rhoeae strains, it is difficult to strictly link *porB* alleles and accordingly NG-MAST STs to antimicrobial susceptibility phenotypes. Interestingly, seven of the eight isolates in the *porB2569* group that showed higher MICs of cefixime belonged to MLST ST7363 and MLST ST1901, which are the two major STs in which cefixime resistance has emerged. This might suggest that these MLST ST7363 and MLST ST1901 isolates have horizontally acquired their *porB2569* group allele from an authentic MLST ST7359 strain, which is the predominant MLST type among isolates within the *porB2569* group.

The first described isolate of NG-MAST ST1407 from San Francisco, CA, displayed a decreased susceptibility to cefixime, and this isolate had a mosaic type PBP 2 encoded by the *penA* mosaic allele SF-A, subsequently named *penA* allele XXXIV (23). The high-level ceftriaxone-resistant NG-MAST ST1407 isolates identified in France (14) and Spain (25) both had an identical mutated *penA* XXXIV allele (*penA* allele CI [14, 23, 25]) that encodes a PBP 2 XXXIV sequence with leucine replaced by proline at amino acid position 501 (L501P) (14). Accordingly, these high-level resistant strains have presumably evolved by a single nucleotide polymorphism in the *penA* XXXIV allele resulting in an A501P alteration in PBP 2 in an NG-MAST ST1407 (MLST 1901) strain. In the present study, although many NG-MAST ST1407 *N. gonorrhoeae* isolates with *penA* XXXIV allele or derivates of this allele were identified, no *penA* allele CI (14, 23, 25) was found. However, some other single-amino-acid-substituted alleles of *penA* XXXIV, i.e., *penA* XXXIV with P551S or A501V, were identified. The P551S and A501V amino acid substitutions have previously been associated with decreased susceptibility to ceftriaxone (10, 37, 38). In the present study, it was shown by transformation experiments that these substitutions in a *penA* XXXIV allele result in a 2- to 4-fold increase in the MICs of cefixime and ceftriaxone.

In conclusion, our intensified surveillance in 2010 to 2012 in the Kyoto and Osaka prefectures, Japan, did not identify any dissemination of the high-level ceftriaxone-resistant *N. gonorrhoeae* strain H041, suggesting that H041 caused only a sporadic case and has not further spread. Furthermore, no other ceftriaxone-resistant strain was identified. The antimicrobial resistance surveillance in this region has continued and should now be expanded nationally.

However, it is cause for great concern that *N. gonorrhoeae* strains with the *penA* XXXIV allele and its derivatives are also shown to be spreading in Japan, as in many other countries (10, 14). The *penA* mosaic XXXIV allele appears also to be evolving, resulting in further-enhanced MICs of ESCs, and it might be only a matter of time before an additional high-level ceftriaxone-resistant strain emerges. If this strain is not detected in a timely fashion and has a retained biological fitness, it will spread internationally and result in a large public health problem. Consequently, it is crucial not only to enhance the phenotypic antimicrobial susceptibility surveillance of *N. gonorrhoeae* but also to perform molecular typing and detection to monitor the spread and evolution of successful *N. gonorrhoeae* clones with decreased susceptibility and resistance to ceftriaxone worldwide.

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Note

Characterization of azithromycin-resistant *Neisseria gonorrhoeae* isolated in Tokyo in 2005–2011

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ABSTRACT

A total of 122 *Neisseria gonorrhoeae* isolated in the Tokyo metropolitan area in 2005–2011 were collected and analyzed by *N. gonorrhoeae* multiantigen sequence typing (NG-MAST) and for their susceptibility to azithromycin and ceftriaxone. All 122 strains were susceptible to ceftriaxone, but 8 strains were azithromycin-resistant, defined as an azithromycin MIC ≥ 1 μg/ml. The 8 azithromycin-resistant strains were in 6 NG-MAST types, 3 strains in NG-MAST type 1407 and each of the other 5 strains in a different NG-MAST type. NG-MAST type 1407 strains are multidrug-resistant and are disseminated worldwide.

Timely revision of treatment guidelines has been essential for control of *Neisseria gonorrhoeae* infections because of the rapid emergence and spread of drug resistant *N. gonorrhoeae* strains. Therefore, continuous surveillance and antimicrobial susceptibility testing of *N. gonorrhoeae* has been required.

Since the withdrawal of cefixime from the treatment guidelines for *N. gonorrhoeae* in Japan in 2006, the recommended drugs have been limited to three injectable antibiotics: ceftriaxone, spectinomycin, and cefodizime. The first report of a ceftriaxone-resistant *N. gonorrhoeae* strain was an isolate in 2009 from Kyoto, Japan. Spread of ceftriaxone-resistant *N. gonorrhoeae* and development of other treatment options then became a concern. Oral azithromycin (2 g) became available for treatment of *N. gonorrhoeae* infections in Japan in 2009. However, emergence of azithromycin-resistant *N. gonorrhoeae* in Japan would be a significant clinical problem because it would limit the utility of the only currently available oral drug treatment for *N. gonorrhoeae* infections in Japan. Indeed, azithromycin hyper-resistant *N. gonorrhoeae* isolates have been reported in several other countries [1–8].

From this background, we performed retrospective analyses of the clinical *N. gonorrhoeae* strains isolated and stocked in the Byoutai-Seiri Laboratory in 2005–2011. These 122 *N. gonorrhoeae* strains (8 strains isolated in 2005, 24 in 2006, 29 in 2007, 12 in 2008, 9 in 2009, 20 in 2010, and 20 in 2011) were analyzed by multiantigen sequence typing (NG-MAST), as described by Martin et al. [9], and for the minimum inhibitory concentrations (MIC) of penicillin G, cefixime, ceftriaxone, ciprofloxacin, spectinomycin, and azithromycin by the agar dilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI; http://www.clsi.org), with utilization of ATCC49226 strain as the quality control of MIC values.

The 122 *N. gonorrhoeae* strains were in 82 NG-MAST types. The largest number of strains were NG-MAST type 2958 ($n = 16$), followed by NG-MAST type 1407 ($n = 14$) and NG-MAST type 247 ($n = 3$). Only 1 or 2 strains were in each of the other 79 NG-MAST types. The high prevalence of NG-MAST type 1407 and 2958 strains in Japan was also reported previously [10,11]. We then determined the MIC of azithromycin, ceftriaxone, and other 4 drugs described above, of the 122 *N. gonorrhoeae* strains. In this study, an antibiotic MIC ≥ 1 μg/ml was defined as azithromycin-resistant following the EUCAST Clinical Breakpoint Table v. 3.1 2013-02-11 (http://www.eucast.org/antimicrobial-susceptibility-testing/breakpoints) and MIC ≥ 0.5 μg/ml as ceftriaxone-

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Table 1
Properties of the 8 azithromycin-resistant *N. gonorrhoeae* strains in this study.

Strain number	Isolation date	NG-MAST ST	*porB* allele	*tbpB* allele	MIC (μg/ml)						Nucleotide at position 2611 in 23S rRNA gene[a]			
					PCG[b]	CFIX[b]	CTRX[b]	CPFX[b]	SPCM[b]	AZM[b]	Allele 1	Allele 2	Allele 3	Allele 4
50	Jun 2007	278	4	27	1	0.06	0.06	4	16	1	C	C	C	C
57	Jul 2007	7023	4222	21	0.5	0.25	0.125	8	16	1	C	C	C	C
112	May 2010	5687	2481	10	0.25	0.25	0.03	16	32	1	C	C	C	C
115	Jun 2010	6762	4	1307	0.5	0.25	0.03	4	16	8	T	T	T	T
139	Jan 2011	1407	908	110	2.0	0.125	0.06	32	32	16	T	T	T	T
142	Feb 2011	1407	908	110	2.0	0.125	0.06	16	16	16	T	T	T	T
148	Aug 2011	7048	4240	1365	1.0	0.06	0.03	8	16	1	C	C	C	C
149	Aug 2011	1407	908	110	4.0	0.25	0.06	16	16	1	C	C	C	C

[a] There were no mutations in of the four alleles of the 23S rRNA gene in these 8 strains except at position 2611 (*E. coli* numbering) of the three strains with an azithromycin MIC >4 μg/ml.
[b] PCG, penicillin G; CFIX, cefixime; CTRX, ceftriaxone; CPFX, ciprofloxacin; SPCM, spectinomycin; AZM, azithromycin.

resistant following the Clinical and Laboratory Standards Institute (CLSI; http://www.clsi.org), respectively, because CLSI has not set the breakpoint of azithromycin yet. All 122 *N. gonorrhoeae* strains were found to be susceptible to ceftriaxone, but 8 strains were azithromycin-resistant (Table 1). Five of these 8 azithromycin-resistant strains had an MIC = 1 μg/ml and the other 3 strains had an MIC >4 μg/ml (Table 1). For these 8 azithromycin-resistant strains, 3 strains were NG-MAST type 1407 (strains 139, 142, and 149) and there was 1 strain in NG-MAST type 278, 5687, 6762, 7023, and 7048 (Table 1). Although more *N. gonorrhoeae* strains in this study were NG-MAST type 2958 than any of the other 81 NG-MAST types, none of the 8 azithromycin-resistant strains was NG-MAST type 2958.

