の主体である男子)の抱えた課題の一つであり，古今東西のこの普遍的命題に教育がどこまで手をさしのべられるかということにも模範回答はない．しかし，ここに一つのブレーキが提示されうる．それが妊娠というリスクであり，性感染症というリスクである．教育者や医療者は，彼ら思春期の中に身を置く若者に必然的に起こってくる性欲が行為までに至った際に起こりうるいわばadverse event（有害事象）を教示し，熱く沸く感情に冷や水をかけることをある程度積極的に行わざるをえない．それは決して脅しというものではなく，scientific society（科学的社会）では常識として伝達すべき事項である．これは性教育の中の性感染症予防教育というべき一単元と捉えるべきである．

Ⅱ 具体的な性感染症予防教育の流れ（対高校生）

1．序（図1）

授業対象となる中高生が今，人生のどういう時期にいるのかということ，また思春期に起こることを具体的に説明し，男女の体型が変わってくることなどにも触れる．

2．性交渉のリスクの提示と授業の主題（図2）

望まざる妊娠と性感染症という，adverse event（有害事象）の存在を指摘．授業では，adverse event(有害事象)という言葉は使わず，“リスク”という語を使用する．

3．性感染症の具体的説明（図3〜5）

具体的疾患（たとえば，性器クラミジア感染症）の症状や感染経路などを解説．無自覚に進展して女子では不妊症や子宮外妊娠の原因となることや流産・早産，垂直感染の問題，男子では精巣上体炎について説明する．

4．無症候性感染が多いことへの警鐘（図6）

ここでもクラミジア感染などを例に挙げて，症状がないまま伝播していく問題を教える．

5．エイズの問題の指摘（図7）

この感染症の本態や経過を理解させ，日本で年々，HIV感染症・エイズ患者が増加していることについてデータをもとに説明する．

6．ヒトパピローマウイルス（HPV）感染と子宮頸癌との関係（図8）

20代の若年女性の子宮頸癌が増加傾向にあることを認識させ，その背景に高リスク型HPV感染が存在すること，すなわち，子宮頸癌の多くも広い意味での性感染症であることを解説する．

7．性パートナーが一人であれば安心か（図9）

実際は否である．相手が一人でも，その背後に性のネットワークが存在し，感染する懸念がある．

8．では，どうすればいいのか（図10，11）

予防が第一である．no sexも一つの予防．あえてセックスするなら必ずコンドームを使うこと．コンドームの正しい付け方は常識として教える．もし，感染している心配があるなら，保健所で無料・匿名でHIVの検査が受けられることを伝える．

9．最後にメッセージ

性交を焦る必要はない．心のつながりを大切にして，ゆっくりと時間をかけて「人間関係」を築くよう伝える．まずは心のコミュニケーションを．

Ⅲ この性感染症予防教育は大人にも通じる（図12）

大人でも，性感染症の正しい知識を有している者は必ずしも多くない．「もし，あえてセックスをするのなら→必ずコンドームを使うこと(ピルなどの適切な使用も，医療機関で相談すること)．コンドームなどを使わずにセックスをしてもよいのは，互いに感染がないとき，愛する相手との間に子どもを産み，育てることができ，しかも相手もそれを望みかつ，それができる条件が整っているときだけです」という結論は，大人にも訴えたい．

