Epidemiology and treatment of gonorrhoea caused by penicillinase-producing strains of *Neisseria gonorrhoeae* in Fukuoka, Japan

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SUMMARY Thirty strains of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) were detected by a rapid iodometric method out of 206 strains isolated from patients with gonorrhoea between January and December 1981. Of the 30 patients, five of the nine women were prostitutes and 14 of the 21 men were infected by prostitutes in or around Fukuoka City, with the exception of one who was infected in Formosa. Treatment with ampicillin or amoxycillin resulted in failure whereas treatment with spectinomycin was successful.

Introduction

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains were isolated for the first time in 1976 in the United Kingdom¹⁻³ and in the United States⁴ and since have been found in many countries all over the world.⁵ Although we reported the antibiotic sensitivity patterns of 25 PPNG strains and 130 non-PPNG strains isolated in Fukuoka, Japan, in 1981⁶ the epidemiology of PPNG strains in Japan has not been reported. In the present study we determined the epidemiology and results of treatment in 30 patients with gonorrhoea due to PPNG strains who attended Urabe Hospital, Fukuoka City, Japan, in 1981.

Patients and methods

All the isolates of penicillinase-producing *N gonorrhoeae* (PPNG) were obtained from patients attending Urabe Hospital between January and December 1981. They were identified by Gram-stained microscopy, the oxidase reaction, and their ability to produce acid from glucose but not from lactose, maltose, and sucrose (tested by the Minitek System, BBL). Their ability to reduce nitrate was also determined. The production of β -lactamase by gonococcal isolates was examined by a rapid iodometric method.⁷

The sensitivity of PPNG strains to penicillin G, amoxycillin, doxycycline, and spectinomycin was determined by the agar dilution method.⁶

Gonorrhoea was treated with four drug regimens as summarised in table I. The results of treatment were evaluated by the following criteria:

Cure—Diplococci were absent in Gram-stained smears, and follow-up cultures gave negative results. When more than 10 pus cells per high power field ($\times 100$ objective) were found in the urethral smear, postgonococcal urethritis (PGU) was considered to be present. In the case of female patients postgonococcal cervicitis (PGC) was also noted.

Failure—Diplococci were present in Gram-stained smears or follow-up culture for *N gonorrhoeae* gave a positive result.

TABLE I Treatment schedules for gonorrhoea

Drug	Dose/day	Route	Duration of treatment (days)*
Ampicillin	1.5 g	Oral	3-7
Amoxycillin	1.0 g	Oral	3-7
Doxycycline	200 mg	Oral	3-7
Spectinomycin	2.0 g	Intramuscular	Single dose

*All patients were required to return within three to four days for follow-up.

Results

EPIDEMIOLOGY

Of 206 isolates of *N gonorrhoeae*, 30 (14.6%) produced penicillinase. The epidemiology of

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gonorrhoea due to PPNG strains is summarised in table II. Of the 30 patients, 21 were men and nine women; five of the nine women were prostitutes, and 14 of 21 infections in men were acquired from prostitutes. With one exception (case No 8), a man who had been infected in Formosa, the men were infected in or around Fukuoka City. The incidence of infection due to PPNG strains was relatively high in September and December. Five pairs of patients were related epidemiologically.

TABLE II *Epidemiological data of patients harbouring PPNG strains isolated in Fukuoka (1981)*

Month	Case No*	Age (years)	Sex	Occupation	Source
March	1	18	F	Prostitute	
	2	22	M		Common-law wife
April	3	21	M		Girlfriend
	4	26	M		Prostitute
May	5	45	M		Prostitute
	6	39	F		Boyfriend
July	7	27	M		Prostitute
	8	48	M		Prostitute
	9	33	M		Prostitute
August	10	25	M		Prostitute
	11	24	M		Prostitute
September	12	22	F	Prostitute	
	13	20	F	Prostitute	
	14	20	F	Prostitute	
	15	21	M		Common-law wife
	16	28	F		Husband
	17	33	M		Prostitute
October	18	31	M		Girlfriend
	19	28	M		Prostitute
	20	27	M		Bar girl
November	21	26	M		Bar girl
	22	27	M		?
	23	21	M		Girlfriend
December	24	32	M		Prostitute
	25	22	F		Boyfriend
	26	28	M		Prostitute
	27	27	F	Prostitute	
	28	22	F		Husband
	29	24	M		Prostitute
	30	28	M		Girlfriend