We noticed that, of the 14 NG-MAST type 1407 strains in this study, the first 11 strains, isolated from 2006 to 2010, were all azithromycin-sensitive (MIC <1 μg/ml). In contrast, the 3 NG-MAST type 1407 strains isolated in 2011 were all azithromycin-resistant. Each of the other 5 azitromycin-resistant strains in this study, isolated from 2007 to 2011, was a different NG-MAST type (Table 1).

The azithromycin-resistant *N. gonorrhoeae* strains detected in this study were different NG-MAST types than the azithromycin-resistant strains isolated in other countries [1–8]. Therefore, we constructed a phylogenetic tree of the *porB* gene sequences of *N. gonorrhoeae* strains from Japan and other countries to investigate the genetic relationships of these strains (Fig.1). No *porB* sequence in the *N. gonorrhoeae* strains from other countries was identical to any of the *porB* sequences of the strains isolated in the Tokyo metropolitan area, except for the *por4* allele that is common in azithromycin-resistant strains from England and Scotland (NG-MAST types 5, 225 and 738) and was found in two of the azithromycin-resistant strains from Tokyo (NG-MAST types 278 and 6762) in this study. The *por908* allele in the NG-MAST type 1407 strains isolated in Japan had only a one nucleotide difference from the *por2237* allele found in an NG-MAST type 3709 strain isolated in the United States [8] and was closely related to the *por971* allele found in an NG-MAST type 1503 strain isolated in Scotland (Fig.1) [4]. Moreover, these NG-MAST type 3709 [8] and type 1503 strains [4] have a *tbpB110* allele that is also in NG-MAST type 1407 strains (Table 1). Therefore, the *por* allele may have diverged in globally disseminated NG-MAST type 1407 strains and some of these NG-MAST type 1407 and related strains subsequently acquired azithromycin resistance.

A point mutation in the *N. gonorrhoeae* 23S rRNA gene has been shown to be responsible for azithromycin resistance [12]. Therefore, we sequenced the four 23S rRNA loci in the 8 azithromycin-resistant *N. gonorrhoeae* strains in this study (Table 1), referring 23S rRNA sequence of strain 20869 in reference 12. The three strains with an azithromycin MIC >4.0 μg/ml (strains 115, 139, and 142) had a C2611T transition (*E. coli* numbering) mutation in all four loci. But, these three strains did not have the A2059G mutation (*E. coli* numbering) found in azithromycin hyper-resistant strains (MIC ≥ 256 μg/ml) [13]. However, the other five *N. gonorrhoeae* strains in this study, with an azithromycin MIC = 1.0 μg/ml, had neither C2611T nor A2059G mutation in any of the four 23S rRNA gene loci.

In this study, we showed that up to the 3 of the 8 azithromycin-resistant *N. gonorrhoeae* strains detected in these analyses were NG-MAST type 1407. This is a public health concern because NG-MAST type 1407 strains have been reported to have reduced susceptibility to cefixime and ciprofloxacin, in several previous studies [11,12]. Moreover, of these three NG-MAST type 1407 strains, two (strains 139 and 142) had an azithromycin MIC as high as 16 μg/ml, the highest value detected in this study.

As an orally administered drug, azithromycin is an attractive treatment choice for *N. gonorrhoeae*. However, it has to be used cautiously because the results of this study indicated that azithromycin-resistant *N. gonorrhoeae* strains have spread, especially as of 2011, with significant clonality in NG-MAST type 1407 strains.

Although azithromycin therapy alone is not recommended in the Japanese Society for Sexually Transmitted Infections guideline, 2 g oral azithromycin is sometimes prescribed for *N. gonorrhoeae* treatment. A recent treatment guideline from the United States CDC recommends dual use of ceftriaxone/azithromycin or ceftriaxone/doxycycline because of their reported efficacy in the treatment of *N. gonorrhoeae* infections [14]. A regimen of azithromycin 2 g orally in a single dose is also proposed as an alternative if ceftriaxone cannot be given because of severe allergy. In this case, the CDC recommended that the patient should return 1 week after treatment for a test-of-cure.

In *N. gonorrhoeae*, the emergence of the initial drug-resistant strains and spread of these strains has been very rapid, partly because they have the high natural transformation ability and intra-species transfer of resistance gene may occur [15]. Therefore, there should be active surveillance to detect the emergence and spread of antibioitc-resistant *N. gonorrhoeae* strains, especially when a new drug is introduced for treatment of *N. gonorrhoeae* infections.

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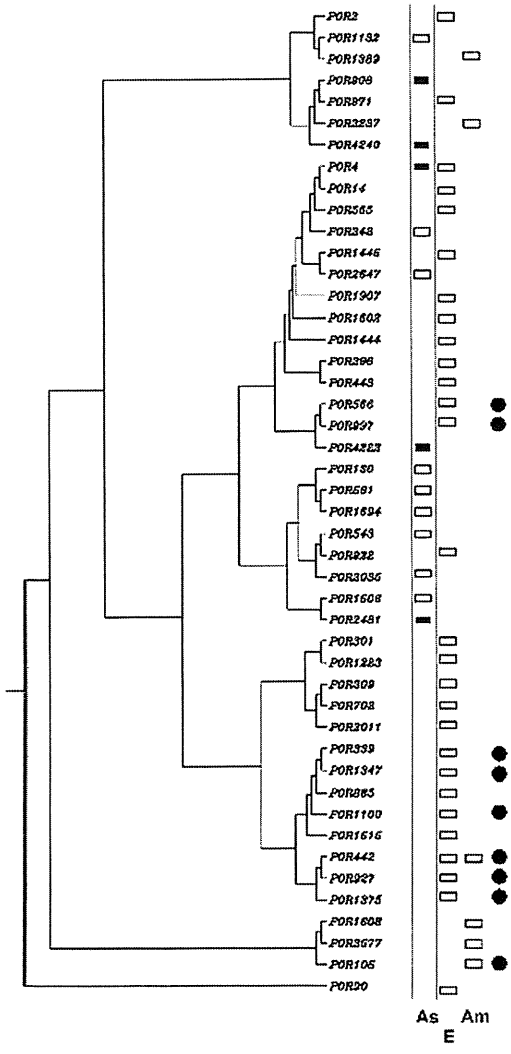

Fig. 1. Phylogenetic tree constructed from sequences of *porB* alleles from *N. gonorrhoeae* strains from Japan (filled boxes in column As) (data from this study), China (open boxes in column As) [6], Europe (open boxes in column E) [1,4,5], and United States and Argentina (open boxes in column Am) [2,3,7,8]. A 490 bp internal region of the *porB* gene, including loops 3, 4 and 5, which was used in NG-MAST, was used to reconstruct the phylogenetic tree using the MEGA 4 program. The numbers are the *porB* allele numbers assigned in the NG-MAST database. The *porB* alleles reported to be in azithromycin hyper-resistant strains (MIC ≥ 256 μg/ml) are marked with circles.

Conflict of interest

None of the authors has any conflicts of interest to declare.

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Treatment failure with 2 g of azithromycin (extended-release formulation) in gonorrhoea in Japan caused by the international multidrug-resistant ST1407 strain of *Neisseria gonorrhoeae*

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Objectives: Antimicrobial resistance in *Neisseria gonorrhoeae* is a major public health concern globally. We report the first verified treatment failure of gonorrhoea with 2 g of azithromycin (extended-release formulation) in Japan and characteristics of the corresponding *N. gonorrhoeae* isolates.

Methods: Pre- and post-treatment isolates ($n=4$) were investigated by Etest for antimicrobial susceptibility. The isolates were examined for molecular epidemiology by multilocus sequence typing (MLST), *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) and multiple-locus variable-number tandem repeat analysis (MLVA), and for the presence of azithromycin resistance determinants (23S rRNA gene mutations, *erm* genes and *mtrR* mutations).

Results: All isolates were resistant to azithromycin (MIC 4 mg/L) and ciprofloxacin, but remained susceptible to cefixime, ceftriaxone and spectinomycin. All isolates were assigned to MLST ST1901 and NG-MAST ST1407 and three of four isolates possessed MLVA profile 8-3-21-16-1. All isolates contained the previously described C2599T mutation (*N. gonorrhoeae* numbering) in all four 23S rRNA alleles and the previously described single-nucleotide (A) deletion in the *mtrR* promoter region.

Conclusions: This verified treatment failure occurred in a patient infected with an MLST ST1901/NG-MAST ST1407 strain of *N. gonorrhoeae*. While this international strain commonly shows resistance or decreased susceptibility to multiple antimicrobials, including extended-spectrum cephalosporins, the strain reported here remained fully susceptible to the latter antimicrobials. Hence, two subtypes of azithromycin-resistant gonococcal MLST ST1901/NG-MAST ST1407 appear to have evolved and to be circulating in Japan. Azithromycin should not be recommended as a single antimicrobial for first-line empirical treatment of gonorrhoea.