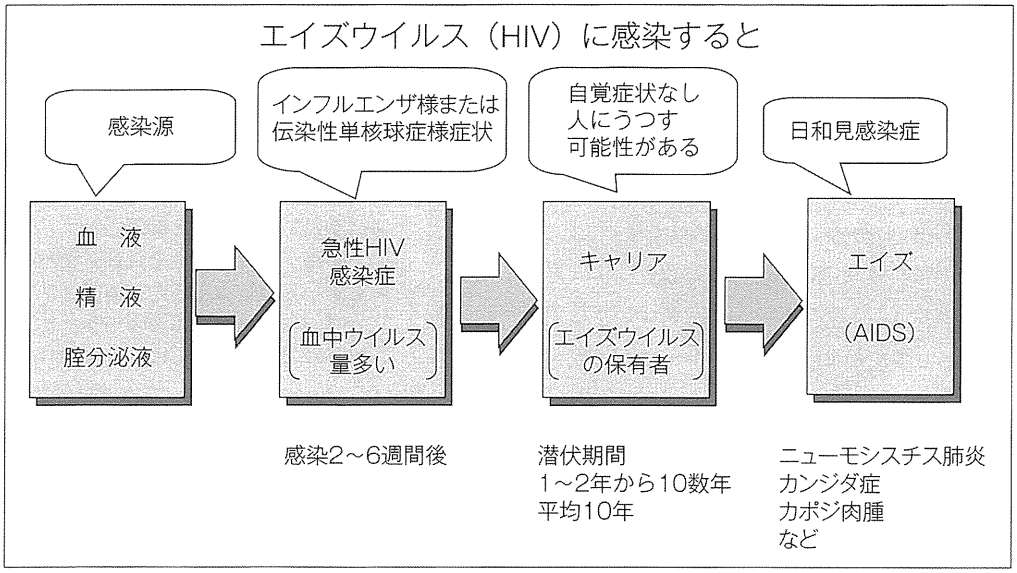

図7　エイズウイルスとは

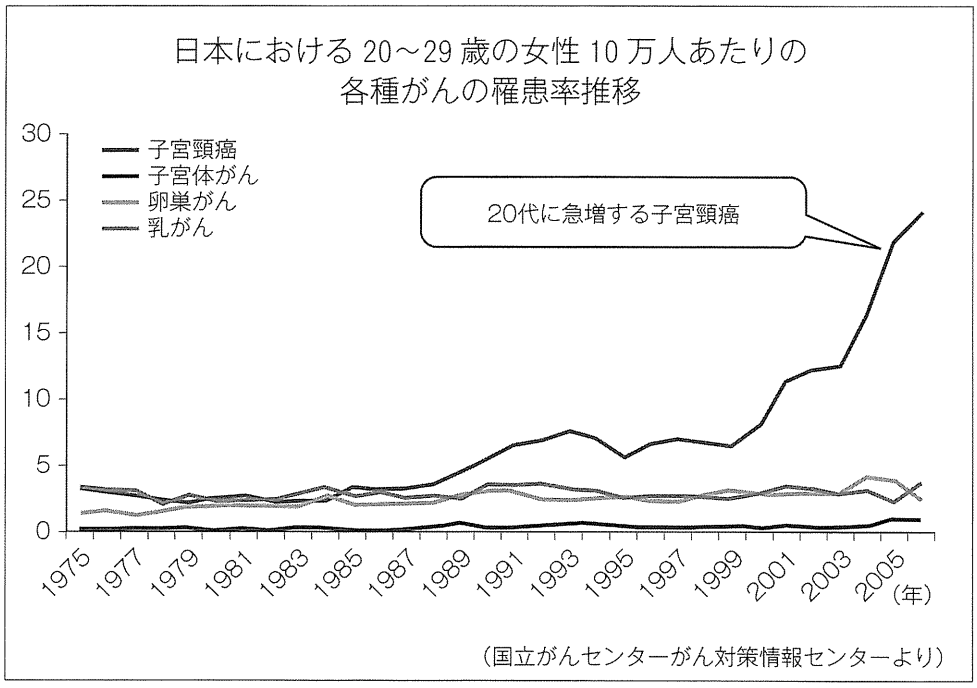

図8　20代に子宮頸癌は急増する

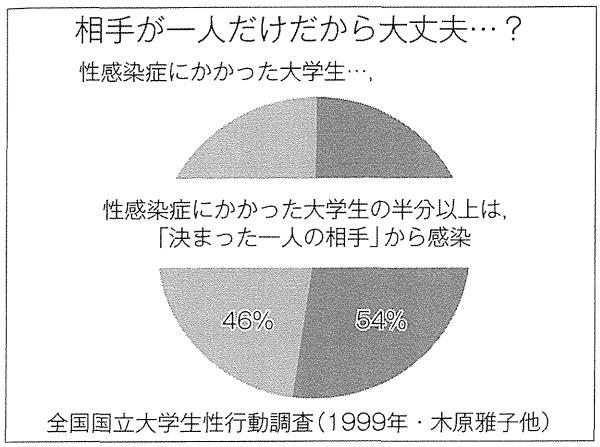

図9　性パートナーが一人のみである人の割合

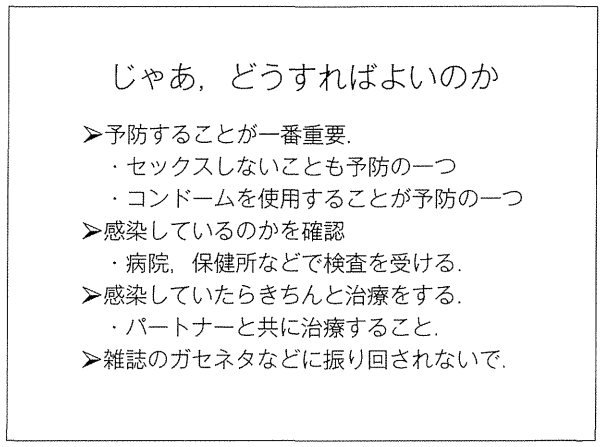

図10　性感染症に悩まないために

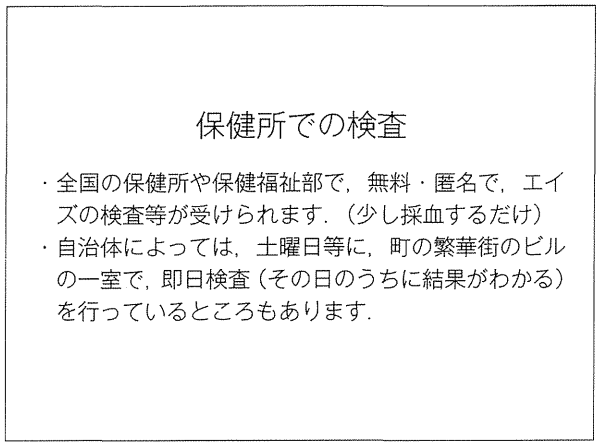

図11　検査実施施設

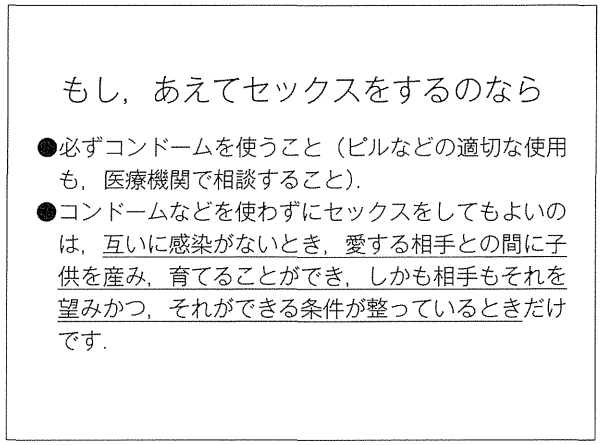

図12　大人にも通じる予防教育

Ⅳ 授業の理解度

筆者は，これらのスライドを使って，2006～2010年の5年間に神戸市内男女共学高校1～2年（もっとも多い年で7校，少ない年で4校）にデリバリー授業をした．その授業の直後に生徒からとった無記名アンケートの集計結果を**図13～17**に示す．おおむね，理解度は良好である．図15（設問3）にある高校生の性行為に対しての考え方はさまざまであり，「考えたことがない」と答えた生徒も多かった．また，神戸市では，中学3年時にも性感染症の授業を行っているが，多くの生徒がそのことを覚えており，2段構えの教育体制は意義があるものと思われた．

おわりに

HIV感染症の増加などの現状に照らし，中高生への性感染症の正確な知識の伝達は社会的にみて，非常に重要な課題である．日本性感染症学会では性感染症認定医（**表1**，細則は文献3）参照）および認定士（**表2**，細則は文献4）参照）制度を2009年度に発足させた．2012年までの4回の認定作業で，認定医は370名あまり誕生しているが，認定士がいまだ20名程度と少な

