Our study revealed that the incidence rate of asymptomatic infection with *C. trachomatis* was 4.7%. The incidence rate was reported to be from 2.3% to 7.6% in studies overseas.[2,5,6,10,11] The study by Imai and colleagues showed infection in 7.0% of sexually active male students in Miyazaki Prefecture, Japan.[7] Although we have often found that different regions or communities have different incidences of STIs, our results on asymptomatic chlamydial infection were similar to others. That is to say, the population with asymptomatic chlamydial infection could be the infectious origin and they might never notice their infections without screening. Generally, the incidence rate of genital *C. trachomatis* infection is higher in females than in males, even if asymptomatic.[1,4,7,12] However, some reports showed that there was little difference in the incidence of asymptomatic infection by sex.[10,11] We should be aware that the rate of *C. trachomatis* infection in younger males without any subjective symptoms is not negligible and they should be targeted for education about and screening for this pathogen.

No subjects had asymptomatic infection with *N. gonorrhoeae* in this study. Kent and colleagues reported that no asymptomatic male had gonorrhoea in screening in San Francisco high schools[4] and none in military populations.[13] The prevalence of asymptomatic gonorrhoea infection was extremely low, 0.2%, 1 of 1837, in a study in Thailand.[6] Currently, we have serious problems in the treatment for antimicrobial-resistant *N. gonorrhoeae* in Japan.[14] Our study showed that no gonorrhoea screening would be needed and we should remedy symptomatic urethritis with *N. gonorrhoeae* adequately using only two or three kinds of antimicrobials intravenously or intramuscularly.

We have had few data on asymptomatic genital HPV infection in men. The detection rate for HPV in men with no apparent genital warts might differ in each country or region. The incidence rates of genital HPV infection in men without genital warts have been reported to be 7.2%, 13%, and 43% in Finland,[15] Sweden,[3] and Mexico,[16] respectively. These studies clearly showed that sexual activity was strongly associated with positive HPV detection. Our previous study[8] showed that HPV DNA was found in 1.3% of 75 healthy male volunteers and in 18.5% of 130 patients with urethritis without genital warts. This study suggested that sexual activity might be a contributory factor for positive HPV. In this study, the detection rate of HPV DNA in sexually active healthy male volunteers was 8.0%. The healthy male volunteers in our previous study and this study were quite similar in age distribution, frequency of sexual intercourse, and number of sex partners; however, these two groups were recruited among a distinct population.

Although we do not have any hypothesis for the difference of the detection rate of HPV DNA between these two groups, it might be affected by factors such as the sexual partners' character and sexual behavior. Although we recruited university students, they might not have been ideal controls or subjects because their lifestyle may have differed from that of young males in general. Indeed, it is impossible to select truly optimal subjects from the population with every background, which is a common limitation in this kind of study, including our study. The bottom line of this study is that there were younger men who were positive for STI pathogens and the incidence was not negligible.

Logistic regression analysis of the risk factors revealed no statistically significant, independent risk factors. The detection rate was relatively low in this study, and this study is a small series from the aspect of a general epidemiological survey. Although we could not find any independent risk factor for asymptomatic males with *C. trachomatis* and HPV in this study, those risk factors, such as number of sex partners and the past history of STIs, were commonly important in this kind of research.

Acknowledgments This study was in part supported by a grant-aid of Research on Emerging and Re-emerging Infectious Diseases by the Ministry of Health, Labor and Welfare.

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男子淋菌性尿道炎由来淋菌の各種抗菌薬に対する感受性

—1999～2004年分離株の比較—

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日本化学療法学会雑誌　VOL.53 NO.8 AUG. 2005

【原著・臨床】

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1999年から2004年までに東京慈恵会医科大学附属病院ならびに首都圏の関連病院を受診した男子淋菌性尿道炎患者の尿道から分離された*Neisseria gonorrhoeae* 277株と咽頭から分離された4株，計281株のcefixime（CFIX），cefteram pivoxil（CFTM-PI），ceftriaxone（CTRX），cefodizime（CDZM），spectinomycin（SPCM），levofloxacin（LVFX）に対する抗菌薬感受性を測定し，年次的推移を検討した。さらに，これらのうちCFIXに対するMICが0.5 μg/mL以上の10株を対象として，その遺伝子パターンをpulsed-field gel electrophoresis（PFGE）により解析した。2004年における各抗菌薬に対する耐性菌の割合はCFIXでは5.9%，CFTM-PIでは20.8%そしてLVFXでは80.2%であったが，CTRX，CDZMそしてSPCMに対する耐性株はなかった。2004年に分離された淋菌に対する各抗菌薬のMIC_{90}は2003年と比較してほぼ変化がなく，経口セフェム系薬の耐性も特に進んでいなかった。咽頭由来淋菌4株のMICは尿道由来株と比較して1管程度高い値であった．β-lactamase産生菌は1999年には2.4%，2003年には5.2%，2004年には5.0%に認められた。CFIX耐性株のPFGEの解析では，4種類のパターンが認められ，このうち同じパターンが10株中7株を占めたが，分離年度あるいは分離地域に特定の傾向を認めなかったため，CFIX耐性株は同じクローンのアウトブレイクではないと考えられた。

Key words: *Neisseria gonorrhoeae*，male urethritis，drug-susceptibility，pulsed-field gel electrophoresis（PFGE）

近年，わが国をはじめとして東アジア地域を中心に淋菌のフルオロキノロン系薬に対する耐性化が大きな問題となってきている。フルオロキノロン系薬耐性淋菌の増加後は経口セフェム系薬が淋菌感染症の重要な治療薬として推奨された[1]．しかし，この経口セフェム系薬に対する耐性淋菌が認められ，治療失敗例も報告されつつある[2]。さらに，性風俗の多様化に伴い口腔性交を介する感染者が増加していることも淋菌感染症の蔓延の一因となっている。そこで，今回われわれは1999年から2004年に淋菌性尿道炎患者から分離された淋菌に対する各種抗菌薬の最小発育阻止濃度（MIC）を測定し，その年次推移について検討した。さらにこれらの臨床分離株のうち，CFIX低感受性株の遺伝子パターンをpulsed-field gel electrophoresis（PFGE）により解析し，疫学的傾向の有無を検討したので報告する。

I. 対象と方法

1. 対象淋菌株

1999年から2004年までの間に東京慈恵会医科大学附属病院ならびに首都圏の関連病院を受診した男子淋菌性尿道炎患者から分離された淋菌281株を対象とした。分離された時期は，1999年が41株，2000年が57株，2001年が24株，2003年が58株そして2004年が101株である。これらのうちの4株は2004年に咽頭から分離され，そのうちの3株については同一症例の尿道からも淋菌が分離された。

2. 検討項目

1) 抗菌薬感受性試験

分離された男子尿道炎由来淋菌株に対する各種抗菌薬の最小発育阻止濃度（minimary inhibitory concentration: MIC）をClinical Laboratory Standards Institute（CLSI）法に準じた寒天平板希釈法[3]で行った。対象とした抗菌薬はcefixime（CFIX），cefteram pivoxil（CFTM-PI），ceftriaxone（CTRX），cefodizime（CDZM），spectinomycin（SPCM）そしてlevofloxacin（LVFX）の6薬剤で，それらのNCCLSによるbreak pointはCFIX，CFTM-PI，そしてCTRXが0.25 μg/mL，CDZMおよびLVFXが0.125 μg/mL，そしてSPCMが32 μg/mLである。なお，薬剤

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Table 1. Distribution of MICs of each antimicrobial agent against *N. gonorrhoeae*

agent	year	No. of strains	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	breakpoint	rate of susceptible strains (%)
cefixime	1999	41	0.002－0.12	0.008	0.03	0.25	100
	2000	57	≦0.001－0.5	0.008	0.25		93.0
	2001	24	0.004－0.25	0.03	0.25		100
	2003	58	0.002－0.5	0.002	0.25		96.6
	2004	101	0.002－0.5	0.015	0.25		94.1
cefteram-pivoxil	1999	41	0.002－0.5	0.06	0.12	0.25 *	92.7
	2000	57	0.004－0.5	0.015	0.5		87.7
	2001	24	0.002－0.25	0.06	0.25		100
	2003	58	0.008－1	0.12	0.5		77.6
	2004	101	0.002－2	0.06	0.5		79.2
ceftriaxone	1999	41	≦0.001－0.06	0.008	0.015	0.25	100
	2000	57	≦0.001－0.06	0.004	0.06		100
	2001	24	0.001－0.06	0.015	0.03		100
	2003	58	0.002－0.12	0.03	0.12		100
	2004	101	0.002－0.12	0.015	0.06		100
cefodizime	1999	41	0.002－0.25	0.03	0.06	0.5 **	100
	2000	57	0.002－0.12	0.015	0.06		100
	2001	24	0.002－0.12	0.01	0.06		100
	2003	58	0.002－0.12	0.03	0.12		100
	2004	101	0.002－0.25	0.03	0.12		100
spectinomycin	1999	41	4－16	8	16	32	100
	2000	57	2－8	2	4		100
	2001	24	4－16	16	16		100
	2003	58	2－16	8	16		100
	2004	101	2－16	8	8		100
levofloxacin	1999	41	0.002－16	0.5	8	0.125 **	41.5
	2000	57	0.004－8	0.5	4		38.6
	2001	24	0.008－＞8	4	＞8		12.5
	2003	58	0.004－16	4	8		17.2
	2004	101	0.004－16	2	8		19.8