*Patients in case Nos 1 and 2, 5 and 6, 14 and 15, 16 and 17, 28 and 29 were epidemiologically related

MINIMUM INHIBITORY CONCENTRATIONS

The distributions of minimum inhibitory concentrations (MICs) of penicillin G, amoxycillin, doxycycline, and spectinomycin for each gonococcal strain are shown in table III. As we reported previously⁶ MICs for PPNG strains of penicillin G, amoxycillin, or doxycycline were very high compared with those for non-PPNG strains. All the isolates were sensitive to spectinomycin.

TREATMENT AND FOLLOW-UP

Treatment and the results of follow-up of each patient are shown in table III and the cumulative data summarised in table IV. Initial treatment with ampicillin of six of seven patients and with amoxycillin of all of 16 patients resulted in failure; one patient who

was cured with ampicillin was a prostitute (case No 12), but postgonococcal urethritis and cervicitis developed. Of the 28 patients treated with spectinomycin, eight did not return for follow-up. In 19 of 20 cases who were available for follow-up the treatment was successful; treatment of one patient, a prostitute (case No 14), was not successful. The incidence of PGU after treatment with spectinomycin was 10%. Doxycycline was successful in the treatment of two of three patients with gonorrhoea.

Discussion

Our present study shows that PPNG strains are becoming an increasing problem in Fukuoka, Japan. Thirty (14.6%) out of 206 isolates produced penicillinase. Furthermore, these PPNG strains appear to have established themselves in the local population, mainly among prostitutes. The role of prostitutes in the spread of PPNG strains has been stressed previously⁸ and has been confirmed by our data on the source of infection. Importation of PPNG strains from other countries no longer plays a major role in the spread of PPNG strains in our patients.

Almost all patients treated with ampicillin or amoxycillin were not cured; spectinomycin was the only drug that produced acceptable cure rates. Spectinomycin was successful in the treatment of gonorrhoea caused by both non-PPNG^{9,10} and PPNG⁸ strains. The Center for Disease Control (Atlanta, Georgia, USA)^{11,12} also recommend spectinomycin as first-line treatment. Our in-vitro susceptibility tests showed that all PPNG isolates were sensitive to spectinomycin, and spectinomycin 2 g intramuscularly proved to be effective in the treatment of 27 of 28 patients.

The default rate of 28.6% illustrates the importance of treatment that will be rapidly successful. It is probable that patients who did not return for follow-up were cured. Treatment failure occurred in one patient, a prostitute, and the possibility of reinfection could not be eliminated.

Although doxycycline was successful in the treatment of two of three patients its efficacy cannot be evaluated in only a few cases. As indicated previously⁶ the MICs of doxycycline for PPNG strains were appreciably higher than for non-PPNG strains. Nayyar *et al*⁸ also reported that PPNG strains seemed to be less sensitive to tetracycline than non-PPNG strains isolated in Rotterdam. Further evaluation of tetracycline in the treatment of gonorrhoea caused by PPNG strains is needed.