Keywords: *N. gonorrhoeae*, *N. gonorrhoeae* multi-antigen sequence typing, NG-MAST, antimicrobial resistance, 23S rRNA, test of cure

Introduction

Neisseria gonorrhoeae infections are major public health concerns worldwide. In 2008, the WHO estimated there were 106 million gonorrhoea cases among adults globally, making it the most prevalent bacterial sexually transmitted infection.[1] In Japan, based on a sentinel surveillance system (~1000 sentinel sites) for gonorrhoea, the number of reported cases peaked (21 921 cases) in 2002, but declined to 10 247 cases in 2011. Resistance in *N. gonorrhoeae* to previously recommended first-line antimicrobials for treatment of gonorrhoea is prevalent worldwide.[2–4] Although attempts have been made to establish surveillance of antimicrobial resistance in *N. gonorrhoeae* in Japan, this has proved difficult due to the low number of isolates obtained for study.[5] Dual antimicrobial therapies have been introduced in the USA[6] and Europe,[7] recommending ceftriaxone (one dose of 250–500 mg intramuscularly) together with azithromycin (one dose of 1–2 g orally) for treatment of uncomplicated gonorrhoea. Furthermore, in the USA one dose of 2 g of azithromycin is recommended if the patient has severe cephalosporin allergy[6] and, despite not being recommended, in several countries, including Japan, azithromycin (one dose of 1–2 g) as single antimicrobial

therapy is occasionally used, due to its wide availability and ease of administration.

Here we report the first verified treatment failure of gonorrhoea with 2 g of azithromycin [extended-release formulation (azithromycin-ER)] in Japan and the phenotypic and genetic characteristics of the corresponding *N. gonorrhoeae* isolates.

Methods

The work was performed at the Department of Bacteriology I, National Institute of Infectious Diseases, Tokyo, Japan.

Case report

In early 201 3, an asymptomatic woman in her late teens presented to a sexually transmitted infection clinic in Osaka city. She sought care because 3 days earlier her male sex partner had been diagnosed with *N. gonorrhoeae* urethritis at another private clinic (no further information regarding this case was available). During the visit she was treated with 2.0 g of azithromycin-ER orally, which is formulated as sustained-release microspheres.[8] Pharyngeal and vaginal culture specimens were also taken, which were confirmed as *N. gonorrhoeae* positive in 2 days (referred to as FC-195 and FC-196, respectively). On the follow-up visit (Day 9), vaginal and pharyngeal culture specimens were taken for test of cure and the patient also received 1 g of ceftriaxone intravenously due to azithromycin resistance (see the Results section) in the isolates cultured on Day 1. The vaginal and pharyngeal test of cure specimens were both confirmed 2 days later as still culture-positive for *N. gonorrhoeae* (isolates designated FC-200 and FC-201, respectively). The patient denied any sexual contacts from the time of receiving azithromycin treatment to test of cure. On Day 22, the patient returned for a test of cure following the ceftriaxone treatment and at this visit vaginal and pharyngeal culture specimens were negative for *N. gonorrhoeae*.

Characterization of isolates

The four clinical isolates were characterized as described below. For comparison, seven additional azithromycin-resistant gonococcal isolates of *N. gonorrhoeae* multi-antigen sequence type (NG-MAST) ST1407 collected in the same geographical region in 2011 and 2012 were analysed.

Antimicrobial susceptibility testing

The MIC (mg/L) of azithromycin was determined using the Etest method (bioMérieux, AB, Solna, Sweden) according to the manufacturer's instructions. MIC values were interpreted in accordance with EUCAST clinical breakpoint criteria (V4.0; www.eucast.org/clinical_breakpoints/; see Table 1).

Genetic characterization

For molecular epidemiology, all isolates were characterized by multilocus sequence typing (MLST), NG-MAST and multiple-locus variable-number tandem repeat analysis (MLVA), as previously described.[9,10]

Azithromycin resistance-associated mutations in the peptidyltransferase region of domain V of the 23S rRNA gene were determined by sequencing, as previously described.[11] The methylase-encoding *ermA*, *ermB*, *ermC* and *ermF* resistance genes were detected with PCR, as previously described.[12] The *mtrR* gene, including the promoter region, and the *penA* gene were sequenced as previously described.[9,13]

Results

The phenotypic and genetic characterization of all four *N. gonorrhoeae* pre- and post-treatment isolates (AZM-TF isolates) is summarized in Table 1, which also includes seven additional azithromycin-resistant NG-MAST ST1407 isolates from the same geographical region (Kyoto/Osaka) for comparison.

Antimicrobial susceptibility testing

All AZM-TF isolates were resistant to azithromycin (MIC 4 mg/L) and ciprofloxacin (MIC ≥32 mg/L), but were susceptible to cefixime (MIC 0.032–0.064 mg/L), ceftriaxone (MIC 0.016–0.032 mg/L) and spectinomycin (MIC 4–8 mg/L). The additional azithromycin-resistant isolates had similar antibiograms; however, the MICs of cefixime (0.125–0.25 mg/L) and ceftriaxone (0.032–0.125 mg/L) for these isolates were 2- to 8-fold higher (Table 1).

Genetic characterization

All AZM-TF isolates were assigned to MLST ST1901 and NG-MAST ST1407. Using MLVA, all isolates, with the exception of FC-196, possessed an identical number of repeat units (8-3-21-16-1) in loci VNTR04-03, VTNR04-10, VNTR07-02, VNTR15-02 and VNTR16-01,[10] respectively. The pre-treatment pharyngeal isolate FC-196 had a closely related MLVA profile, 10-3-21-16-1, i.e. a single-locus variant with slight differences in the VNTR04-03 locus. The additional azithromycin-resistant NG-MAST ST1407 isolates were all assigned as MLST ST1901, with one exception (IT-027: ST10241). These isolates had four different MLVA profiles, which differed from those of the AZM-TF isolates with at least two loci (Table 1).

All AZM-TF isolates contained the previously described C2599T mutation in all four alleles of the 23S rRNA gene (Table 1),[11] but did not have any A2143G mutation.[14] Among the additional seven azithromycin-resistant isolates, HI-015 also possessed the C2599T mutation in all four alleles, but the others had the C2599T mutation in two or fewer alleles. All isolates analysed here, except FC-107, also contained the previously described single-nucleotide (A) deletion in the *mtrR* promoter region; however, no isolates contained the *ermA*, *ermB*, *ermC* or *ermF* genes.

With regard to the main cephalosporin resistance determinant,[4] the AZM-TF isolates and HI-015 possessed the *penA* XXXIV allele and the remaining six isolates had a *penA* XXXIV variant with an additional P551S or A501V mutation (Table 1). These latter alleles are known to result in higher MICs of cephalosporins,[4,9,15] in accordance with the results of this study.

Discussion

This is the first reported case of failure of gonorrhoea treatment with azithromycin in Japan, which was strictly verified in accordance with WHO criteria, i.e. a detailed clinical history was recorded, reinfection was ruled out, the pre-treatment and post-treatment isolates were mainly phenotypically and genetically indistinguishable by highly discriminatory molecular epidemiological typing methods, and the isolates were resistant to azithromycin and contained genetic resistance determinants causing the azithromycin resistance.[2,4,16] The clinical failure occurred after using a 2 g dose of azithromycin-ER (an extended-release

Table 1. Antimicrobial susceptibility and molecular characteristics of *N. gonorrhoeae* isolates with low-level resistance to azithromycin in Japan

		MIC (mg/L)[a]								MLVA repeat number					23S rRNA gene (C2599 position)[b]					*mtrR*	
Isolate	Date	AZM	CRO	SPT	PEN	CFM	CIP	MLST	NG-MAST	04-03	04-10	07-02	15-02	16-01	allele 1	allele 2	allele 3	allele 4	*penA*	promoter region[c]	CDS
FC-195	2013	4	0.032	8	1	0.032	32	1901	1407	8	3	21	16	1	T	T	T	T	XXXIV	A deletion	WT
FC-196	2013	4	0.032	8	1	0.032	32	1901	1407	10	3	21	16	1	T	T	T	T	XXXIV	A deletion	WT
FC-200	2013	4	0.016	4	1	0.032	32	1901	1407	8	3	21	16	1	T	T	T	T	XXXIV	A deletion	WT
FC-201	2013	4	0.032	8	1	0.064	>32	1901	1407	8	3	21	16	1	T	T	T	T	XXXIV	A deletion	WT
KM-026	2011	1	0.125	8	2	0.25	16	1901	1407	6	3	3	17	1	T	T	WT	WT	XXXIV_P551S	A deletion	WT
KM-029	2011	1	0.125	8	4	0.25	16	1901	1407	6	3	3	17	1	T	T	WT	WT	XXXIV_P551S	A deletion	WT
HI-015	2011	8	0.125	8	1	0.125	>32	1901	1407	11	3	21	18	1	T	T	T	T	XXXIV	A deletion	WT
IT-027	2011	1	0.125	8	4	0.25	>32	10241	1407	4	3	4	17	1	WT	WT	WT	WT	XXXIV_P551S	A deletion	WT
HI-018	2012	1	0.125	8	2	0.25	>32	1901	1407	4	3	4	17	1	WT	WT	WT	WT	XXXIV_P551S	A deletion	WT
IT-030	2012	1	0.125	8	1	0.25	>32	1901	1407	4	3	4	17	1	WT	WT	WT	WT	XXXIV_P551S	A deletion	WT
FC-107	2012	1	0.032	8	0.25	0.125	>32	1901	1407	7	3	5	13	1	WT	WT	WT	WT	XXXIV_A501V	new	L47R