* breakpoint of cefixime was substituted
** breakpoint of cefotaxime was substituted
** twice value of breakpoint of ofloxacin

耐性淋菌の定義は米国疾病管理予防センター（Centers for Disease Control and Prevention: CDC）の淋菌抗菌薬感受性サーベイランスプロジェクト[4]に準じた。

2) β-lactamase の検出

β-lactamase の検出はニトロセフィン法で行った。

3) PFGE 解析

今回の臨床分離株のうちで，CFIX の MIC が 0.5 μg/mL 以上であった 10 株について，この遺伝子パターンを pulsed-field gel electrophoresis (PFGE) により解析した。方法は菌をアガロースゲルに包埋後，lysozyme を用いて溶菌し，proteinase k により蛋白分解した後，制限酵素 *Spe*I (Takara) で 35℃，8 時間処理をした。泳動は，パルスフィールドゲル電気泳動システム (CHEF-DRII, Bio-Rad Laboratories) を用い，1% アガロースゲル，パルスタイム 5～15 秒，電圧 200V で 20 時間行い，泳動後のゲルをエチジウムブロマイドで染色し，泳動パターンを比較した。

II. 結　　果

1. 淋菌の抗菌薬感受性の推移

1999 年から 2004 年にかけての各抗菌薬の MIC および感受性についての結果を示す (Table 1)。CFIX に関しては，1999 年から 2000 年にかけて MIC_{90} が 0.03 μg/mL から 0.25 μg/mL に上昇したものの，それ以降は変動せず，MIC_{50} も 1999 年以降大きな変動は認められず，感受性率は 90% 以上を維持していた。CFTM-PI も CFIX 同様 1999 年から 2000 年にかけて MIC_{90} は 0.12 μg/mL から 0.5 μg/mL に上昇したが，それ以降は大きな変化はなく，MIC_{50} もほぼ一定であった。しかし，CFTM-PI に対する感受性率は 2003 年以降に 70% 台にまで低下した。CTRX は 1999 年から 2000 年にかけて MIC_{90} が 0.015 μg/mL から 0.06 μg/mL に上昇したが，それ以降はほぼ一定であり，MIC_{50} は 1999 年には 0.008 μg/mL であったものが 2003 年には 0.03 μg/mL まで上昇したが 2004 年には 0.015 μg/mL となっていた。CTRX の MIC_{90} は 1999 年以降上昇傾向にあるが breakpoint より低値であり 2004 年

Table 2. Comparison of MICs of each antimicrobial agent against *N. gonorrhoeae* strain isolated from urethra and pharynx

Case No.	Sample	antimicrobial agent						β-lactamase
		Cefixime	Cefteram-pivoxil	Ceftriaxone	Cefodizime	Spectinomycin	Levofloxacin	
9	urine	0.015	0.06	0.015	0.03	8	2	—
	pharynx	0.015	0.06	0.015	0.03	8	4	—
17	pharynx	0.015	0.12	0.03	0.06	16	4	—
29	urine	0.008	0.06	0.008	0.015	8	2	—
	pharynx	0.008	0.06	0.015	0.03	16	2	—
35	urine	0.25	0.5	0.06	0.06	4	2	—
	pharynx	0.25	0.5	0.06	0.06	8	4	—

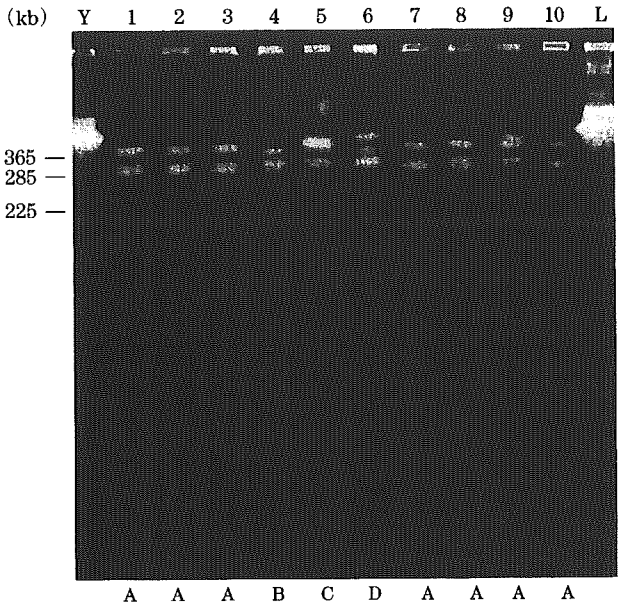

Fig. 1. PFGE patterns of CFIX-resistant *N. gonorrhoeae* strains.

の時点ではまだCTRX耐性淋菌は認められなかった。CDZMは1999年以降MIC_{50}，MIC_{90}ともにほぼ一定であり，CDZM耐性淋菌は2004年の時点では認めなかった。SPCMのMIC_{50}とMIC_{90}もCDZMと同様に1999年以降変化を認めず，2004年の時点でSPCM耐性淋菌は認められなかった。LVFXのMIC_{50}とMIC_{90}はともに調査した5年間を通じて高値であり，感受性率は2001年以降10%台まで低下した。

咽頭由来の淋菌は4株あり，同一症例の尿道から分離された3株との各抗菌薬に対する感受性の比較を行ったところ，両者はほぼ同等であった（Table 2）。

β-lactamase産生菌は9株認め，すべて尿道からの分離株であった。分離年度別では，1999年が1株(2.4%)，2003年が3株(5.2%)，2004年が5株(5.0%)であった。

2. CFIX耐性淋菌のPFGEパターン

CFIXに対するMICが0.5 μg/mL以上のCFIX耐性株の遺伝子パターンをPFGEにより解析したが，その結果Fig. 1に示すように，A～Dの4パターンが認められ，このうちパターンAが7株と最も多かった。Aパターンの年度別内訳は1999年が2株，2000年が3株そして2003年が2株であり，特定の年度に集中することはなかった。さらに，このAパターンは特定の地域に偏ることなく東京23区および横浜地区の広範囲に分布していた。また，PFGEパターンと抗菌薬感受性には相関性が認められなかった（Table 3）。

III. 考　　察

近年，性活動の若年化や多様化に伴い淋菌感染症やクラミジア感染症をはじめとした性感染症の増加が問題視されている。1988年以来行われている厚生労働省STD定点動向調査[5]では淋菌感染症は1991年から1994年にかけて一度減少したものの，1995年から再び増加傾向にある。田中らは福岡市において1994年から2000年にかけて男性の淋菌感染症は3.6倍に増加していると報告している[6]。このようなわが国における淋菌感染症の蔓延の原因としては口腔性交を介した感染者の増加やフルオロキノロン系薬耐性をはじめとする薬剤耐性淋菌の増加が指摘されている[7]。近年の検討ではペニシリン系薬に関し，β-lactamase産生淋菌（penicillinase-producing *Neisseria gonorrhoeae*: PPNG）は非常に少なく，そのほとんどがCDCの淋菌抗菌薬感受性サーベイランスプロジェクト[8]で定義されている染色体性ペニシリン系薬耐性淋菌であった。フルオロキノロン系薬耐性淋菌の出現は1993年に岡崎らが報告[9]して以来増加傾向にある。1980年代に登場したフルオロキノロン系薬は，当時ペニシリン系薬耐性淋菌やテトラサイクリン系薬耐性淋菌にも強い抗菌力を示しただけではなく，同時期に非淋菌性尿道炎の起炎菌として明らかとなった *Chlamydia trachomatis* に対しても有効であったため，淋菌性尿道炎に対する第一選択薬として使用されるようになった。しかし，このようなフルオロキノロン系薬の繁用がフルオロキノロン系薬耐性淋菌を蔓延させ[10]，1999年に日本性感染症学会の淋菌感染症に対するガイドライン[11]ではフル

Table 3 PFGE patterns of CFIX-resistant *N. gonorrhoeae* strains and their drug-susceptibility

No	year of isolation	PFGE pattern	MIC (μg/mL)					
			CFIX	CFTM-PI	CTRX	CDZM	LVFX	SPCM
1	2000	A	0.5	0.5	0.06	0.06	8	4
2	2000	A	0.5	0.5	0.12	0.12	8	4
3	2000	A	0.5	0.5	0.06	0.06	8	4
4	2000	B	0.5	0.5	0.06	0.06	4	4
5	2000	C	0.5	0.5	0.06	0.12	0.5	4
6	1999	D	0.5	0.5	0.06	0.06	4	4
7	1999	A	0.5	1	0.06	0.06	0.25	4
8	1999	A	0.5	0.5	0.06	0.06	8	4
9	2003	A	0.5	1	0.12	0.12	16	8
10	2003	A	0.5	0.5	0.12	0.12	8	8