Because of the urgent need for alternative treatment for patients infected with PPNG strains β -lactamase-resistant cephalosporins or cefamycins have been used recently. Cefotaxime,^{13,14} cefuroxime,^{15,16} and

TABLE III MICs of antibiotics and results of treatment of gonorrhoea due to PPNG strains (1981)

Case No	MIC ($\mu\text{g/ml}$) of:										Second treatment			
	First treatment					Second treatment					Drug	Days*	Result†	Result‡
	Penicillin G	Amoxycillin	Doxycycline	Spectinomycin	Drug	Days*	Result†	Days*	Result†	Drug				
1	6-25	3-13	12-5	6-25	Ampicillin	8	Failure			Doxycycline	9		Cured	
2	6-25	25	12-5	3-13	Spectinomycin	15	Cured							
3	6-25	25	12-5	3-13	Amoxycillin	7	Failure			Spectinomycin	ND		Defaulted	
4	25	25	25	3-13	Amoxycillin	2	Failure			Spectinomycin	ND		Failure#	
5	12-5	12-5	6-25	1-56	Amoxycillin	3	Failure			Doxycycline	4		Cured	
6	12-5	25	12-5	3-13	Amoxycillin	3	Failure			Spectinomycin	10		Cured (PGU)	
7	6-25	50	25	12-5	Amoxycillin	3	Failure			Spectinomycin	3		Cured	
8	ND	ND	ND	ND	Amoxycillin	4	Failure			Spectinomycin	3		Cured	
9	50	>100	50	12-5	Amoxycillin	4	Failure			Spectinomycin	7		Cured (PGU)	
10	50	>100	25	12-5	Amoxycillin	4	Failure			Spectinomycin	17		Cured	
11	6-25	12-5	25	12-5	Ampicillin	7	Cured (PGC)							
12	6-25	50	12-5	25	Spectinomycin	17	Cured							
13	100	>100	50	25	Ampicillin	4	Failure			Spectinomycin	10		Failure#	
14	100	>100	50	25	Ampicillin	4	Failure			Spectinomycin	14		Cured	
15	100	>100	50	25	Amoxycillin	4	Failure			Spectinomycin	5		Cured	
16	50	>100	50	25	Amoxycillin	3	Failure			Spectinomycin	6		Cured	
17	>100	>100	50	25	Amoxycillin	3	Failure			Spectinomycin	7		Cured	
18	25	100	1-56	25	Amoxycillin	4	Failure			Spectinomycin	11		Cured	
19	50	>100	1-56	25	Amoxycillin	4	Failure			Spectinomycin	3		Cured	
20	100	>100	12-5	25	Amoxycillin	3	Failure			Spectinomycin	ND		Defaulted	
21	100	>100	12-5	25	Amoxycillin	4	Failure			Spectinomycin				
22	50	100	6-25	25	Spectinomycin	3	Cured							
23	25	50	12-5	12-5	Amoxycillin	3	Failure			Spectinomycin	7		Cured	
24	100	>100	12-5	25	Ampicillin	5	Failure			Spectinomycin	4		Cured	
25	100	100	3-13	25	Amoxycillin	7	Failure			Spectinomycin	ND		Defaulted	
26	50	100	25	25	Amoxycillin	4	Failure			Spectinomycin	ND		Defaulted	
27	25	100	50	25	Spectinomycin	ND	Defaulted							
28	ND	ND	ND	ND	Spectinomycin	ND	Defaulted							
29	25	>100	25	25	Spectinomycin	10	Cured							
30	ND	ND	ND	ND	Spectinomycin	ND	Defaulted							

* Intervals between beginning of treatment and follow-up examination

† See text for evaluation of result

‡ Patients in case Nos 5 and 14 were cured of gonorrhoea by treatment with spectinomycin (in a single dose) and doxycycline (for 12 days) respectively. ND = not determined; PGC = postgonococcal cervicitis, PGU = postgonococcal urethritis

TABLE IV Cumulative data on the results of treatment of 30 patients with gonorrhoea due to PPNG strains

Drug	Total No of cases	Results of follow-up*			
		Cure	PGU/C†	Failure	Defaulted
Ampicillin	7	1	1	6	0
Amoxycillin	16	0	0	16	0
Doxycycline	3	2	0	1	0
Spectinomycin	28	19	2	1	8

*See text for evaluation of results

†Postgonococcal urethritis/cervicitis

cefoxitin¹⁷ have proved to be very successful in the treatment of gonorrhoea due to PPNG strains.

