Susceptibility to antimicrobials of *Neisseria gonorrhoeae* isolated in Singapore: implications on the need for more effective treatment regimens and control strategies

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SUMMARY The antimicrobial susceptibility of gonococci isolated in Singapore has been studied over several years. In 1983, the prevalence of penicillinase producing *Neisseria gonorrhoeae* (PPNG) was 33.5% and 64% of non-PPNG isolates had minimum inhibitory concentrations (MICs) of penicillin of ≥ 0.5 mg/l. After a control programme, the isolation of the gonococcus from prostitutes was reduced and there was improvement in its susceptibility to antimicrobials. The incidence of PPNG strains was stabilised with a change in the treatment regimen. An influx of foreign prostitutes, however, had an unfavourable impact on these variables. Countries in South East Asia have a high prevalence of PPNG and non-PPNG strains that have reduced susceptibility to antimicrobials. In view of increased air travel the problem should be seen from a global perspective. Better treatment regimens and control strategies are urgently needed.

Introduction

Since penicillin was first used in the treatment of gonorrhoea the gonococcus has shown a remarkable ability to develop resistance to the drug. The percentage of strains with chromosomally determined resistance has been increasing over the years, requiring the administration of increasing doses of penicillin to achieve a satisfactory response. With the appearance of penicillinase producing *Neisseria gonorrhoeae* (PPNG) strains and spectinomycin resistant strains there is growing concern about the adequacy of current treatment regimens.

In Singapore we have been monitoring the susceptibility to antimicrobials of the gonococcus for several years. Singapore is located in a region where gonorrhoea is rife, and our findings reflect the situation in this part of the world. In a previous paper we studied the factors responsible for the changes up to 1981.¹ We now report on the changes that have occurred since then. Analysis of the data indicates that there is an urgent need for more effective treatment regimens and control strategies.

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Materials and methods

The isolates for measuring minimum inhibitory concentrations (MICs) of antimicrobials were from routine specimens sent to the laboratory. Before 1980 patients providing most of the specimens were mainly prostitutes. Later, when it was found that the isolates from prostitutes were less susceptible to antibiotics than those from male patients,² the strains tested each time consisted of an equal number of non-PPNG and PPNG strains from men and women. The specimens were from the anogenital region and were inoculated directly on to modified Thayer-Martin medium. They were incubated in candle extinction tins at 36°C, and were identified by their colonial morphology, oxidase reaction, and Gram stained appearance on microscopy. Detection of penicillinase production was initially by the rapid iodometric method, followed by the paper iodometric method, and then by the paper acidometric method.³

MIC determinations were performed every two weeks throughout the year randomly on strains that had been isolated during the period preceding the test. Details of the agar plate dilution method used have been described elsewhere.² The Mann-Whitney U test was used to compare the MIC distribution patterns of the strains isolated in 1983.

Results

Table I shows the susceptibility to five common antibiotics of 300 non-PPNG and 300 PPNG strains isolated in 1983. Unimodal distribution patterns were found for all the antibiotics. In 64% of non-PPNG strains MICs of penicillin were ≥ 0.5 mg/l, while 61.8% of all strains required at least 2 mg/l of tetracycline for inhibition. High treatment failure rates may be expected for strains with such high MICs.⁴

Although the median MIC of penicillin for non-PPNG strains isolated from women (0.39 mg/l) was only slightly higher than the median MIC for such strains from men (0.37 mg/l), the distribution patterns of the two groups of gonococci were significantly different ($t = 4.584$; $p < 0.001$). Similarly the strains isolated from women were slightly less susceptible to ampicillin than those from men ($t = 3.4949$; $p < 0.001$). There were, however, no appreciable differences in the distribution patterns of the two groups with regard to

tetracycline, kanamycin, or spectinomycin at the 0.05 level.

PPNG strains were more resistant than non-PPNG strains to tetracycline ($t = 2.939$; $p < 0.01$). The difference was less significant with regard to kanamycin ($t = 1.966$; $p < 0.05$), and there was no significant difference in the spectinomycin distribution patterns ($t = 0.28$; $p > 0.50$). None of the strains was resistant to kanamycin or spectinomycin.