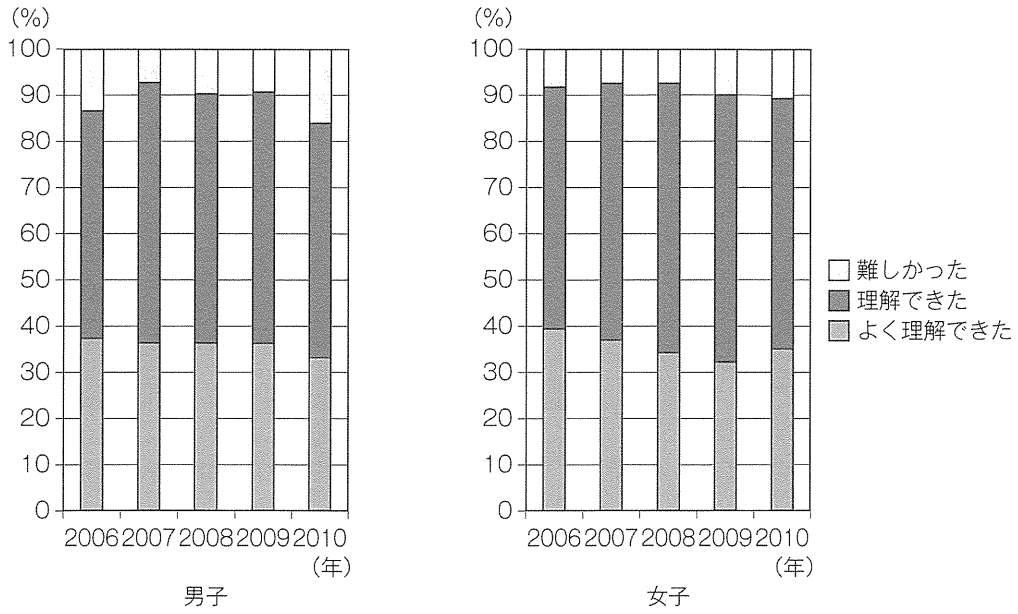

図 13　設問 1：講演会の内容が理解できましたか

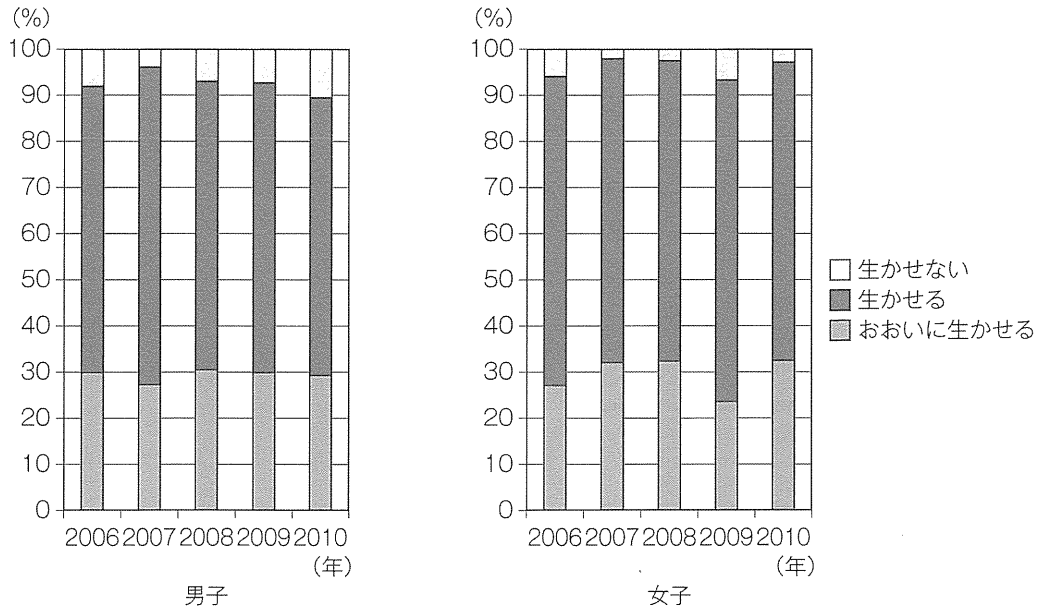

図 14　設問 2：自分の今後の性行動に生かせると思いましたか

い．今後，認定士の応募が増え増員され，日本各地区で中高生への性感染症教育を担当することにより，その推進を期待するものである．少子高齢化社会の中にあって，性感染症は日本民族にとっては脅威である．すなわち，クラミジア→不妊，HPV→子宮頸癌など，少子社会にさらにネガティブな要素をもたらす無症候性感染の怖さを，もっと社会が理解するべきである．10 代半ばでの学校現場における教育が最大の防波堤であり，教育現場と医療者の協調が必要