AZM, azithromycin; CRO, ceftriaxone; SPT, spectinomycin; PEN, penicillin G; CFM, cefixime; CIP, ciprofloxacin; CDS, coding sequence; WT, wild-type.
FC-195/FC-196 and FC-200/FC-201 are pre- and post-treatment isolates, respectively, from the first verified treatment failure with 2 g of azithromycin in Japan.
[a]Susceptibility (S) and resistance (R) according to EUCAST breakpoints (www.eucast.org): azithromycin, S ≤0.25 mg/L and R >0.5 mg/L; ceftriaxone, S ≤0.125 mg/L and R >0.125 mg/L; spectinomycin, S ≤64 mg/L and R >64 mg/L; penicillin, S ≤0.064 mg/L and R >1 mg/L; cefixime, S ≤0.125 mg/L and R >0.125 mg/L; and ciprofloxacin, S ≤0.032 mg/L and R >0.064 mg/L.
[b]A C2599T mutation in 23S rRNA alleles results in decreased target affinity and increased MICs of azithromycin.[10]
[c]Two different sequences of the promoter region of the *mtrR* gene were identified, i.e. the previously described deletion of one nucleotide (A)[8,12] and a new sequence, GGTTACAAAGTCTTTTTTATAATCCGCCCTCAT (accession number AB914770), in which underlined nucleotides differ from those in the wild-type sequence.

formulation using microspheres that results in an extended duration of effect and less severe adverse effects), which is the highest dose of azithromycin used for treatment of gonorrhoea. All four AZM-TF isolates belonged to MLST ST1901 and NG-MAST ST1407, and all isolates, with the exception of one, were also assigned to an identical MLVA profile. The single-locus MLVA variant of the remaining isolate most likely only represents the intra-strain variability and instability of the VNTR04-03 locus. The C2599T mutation was identified in all four alleles of the 23S rRNA gene, which has been associated with low-level resistance to azithromycin,[11] in all AZM-TF isolates and the HI-015 isolate (azithromycin MIC 4–8 mg/L). The additional examined azithromycin-resistant isolates with this mutation in two or fewer alleles had an azithromycin MIC of only 1 mg/L. All these results are in accordance with previous publications.[14] The single-nucleotide deletion (A) in the inverted repeat region of the *mtrR* promoter, which has been shown to increase azithromycin MICs by causing overexpression of the MrCDE efflux pump,[13] was also present in the AZM-TF isolates.

As mentioned earlier, the treatment failure was caused by *N. gonorrhoeae* MLST ST1901 and NG-MAST ST1407, which is, together with its evolved genetic subtypes, a multidrug-resistant gonococcal clone accounting for a high proportion of the decreased susceptibility and resistance to extended-spectrum cephalosporins in many settings, including the Kyoto/Osaka area, worldwide.[4,9,17,18] Interestingly, the azithromycin-resistant gonococcal MLST ST1901 and NG-MAST ST1407 strain causing the treatment failure in Osaka was fully susceptible to extended-spectrum cephalosporins (e.g. cefixime MICs were 0.032–0.064 mg/L) and instead had substantially higher MICs of azithromycin compared with conventional ST1901/ST1407 isolates.[4,9,17,18] In the ongoing gonococcal surveillance in the Kyoto/Osaka area, among 413 isolates collected from April 2010 to March 2013, 12 additional isolates showing azithromycin resistance have been identified. Of these 12 isolates, 7 were assigned to NG-MAST ST1407, but all 7 had decreased susceptibility to cefixime (MICs 0.125–0.25 mg/L) (Table 1). Furthermore, three azithromycin-resistant NG-MAST ST1407 isolates were found in the Tokyo area in 2011.[19] Two of these three isolates had an MIC of 16 mg/L and possessed the C2599T mutation in all four 23S rRNA alleles. Both of these two isolates also showed decreased susceptibility to cefixime (MIC 0.125 mg/L), in accordance with conventional gonococcal NG-MAST ST1407 isolates. Accordingly, two subtypes of azithromycin-resistant gonococcal NG-MAST ST1407 appear to have evolved and to be circulating in Japan.

Azithromycin-ER has been approved for gonorrhoea treatment since 2009 in Japan. This drug has high activity against many Gram-positive and Gram-negative bacteria, high tissue penetration (making it effective for intracellular pathogens), a single-dose oral regimen, less severe adverse effects compared with conventional azithromycin [immediate-release formulation (azithromycin-IR)] and ease of administration, increasing compliance. According to pharmacokinetic/pharmacodynamic investigations, a 2 g dose of azithromycin-ER results in 3- to 4-fold higher AUC in serum than a 500 mg dose of azithromycin-IR.[20] As the efficacy of azithromycin is best correlated with the parameter AUC/MIC, azithromycin-ER (in a single dose of 2 g) might be a more effective option than azithromycin-IR (in a single dose of 2 g) for treatment of gonorrhoea. However, appropriate comparisons between a 2 g dose of each formulation, taking into account selection of resistance, are crucial. Gonococcal strains with high-level resistance to azithromycin, due to an A2143G mutation in three or four of the 23S rRNA alleles, have been isolated in several countries worldwide,[21–24] though not yet in Japan. Nevertheless, data from the gonococcal antimicrobial resistance surveillance in the Kyoto/Osaka area[9] showed that 3.2% of the gonococcal isolates from April 2010 to March 2013 were resistant to azithromycin. Previously, levels of azithromycin-resistant *N. gonorrhoeae* isolates between 0.4% and 6.6% have been reported in Japan.[5,19,25] However, additional data, including clinical trial data, are needed for the determination of an evidence-based resistance breakpoint for azithromycin-ER, as illustrated in the present study, which shows that *N. gonorrhoeae* strains with low-level azithromycin resistance can cause gonorrhoea treatment failures. Given the occurrence of azithromycin resistance in many countries globally already and the rapid selection of azithromycin resistance when it is widely used (including at doses of 2 g using an extended-release formulation), azithromycin should not be recommended as monotherapy for first-line empirical treatment of gonorrhoea.

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Transparency declarations

None to declare.

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淋菌の咽頭感染，クラミジアの咽頭感染に関する更新，改訂について

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要旨：淋菌・クラミジアの咽頭感染の多くは無症候性感染で，男性のクラミジアは少ないが，女性のクラミジア，そして淋菌では男女ともに性器感染の有無にかかわらず咽頭への感染者が少なくない。診断は，咽頭スワブまたはうがい採取し核酸増幅法で検出する。淋菌の咽頭感染への推奨治療は，CTRX 1g 単回静注，CDZM 1 または 2g を 1～2 回 / 日で 1～3 日間静注のみである。しかし，第 1 選択薬の CTRX 耐性株の報告をうけ，今後治療不成功例発生への注意が求められる。

key words　咽頭感染，淋菌，クラミジア

はじめに

感染症発生動向調査では 1990 年以降，性感染症の患者報告数第 1 位は性器クラミジア，第 2 位は淋菌感染症，という状況が続いている。

この二つの性感染症患者が多い原因として，淋菌，クラミジアともに感染していても無症状で他覚的所見が認められない無症候性感染者が少なくないこと，そしてその無症候性感染者が感染源となって新たな感染が拡がることがあげられている。淋菌は性風俗従業女性の咽頭からの検出率が性器よりも高く，男性の淋菌性尿道炎の約半数が性風俗従業女性の咽頭からの感染であること[1,2]，クラミジアは無防備で活発な性行動をとりがちな若年層における罹患率が高いことから，近年の性行動の多様化を背景に，淋菌，クラミジアともに咽頭を介した感染例の増加が指摘されている。

Upgraded information in the latest edition of the guideline about pharyngeal infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

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key words : pharyngeal infection, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*

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I　淋菌およびクラミジアの咽頭感染の実態

「性感染症 診断・治療 ガイドライン 2011」では，淋菌およびクラミジアの咽頭感染はその多くが無症候性感染（**図 1**）であり，咽頭の症状が無くても男性の淋菌性尿道炎の 10～30％の人の咽頭から淋菌が，子宮頸管からクラミジアが検出された女性の 10～20％の人の咽頭からクラミジアがそれぞれ検出されることが示されている。