As suggested by Thin¹⁸ careful follow-up and rapid and vigorous contact tracing are essential also in the Fukuoka area. Sng *et al*¹⁹ advised that it would be prudent to screen all gonococcal isolates for β -lactamase in an area where the prevalence of PPNG is 1% or more. Recently, rapid and simple methods for the detection of β -lactamase production have been available commercially. Such tests should be available for both hospital and clinic use.

References

1. Phillips I. β -lactamase-producing, penicillin-resistant gonococcus. *Lancet* 1976;ii:656-7.
2. Percival A, Rowlands J, Corkill JE, *et al*. Penicillinase-producing gonococci in Liverpool. *Lancet* 1976;ii:1379-82.
3. Perine PL, Thornsberry C, Schalla W, *et al*. Evidence for two distinct types of penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1977;ii:993-5.
4. Ashford WA, Golash RG, Hemming VG. Penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1976;ii:657-8.
5. Center for Disease Control. Global distribution of penicillinase-producing *Neisseria gonorrhoeae* (PPNG). *Morbidity Mortality Weekly Rep* 1982;31:1-3.
6. Yoshida S, Urabe S, Mizuguchi Y. Antibiotic sensitivity patterns of penicillinase-positive and penicillinase-negative strains of *Neisseria gonorrhoeae* isolated in Fukuoka, Japan. *Br J Vener Dis* 1982;58:305-7.
7. Anonymous. *Neisseria gonorrhoeae* producing penicillinase. *Wkly Epidem Rec* 1976;51:293-4.
8. Nayyar KC, Noble RC, Michel MF, Stolz E. Gonorrhoea in Rotterdam caused by penicillinase-producing gonococci. *Br J Vener Dis* 1980;56:244-8.
9. Finger AH. Spectinomycin in the treatment of gonorrhoea in females and males. *Br J Vener Dis* 1975;51:38-40.
10. Grunder K, Petzoldt D. Sensitivity of *Neisseria gonorrhoeae* to spectinomycin and thiamphenicol. *Br J Vener Dis* 1980;56:252-4.
11. Center for Disease Control. Gonorrhea: CDC-recommended treatment schedules, 1979. *J Infect Dis* 1979;139:496-501.
12. McCormack WM. Treatment of gonorrhea. *Ann Intern Med* 1979;90:845-6.
13. Rajan VS, Sng EH, Pang R, Tan NJ, Thirumoorthy T, Yeo KL. HR756 — a new cephalosporin in the treatment of gonorrhoea caused by ordinary and penicillinase-producing strains of *Neisseria gonorrhoeae*. *Br J Vener Dis* 1980;56:255-8.
14. Slack RC, Bittner JB, Finch R. Treatment of gonorrhoea caused by β -lactamase-producing strains of *Neisseria gonorrhoeae* with cefotaxime. *Lancet* 1980;i:431-2.
15. Nayyar KC, Michel MF, Stolz E. Antibiotic sensitivities of gonococci isolated in Rotterdam and results of treatment with cefuroxime. *Br J Vener Dis* 1980;56:249-51.
16. Normark S, Elmros T, Norlander L, *et al*. Cefuroxime treatment of urethritis caused by β -lactamase-producing strain of *Neisseria gonorrhoeae*. *Acta Derm Venereol (Stockh)* 1980;60:277-9.
17. Berg SW, Kilpatrick ME, Harrison WO, McCutchan JA. Cefoxitin as a single-dose treatment for urethritis caused by penicillinase-producing *Neisseria gonorrhoeae*. *N Engl J Med* 1979;301:509-11.
18. Thin RN. Gonorrhoea: a continuing problem in the 1980s. *Br J Vener Dis* 1980;56:193.
19. Sng EH, Yeo KL, Rajan VS, Lim AL. Comparison of methods for the detection of penicillinase-producing *Neisseria gonorrhoeae*. *Br J Vener Dis* 1980;56:311-3.