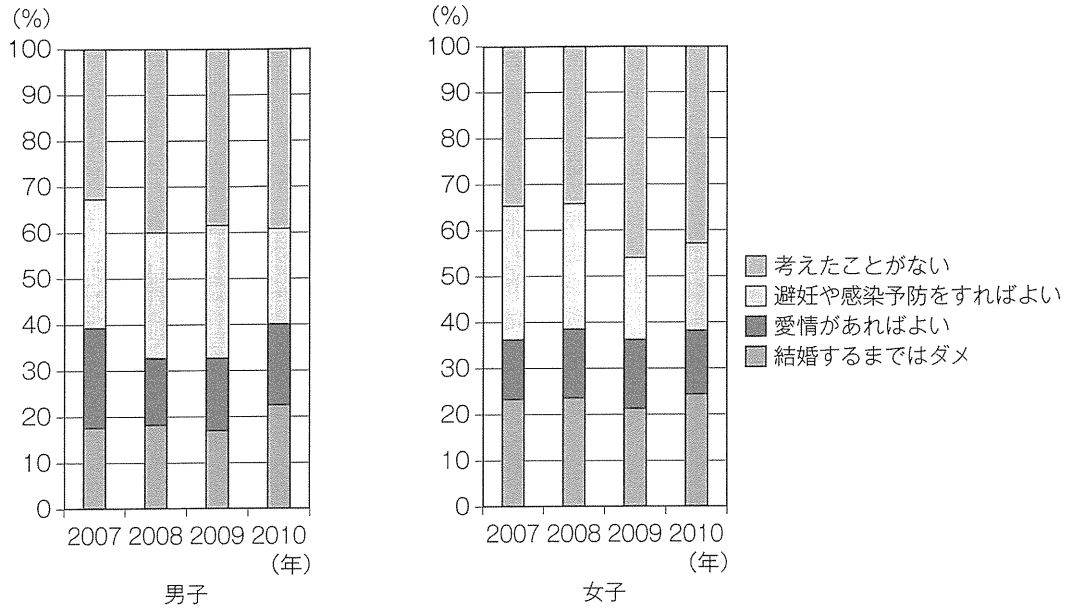

図 15　設問 3：高校生の「性行為」に対して，あなたはどう思いますか

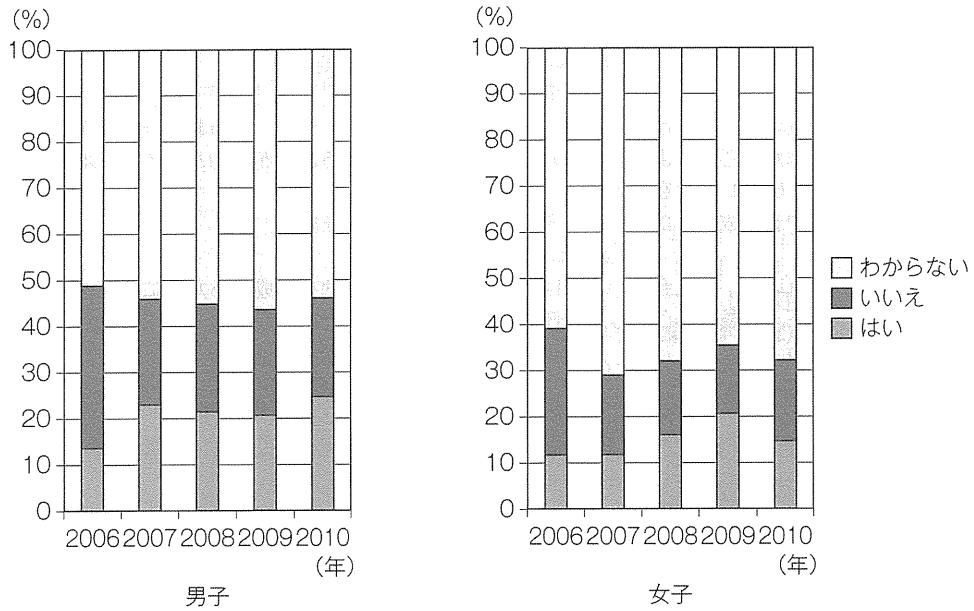

図 16　設問 4：今後，機会があれば「性感染症」の検査を受けますか

である．

感染症学と疫学とのドッキングにより，詳細な実態調査が継続的に行われ，それが国民・若者に広報され，有効な対策がとられるべきである．日本性感染症学会が，その橋渡し役を担い，認定士制度等の意義を深め，標準教育用スライドが活用されることが期待される．

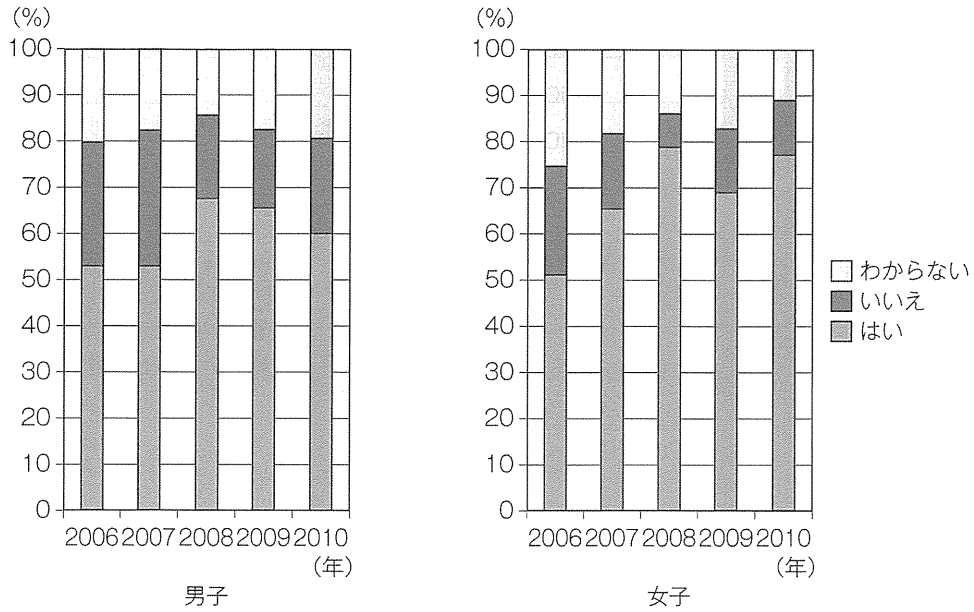

図 17　設問 5：中学生の時に，今回のような医師や助産師による性教育講演会を聞いたことがありますか

表 1　認定医制度規則

日本性感染症学会 認定医制度規則

第 1 章　総　則

第 1 条　日本性感染症学会（以下，本会という）は，性感染症の病態解明，予防，診断および治療の進歩に即応した優秀な医師の養成をはかることにより，国民の衛生，福祉に貢献することを目的として，日本性感染症学会認定医（以下，認定医という）制度を設ける．