われわれが，2005 年から 2009 年に，性感染症クリニック受診者の男性 335 人，女性 519 人を対象に，性器と咽頭から同時に淋菌とクラミジアの検査を実施した前向き研究の結果[3,4]では，淋菌およびクラミジアの性器と咽頭それぞれの陽性者数（**図 2**）は，咽頭の陽性者数が性器の陽性者数に比べて有意に少なかったのは男性のクラミジア検査のみであった。男性の淋菌検査と女性のクラミジア検査では，咽頭の陽性者数は性器の陽性者数に比べて少ないものの有意差はなく，女性の淋菌検査ではやはり有意差はないが咽頭の陽性者が性器の陽性者数を上回る結果であった。この傾向

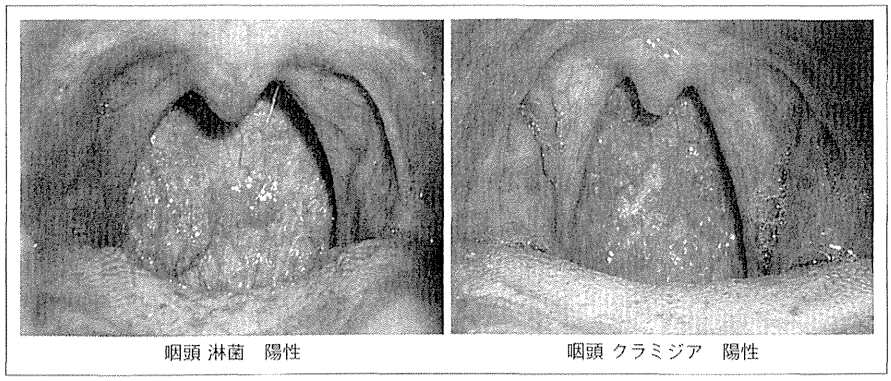


図1　淋菌・クラミジア咽頭感染者の臨床所見
感染者の多数は無症状。咽頭発赤や扁桃腫脹など他覚的所見が認められないことが多い。

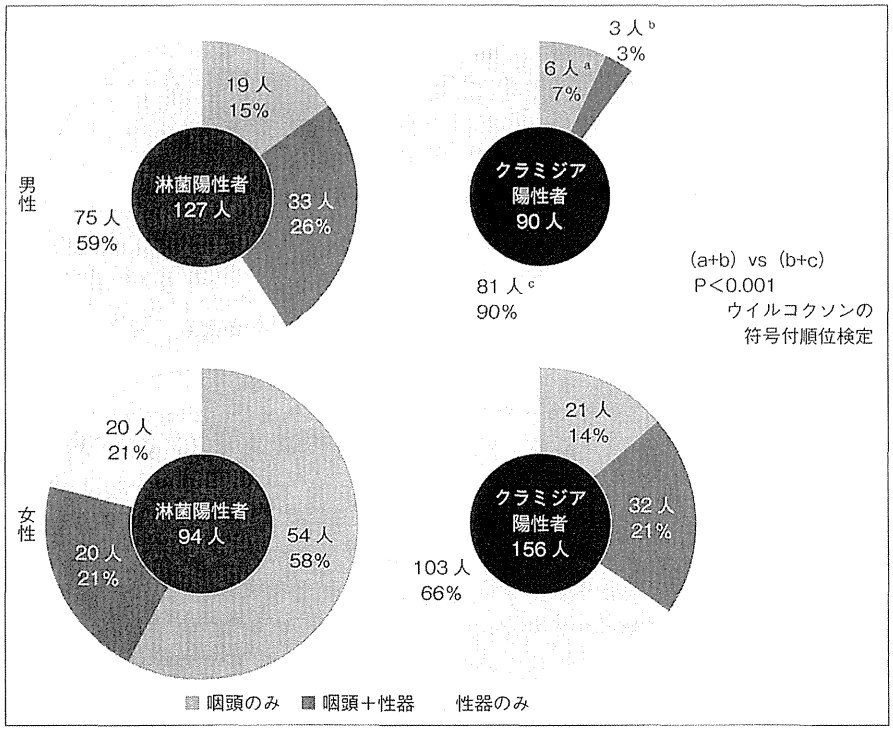


図2　性感染症クリニックにて男性335人，女性519人に実施した淋菌・クラミジアの咽頭・性器同時検査の陽性者数

は，淋菌とクラミジアの咽頭感染に関する諸家の報告でも同様であり，淋菌，クラミジアともに性器に感染している人は咽頭にも感染している可能性が高く，男性の咽頭クラミジア感染症者は少ないが，女性のクラミジア，そして淋菌では男女ともに性器に感染がなくても咽頭には感染している人が少なからず存在する。

日本性感染症学会においても，淋菌およびクラミジアの咽頭感染はここ数年トピックスとして毎年取り上げられており，咽頭感染に関する最新のデビデンスや検査方法をうけて，「性感染症 診断・治療 ガイドライン 2011」では，淋菌とクラミジアの咽頭感染に関する診断と治療の内容の一部が更新・改訂されている。

Ⅱ　咽頭からの淋菌およびクラミジア検査

淋菌の罹患部の菌量は，尿道，子宮頸管，直腸，咽頭の順に少ないことが「性感染症 診断・治療 ガイドライン 2004」から示されている。また，

表1 咽頭からの淋菌・クラミジア検査

	分離培養同定	酵素抗体法	核酸検出法		核酸増幅法		
		IDEIA	DNAプローブ法	ハイブリッドキャプチャー法	PCR* アンプリコア	SDA# プローブテック	TMA$ アプティマコンボ2
Neisseria gonorrhoeae	専用培地	×	△	△	●	◎	◎
Chlamydia trachomatis	不可	○	△	△	◎	◎	◎

◎ → 咽頭検査で推奨ランクA（咽頭以外の検査では推奨ランクB）。
● → 咽頭検査では適応されない。
○ → 推奨ランクAであるが，咽頭検査では菌量が少ないため検出率が低い。
△ → 咽頭検査の適応はあるが，ガイドラインでは推奨されていない。
× → 検査項目として存在しない。
* PCR：Polymerase chain reaction　ポリメラーゼ連鎖反応
# SDA：Strand Displacement Amplification　鎖置換増幅
$ TMA：Transcription-Modiated Amplification　転写介在増幅

表2 淋菌・クラミジア核酸増幅法（性感染症 診断・治療 ガイドライン2011 より引用）

	PCR法	TMA法	SDA法
製品名	アンプリコア STD-1 クラミジアトラコマチス ナイセリアゴノレア	アプティマ Combo2 クラミジア/ゴノレア	BD プローブテック クラミジア・トラコマチス ナイセリア・ゴノレア
検体の種類	男性尿道擦過物・子宮頸管擦過物・尿	男性尿道擦過物・子宮頸管擦過物・尿・咽頭擦過物	男性尿道擦過物・子宮頸管擦過・尿・咽頭擦過物
ターゲット	DNA	rRNA	DNA
検査時間	約5時間	約4.5時間	約2.5時間
最小検出感度 クラミジア・トラコマチス	1 IFU/Assay	1 IFU/Assay	1 IFU/Assay
最小検出感度 ナイセリア・ゴノレア	5 CFU/Assay	50 cell/Assay	10 cell/Assay
増幅・検出	増幅したものを別工程で検出	増幅したものを別工程で検出	同時に行う

咽頭は唾液や飲食によって表面が常にクリアランスされている部位であるため，クラミジアについても同様に他の感染部位に比べて咽頭では上皮に存在する病原体数が少ないことが推察される。淋菌・クラミジアの検出検査（**表1**）として，分離培養（淋菌のみ），酵素抗体法（クラミジアのみ），核酸検出法，核酸増幅法があるなかで，「性感染症 診断・治療 ガイドライン2008」より，咽頭からの検出には感度が高い核酸増幅法のSDA（Strand Displacement Amplification：鎖置換増幅）法のBD プローブテック ET CT/GC（日本ベクトン・デッキンソン，以下SDAと略す）と，TMA（Transcription-Mediated Amplification：転写介在増幅）法のアプティマコンボ2（富士レビオ，以下TMAと略す）を推奨している（**表2**）。

ほかに，淋菌，クラミジアに現在保健収載されている核酸増幅検査としてPCR（Polymerase chain reaction：ポリメラーゼ連鎖反応）法のアンプリコアSTD-1ナイセリアゴノレアおよびアンプリコアSTD-1クラミジアトラコマティス（ロ

表3　淋菌・クラミジア　核酸増幅検査の保険収載されている咽頭の適応材料

PCR アンプリ コア*	SDA ブローブテック	TMA アプティマ コンボ2	realtime PCR コバス4800 システム
スワブ うがい	スワブ	スワブ	うがい

*クラミジア検査のみ

シュ・ダイアグノスティックス，以下PCRと略す）があるが，PCRによる淋菌検査では口腔咽頭の常在性ナイセリアとの交叉反応が生じるため咽頭検体に対する検査は適応外のため，ガイドラインでは推奨していない。

