence of HIV infection[15,16].

However, its resistance to antibiotics has been continuously brought about, so adequate choice of antibiotics is important. Its resistance development toward antibiotics and its further spread has several factors. Antibiotic-resistance is usually involved with the introduction of new strains to a community through infection and its spread in high risk groups[17-20]. Its medications may add resistance to a part of strains through selective pressure[11,21-23]. In addition, non-compliancy of the patients and self-treatment may promote its development[17,19,20,23]. Antibiotic-resistance varies in regions a great deal. Therefore, for physicians to make a better choice of medications, there needs to be a surveillance data based on regions, nations, and the world. Currently countries like the United States[8], Canada[24], Australia[25], Netherlands[5] and some others are continuously doing a surveillance data on the sensitivity of gonorrhea. And through the GASP (global antimicrobial susceptibility programme) which collects data from the American Continent, the Caribbean, the western Pacific and south east Asia[26], we can gather data of sensitivity.

In many cases, PPNG shows resistance to other antibiotics like tetracycline. Its examination is important in the elimination of gonorrhea. Our institution has been examining and reporting the development rate of PPNG in the venereal disease clinic in Jung-gu Community Health Center since 1981.

In this surveillance, we have found that the frequency rate in the current five years has declined significantly. Its possible reasons may be the use of quinolones or ceftriaxone as medications, the relative possibility of development diminishing, the growing recognition of PPNG by physicians or the increase of the patients going to clinics instead of pharmacies. Perhaps the number of subjects of the surveillance was too few, and the development was tentatively preponderant.

There are four reasons why the government should continue the surveillance. Firstly, it is the microbiologically instability of N. gonorrhoeae and its possibility of antibiotics-resistance development. Secondly, it is possible that N. gonorrhoeae that shows resistance to penicillin may show resistance to other antibiotics. Thirdly, it works as a guiding index to the nation's condition of medical service and public health. Finally, it can contribute to the elimination of gonorrhea by helping to choose adequate medication for the most common venereal disease, gonorrhea.

On the basis of this surveillance data, we can predict that the more people recognize venereal diseases, more people will go to clinics and hospitals, and as a result, physicians will be more discreet in the treatment of gonorrhea. Moreover, because sexual patterns, such as the use of condoms, are changing due to the increase of AIDS development, PPNG development will gradually decrease even though it may increase a bit in the future.

Though the frequency rate of PPNG development in the recent five years is still over 50%, it has declined from the past years. To eliminate gonorrhea, physicians must use a dose of adequate antibiotics and give their patients insight of the dangerous factors that may be infected by resistant strains. Moreover, the government must provide education on high risk groups and continue the test of sensitivity of the medications in use like cephalosporins and fluoroquinolones along with the PPNG surveillance.

## REFERENCES

1. Phillips I. Beta-lactamase producing, penicillin-resistant gonococcus. Lancet 2:656-657, 1976.
2. Ashford WA, Golash RG, Hemming VG. Penicillinase-producing Neisseria gonorrhoeae. Lancet 2:657-658, 1976.
3. Hernandez FI. Penicillinase producing Neisseria gonorrhoeae (PPNG) among US military in Korea. Yonsei Reports on Tropical Medicine 9:107, 1978.
4. Chong YS, Park KJ, Kim HS, et al. Isolation of beta-lactamase producing Neisseria gonorrhoeae. Yonse Med J 20:133-137, 1979.
5. Laar MJW van de, Duynhoven YTHP van, Dessens M, et al. Surveillance of antibiotic resistance in Neisseria gonorrhoeae in the Netherlands, 1977-95. Genitourin Med 73:510-517, 1997.
6. Centers for Disease Control. Antibiotic-resistant strains of Neisseria gonorrhoeae. Policy guidelines for detection, management and control. MMWR 36(suppl 5S):1S-18S, 1987.
7. Centers for Disease Control. 1985 STD treatment guidelines. MMWR 34(suppl 4S): 83S-86S, 92S-94S, 1985.
8. Schwarcz SK, Zenilman JM, Schnell D, et al. Na-