オロキノロン系薬は淋菌感染症の治療薬として推奨されず経口薬ではセフェム系薬が推奨されている。その後，経口セフェム系薬耐性菌も徐々に増加しつつあり，2004年の性感染症診断・治療ガイドライン[12]ではSPCM 2.0 g単回投与，CTRX 1.0 g単回投与，CDZM 1.0 g単回投与が推奨されており，経口セフェム系薬に関してはCFIX 400 mg 1～3日投与も代替治療法として提示されているが，投与後に淋菌の消失を確認することを奨めている。今回のわれわれの検討でも淋菌に対して調査した5年間を通じて100%の感受性を示したものは，CTRX，CDZM，SPCMの3薬剤であったが，これらのうちCTRXはそのMIC_{90}が徐々に上昇しつつあり，CTRX耐性淋菌の出現が懸念される。

欧米先進諸国と比べてわが国でフルオロキノロン系薬耐性をはじめとする抗菌薬耐性淋菌が蔓延している理由として淋菌感染症に対する薬剤の投与量ならびに投与法に問題があるためと考えられる。CDCでは淋菌感染症の治療には注射薬，経口薬いずれの場合にも単回投与での治療を推奨している[13]。単回で十分量を投与することで確実に淋菌を除菌するということである。一方，わが国では経口抗菌薬を1日2～3回に分けて7～14日間連続投与する方法が一般的であったため，服薬の忘れや自己判断による服薬中断などにより，その結果生き残った淋菌が薬剤耐性を獲得し蔓延していったとの指摘もある[14]。今回の検討により，ガイドラインにあるように単回投与で確実に除菌する方法を普及させていく必要があると考えられた。咽頭に存在する淋菌は抗菌薬の種類によっては抗菌化学療法に対して抵抗性を示すことが少なくないといわれており[15]，性器と咽頭に淋菌が同時に感染している患者に対しては治療により性器の淋菌は消失しても咽頭の淋菌は残存して潜伏感染する可能性がある[16]。このような理由により特に風俗女性が無自覚のまま口腔性交を介して淋菌を拡散していることも考えられる。エイズ予防キャンペーンの影響によりソープランド女性においてはコンドームの使用頻度が増加し，これらの女性における淋菌およびクラミジア感染率が有意に減少しており，コンドームの適正使用などの啓蒙活動は重要かつ意義のあるものと考えられる[17]。今後われわれ医療従事者は口腔性交による感染者が減少するよう，STDの危険性を患者に説明することはいうまでもなく，口腔性交のみでもSTDに感染することを社会一般へも啓蒙していくことが重要であると考えられた。

今回，CFIXに対するMICが0.5 μg/mL以上の10株のPFGEタイプには4パターンが認められたがこのうちAパターンが10株中7株に認められ，分離された年度に特定の傾向を認めず，東京23区および横浜地区の広範囲に分布し，CFIX以外の薬剤感受性パターンも一定ではなかった。したがって，これらのCFIX耐性淋菌は同一クローンによるアウトブレイクではないと考えられた。雑賀ら[18]は特定の一地域に存在する株と，地域に関係なく広く分布している株も存在し，これは人の流動形態が関与しているのであろうと示唆している。今後は抗菌薬耐性淋菌の分布状況を把握するうえで，抗菌薬耐性株の分布率と遺伝子パターンの解析をさらに進めていくことが重要であると考えられた。

本論文の要旨は日本性感染症学会第17回学術大会（2004年12月5日，東京）において発表した。

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Drug-susceptibilities of *Neisseria gonorrhoeae* strains isolated from male patients with gonococcal urethritis against antimicrobial agents

—Their comparisons from 1999 to 2004—

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We investigated drug-susceptibility of *Neisseria gonorrhoeae* strains, which were isolated from the urethras and pharynx of the male patients with urethritis between 1999 and 2004, against cefixime (CFIX), cefteram pivoxil (CFTM-PI), ceftriaxone (CTRX), cefodizime (CDZM), spectinomycin (SPCM), levofloxacin (LVFX). Among these strains, 10 strains, which were highly resistant to CFIX (MIC≧0.5 μg/mL), were analyzed their gene pattern using pulsed-field gel electrophoresis (PFGE). Drug-resistant rates in 2004 against CFIX, CFTM-PI, CTRX, CDZM, SPCM and LVFX were 5.9%, 20.8%, 0%, 0%, 0%, and 80.2%, respectively. MICs 90 against the strains isolated in 2004 did not change compared to those in 2003. MICs against four strains isolated from pharynx were twice higher than those from urethras. The incidences of β-lactamase producing strain were 2.4% in 1999, 5.2% in 2003, 5.0% in 2004, respectively. From gene analysis using PFGE, four gene patterns were recognized. Among them, 7 had the same gene pattern, which was detected from the strains isolated in each year and from different areas, indicating that this appearance of CFIX-resistant strains was not due to an outbreak of the same clone.

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International Journal of Antimicrobial Agents 27 (2006) 20–26

INTERNATIONAL JOURNAL OF
Antimicrobial
Agents

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Analysis of mutations within multiple genes associated with resistance in a clinical isolate of *Neisseria gonorrhoeae* with reduced ceftriaxone susceptibility that shows a multidrug-resistant phenotype

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Received 10 June 2005; accepted 27 August 2005

Abstract

A *Neisseria gonorrhoeae* strain with a reduced susceptibility to ceftriaxone (minimum inhibitory concentration (MIC) = 0.5 μg/mL) was isolated among 398 clinical isolates obtained from 2000–2001 in Fukuoka City, Japan. The *N. gonorrhoeae* strain was negative for penicillinase production but it showed multidrug resistance against penicillin (MIC = 8 μg/mL), tetracycline (MIC = 4 μg/mL), azithromycin (MIC = 0.5 μg/mL) and ciprofloxacin (MIC = 16 μg/mL). The molecular mechanisms of the multidrug-resistant phenotype in this strain were analysed. Polymerase chain reaction and direct DNA sequencing were performed to identify mutations within the *penA*, *ponA*, *mtrR*, *penB*, *gyrA* and *parC* genes of the gonococcal strain, which thus explain the multidrug-resistant phenotype. The *N. gonorrhoeae* strain contained a significantly different sequence of the *penA* gene from that of the ceftriaxone-susceptible strains. Some regions of the transpeptidase domain within this *penA* gene were closely similar to those found in other *Neisseria* species such as *Neisseria subflava*, *Neisseria flavescens* or *Neisseria perflava/sicca*. This strain also included a *ponA* mutation that is associated with high-level resistance to penicillin, *mtrR* mutations that mediate overexpression of the MtrCDE efflux pump responsible for resistance to hydrophobic agents such as azithromycin, and *penB* mutations that reduce porin permeability to hydrophilic agents such as tetracycline. Moreover, this strain contained *gyrA* and *parC* mutations that confer high-level resistance to ciprofloxacin. These results indicate the emergence of a *N. gonorrhoeae* strain with reduced susceptibility to ceftriaxone, which also showed a multidrug-resistant phenotype that can be explained by the presence of multiple loci mutations associated with antibiotic resistance.

Keywords: *Neisseria gonorrhoeae*; Ceftriaxone; Resistance; Susceptibility; Mutation

1. Introduction

The evolution of resistance to antimicrobial agents in *Neisseria gonorrhoeae* isolates is a global problem in the treatment of gonococcal infections. The gonococcal resistance level to penicillins, tetracyclines, fluoroquinolones and oral cephalosporins has recently begun to increase in Japan [1,2]. Therefore, a regimen of parenteral cephalosporin such as ceftriaxone or spectinomycin is now generally recommended as a first-line treatment for uncomplicated gonococcal infections, and this regimen has also been proven to show an excellent clinical efficacy in Japan. However, we have recently isolated a *N. gonorrhoeae* strain with a reduced susceptibility to ceftriaxone in Fukuoka City, Japan. This gonococcal strain was also found to demonstrate a chromosomally-mediated multidrug-resistant phenotype. The treatment of gonorrhoea may therefore become increasingly more complicated owing to its resistance to a variety of antimicrobial agents, including parenteral cephalosporins.

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0924-8579/$ – see front matter © 2005 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
doi:10.1016/j.ijantimicag.2005.08.021

The genetic mechanisms of chromosomally-mediated penicillin and tetracycline resistance in *N. gonorrhoeae* have been investigated in laboratory mutants and clinical isolates, and the mechanisms are thought to be due to mutations in the three loci of *penA*, *mtrR* and *penB* genes [3]. Mutations in the *penA* gene are associated with a reduced binding of penicillin by penicillin-binding protein (PBP)2, which is a very important target for penicillin [4,5]. Mutations in the *mtrR* gene confer non-specific resistance to erythromycin, azithromycin, rifampicin and hydrophobic agents owing to increased expression of the MtrCDE efflux pump system [6]. The *penB* mutations reduce porin permeability of the outer membrane to hydrophilic antibiotics such as penicillin and tetracycline [7,8]. The *penB* phenotype is apparent only in strains with the MtrR phenotype. In addition to affecting resistance to penicillin, the *penA*, *mtrR* and *penB* loci appear to increase resistance to cephalosporins in *N. gonorrhoeae*. Moreover, recent studies have indicated that alterations in PBP1, encoded by the *ponA* gene, are involved in high-level penicillin resistance in chromosomally-mediated resistant *N. gonorrhoeae* [9,10].