Ⅲ　核酸増幅法におけるうがい液検体の有用性

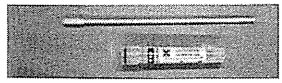
核酸増幅法は，他の検査法に比べて格段に感度が高い検査であるが，現在のSDA，TMAともに咽頭検査専用の検査キットはつくられておらず，尿道用スワブキットまたは子宮頸管用スワブキットのいずれかで，咽頭からスワブを採取し検査しなければならない。しかし，咽頭の内腔は，尿道や膣・子宮頸管に比べて格段に広く，尿道または子宮頸管スワブ用の綿棒では咽頭全体からみるとほんの一部の粘膜上皮しか採取できない。また図1に示したように病的所見に乏しい淋菌およびクラミジア感染症の場合，先の細い綿棒で広い咽頭内を盲目的に擦過したのでは病原微生物を捕らえていない可能性も否定できない。一方，うがい液は咽頭反射が強く視診もできない症例でも侵襲を与えず咽頭全体の粘膜上皮を確実に採取でき，被験者側の協力性や採取側の手技による影響を受けにくいというメリットがある。「性感染症 診断・治療 ガイドライン2008」では，咽頭スワブとの優劣について判断できないという理由で，うがい液は推奨ランクBであったが，その後，うがい液を検体とした核酸増幅検査の検出性はスワブと同等であることを示す研究結果が次々と示され，「性感染症 診断・治療 ガイドライン2011」では咽頭スワブと並んでうがい液は推奨ランクAとなっている。しかし，SDA，TMAともに，咽頭の適応材料として保険収載されているのは咽頭スワブのみで（表3，4a），うがい液は検体として保険収載されていない。うがい液で検査する場合には尿用のキットを用いて行うことができるが（表4b）が，適応外材料のため事前に提出先の検査センターへ問い合わせる必要がある。ちなみに，PCRの咽頭淋菌検査の交叉反応の問題を解消した後継品の，real-time PCR法（コバス4800システムCT/NG，ロシュ・ダイアグノスティックス）が適応材料としてうがい液を材料とした咽頭検査として今年7月1日に保険収載され（逆に咽頭スワブは適応外），おそらく10月以降から各検査センターにて受託可能となる見込みである。

Ⅳ　淋菌の抗菌薬多剤耐性化問題

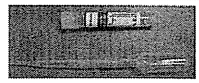
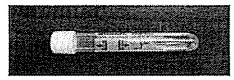
以前から問題とされてきた淋菌の抗菌薬多剤耐性化が，ここ数年さらに深刻化している。淋菌は抗菌薬耐性化を獲得しやすい性質があり，すでに多くの抗菌薬に耐性を持つ。感受性のある抗菌薬でも，投与量・方法を誤ると薬剤耐性化が進む恐れが常にある。特に，抗菌薬の組織移行性の違いから性器感染に有効でも，咽頭感染では効果がない薬剤があるため，感染部位によって推奨薬剤選択が異なることに留意しなければならない。日本性感染症学会では性感染症 診断・治療ガイドラインのなかで推奨する淋菌の抗菌薬処方を，淋菌の最新の薬剤耐性にあわせて改訂の度に改正している。性器感染にも咽頭感染にもほぼ100％有効な処方として，セフトリアキソン（CTRX：ロセフィン）静注1g単回投与（推奨ランクA），セフォジジム（CDZM：ケニセフ，ノイセフ）静注1または2gを1～2回/日を1～3日間投与（推奨ランクB）が提示されている。スペクチノマイシン（SPCM：トロビシン）筋注2g単回投与（推奨ランクB）は性器感染にはほぼ100％有効であるが，咽頭感染には効果が劣るため推奨から外されている。経口薬として，セフィキシム（CFIX：セフスパン）の抗菌力が最も強く，注射薬による

表4　淋菌・クラミジア　核酸増幅法検査

a：咽頭擦過検体用キット

	採取容器	項目
PCR アンプリコア 滅菌スワブ		クラミジア のみ
SDA プローブテック wet スワブ黄色		淋菌 クラミジア
TMA コンボ2 wet スワブ白色		淋菌 クラミジア

b：咽頭 うがい液*用キット

	採取容器	項目
SDA プローブテック* 尿採取用容器		淋菌 クラミジア
TMA コンボ2* 尿採取用容器		淋菌 クラミジア
RT-PCR コバス うがい液採取用容器		淋菌 クラミジア

*うがい液は保健適応外材料のため，提出する検査会社との相談が必要

治療困難な症例に使用可能である。しかし，400mg/分2/日を3日間投与で30～40%の治療無効例があるので，治療後の治癒確認再検査が必要となる。

クラミジアの咽頭感染に関しては，性器と同じレジメとなっており，また現在まで耐性株の報告もない。

おわりに

日本の性風俗従業女性の咽頭からCTRXに高度耐性を示す株が分離されたことが2009年に報告された。それを受けてCDCは，2000年から2010年の淋菌感染症サーベイランスシステムのデータを解析し，2009年7月のweekly reportのなかで淋菌のセファロスポリン系薬に対する耐性化の急速な進行を取り上げ，「2007年にフルオロキノロンへの耐性化が進んだときと似た状況で，前回は推奨レジメンを変更して対応できたが，現在の治療方針を越える効果ある治療の選択肢がない」と警鐘を鳴らしている。淋菌の咽頭感染への第1選択薬であるCTRXに対して，PK/PDに則った適切な投与量，方法を厳守し，治療不成功例の発生が確認された場合は直ちにご報告いただきたい。

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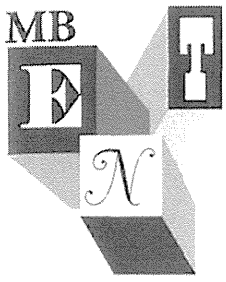

◆特集・痛みの性状からわかる耳鼻咽喉科疾患

Ⅱ. 各 論
3. STIと咽喉頭の痛み

余田敬子*

Abstract 梅毒の第1期病変である硬結や潰瘍は無痛性で，第2期病変の粘膜斑や口角炎は，軽い痛みまたは違和感を訴える．HSVは初感染時に口腔咽頭粘膜に特徴的なアフタ・びらん・白苔を伴う咽頭炎や扁桃炎を発症し，激しい痛みと高熱がみられる．HIVは，感染から2～4週間頃の急性初期感染期に，インフルエンザまたは伝染性単核球症様の非特異的な咽頭痛を訴える．HIV感染の中期以降にあらわれる口腔咽頭病変には，カンジダ症，再発性アフタ性口内炎，多形性紅斑，台癬，非特異的口腔潰瘍，カポジ肉腫，非ホジキンリンパ腫，扁平上皮癌等があり，それぞれ病変に伴う痛みや，違和感を訴える．淋菌とクラミジアは感染者数の多い性感染症で，どちらも咽頭に感染すると大多数は無症候性に感染する一方で，ごく一部に非特異的な咽頭炎，扁桃炎，上咽頭炎による痛みを訴える．HPVは中咽頭癌との関連性が指摘されているが，HPV感染そのものは無症候性である．

Key words 性感染症(sexually transmitted infection)，梅毒(syphilis)，単純ヘルペスウイルス感染症(herpes simplex virus infection)，ヒト免疫不全ウイルス感染症(human immunodeficiency virus infection)，淋菌感染症(gonococcal infection)，クラミジア感染症(chlamydial infection)，ヒトパピローマウイルス感染症(human papillomavirus infection)

はじめに

性感染症は従来よりSTD(sexually transmitted diseases)の略が普及しているが，多くの性感染症において無症候性感染者がキャリアとなって感染拡大に大きく関与していることが指摘されるようになり，性感染症をsexually transmitted diseasesではなく，sexually transmitted infection；STIと呼ぶようになっている．STIの原因微生物のうち，咽喉頭疾患に関連するものとして，梅毒トレポネーマ，単純ヘルペスウイルス(herpes simplex virus；HSV)，ヒト免疫不全ウイルス(human immunodeficiency virus；HIV)，淋菌，クラミジアトラコマティス(*Chlamydia trachomatis*；以下，クラミジア)，ヒトパピローマウイルス(human papillomavirus；HPV)が挙げられる．

これらの咽喉頭に関連する性感染症には，その特徴的な臨床像から診断しやすいものと，特徴に乏しく他の疾患との鑑別が難しいものとがある．本稿ではHSV感染症，梅毒，淋菌およびクラミジア感染症，HPV感染症について，咽喉頭の痛みの性状からみた臨床像，診断，治療について概説する．

梅 毒

梅毒はスピロヘータの一種である梅毒トレポネーマ(*Treponema pallidum subspecies pallidum*；以下，Tp)を病原体とする慢性感染症[1]で，体のあらゆる部分または全身の皮膚や粘膜，時に臓器に病変を生じる．胎児が経胎盤的に感染する先天性梅毒と，経胎盤感染以外の感染経路で梅毒