Table II shows the changes in the susceptibility to antimicrobials over seven years. The median MIC was used to reflect the changes because unlike the geometric mean there was no necessity to measure the MICs of all the strains at the extreme ends of the distribution. Only results from women were considered because routine monitoring of isolates from men only started in 1980. On the whole certain trends could be seen. There was decline in the MICs of all the antibiotics during the first three to four years, but in the last two to three years a slight increase in MICs was detected. Although high MICs of penicillin were

TABLE 1 Susceptibility to five common antibiotics of *Neisseria gonorrhoeae* isolated in Singapore in 1983

Antibiotics	MICs (mg/l)	No of non-PPNG strains		No of PPNG strains	
		Men	Women	Men	Women
Penicillin	≤ 0.03	1			
	0.06	8	5		
	0.12	17	22		
	0.25	29	26		
	0.5	42	41		
	1.0	24	24		
	2.0	24	23		
	4.0	5	7		
	8.0		2		
Median MIC		0.37	0.39		
Ampicillin	≤ 0.06	14	9		
	0.12	31	35		
	0.25	46	41		
	0.5	30	31		
	1.0	23	22		
	2.0	5	9		
	4.0	1	1		
	8.0		2		
Median MIC		0.21	0.22		
Tetracycline	≤ 0.25	6	2	1	2
	0.5	32	32	19	23
	1.0	34	36	22	20
	2.0	42	46	72	71
	4.0	34	32	35	34
	8.0	2	2	1	
Median MIC		1.08	1.12	1.47	1.43
Kanamycin	≤ 4.0	5	5	1	3
	8.0	28	18	29	31
	16.0	109	115	82	88
	32.0	8	14	38	28
Median MIC		11.1	11.8	12.4	11.8
Spectinomycin	8.0	9	6	6	5
	16.0	138	141	142	141
	32.0	3	3	2	4
Median MIC		11.9	11.9	11.9	12.0

MIC = minimum inhibitory concentration.

TABLE II Median minimum inhibitory concentrations of five common antibiotics for non-PPNG and PPNG strains from female prostitutes in Singapore over seven years

Antibiotics	Strains	Median minimum inhibitory concentrations (mg/l) in:						
		1977	1978	1979	1980	1981	1982	1983
Penicillin	Non-PPNG	0.48	0.52	0.38	0.33	0.34	0.35	0.39
	PPNG							
Ampicillin	Non-PPNG	0.38	0.38	0.26	0.20	0.22	0.19	0.22
	PPNG							
Tetracycline	Non-PPNG	1.03	1.53	0.97	1.03	0.98	1.18	1.12
	PPNG	2.25	3.29	1.94	1.36	1.30	1.60	1.43
Kanamycin	Non-PPNG	9.2	10.3	11.1	8.0	10.2	10.4	11.8
	PPNG	20.0	13.3	13.4	7.5	10.0	10.3	11.8
Spectinomycin	Non-PPNG	12.6	11.6	10.7	11.3	11.0	11.5	11.9
	PPNG	12.3	12.6	12.5	11.4	10.7	11.6	12.0
No of strains tested	Non-PPNG	321	335	358	150	150	150	150
	PPNG	19	268	377	150	150	150	150

seen over the years, none of the non-PPNG strains had MICs of penicillin exceeding 8 mg/l. It is not clear what caused the slight drop in MICs of ampicillin in 1982. It is interesting that throughout the whole period of study the non-PPNG strains were more susceptible than PPNG strains to tetracycline.

Comparison of MICs between countries was not simple because of the lack of uniformity in methodology. In order to construct Table III it was necessary to recalculate the MICs for some of the studies using the raw data provided. The countries are listed in

decreasing order of susceptibility to penicillin. Although the studies were carried out over several years, certain general observations may be made. Less than 20% of strains from developed countries (other than Japan) required ≥ 0.5 mg/l penicillin for inhibition. However, 50% or more of the strains from several countries in South East Asia had MICs of ≥ 0.5 mg/l.

Table IV shows that there has been a steady decline in the isolation of gonococci from prostitutes since 1978. In 1982 no appreciable decline was noted but in

TABLE III Penicillin susceptibility of *Neisseria gonorrhoeae* from different countries

Country	Author	No of strains	% of strains with MICs (mg/l) of:		
			≤ 0.03	0.06-0.25	≥ 0.5
Canada	Stewart, 1979 5	885	49.1*	50.7*	0.2*
Ethiopia	Gedebou, 1980 6	500	59.0*	40.2*	0.8*
Australia	Finger, 1977 7	947	87.7†	10.1†	2.2†
South Africa	Liebowitz, 1982 8	100	73.0	22.0	5.0
United Kingdom	Seth, 1979 9	274	61.0	32.5	6.6
Netherlands	Nayyar, 1980 10	147**	51.7*	41.5*	6.8*
New Zealand	Green, 1978 11	442	72.2	18.8	9.0
Saudi Arabia	Chowdhury, 1981 12	73**	45.2	39.7	15.1
Nigeria	Osoba, 1977 13	80	17.5‡	66.3‡	16.3‡
United States	Jaffe, 1976 14	4405	31.0	51.6	17.4
Belgium	Piot, 1979 15	168	53.6	28.6	17.9
Iran	Zirak-Zadah, 1977 16	78		74.4	25.6
Central African Republic	Widy-Wirski, 1982 4	70	31.4	41.4	27.1
Swaziland	Piot, 1979 15	54	53.7	18.5	27.8
India	Gopalan, 1982 17	118	29.7‡	42.4‡	28.0‡
Hong Kong	Ng, 1981 18	49	22.4	49.0	28.6
Rwanda	Piot, 1979 15	41	14.6	43.9	41.5
Puerto Rico	Rodriguez, 1983 19	50		58.0	42.0§
Zambia	Ratnam, 1982 20	224**	17.8	39.7	42.4
Japan	Yoshida, 1982 21	130	1.5¶	49.2¶	49.2¶
Malaysia	Ngew, 1979 22	60		48.0	52.0
Singapore	Sng (this paper)	300	0.3	35.7	64.0
Philippines	Tupasi, 1980 23	85		27.1	72.9
Korea	Wilson, 1976 24	67	1.5	17.9	80.6
Thailand	Brown, 1982 25	116		18.1	81.9