However, little is known about the molecular mechanisms for cephalosporin resistance in *N. gonorrhoeae*. The aim of this study was to determine the molecular basis for ceftriaxone resistance with a multidrug-resistant phenotype in a strain of *N. gonorrhoeae* isolated from our patient population.

2. Materials and methods

2.1. Neisseria gonorrhoeae strains

Antimicrobial susceptibility testing was performed on a total of 398 clinical isolates of *N. gonorrhoeae* that had been obtained from January 2000 to December 2001. All isolates of *N. gonorrhoeae* were collected from male patients with urethritis attending a sexually transmitted disease clinic in Fukuoka City, Japan. None of the isolates were either post-treatment isolates or repeat isolates from the same patient. The clinical efficacy of ceftriaxone or other antibiotics against *N. gonorrhoeae* isolates was not known. The organisms were identified by Gram staining, oxidase activity and reaction using the Gonochek II test (EY Laboratories, San Mateo, CA). The isolates were suspended in a cryoprotective medium [11] and stored at −80 °C until they were tested. After antimicrobial susceptibility testing, the identities of five isolates (GP853, GP984, GP986, GP998 and A69W) were further confirmed using the biochemical test Vitek NHI (bioMerieux, Tokyo, Japan).

2.2. Antimicrobial susceptibility testing

The minimum inhibitory concentration (MIC) for all isolates was determined by an agar dilution technique with a GC agar base (Becton Dickinson, Sparks, MD) containing 1% Iso VitaleX (Becton Dickinson) and two-fold dilutions of antibiotics as specified in the National Committee for Clinical Laboratory Standards (NCCLS) protocol [12]. Briefly, the plates were inoculated with ca. 10^4 colony-forming units/spot of each isolate with a multipoint inoculator. The World Health Organization reference *N. gonorrhoeae* strains A, B, C, D and E, and *N. gonorrhoeae* ATCC 49226 strain were included as quality controls. The plates were incubated for 24 h at 35 °C in a 5% CO_2 atmosphere. MICs were defined as the lowest antibiotic concentration observed to inhibit bacterial growth. The antimicrobial agents tested were penicillin G (Sigma Chemical Co., St Louis, MO), tetracycline (Wyeth Ledere Japan, Tokyo, Japan), ceftriaxone (Nippon Roche, Tokyo, Japan), cefixime (Astellas Pharma, Tokyo, Japan), ciprofloxacin (Bayer Yakuhin, Osako, Japan), azithromycin (Pfizer Pharmaceuticals, Tokyo, Japan) and spectinomycin (Sigma Chemical Co.). All of the antibiotics were obtained in powder form at the stated potencies determined by their manufacturers. The antimicrobial susceptibility was determined according to the breakpoint criteria defined by the NCCLS [12].

2.3. Polymerase chain reaction (PCR) amplification and DNA sequencing

For the PCR amplification of the *penA* gene, three sets of oligonucleotide primers (1S 5′-CGAATATAAGCCCCGGAT-3′, PA2 5′-ACAATCTCGTTGATACTCG-3′ [13]; B1 5′-TGCCGGAATCGGATTCCT-3′, B2 5′-CGATGACGTGTGCAAAGA-3′; and C1 5′-TTACGGCCTGCAATTGAG-3′, C2 5′-GGTCGGGATGCCGGTTTC-3′) were used. The *ponA* gene was amplified with the following primers: 5′-CGCGGTGCGGAAAACTGATATCGAT-3′ (nucleotides 955–978 of the *ponA* open reading frame) and 5′-AGCCCGGATCGGTTACCATACGTT-3′ (nucleotides 2218–2195 of the *ponA* open reading frame) [10]. To amplify the promoter and coding regions of the *mtrR* gene (nucleotides 860–1175; GenBank accession no. Z25796), primers MTR1 (5′-AACAGGCATTCTTATTTCAG-3′) and MTR2 (5′-TTAGAAGAATGCTTTGTGTC-3′) published by Mavroidi et al. [13] were used. Primers PorB1 (5′-AAAGGCCAAGAAGACCTCGGC-3′) and PorB2 (5′-GAGAAGTCGTATTCCGCACCG-3′) were used for amplification of a part of the *por* gene (nucleotides 160–917; EMBL accession no. AJ004943) [13].

PCR amplification was performed in a reaction mixture containing 5.0 μL of 10× *Taq* polymerase buffer (500 mM KCl, 100 mM Tris–HCl (pH 8.3), 15 mM $MgCl_2$, 0.1% gelatin), 2.0 μL of each of the two primers (25 pmol/μL), 1.0 μL of each of the four deoxynucleotide triphosphates (10 mM), 0.25 μL of *Taq* DNA polymerase (5 U/μL) (Takara Biomedicals, Otsu, Shiga, Japan) and 1.0 μL of template DNA (100 ng/μL). Thirty-five cycles were performed for each reaction. Each cycle consisted of denaturation at 96 °C for 0.5 min, annealing at 56 °C for 0.5 min and extension at 74 °C for 0.5 min. The PCR amplification products were directly sequenced using a DYEnamic ET Terminator Cycle

Sequencing Kit (Amersham Biosciences, Piscataway, NJ) and ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

We also examined mutations in the quinolone resistance-determining regions (QRDRs) within the *gyrA* and *parC* genes, as described previously [1].

3. Results

3.1. Susceptibility to antimicrobial agents

Of the 398 clinical isolates of *N. gonorrhoeae* tested, only one (0.3%) showed a reduced susceptibility to ceftriaxone (MIC = 0.5 μg/mL). The antimicrobial susceptibilities of the strain GP853 with a reduced susceptibility to ceftriaxone and of four ceftriaxone-susceptible strains (GP984, GP986, GP998 and A69W), which were chosen as control strains in the molecular investigations, are shown in Table 1. Strain GP853 was negative for penicillinase production and showed a reduced susceptibility to other cephalosporins such as cefixime. Strain GP853 was also resistant to penicillin, tetracycline, azithromycin and ciprofloxacin, but it was susceptible to spectinomycin. Our results suggested that the *N. gonorrhoeae* strain GP853 with a reduced susceptibility to ceftriaxone showed a multidrug-resistant phenotype for antimicrobial susceptibility and might contain mutations in multiple loci of *penA*, *ponA*, *mtrR*, *penB*, *gyrA* and *parC* genes, which induce microorganism resistance to various antimicrobial agents.

3.2. Mutations in the penA gene

Mutations in the *penA* gene are associated with a reduced binding of penicillin to PBP2, which is a very important target for penicillin in gonococci. Full-length *penA* sequences were determined using five *N. gonorrhoeae* strains including four isolates (GP984, GP986, GP998 and A69W) susceptible to ceftriaxone (MIC = 0.001 or 0.004 μg/mL) as well as strain GP853 with a reduced susceptibility to ceftriaxone. The amino acid sequences of PBP2 of GP853 (Fig. 1B) and GP998 (Fig. 1C) are shown in Fig. 1. The PBP2 sequence of GP998 susceptible to ceftriaxone was identical to that of penicillin-susceptible strain LM306 (GenBank accession no. M32091; Fig. 1A). However, the PBP2 sequence of the strain GP853 did not have the extra codon (345a) and the sequence was very different from that of penicillin-susceptible strain LM306. Multiple substitutions of a mosaic-like structure were identified mainly within the region of the transpeptidase domain in the PBP2 of strain GP853, which is predicted to extend from ca. residues 260–581 [5,14]. Of the 581 amino acids (1–581) in the PBP2 sequence of GP853, 520 (89.5%) were identical and 61 (10.5%) were different from those in the sequence of strain LM306.

Next we compared the amino acid sequence (330–552) included in the transpeptidase domain of the PBP2 of GP853 with those of various *Neisseria* species, including *N. gonorrhoeae* LM306, *Neisseria subflava* ATCC 14799, *Neisseria flavescens* IID592, *Neisseria perflava/sicca* 1654/1659 (GenBank accession no. X67442), *Neisseria meningitidis* MC58 (GenBank accession no. NC-003112), *Neisseria polysaccharea* NCTC 11858 (GenBank accession no. X59626) and *Neisseria cinerea* NCTC 10294 (GenBank accession no. X59540). Surprisingly, the sequence of this region within the transpeptidase domain of the PBP2 of GP853 was closely similar to those of *N. subflava* ATCC 14799, *N. flavescens* IID592 and *N. perflava/sicca* 1654/1659 (Table 2).

Table 2
Differences in the PenA sequence between *Neisseria gonorrhoeae* GP853 and other *Neisseria* species[a]

Strain (GenBank accession no.)	Different	Identical (%)
N. gonorrhoeae LM306 (M32091)	36	187 (83.9)
N. subflava ATCC 14799	5	218 (97.8)
N. flavescens IID592	6	217 (97.3)
N. perflava/sicca 1654/1659 (X76422)	7	216 (96.9)
N. meningitidis MC58 (NC-003112)	36	187 (83.9)
N. polysaccharea NCTC 11858 (X59626)	35	188 (84.3)
N. cinerea NCTC 10294 (X59540)	30	193 (82.1)

[a] The amino acid sequences (330–552) that are included in the transpeptidase domain of PenA of *Neisseria* species were compared.