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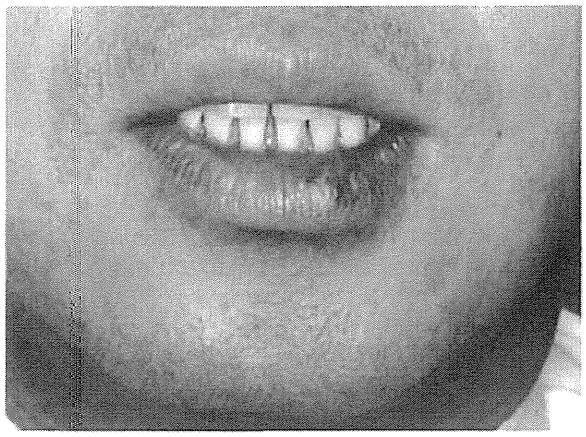

図 1. 口唇の初期硬結(41 歳，男性)文献 2 より転載
暗赤色で，無痛性の硬い腫瘤を下口唇左側に触れる(文献 2 より転載)

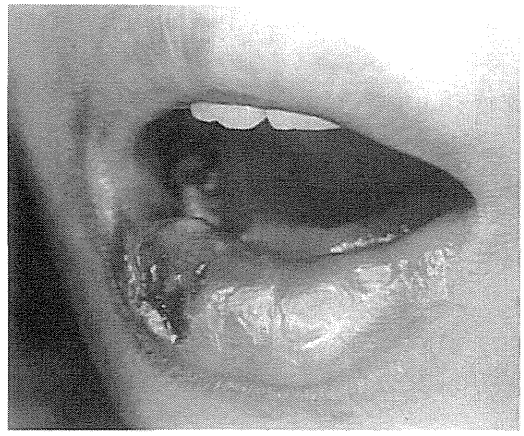

図 2. 口唇の硬性下疳(16 歳，女性)
初期硬結が潰瘍化したもの．無痛性．潰瘍面のスワブの鏡検にて，ラセン状のトレポネーマが検出される(文献 2 より転載)

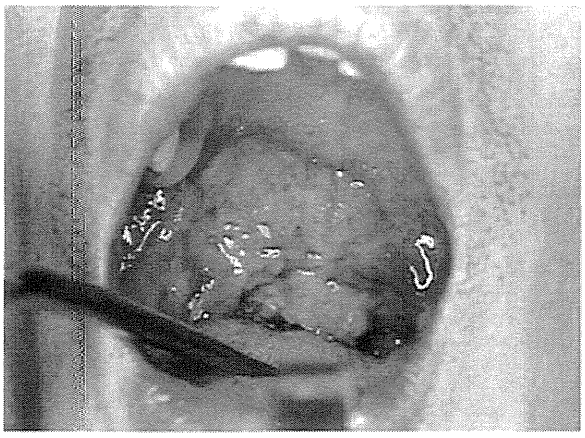

図 3. 梅毒 2 期の咽頭粘膜斑(43 歳，男性)
口蓋垂から口蓋粘膜に拡大した粘膜斑．粘膜斑は扁平で若干の隆起があり，周囲は薄い赤色の紅暈で囲まれ青みがかった白灰色で「乳白斑」とも呼ばれる(文献 2 より転載)

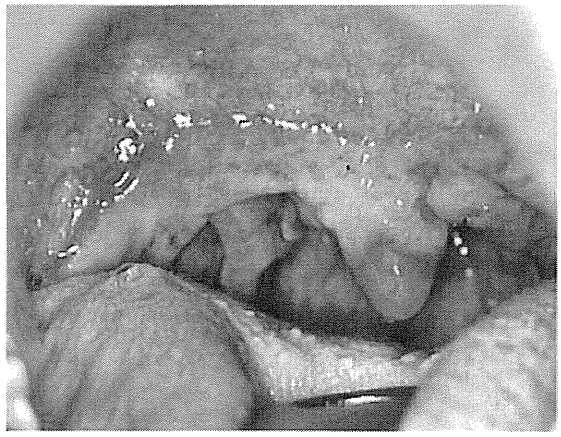

図 4. 梅毒 2 期の咽頭粘膜斑(27 歳，女性)
粘膜斑が口峡部に沿って弧状に拡大融合して，蝶が羽を広げたような "butterfly appearance" を呈している(文献 3 より転載)

に感染する後天梅毒に分けられ，後天梅毒には血清梅毒検査は陽性であるが臨床症状のない無症候梅毒と，皮膚や粘膜に病変がみられる顕症梅毒とがある．顕症梅毒は Tp に感染してからの時期(第 1～4 期)によってあらわれる病変，疾患が異なる．

耳鼻咽喉科領域では，第 1 期の初期硬結，硬性下疳，第 2 期の粘膜斑，口角炎が口腔，咽頭にみられる場合がある[1)～4)]．

1．痛みの性状

1）初期硬結・硬性下疳

感染後 3ヶ月頃まで(第 1 期)にみられる病変で，Tp が侵入した部位にしこりが生じ(初期硬結，図 1)，数日後には硬結の中央に潰瘍ができる(硬性下疳，図 2)．初期硬結・硬性下疳は痛みがないのが特徴で，アズキ大から指頭大の大きさで暗赤色を呈し軟骨のように硬く触れる．耳鼻咽喉科領域では口唇，舌，扁桃[1)2)]に 1 個，時に 2～3 個現れる．患側頸部に軟骨様に硬く触れるリンパ節腫脹を伴い，これも無痛性[4)]である．

2）口角炎・粘膜斑

感染後 12 週目頃(第 2 期)には，口腔・咽頭の粘膜斑(乳白斑ともいう)と口角炎がみられる．咽頭の粘膜斑(図 3)は，扁平で若干の隆起があり，青みがかった白または灰色を呈して周囲は薄い赤色

表 1. 梅毒血清反応　定性検査の結果の解釈

STS	TPHA 抗原法	結果の解釈
−	−	非梅毒 稀に感染初期#
+	−	生物学的偽陽性(BFP)* 稀に感染初期#
+	+	梅毒(早期から晩期) 梅毒治癒後の抗体保有者
−	+	梅毒治癒後の抗体保有者

(文献 1 より転載)

第 1 期の梅毒感染初期が疑われる場合は，2〜4 週後に再検査が必要となる

*生物学的偽陽性(BFP)梅毒に感染していなくても，ウイルス・細菌などによる感染症，膠原病，妊娠，担癌状態，老齢，静注薬物乱用者などで STS が陽性を示す場合をいう

表 2. 梅毒血清反応　定性検査(用手法)の結果の解釈

	検査法	抗体価(血清希釈倍数)									
STS	RPR 法	1○	2	4	8	16	32	64	128	256	512
	ガラス板法	1○	2	4	8	16	32	64	128	256	512
Tp 抗原	TPHA		80		320	1,280		5,120	20,480		81,920
	FTA-ABS		20			定性法のみ					
抗体価の読み方					低い←	中等度		→高い			

(文献 1 より転載)

○印は定性検査の血清希釈倍数
感染初期には STS 群抗体価が TPHA 法の抗体価に先行して陽性となる

の紅暈で囲まれる．乳白斑が拡大・融合すると軟口蓋に特徴的な“butterfly appearance”を呈する(図 4)．梅毒性口角炎は口角に白斑を伴う所見で，カンジダ性口角炎に似ているが梅毒の白斑は擦過にて剝離されない．粘膜斑，口角炎ともに，病変部の比較的軽い痛みや違和感を訴える[4]．自覚症状がなく，病変に気づいて受診する場合もある．

2．検査・診断

Tp は分離培養ができないため，直接検出する直接法または梅毒血清反応によって診断する．

臨床所見からカンジダ症との鑑別を要する場合は，病変部から採取したスワブを鏡検とともに真菌培養へ提出する．

1）直接法

硬性下疳や粘膜斑などの口腔咽頭の梅毒病変には Tp が多く存在するため直接法での検出が有用である．硬性下疳や粘膜斑の表面を擦って採取した漿液をスライドグラスに塗抹，染色し観察する．ただし，Tp と口腔内常在性トレポネーマとの鑑別は困難，必ず梅毒血清反応の結果とあわせて診断する．また，抗菌薬がいったん投与されると病変部の Tp が減少し検出率が低下するため，直接法は必ず抗菌薬投与前に行う．

2）梅毒血清反応

梅毒血清反応には，リン脂質のカルジオリピンを抗原とする脂質抗原試験(serologic tests for syphilis；STS)と，Tp 抗原法がある．STS にはガラス板法や RPR(rapid plasma reagin)があり，抗原法には TPHA (treponema pallidum heamagglutination assay) と FTA-ABS (fluorescent treponemal antibody absorption test) 法がある．はじめに STS の 2 法と TPHA の定性検査を行い(表 1)，陽性の場合に STS および TPHA の定量検査で確定診断する(表 2)．梅毒血清反応は血行性感染が始まる第 2 期以降の診断に有用である．血清梅毒反応陰性でも，問診や臨床所見から第 1 期が疑われる場合は，2〜4 週後に再検査を行う．

これまで用手法で行われていた STS，TPHA の定量検査は，近年高感度の自動定量測定が開発され，各医療施設に導入されつつある．自動定量測定と従来の用手法による定量検査の数値との相関性は自動測定キットのメーカーにより異なるの

で注意する.