tional surveillance of antimicrobial resistance in Neisseria gonorrhoeae. JAMA 264:1413-1417, 1990.
9. Centers for Disease Control. 1993 STD treatment guidelines. MMWR 42(RR-14):4-5, 1993.
10. Centers for Disease Control. Tetracycline-resistant Neisseria gonorrhoeae-Georgia, Pennsylvania, New Hampshire. MMWR 34:563-564, 569-570, 1985.
11. Knapp JS, Zenilman JM, Biddle JW, et al. Frequency and distribution in the United States of strains of Neisseria gonorrhoeae with plasmid-mediated high-level resistance to tetracycline. J Infect Dis 155: 819-822, 1987.
12. Klingeren B van, Dessens-Kroon M, Verheuvel M. Increased tetracycline resistance in gonococci in the Netherlands. Lancet ii:1278, 1989.
13. Lewis DA, Ison CA, Forster GE, Goh BT. Tetracycline-resistant Neisseria gonorrhoeae. Characteristics of patients and isolates at a London genitourinary medicine clinic. Sex Transm Dis 23:378-383, 1996.
14. Laar MJW van de, Pickering J, Hoek JAR van den, Griensven GJP van, Coutinho RA, Water HPA van de. Declining gonorrhoea rates in the Netherlands, 1976-1988: consequences for the AIDS epidemic. Genitourin Med 66:148-155, 1990.
15. Catchpole MA. The role of epidemiology and surveillance systems in the control of sexually transmitted diseases. Genitourin Med 72:321-329, 1996.
16. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment sexually transmitted diseases on HIV infection in rural Tanzania: randomized controlled trial. Lancet 346:530-536, 1995.
17. Zenilman JM, Bonner M, Sharp KL, Rabb JA, Alexander ER. Penicillinase-producing Neisseria gonorrhoeae in Dade County, Florida: evidence of core-group transmitters and the impact of illicit antibiotics. Sex Transm dis 15:45-50, 1988.
18. Rothenberg R, Voigt R. Epidemiologic aspects of control of penicillinase-producing Neisseria gonorrhoeae. Sex Transm Dis 15:211-216, 1988.
19. Hook EW 3d, Brady WE, Reichart CA, Upchurch DM, Sherman LA, Wasserheit JN. Determinants of emergence of antibiotic-resistant Neisseria gonorrhoeae. J Infect Dis 159:900-907, 1989.
20. Handsfield HH, Rice RJ, Roberts MC, Holmes KK. Localized outbreak of penicillinase-producing Neisseria gonorrhoeae; paradigm for introduction and spread of gonorrhea in a community. JAMA 261: 2357-2361, 1989.
21. Boslego JW, Tramont EC, Takafuji ET, et al. Effects of spectinomycin use on the prevalence of spectinomycin-resistant and of penicillinase-producing Neisseria gonorrhoeae. N Engl J Med 317:272-278, 1987.
22. Telzak EE, Spitalny KC, Faur YC, et al. risk factors for infection with plasmid-mediated high-level tetracycline resistant Neisseria gonorrhoeae. Sex Transm Dis 16:132-136, 1989.
23. Reichart CA, Neumann T, Foreman P, Zenilman JM, Hook EW 3d. Temporal trends in gonococcal antibiotic resistance in Baltimore. Sex Transm Dis 19:213-218, 1992.
24. Dillon JR. National microbiological surveillance of the susceptibility of gonococcal isolates to antimicrobial agents. Can J Infect Dis 3:202-206, 1992.
25. Members of the Australian Gonococcal Surveillance Programme. Penicillin sensitivity of gonococci in Australia: development of Australian gonococcal surveillance programme. Br J Vener Dis 60: 226-230, 1984.
26. Ison CA, Dillon JR, Tapsall J. The epidemiology of global antibiotic resistance among Neisseria gonorrhoeae and Haemophilus ducreyi. Lancet 351(Suppl III):8-11, 1998.