Table 1
Comparison of the antimicrobial susceptibility of a *Neisseria gonorrhoeae* strain showing reduced susceptibility to ceftriaxone with the minimum inhibitory concentrations (MICs) of ceftriaxone-susceptible strains

Strain	MIC (μg/mL)							
	CTRX	CFIX	PCG	TC	AZM	CPFX	SPCM	β-Lactamase
Reduced susceptibility to ceftriaxone								
GP853	0.5	0.5	8	4	0.5	16	8	Negative
Susceptible to ceftriaxone								
GP984	≤0.001	0.004	0.06	0.03	0.03	0.06	8	Negative
GP986	0.004	0.008	0.03	0.25	0.12	0.002	16	Negative
GP998	≤0.001	0.002	0.008	0.06	0.015	0.002	2	Negative
A69W	0.004	0.008	0.06	0.25	0.03	0.004	4	Negative

CTRX: ceftriaxone; CFIX: cefixime; PCG: penicillin G; TC: tetracycline; AZM: azithromycin; CPFX: ciprofloxacin; SPCM: spectinomycin.

```
                1                                                  50                                                 100
A: LM306        MLIKSEYKPRMLPKEEQVKKPMTSNGRISFVLMAMAVLFACLIARGLYLQTVTYNFLKEQGDNRIVRTQALPATRGTVSDRNGAVLALSAPTESLFAVPK
B: GP853        ----------------------------------------------------------------------------------------------------
C: GP998        ----------------------------------------------------------------------------------------------------
              101                                                 150                                                 200
A: LM306        DMKEMPSAAQLERLSELVDVPVDVLRNKLEQKGKSFIWIKRQLDPKVAEEVKALGLENFVFEKELKRHYPMGNLFAHVIGFTDIDGKGQEGLELSLEDSL
B: GP853        E-------------------------------------------------------A-----------S----------------------------
C: GP998        ----------------------------------------------------------------------------------------------------
              201                                                 250                                                 300
A: LM306        YGEDGAEVVLRDRQGNIVDSLDSPRNKAPQNGKDIILSLDQRIQTLAYEELNKAVEYHQAKAGTVVVLDARTGEILALANTPAYDPNRPGRADSEQRRNR
B: GP853        HAGE---------E-------------------------------------------------------------V-----E--K--Q---------
C: GP998        ----------------------------------------------------------------------------------------------------
              301                                                 350                                                 400
A: LM306        AVTDMIEPGSAIKPFVIAKALDAGKTDLNERLNTQPYKIGPSPVR? DTHVYPSLDVRGIMQKSSNVGTSKLSARFGAEEMYDFYHELGIGVRMHSGFPGET
B: GP853        -----------M---T------S--V-ATDTF--L-----SAT-Q-------T-------------------M-TPK-------D--V------------
C: GP998        ----------------------------------------------------------------------------------------------------
              401                                                 450                                                 500
A: LM306        AGLLRNWRRWRPIEQATMSFGYGLQLSLLQLARAYTALTHDGVLLPLSFEKQAVAPQGKRIFKESTAREVRNLMVSVTEPGGTGTAGAVDGFDVGAKTGT
B: GP853        -----S----QK-----------------------V-----E---V---------K---VI-A---KK--E-------A-------------------
C: GP998        ----------------------------------------------------------------------------------------------------
              501                                                 550                                581
A: LM306        ARKFVNGRYADNKHVATFIGFAPAKNPRVIVAVTIDEPTAHGYYGGVVAGPPFKKIMGGSLNILGISPTKPLTAAAVKTPS*
B: GP853        ---L-----V-Y---------------------------N---S---T--V--QV---------V----------------
C: GP998        ------------------------------------------------------------------------------
```

Fig. 1. The amino acid sequences of penicillin-binding protein (PBP)2 of (A) a penicillin-susceptible *Neisseria gonorrhoeae* strain LM306 (GenBank accession no. M32091), (B) *N. gonorrhoeae* strain GP853 with a reduced susceptibility to ceftriaxone and (C) *N. gonorrhoeae* strain GP998 that is susceptible to ceftriaxone. The PBP2 sequence of strain GP853 does not have the extra codon (345a) and the sequence is extremely different from that of penicillin-susceptible strain LM306. The dashes indicate amino acid residues identical to those of LM306.

3.3. Mutations in the ponA gene

Alterations in PBP1 related to high-level penicillin resistance in chromosomally-mediated resistant *N. gonorrhoeae* have been reported [9]. We examined the sequence of the *ponA* gene coding PBP1 of the GP853 strain with reduced ceftriaxone susceptibility and high-level penicillin resistance (MIC = 8 μg/mL) according to the method published by Ropp et al. [10]. In this study, we identified only a single mutation of Leu-421 → Pro in the PBP1 in strain GP853, whilst there were no such mutations in the four ceftriaxone-susceptible strains (GP984, GP986, GP998 and A69W).

3.4. Mutations in the mtrR gene

The strain GP853 with a reduced ceftriaxone susceptibility showed a decreased susceptibility to azithromycin (MIC = 0.5 μg/mL). We next determined whether *N. gonorrhoeae* strain GP853 contained mutations within the *mtrR* coding region or the 13 bp inverted repeat of the *mtrR* promoter [6]. Strain GP853 had a single base pair (A/T) deletion (−AAAGTCTTTTT) in the 13 bp inverted repeat positioned between −10 and −35 sequences of the *mtrR* promoter, whilst the four isolates susceptible to ceftriaxone had no deletion (AAAAAGTCTTTTT) within the *mtrR* promoter. Moreover, two point mutations as a result of the following amino acid substitution were identified within the *mtrR* coding region in strain GP853: Gly-45 → Asp and Tyr-105 → His. Of the four strains susceptible to ceftriaxone, only one contained the Gly-45 → Asp substitution, whilst the remaining three had the Tyr-105 → His substitution in the *mtrR* coding region.

3.5. Mutations in the penB gene

Mutations in *penB* have been reported to be in loop 3 of the *por* gene and reduce porin permeability to hydrophilic antibiotics. They are known to play an important role in the development of chromosomally-mediated resistance to penicillins and tetracyclines in *N. gonorrhoeae* [7,8]. We asked whether the GP853 strain carried *penB* mutations in loop 3 of the *por* gene. In this study, the amplified *por* segment included putative loop 3 (residues 100–128) of the Por protein [10]. Both Asp-120 and Asp-121 mutations, the presence of which may be associated with a reduced permeability to penicillins and tetracyclines [7], were identified in strain GP853. These

mutations were not identified in the four strains susceptible to ceftriaxone.

3.6. Mutations in the gyrA and parC genes

Because strain GP853 was resistant to ciprofloxacin (MIC = 16 μg/mL), we also investigated genetic alterations within the QRDR in the *gyrA* and *parC* genes, which confer fluoroquinolone resistance to the microorganism. The GP853 strain contained a total of four amino acid substitutions, including Ser-91 → Phe and Asp-95 → Asn mutations within the GyrA protein, and Ser-87 → Arg and Ser-88 → Pro mutations within the ParC protein. Of the four isolates that were susceptible to ceftriaxone, only one strain (GP984), with a decreased susceptibility to ciprofloxacin (MIC = 0.06 μg/mL), contained a single amino acid mutation of Ser-91 → Phe within the GyrA protein.

4. Discussion

Ceftriaxone is a highly potent antimicrobial agent against *N. gonorrhoeae* and it is recommended to be used as the first-line agent in the treatment of gonococcal infections worldwide. As shown previously, ceftriaxone MIC_{50}, MIC_{90} and the MIC range were 0.015 μg/mL, 0.06 μg/mL and 0.001–0.5 μg/mL, respectively [2]. However, we recently isolated a *N. gonorrhoeae* strain (GP853) with a reduced susceptibility to ceftriaxone in Fukuoka City, Japan, where gonococci have been developing resistance to various antimicrobial agents [1,2]. Isolation of *N. gonorrhoeae* with either resistance or a decreased susceptibility to ceftriaxone is very rare [15–17]. Furthermore, to our knowledge, so far there have been no reports or investigations that have elucidated the molecular mechanisms of ceftriaxone resistance in clinical isolates of *N. gonorrhoeae*.

In this study we examined the molecular mechanisms of resistance to ceftriaxone in *N. gonorrhoeae*. The GP853 strain was negative for β-lactamase production and also showed a multidrug-resistant phenotype. Therefore, the mechanism of this gonococcal resistance to ceftriaxone is not considered to be due to plasmid-mediated resistance but instead due to chromosomally-mediated resistance. Mutations in the three loci of *penA*, *mtrR* and *penB* in *N. gonorrhoeae* are well known to be associated with low-level chromosomally-mediated resistance to penicillin and tetracycline [3–8]. Moreover, recent studies demonstrated that alterations in PBP1 owing to a point mutation in the *ponA* gene were involved in high-level chromosomally-mediated penicillin resistance [9,10]. It appears that the *penA*, *mtrR*, *penB* and *ponA* mutations that confer high-level resistance to penicillin also increase the resistance level to cephalosporins such as ceftriaxone in gonococci.