*MICs ≤ 0.04 ; 0.08-0.32; ≥ 0.32 .

†MICs ≤ 0.06 ; 0.12-0.5; ≥ 1.0 units/ml.

‡MICs ≤ 0.04 , 0.08-0.3; ≥ 0.6 .

§MICs ≥ 0.5 based on MIC₉₀ of intermediate resistant strains.

||MICs ≤ 0.05 .

¶MICs ≤ 0.03 ; 0.05-0.39; ≥ 0.78 .

**adjusted for non-PPNG strains.

TABLE IV Isolation of *Neisseria gonorrhoeae* over eight years from prostitutes and from the total population of Singapore showing the percentage of PPNG strains

	Isolation from prostitutes		Total isolation	
	No of cultures	No (%) positive	No of isolates	No (%) of PPNG strains
1976	15 326	1 485 (9.7)	1 250*	3 (0.2)
1977	43 735	5 204 (11.9)	8 597	22 (0.3)
1978	57 806	6 491 (11.2)	10 100	1 016 (10.1)
1979	61 576	6 530 (10.6)	11 741	1 947 (16.6)
1980	61 218	5 828 (9.5)	9 672	2 784 (28.8)
1981	56 833	5 006 (8.8)	8 040	2 369 (29.5)
1982	57 276	5 010 (8.7)	8 523	2 948 (34.6)
1983	59 198	3 695 (6.2)	6 141	2 058 (33.5)

*November and December only.

1983 a notable decline was seen. On the other hand, the incidence of PPNG strains showed a sharp rise in 1978, which continued until 1980, when it stabilised somewhat. A further slight increase occurred in 1982 and the incidence has since remained at 33.5% in 1983.

Discussion

The data gathered from various studies show that there is wide variation in the susceptibility to penicillin of non-PPNG strains isolated from different countries (table III). There appear to be differences in the susceptibility patterns of countries in different regions. Countries in South East Asia have the highest percentage of strains with reduced susceptibility. The six countries with the highest percentage of strains requiring ≥ 0.5 mg/l for inhibition were all from this region. On the other hand, gonococci from developed countries (other than Japan) had the largest percentage of susceptible strains. Certain developing countries that are not situated along major tourist routes also had a fairly high percentage of susceptible strains.

Two features may account for the high prevalence of such resistant strains in this region. The first is the dominant role of prostitutes in transmission of disease. Their anonymity and the rapidity with which they can transmit disease make any control effort difficult. The second is the improper use of antibiotics, especially by prostitutes and their clients.¹ The lack of adequate control of the sale of antibiotics in several countries in the region has resulted in self medication and using inadequate doses for prophylaxis and treatment. Furthermore, the lack of standardised treatment regimens may have resulted in the adoption of subcurative treatment regimens by medical practitioners. If any control effort is to be successful, these aspects must therefore be adequately addressed.

It should be noted that the gonococci isolated in the region are also relatively resistant to several other common antibiotics.²⁵⁻²⁷ Many of them show significant positive correlation to penicillin.^{1 8 11 27} In Thailand the percentages of resistant strains have reached such levels that penicillin, ampicillin, and kanamycin were found to yield high treatment failure rates, while tetracycline and erythromycin were considered to be unacceptable on the basis of high expected failure rates.²⁵

The strains isolated in Singapore were slightly less resistant, with 64% and 61.8% (PPNG strains included) of them having MICs of penicillin and tetracycline of 0.5 mg/l and ≥ 2 mg/l respectively, compared with 81.9% and 70.1% of strains from Thailand. There are no recent published data on the efficacy of penicillin, ampicillin, and tetracycline using currently recommended doses in Singapore. Calculations based on the expected failure rates at different MICs,^{4 28} however, indicate that the expected failure rate for penicillin is 7.8%, while the rates for ampicillin and tetracycline are over 10%. These are higher than have been found for countries outside the region, such as the United States of America.²⁸ Failure rates of 11.1% and 16% have been reported for kanamycin²⁹ and thiamphenicol.³⁰ A higher failure rate for cotrimoxazole (30%) was also found,³⁰ compared with studies conducted elsewhere using equivalent dosages,^{31 32} and this was probably due to the higher MICs of the drug.²⁷ It may thus be seen that, even in the treatment of non-PPNG strains, countries in the region have only a limited number of inexpensive drugs available.