第 2 条　本会は，前条の目的を達成するため，本会内に認定医制度委員会を置く．

第 2 章　認定医制度委員会

第 3 条　認定医制度委員会（以下，委員会という）は，第 1 条に掲げる目的を達成するために必要な事項を取り扱う．

第 4 条　委員会の委員（以下，委員という）は，常任理事会の議を経て，理事長が指名する本会理事及び代議員各若干名をもって構成する．

第 5 条　委員会の委員長（以下，委員長という）は，委員の互選により選出する．委員長は，委員会を招集し，本制度の円滑な運営を図る．

第 6 条　委員の任期は 2 年とし，2 期までの再任は妨げない．

第 7 条　委員会には，業務の運営に必要な各種小委員会をおくことができる．

第 8 条　委員会の事務は，日本性感染症学会事務局が取り扱う．

第 3 章　認定医の資格

第 9 条　認定医の資格を申請するものは，次の各項の条件を満足していなければならない．

1．日本国の医師免許証を有すること．

2．申請時において，3 年以上，本会の会員であること．

3．日本内科学会において定められたいずれかの認定医，日本泌尿器科学会専門医，日本産科婦人科学会専門医，日本皮膚科学会専門医，日本小児科学会専門医，日本耳鼻咽喉科学会専門医，日本眼科学会専門医であること，または委員会が性感染症と関連が深いと認める学会の認定医あるいは専門医の資格を有し，5 年以上，性感染症に対する基礎的研究または臨床の経験を有すること．ただし，これらに該当しない場合でも，性感染症に対し十分な臨床経験を 5 年以上積んでいると判断される者は，委員会の議を経て，同等の資格を有するものとみなすことができる．

4．本会の定める教育研修の必要単位を取得していること．〔細則 § 1 参照〕

5．本会が行う認定医資格試験に合格していること．〔細則 § 2 参照〕

（文献 3）より引用）

表2　認定士制度規則

日本性感染症学会 認定士制度規則

第1章　総　則

第1条　日本性感染症学会（以下，本会という）は，性感染症の相談・検査，予防・啓発等に携わることにより，国民の衛生，福祉に貢献することを目的として，日本性感染症学会認定医（以下，認定医という）制度とともに，日本性感染症認定士（以下，認定士という）制度を設ける．

第2条　本会は，前条の目的を達成するため，本会内に認定士制度委員会を置く．

第2章　認定士制度委員会

第3条　認定士制度委員会（以下，委員会という）は，第1条に掲げる目的を達成するために必要な事項を取り扱う．

第4条　委員会の委員（以下，委員という）は，常任理事会の議を経て，理事長が指名する本会の理事及び代議員各若干名をもって構成する．

第5条　委員会の委員長（以下，委員長という）は，日本性感染症学会認定医委員会委員長が兼務する．委員長は，委員会を招集し，本制度の円滑な運営を図る．

第6条　委員の任期は2年とし，2期までの再任は妨げない．

第7条　委員会には，業務の運営に必要な各種小委員会をおくことができる．

第8条　委員会の事務は，日本性感染症学会事務局が取り扱う．

第3章　認定士の資格

第9条　認定士の資格を申請するものは，次の各項の条件を満足していなければならない．

1．薬剤師，保健師・助産師・看護師，学校教諭・養護教諭，臨床検査技師等の日本国内の公的資格を有する者．ただし，これらに該当しない場合でも，性感染症の相談・検査，予防・啓発等に関し十分な経験を5年以上積んでいると判断される者は，委員会の議を経て，同等の資格を有するものとみなすことができる．

2．申請時において，3年以上，本会の会員であること．

3．性感染症に関する相談・検査，予防・啓発等の経験を有すること．

4．本会の定める教育研修の必要単位を取得していること．〔細則§1参照〕

5．本会が行う認定士資格試験に合格していること．〔細則§2参照〕

（文献4)より引用）

文献

1) 荒川創一，白井千香：日本性感染症学会第22回学術集会（京都，2009年12月12日），性感染症に関する中高生教育の現状（新型インフルエンザの影響を含めて）．日本性感染症学会誌 2009；20：51

2) 荒川創一：日本性感染症学会第24回学術集会（東京，2011年12月4日），卒後・生涯学習プログラム講演2（STI予防についての中高生啓発スライドについて）．日本性感染症学会誌 2011；22：39