In this investigation we found that the sequence of some regions of the transpeptidase domain of the PBP2 of strain GP853 were identical to those of other *Neisseria* spp. such as *N. subflava*, *N. flavescens* and *N. perflava/sicca*. Similar results have recently been reported from other investigations on the mechanisms of cefixime-resistant *N. gonorrhoeae* in Japan [18,19]. Ameyama et al. [18] indicated that *N. gonorrhoeae* with a reduced susceptibility to cefixime (MIC = 0.5 μg/mL) had a mosaic-like structure in the *penA* gene, and some regions in the transpeptidase domain of the *penA* gene of the *N. gonorrhoeae* strain were similar to those of *N. perflava/sicca*, *N. cinerea*, *N. flavescens* and *N. meningitidis* [18]. They also showed that gonococcal resistance to cephalosporins was transferred to a susceptible recipient by transformation of the *penA* gene that had been amplified by PCR from a strain with a reduced susceptibility to cefixime [18]. The mosaic-like structure in the *penA* gene may induce a reduction in the level of susceptibility of *N. gonorrhoeae* to β-lactam antibiotics such as penicillins or cephalosporins. Interestingly, the sequence of the transpeptidase domain in our strain GP853 was very similar to that of *N. gonorrhoeae* with a reduced susceptibility to cefixime as reported by Ameyama et al. [18]. Furthermore, some reports have proposed that *Neisseria lactamica* plays a role in the emergence of *N. meningitidis* strains with intermediate resistance to penicillin by horizontal genetic exchange of the *penA* genes [20,21]. Intragenic recombination of the meningococci chromosomal gene *penA* with related genes of *N. lactamica* and other commensal *Neisseria* spp. may have generated mosaic genes that encode proteins with a reduced affinity for penicillin, thus resulting in the emergence of intermediately-resistant meningococcal strains [22]. These findings thus suggest that the horizontal genetic exchange of antimicrobial resistance determinants in the transpeptidase domain of the *penA* gene between commensal *Neisseria* species, such as *N. perflava/sicca*, *N. cinerea* or *N. gonorrhoeae*, may be one of the most significant mechanisms in resistance to cephalosporins in the GP853 *N. gonorrhoeae* strain. Previous reports indicated that among the multiple amino acid changes in PBP2 of chromosomally-mediated penicillin-resistant *N. gonorrhoeae*, the most important change was an amino acid insertion (Asp-345a) into PBP2, which lowers the rate of acylation of PBP2 with penicillin by four- to five-fold [23,24]. However, in the present study, neither strain GP853 with a reduced susceptibility to ceftriaxone nor strain GP998 that is susceptible to ceftriaxone contained this insertion in PBP2.

Ropp et al. [10] demonstrated that alterations in PBP1 were involved in high-level penicillin resistance in chromosomally-mediated resistant *N. gonorrhoeae*, although an additional locus, *penC*, is required to achieve high-level penicillin resistance. They identified a single amino acid mutation of Leu-421 → Pro in PBP1 located 40 amino acids N-terminal to the active site serine residue (Ser-461). This mutation was found in chromosomally-mediated resistant *N. gonorrhoeae* strains for which the MICs for penicillin were 1 μg/mL. This point mutation in the *ponA* gene had a three- to four-fold lower rate of acylation than wild-type PBP1 with β-lactam antibiotics, and replacement of the altered *ponA*

gene in several chromosomally-mediated resistant *N. gonorrhoeae* strains with the wild-type *ponA* gene resulted in a two-fold decrease in the MIC [10]. We also identified the same mutation of Leu-421 → Pro in PBP1 in strain GP853, with MICs of 8 μg/mL and 0.5 μg/mL for penicillin and ceftriaxone, respectively. These results suggest that a mutation of Leu-421 → Pro in PBP1 might be important in high-level penicillin and cephalosporin resistance in chromosomally-mediated resistant *N. gonorrhoeae*.

The MtrCDE-encoded efflux pump has been suggested to be one mechanism by which certain *N. gonorrhoeae* strains could express resistance to erythromycin and azithromycin, and the efflux pump system may be one of the essential mechanisms for multidrug resistance. Mutations within the *mtrR* coding region or the 13 bp inverted repeat positioned between −10 and −35 sequences of the *mtrR* promoter have been reported possibly to result in a reduced susceptibility of gonococci to erythromycin and azithromycin as well as to other hydrophobic agents [6,25,26]. Zarantonelli et al. showed *N. gonorrhoeae* isolates with a decreased azithromycin susceptibility (MIC = 0.25 or 0.5 μg/mL) to have a single base pair (A/T) deletion in the 13 bp inverted repeat in the *mtrR* promoter as well as a single point mutation of Gly-45 → Asp within the *mtrR* coding region [26]. Another study demonstrated a single base pair (A/T) deletion in the *mtrR* promoter and a single substitution of Tyr-105 → His in the *mtrR* coding region in a gonococcal isolate with resistance to penicillin, tetracycline, erythromycin and chloramphenicol [13]. Our GP853 strain also had an A/T deletion in the *mtrR* promoter and a double mutation of Gly-45 → Asp and Tyr-105 → His within the *mtrR* coding region. This double substitution of Gly-45 → Asp and Tyr-105 → His in the *mtrR* coding region may therefore result in a more efficient pump production, thereby increasing resistance to hydrophobic antibiotics such as azithromycin or erythromycin compared with a single substitution of Gly-45 → Asp or Tyr-105 → His. In the present study, although only one of the four strains susceptible to ceftriaxone contained the Gly-45 → Asp substitution whilst the remaining three had the Tyr-105 → His substitution in the *mtrR* coding region, none had a single base pair (A/T) deletion within the *mtrR* promoter. As previously reported, these results suggest that resistance due to a single base pair deletion within the 13 bp inverted repeat sequence within the *mtrR* promoter was substantially greater than that due to mutations in the *mtrR* coding region [26].

The *penB* mutation has been reported to be a mutation in loop 3 of the *por* gene that reduces porin permeability to hydrophilic antibiotics and it is considered to play an important role in the development of chromosomally-mediated resistance to penicillins, cephalosporins, tetracyclines and fluoroquinolones in *N. gonorrhoeae* [7]. It is only apparent in strains with the Mtr phenotype [8]. Gill et al. found both Gly-101 → Asp and Ala-102 → Asp mutations in the putative gonococcal equivalent of the pore-constricting loop 3 of *Escherichia coli* OmpF [8]. These mutations result in an increased negative charge at this position in loop 3 of *por* and they are responsible for reduced porin permeability to antibiotics such as penicillin and tetracycline in gonococci. The present investigation indicated that strain GP853 with a reduced susceptibility to ceftriaxone demonstrated the Mtr phenotype and also had both Gly-120 → Asp and Ala-121 → Asp mutations in loop 3 of Por (Gly-120 and Ala-121 of Por in *N. gonorrhoeae* corresponding to Gly-101 and Ala-102, respectively, of *E. coli* OmpF).

In conclusion, in this study we examined the mechanisms of ceftriaxone resistance in gonococcal isolates with a multidrug-resistant phenotype. A strain with reduced susceptibility to ceftriaxone and multidrug-resistant phenotype had mutations in multiple loci from which *N. gonorrhoeae* acquired resistance to various antimicrobial agents. In Japan, a decrease in the susceptibility to a variety of antimicrobial agents including cephalosporins in *N. gonorrhoeae* isolates has recently been occurring nationwide. Continued surveillance and monitoring of antibiotic susceptibility patterns are therefore strongly needed to detect the increasing number of multidrug-resistant strains.

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泌尿器科領域の性感染症の現状

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性感染症

性感染症（sexually transmitted disease；STD）とは性交または性交に類似する性的接触によって感染伝播する疾患の総称であり，多数の疾患が性感染症に含まれている。**表1**に主な性感染症とその病原体を列挙した。泌尿器科領域の主な性感染症は男性の尿道炎である。尿道炎は淋菌による淋菌性尿道炎とそれ以外の非淋菌性尿道炎に大別される。また，厳密には皮膚科領域ともいえるが，尖圭コンジローマと性器ヘルペスは泌尿器科でもよくみられる疾患である。ケジラミ，疥癬，梅毒など比較的まれな性感染症患者も泌尿器科を訪れることもあるので知っておくべき疾患である。**図1**に性感染症サーベイランス（詳しくは後述）においての泌尿器科を訪れた患者の割合を示す。尿道炎が最も多いが性器ヘルペスや尖圭コンジローマも受診していることがわかる。

性感染症のサーベイランス

わが国で，性感染症のうち梅毒とHIV感染症は感染症法により全例報告の対象となっており，報告が義務付けられている。また，厚生労働省・国立感染症情報センターで集計している定点把握対象疾患に性器クラミジア感染症，淋菌感染症，性器ヘルペス，尖圭コンジローマが含まれている。しかし，これらの統計は，性感染症定点の約900の医療機関での症例数であり患者の増減つまり動向はわかるが，罹患率はわからない[1]。そこで，わが国の性感染症の動向と罹患率を正確に把握するために，熊本らにより厚生労働省班研究として，1998年から，全国からモデル7県（1999年から8県，2001年から9モデル県）を選び，各県下の受診した全症例を把握する性感染症サーベイランスが行われた[2]。このサーベイランスでは，産婦人科，泌尿器科，皮膚科，性病科の全医療機関が調査対象となり，軟性下疳，梅毒，尖圭コンジローマ，性器ヘルペス，淋菌感染症，性器クラミジア感染