梅毒患者ではHIV感染を合併する率が高いため，梅毒血清反応陽性者の場合は必ずHIV検査を追加する.

3．治　療

Tpはほとんどの抗菌薬に感受性がある．診断に先行したむやみな抗菌薬の投与は病変のみが消失して見逃され，潜伏梅毒に移行させてしまうおそれがあるため注意する.

最も推奨される抗菌薬はペニシリンで，経口合成剤AMPC，ABPCなどを1回500 mg，またはDEBCPCG(ベンジルペニシリンベンザチン；バイシリンG®)1回400万単位を1日3回投与する．ペニシリンアレルギーの場合は塩酸ミノサイクリンを1回100 mg，1日2回投与する.

治療期間は，第1期では2〜4週間，第2期では4〜8週間投与を継続する．抗体価が高い症例や，感染時期が不明な場合には投与期間を延長する.

治療開始にあたり，内服開始直後の2〜12時間後に，悪寒戦慄・発熱・倦怠感・咽頭痛・筋肉痛・頭痛・頻脈などの症状が一過性に現れ，ほぼ8時間以内に消失する．この現象はJarish-Herxheimaer反応と呼ばれ，第1期で50%，第2期では75%現れる．Tpが多量に死滅し菌体のリポ多糖類が放出されて生じるエンドトキシン反応で，駆梅療法を中止する必要はない．投薬開始時にこの現象を説明し，副作用と誤って薬の服用を中断しないように患者を指導しておくことは重要で，解熱薬も頓用で予め処方しておいてもよい.

治療後，体内のTpが消失するとSTS抗体価は下がりはじめるので，STS定量値は治療効果判定に用いられる．一方，TPHA定量値は治療後に必ずしも低値にならず，治療効果を反映しない．病期に応じた十分な投薬を行った後，臨床症状の持続や再発がないことと，STS抗体価を定期的に追跡して定量値が8倍以下に低下するまで確認する必要がある．治療後半年過ぎてもSTS定量値が16倍以上示す例は，治療が不十分または再感染例が疑われるため，検査と治療を追加する.

HSV性咽頭・扁桃炎

HSVには，1型(HSV-1)と2型(HSV-2)がある．HSV-1，HSV-2ともに，初感染の90%以上は不顕性感染し，潜伏感染に移行する．残りの約10%に，歯肉口内炎，咽頭・扁桃炎，性器ヘルペスの発症がみられる．主にHSV-1は口唇・顔面・眼に，2型は性器に病変を生じるが，HSV-1による性器ヘルペスや，HSV-2による口唇ヘルペスの報告もある.

HSV性咽頭・扁桃炎は，10歳代後半〜30歳代前半の青壮年期にHSVに初感染した場合にみられることが多く，HSV-1，HSV-2，どちらも原因となる[5]

1．痛みの性状

著明な咽頭痛を訴え，咽頭痛・嚥下痛のため摂食障害をきたす患者が多い．38〜40℃の弛張熱と，上頸部リンパ節の高度腫脹を伴う．口蓋扁桃・舌扁桃・咽頭後壁のリンパ濾胞に白苔をともなう発赤腫脹がみられる(図5)．陰窩性扁桃炎と異なり，HSV性扁桃炎の口蓋扁桃の白苔は必ずしも陰窩に一致しない．白苔の周囲の口蓋扁桃(図5)，舌扁桃，口腔粘膜，口唇(図6)にヘルペス特有のアフタがみられる.

口腔・咽頭の帯状疱疹と鑑別を要するが，帯状疱疹は正中を越えず一側性のことが多い．性器ヘルペスや皮膚のヘルペス疹を併発する場合もある.

2．検査・診断

HSV性咽頭・扁桃炎の診断には，抗原検査(モノクローナル抗体による蛍光抗体法)が簡便で，迅速に結果が得られる．特異性が高く型判定も可能でありきわめて有用である．綿棒で擦過採取したアフタや潰瘍病変の細胞をスライドグラスに塗抹し，抗HSV-1および抗HSV-2モノクローナル抗体を用いて，ウイルス感染細胞を同定する.

抗原検査ができない施設においては，他に保険適応である血清抗体検査による診断には時間がかかるため，臨床症状，問診，視診から総合的に診

断し，抗ウイルス薬の投与を判断することが求められる．しかし，症例経験のある医師であれば，その特徴的な所見から，臨床診断は難しくない．HSV 性咽頭扁桃炎であれば，抗ウイルス薬の投与を開始して3日目頃から症状が急速に改善し始める．

移植後患者など重篤化の恐れがある患者で，治療上他の疾患との鑑別診断が必須となる場合は，下記の方法で咽頭の病変から採取した擦過細胞や生検組織から HSV 感染の証拠を検索する．

1）ウイルス分離培養：ゴールドスタンダード，特異性が高く，型判定が可能．

2）核酸増幅法(PCR 法，LAMP 法)：特異性が高く型判定が可能．

3）Tzanck 試験：外来で迅速簡便に検査が可能，感染細胞に特徴的な full 型または Cowdry 型の核内封入体，またはウイルス巨細胞を確認する．HSV と VZV の判別は不可．

4）血清抗体検査：単回検査では臨床的意義が低い．急性期と回復期のペア血清で有意の抗体上昇によって診断することが可能である．HSV 初感染後は生涯持続感染するので，血清抗体価が陽性であることだけでは診断的意味はない．HSV は同一個体において HSV-1 初感染，HSV-2 初感染，潜伏持続感染，再発といった様々な病態があり，また HSV-1 と HSV-2，また HSV と水痘帯状疱疹ウイルス(varicella zoster virus：VZV)間で交叉反応が存在するため，血清抗体価から HSV-1, HSV-2, VZV を判別できない場合もある．

3．治　療

バラシクロビル1回 500 mg，1日2回を経口で5日間，またはアシクロビル1回 200 mg，1日5回を経口で5日間，のどちらかで治療する．経口摂取困難な重症例では，アシクロビル注 5 mg/kg/回，1日3回8時間毎，7日間投与する．腎機能障害合併例では，表3[6]に従い，クレアチニンクリアランス値(CCr)により投与量を決定する．

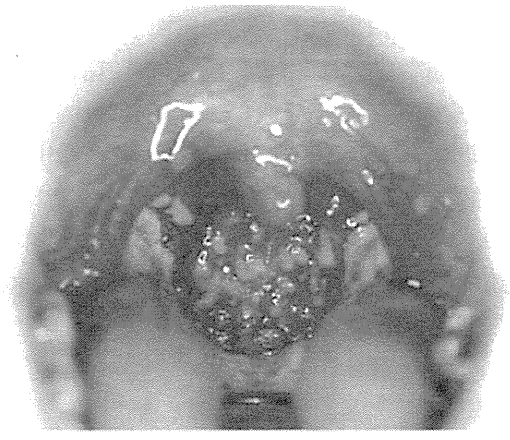

図 5. HSV 咽頭扁桃炎(20 歳，女性)
口蓋扁桃陰窩の白苔，咽頭後壁リンパ濾胞の白苔を伴う発赤腫脹を認める(文献6より転載)

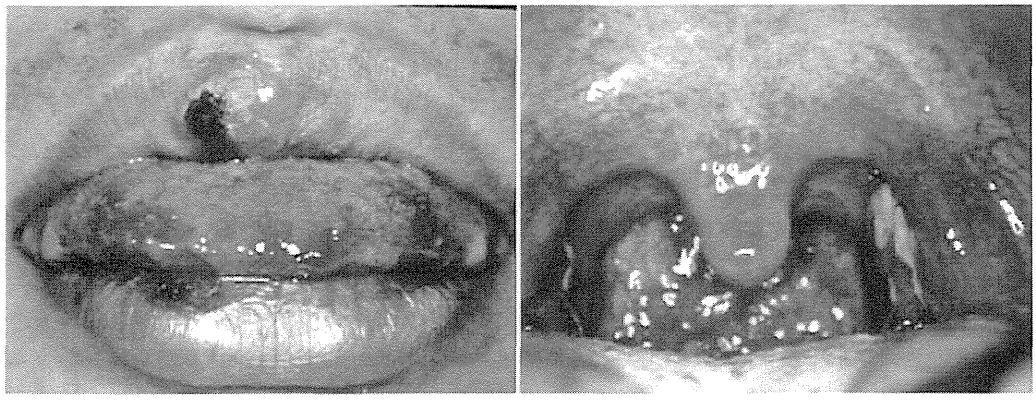

図 6. HSV 性扁桃炎(25 歳，男性)
血清抗体価および扁桃組織生検により HSV-1 初感染による扁桃炎と診断された．偽膜性扁桃炎にアフタを伴う歯肉口内炎の併発がみられる