3) 日本性感染症学会認定医制度規則
http://jssti.umin.jp/pdf/cd_bylaw.pdf

4) 日本性感染症学会認定士制度規則
http://jssti.umin.jp/pdf/cm_bylaw.pdf

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Review Article

Mycoplasma genitalium in male urethritis: Diagnosis and treatment in Japan

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Abbreviations & Acronyms
FVU = first voided urine
GU = gonococcal urethritis
MIC = minimum inhibitory concentrations
NCNGU = non-chlamydial non-gonococcal urethritis
NGU = non-gonococcal urethritis
PCR = polymerase chain reaction
STI = sexually transmitted infections
WBC = white blood cells

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Abstract: Male urethritis is a common disease for urologists, with the most common pathogens being, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. When the tests fail to detect these pathogens, the presented urethritis is called non-chlamydial non-gonococcal urethritis. *Mycoplasma genitalium* is one of the pathogens for non-chlamydial non-gonococcal urethritis. The test for detecting *M. genitalium*, which is commercially available in Japan, is not accepted by the Japanese insurance system now. The detection rate of *M. genitalium* from patients with non-gonococcal urethritis is 10–20% in Japan. Antimicrobial susceptibility testing for *M. genitalium* showed that macrolide has the strongest activity and the minimum inhibitory concentrations of tetracyclines were not substantially lower. Some kinds of fluoroquinolones, such as sitafloxacin and moxifloxacin, have stronger activities against *M. genitalium*. For non-gonococcal urethritis, macrolides and tetracycline are recommended in some guidelines. In clinical studies, tetracyclines are less effective against *M. genitalium* than azithromycin, and azithromycin regimens including 1 g stat or 2 g stat are now recommended for urethritis with *M. genitalium*. However, macrolide-resistant *M. genitalium* strains have recently emerged and are spreading worldwide. This macrolide-resistance is closely related to mutations on the 23S *r*RNA gene. Sitafloxacin and moxifloxacin have shown good efficacies for *M. genitalium* in some clinical studies. If the azithromycin regimens fail, we must consider the use of fluoroquinolones, such as sitafloxacin, in Japan. The most important issues include the acceptance of *M. genitalium* examinations by the national insurance system and the individual treatment of *C. trachomatis* and *M. genitalium* in the not-too-distant future.

Key words: antimicrobial susceptibility, infection, *Mycoplasma genitalium*, treatment, urethritis.

Introduction

Male urethritis is a commonly encountered disease for Japanese urologists, with the most common pathogens being *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. However, there are many cases in which no pathogens are detected by the microbiological tests that are accepted by the Japanese insurance system; that is, the nucleic acid amplification tests for *C. trachomatis* or *N. gonorrhoeae*. When the tests fail to detect these pathogens, the presented urethritis is known as NCNGU. Other previously reported potential pathogens for NCNGU include *Trichomonas vaginalis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, *Niesseria meningitidis*, *Haemophilus* species, herpes simplex virus, adenovirus and others.[1] Among these microorganisms, *T. vaginalis* and *M. genitalium* have been confirmed to exhibit pathogenicity to the male urethra, and treatment strategies for these pathogens are described in some guidelines for STI.[2–5]

In many countries, urologists diagnose and treat male urethritis as STI. The clinical state of NCNGU in which *N. gonorrhoeae* or *C. trachomatis* are detected by known tests are well understood by urologists. However, *M. genitalium* is not recognized, because the commercially available tests to detect this pathogen are not accepted by the national insurance system, especially in Japan. In the present review, to understand the diagnosis and treatment of male urethritis with *M. genitalium* for urologists, literature from peer-reviewed journals

and conference proceedings that show evidence regarding *M. genitalium*-infection were searched.

How or when was *M. genitalium* discovered?

Before the discovery of *M. genitalium*, clinicians knew that some types of microorganisms besides *C. trachomatis* or *N. gonorrhoeae* participated in male urethritis, because male patients testing negative for the two bacteria had symptoms of urethritis, such as urethral discharge and urethral pain. The patients also suffered from inflammatory responses including an increase in WBC in the urinary sediment or urethral smears. These patients responded to antimicrobials, such as tetracyclines, and their findings suggested the presence of unidentified bacterial pathogens in the urethra.[6]

Taylor-Robinson, who worked at St. Mary's Hospital in London, UK, observed motile spiral forms in the urethral smears of patients with NGU using dark-field microscopy.[6,7] He thought that these forms resembled spiroplasmas, which can infect plants or insects. In 1980, urethral swabs were collected from 13 male patients with NGU. These specimens were transported to Tully's laboratory at the National Institutes of Health in Bethesda, MD, USA, and Tully developed a new medium, called SP4 medium, in which any spiroplasma or mycoplasma could grow.[8] The specimens from the urethral swabs were inoculated into SP4 medium and two new mycoplasma strains were identified from the two specimens approximately a month after the initial incubation. These strains were named G-37^T and M-30, and were found to be closely related to, but serologically different from, all other known mycoplasma.[9] Finally, these strains were confirmed as a new species, *M. genitalium*, the 11th species of human originated mycoplasma.[7]

What is *M. genitalium*?