1347-9636/05/￥400/論文/JCLS

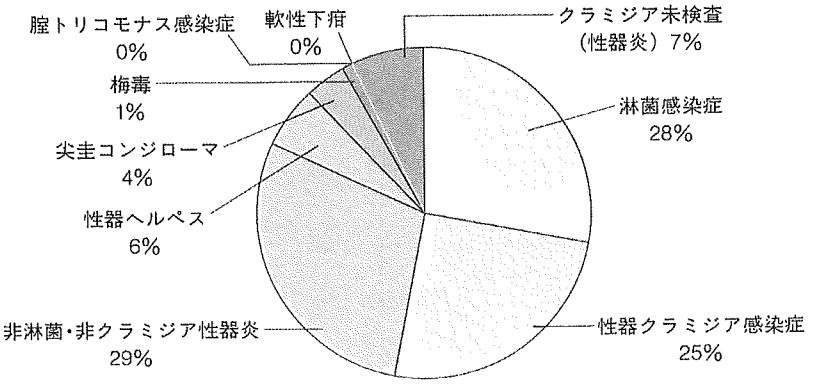
表1　性感染症

性的接触で感染する疾患群を性感染症という。さまざまな疾患があり，診療科も多岐にわたる。

疾患	病原体
尿道炎	淋菌(*Neisseria gonorrhoeae*)
	髄膜炎菌(*Neisseria meningiditis*)
	クラミジア・トラコマチス(*Chlamydia trachomatis*)
	ウレアプラズマ(*Ureaplasma urealyticum*)
	マイコプラズマ(*Mycoplasma genitalium*)
	(*Mycoplasma homunis*)
精巣上体炎	淋菌(*Neisseria gonorrhoeae*)
	クラミジア・トラコマチス(*Chlamydia trachomatis*)
子宮頸管炎	淋菌(*Neisseria gonorrhoeae*)
	クラミジア・トラコマチス(*Chlamydia trachomatis*)
卵管炎・PID・肝周囲炎	淋菌(*Neisseria gonorrhoeae*)
	クラミジア・トラコマチス(*Chlamydia trachomatis*)
カンジダ性腟炎・外陰炎	カンジダ(*Candida albicans*)
腟トリコモナス症	腟トリコモナス(*Trichomonas vaginalis*)
細菌性腟炎	*Gardnerella vaginalis*
	B群レンサ球菌
梅毒	梅毒トレポネーマ(*Treponema pallidum*)
軟性下疳	軟性下疳菌(*Heamophilus ducreyi*)
鼠径肉芽腫	*Calymmatobacterium granulomatis*
鼠径リンパ肉芽腫	クラミジア・トラコマチス(*Chlamydia trachomatis*)
性器ヘルペス	単純ヘルペスウイルス(herpes simplex virus)
尖形コンジローマ	ヒト乳頭腫ウイルス(human papillomavirus)
伝染性軟属腫	伝染性軟属腫ウイルス(mollusucum contagiosum virus)
ケジラミ症	ケジラミ(*Phthirus pubis*)
疥癬	ヒゼンダニ(*Sarcoptes scabiei*)
亀頭包皮炎	レンサ球菌，カンジダ
肝炎	A型肝炎ウイルス
	B型肝炎ウイルス
腸管感染症	*Shigella*, *Salmonella*, *Campylobacter*
アメーバ赤痢	赤痢アメーバ(*Entamoeba histolica*)
AIDS	ヒト免疫不全ウイルス(HIV)
サイトメガロウイルス感染症	サイトメガロウイルス(cytomegalovirus)
伝染性単核症	EBウイルス(Epstein-Barr virus)

図1　泌尿器科を受診する性感染症

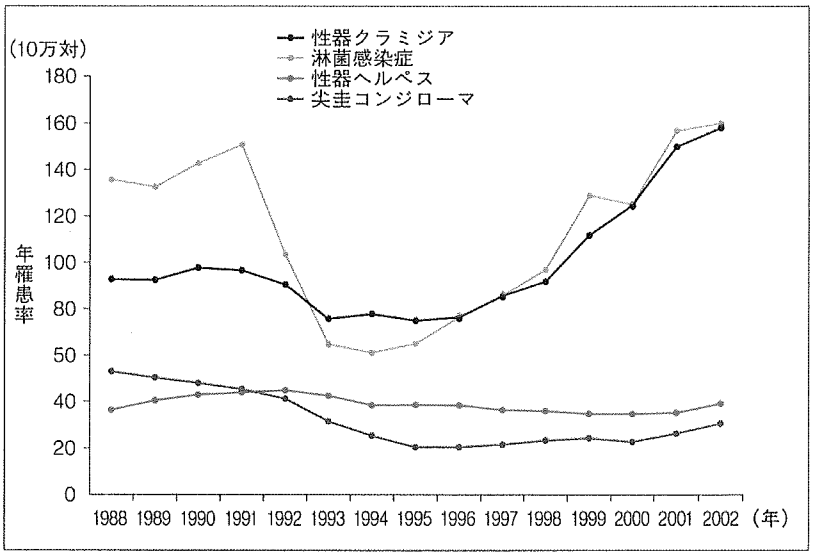
性感染症サーベイランスにおいて泌尿器科を受診した性感染症患者の割合。尿道炎（淋菌感染症，クラミジア感染症，非淋・非クラミジア性器炎，クラミジア未検査性器炎）が大部分を占めるが，尖圭コンジローマや性器ヘルペスも受診している。



症，非淋・非クラミジア性性器炎（男性尿道炎・女性子宮頸管炎で淋菌およびクラミジア検査陰性例），および腟トリコモナス感染症の発症例数を調査した。このサーベイランスでは受診した全症例を把握できるので有病罹患率が明らかとなり，わが国でどのくらいの患者が発生しているかを推定できる[1,2]。熊本らはこの性感染症サーベイランス資料に基づき厚生省性感染症動向調査の疫学的調査から10万人年対罹患率を算出し，推移をまとめている[2]（図2，3）。以下本稿ではこのサーベイランスをもとに各種性感染症の動向について述べる。

図2　罹患率の動向（男性）

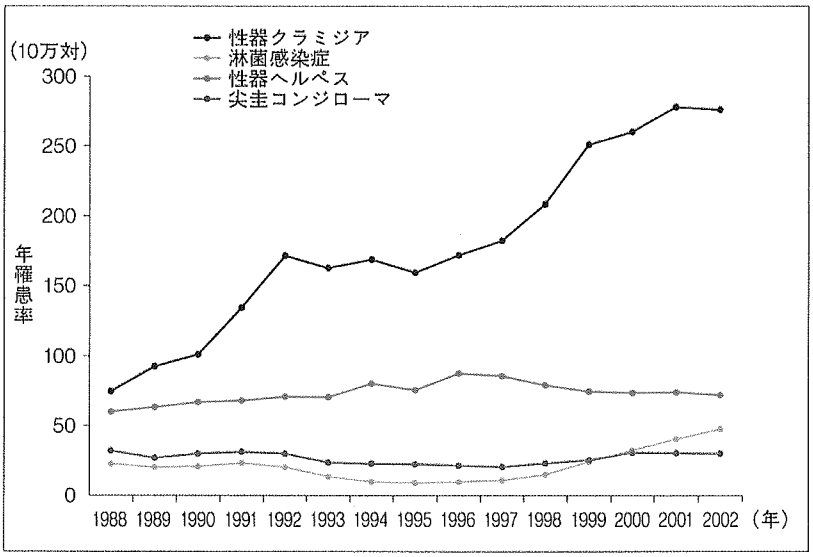
淋菌感染症とクラミジア感染症は1992年以降急減したが，1996年ごろから増加傾向にある。



(文献2より作成)

図3　罹患率の動向（女性）

クラミジア感染症と性器ヘルペスは罹患率が男性に比べ高い。クラミジア感染症の増加が著しい。



(文献2より作成)

図4　淋菌性尿道炎

a：局所所見。外尿道口に膿性分泌物を認める。排尿痛が激しい。
b：分泌物のグラム染色。白血球内にグラム陰性双球菌を認める。
淋菌性尿道炎はエイズショックの影響で1992年から減少傾向にあったが，1996年ごろより増加に転じている。特にフェラチオのみで感染する症例が増加している。