Studies on the trend of susceptibility to antibiotics in Singapore show that the susceptibility patterns were not static. Soon after the introduction of the Medical Scheme³³ in 1976-7 to control syphilis and gonorrhoea in the prostitute population there was a decline in the isolation rate of the gonococcus from prostitutes (table IV) and an improvement in the susceptibility of the organism to antibiotics,

especially to penicillin, ampicillin, and tetracycline (table II). In the past two years, however, a slight increase in resistance has been seen. This is probably related to an influx of prostitutes from Thailand in 1982 and early in 1983. This may also explain the lower susceptibility to penicillin and ampicillin of strains isolated in 1983 from women compared with strains from men. In 1981 no appreciable differences were noted in the patterns of susceptibility to penicillin and ampicillin of strains isolated from men or women.¹

The influx of Thai prostitutes also temporarily arrested the steady decline in isolation rate of gonococci, and caused a slight increase in the prevalence of PPNG strains in 1982 (table IV). The sharp decline in isolation rate in 1983 was largely due to intensive action by the Anti-Vice Enforcement Unit to repatriate the large number of foreign prostitutes to their countries of origin. It is interesting that the vigorous police action did not cause the prostitutes to go underground, as there was no decline in the number of prostitutes attending for routine examination. Other reasons that may have contributed to the reduction are the recession and the fear of acquiring diseases such as genital herpes and the acquired immune deficiency syndrome. Both these conditions received wide publicity in the local press in 1983. These data illustrate the importance of social and psychological factors in determining the transmission of gonorrhoea within a community.

Before 1978 the isolation of PPNG strains was only sporadic. In 1978, however, an outbreak of infection with PPNG strains occurred and the incidence increased from 0.3% to 10.1% (table IV). The increase occurred at a time when the isolation rate of gonococci from prostitutes was falling and the non-PPNG strains were becoming more susceptible to penicillin, ampicillin, and tetracycline. The reason for the paradox was that the antibiotic selective pressures (both prophylactic and therapeutic) favoured an increase in the PPNG strains at the expense of non-PPNG strains.¹ When kanamycin was introduced as a first line drug in 1980, the percentage of PPNG strains isolated levelled off. This underlines the importance of using an appropriate antimicrobial agent in preventing a further selection of PPNG strains. The data of 1983 show that a general decrease in transmission of disease did not necessarily result in a decline in prevalence of PPNG strains.

Similar outbreaks of PPNG strains have occurred in other countries inside and outside South East Asia.^{22-34, 35} In countries with adequate medical facilities such increases have been successfully controlled by various measures aimed at the PPNG strains. These have included surveillance, contact

tracing, epidemiological treatment, prompt use of spectinomycin, and screening of high risk groups. In countries in South East Asia, however, the isolation rates of PPNG strains have remained high with no evidence of decline. Thus high incidences have been recorded in Japan (16.1%),²¹ Malaysia (37.2%),²² Thailand (42%),²⁵ South Korea (40+ %),³⁴ the Philippines (30-40%),³⁶ and Indonesia (25%)³⁷ as well as in Singapore. It appears that the factors which are favourable to the resistant non-PPNG strains also favour PPNG strains.

With the large number of air travellers today, the high incidence of PPNG strains and resistant non-PPNG strains is no longer only a regional problem of South East Asia. In a report by the World Health Organisation 29.4% of 3177 infections with PPNG strains detected in Europe over 18 months were presumed to have been contracted outside the reporting country.³⁸ Of the 639 cases in which the exporting country was known, 59.8% were from countries in South East Asia.

So far no strain resistant to spectinomycin has been found in Singapore. With reports of such strains being found in several countries, however, coupled with the global spread of PPNG strains and the increasing problem of non-PPNG strains with reduced susceptibility to antimicrobials, there is a pressing need for alternative antibiotics that are both effective and inexpensive. Many of the newer cephalosporins are highly effective though expensive. Of these the most promising appears to be ceftriaxone, which has been shown to be antitreponemical.³⁹ This may be an important asset in view of the reported increase in the incidence of early syphilis after the wide use of kanamycin instead of penicillin to treat gonorrhoea in Singapore,²⁹ because, unlike penicillin, kanamycin does not abort incubating syphilis.

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