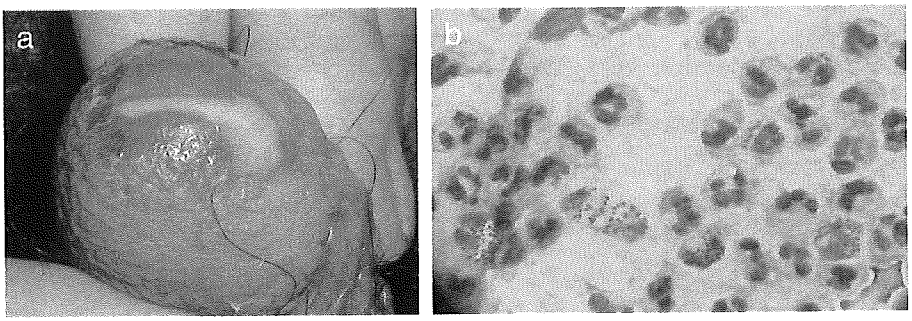
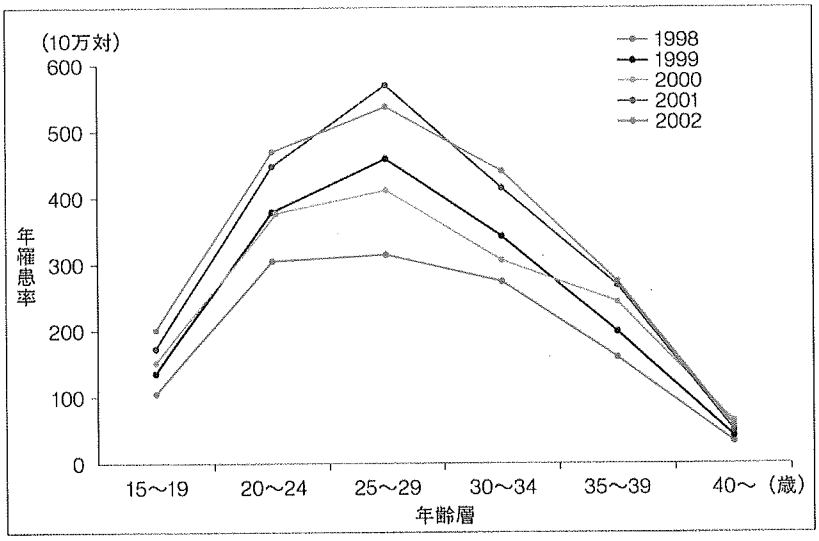


図5　男性淋菌感染症の年代別罹患率の推移

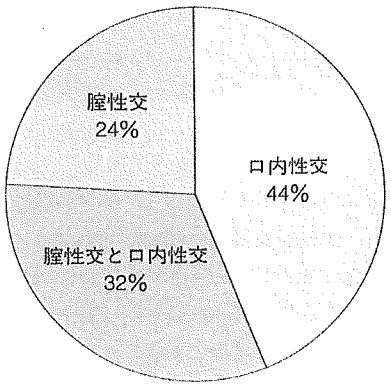
20歳から30歳前半での増加が著しい。



（文献2より作成）

図6　淋菌性尿道炎の性交形態（感染経路）

フェラチオのみでの感染が約半数みられる。



（文献3より引用）

しかし，性感染症は無症候に経過することも多く，実際には医療機関に受診しない患者を含め全数を把握することは不可能であり，潜在的にはこのサーベイランスによる推定数よりも多くの感染者が存在すると考えられる。

性感染症の動向

淋菌性尿道炎（図4）

淋菌（*Neisseria gonorrhoeae*）による淋菌性尿道炎は，エイズショックの影響で1992年から減少傾向にあったが，1996年ごろより増加に転じている。（図2）。男女比では男性が女性の3～4倍多い[2]。年齢別では，20歳から30歳前半が最も多いが，最近では男女とも10歳代の若者の増加率が高いことが懸念されている（図5）。また，最近風俗女性とのオーラルセックスにより感染した淋菌性尿道炎が増加している[3]（図6）。咽頭に淋菌が感染しても症状を呈さないことが多いので，患者が知らずに感染源となってしまうことが原因となっている。

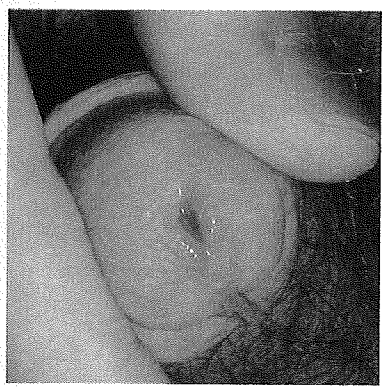
淋菌は薬剤耐性を獲得しやすい細菌で，わが国では最近キノロン耐性株の増加が著しい[4]。また，経口セフェム系薬剤に対しても耐性を示す株も増加している。本疾患の治療上きわめて重要な問題となっている[5]が，詳しくは本特集のPracticeの「性感染症」の各項目を参照していただきたい。

性器クラミジア感染症（図7）

非淋菌性尿道炎のうち半数はクラミジア・トラコマチス（*Chlamydia trachomatis*）によるものである。また，クラミジア性尿道炎の5％は精巣上体

図7　クラミジア性尿道炎

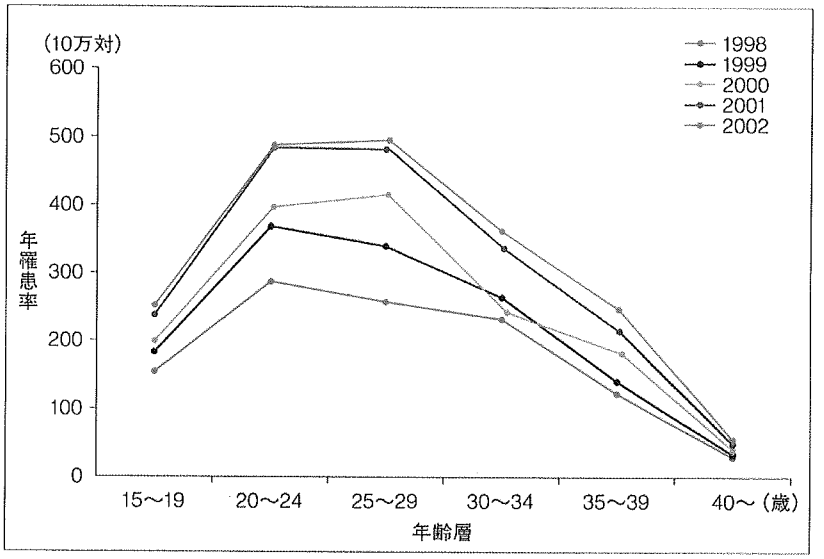
淋菌性尿道炎とは異なり，症状は軽微で，外尿道口から透明な粘液性の分泌物が認められる。1996年から増加に転じている。男性においては20歳代での増加傾向が著しい。フェラチオのみで感染する症例も増加している。



炎を併発する[5]。性器クラミジア感染症は，淋菌性尿道炎と同様に1996年から増加に転じている。男性においては20歳代での増加傾向が著しい（図8）。なお，淋菌性尿道炎と異なり女性に多い（図3）。特に女性においてクラミジア感染の若年化が問題となっている[2]（図9）。なお女性においてクラミジア感染症の罹患率が急増していることについては検査法の進歩やスクリーニング検査の普及によることも一因となっている。クラミジアについても咽頭感染によりオーラルセックスでの感染が増加している。女性の性器にクラミジアが検出された場合は無症状であっても10～20％に咽頭からもクラミジアが検出される[5]。また，性器に比べ治療に時間がかかるといわれ，治療上，問題となっている[5]。クラミジア感染症は淋菌感染症に比べ男女とも症状が軽微で，無症候感染者が多く存在する。熊本は，生殖年齢を中心に男女あわせて100万人

図8　男性クラミジア感染症の年代別罹患率の推移

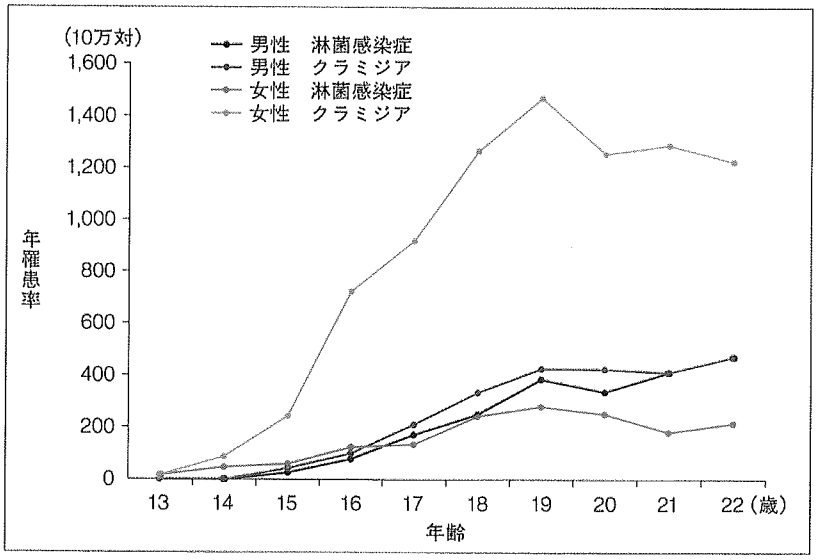
20歳から30歳前半での増加が著しい。



(文献2より作成)

図9　年齢別罹患率

女性ではクラミジアの罹患率が15歳から急に上昇し，20歳で一定となる。男性は女性に比べ上昇傾向が遅れる。



(文献2より作成)