As shown through electron microscopy, *M. genitalium* is shaped like a flask or bottle, measures 0.6–0.7 μm in length and has tip-like structures that attach to the surface of cells.[7,10] This bacterium can grow on axenic culture media, such as SP4 medium or Friis's medium, or on agar to make small colonies called "fried-egg colonies". However, its isolation from clinical specimens has proven extremely difficult. G-37^T and M30 could grow in SP4 medium at the initial cultivation. After the recovery of *M. genitalium*, many researchers have tried to isolate *M. genitalium* from genital specimens, but all failed to directly inoculate the genital specimens to the SP4 medium.[11]

Jensen reported a new method for the isolation of *M. genitalium* from the clinical specimens using co-cultivation with Vero cell in Eagle's minimal essential medium supplemented with serum substitute and glutamine.[12] This method was reasonable, because the *M. genitalium* attaches to animal cells by adhesin and invades them. After *M. genitalium* grew adequately, an adaptation for the axenic culture medium was attempted. Through this method, more than 30 strains were reported to be isolated from clinical specimens.[12–15] However, the success rates for their initial growth in Vero cell culture were not high; the success rate for adaptation to the axenic culture medium was even lower. The isolation of *M. genitalium* from clinical specimens has been obviously difficult and time-consuming.

M. genitalium has the smallest known genome size of a self-replicating organism, at 580 kbp. The full sequence of the *M. genitalium* gene was reported in 1995,[16] and the synthesis of the complete genome was carried out in 2008.[17] It is thought that *M. genitalium* possesses the minimum functional genes to maintain life.

Pathogenicity of *M. genitalium*

To establish that *M. genitalium* is a cause of disease in humans, Taylor-Robinson proposed a modification to the Henle-Koch postulates.[18] This proposal focused on epidemiological studies, studies in animal models, antimicrobial susceptibility testing *in vitro*, clinical responses to antimicrobials and transmissibility. In a chimpanzee animal model, *M. genitalium* grew at the urethra or vagina, induced inflammatory responses and caused an elevation of serum antibodies.[19] The sexual transmission of *M. genitalium* between couples was shown using DNA sequence typing.[20] Many epidemiological studies have shown a prevalence of *M. genitalium* among patients with male urethritis, cervicitis and other diseases. Now, *M. genitalium* is considered an established cause of male NGU[7,10,21] and female cervicitis.[7,10,22,23] Furthermore, acute epididymitis,[24,25] chronic prostatitis[26,27] and balanoposthitis[28] in males, in addition to pelvic inflammatory disease,[29–31] female urethritis[32] and adverse pregnancy events[33] in females, are considered to be related to *M. genitalium* infections; however, further studies are required to determine that *M. genitalium* can cause these diseases.[23,29,34]

Prevalence of *M. genitalium* in male patients with urethritis in Japan

Nucleic acid amplification tests have been used to detect *M. genitalium* in the clinical specimens of patients. Taylor-Robinson analyzed 38 papers on male urethritis between 1993 and 2010 that showed the prevalence rates of *M. genitalium* in male urethritis.[7] *M. genitalium* was detected from the urethras of 15–25% of male patients with the NGU symptoms of discharge and urethral pain. The prevalence of *M. genitalium* among males without symptoms was 5–10%. The odds ratios and 95% confidence intervals of the association between *M. genitalium* and male NGU or NCNGU were 5.5 (95% CI 4.3–7.0) and 7.6 (95% CI 5.5–10.5), respectively. These data support that *M. genitalium* is a pathogen for male urethritis, including cases of NGU and NCNGU.

In Japan, the test to detect *M. genitalium* in patients has not been accepted by the national insurance system. There-

fore, the data for the prevalence rates of *M. genitalium* are limited. Table 1 shows the prevalence of *M. genitalium* and *C. trachomatis* among male patients in Japan.[35–48] The study of *M. genitalium* in Japan began with Deguchi *et al.* at Gifu University. These researchers carried out many early studies and developed a new phylogeny-based real-time PCR test that amplifies a portion of the 16s *r*RNA gene, and can detect *M. genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Ureaplsma parvum*.[49,50] This test is supported by an examination company and commercially available. The detection rate of *M. genitalium* in patients with NGU was 10–15%, and although the rates in recent studies increased slightly to approximately 20%, it can be said that the detection rates of *M. genitalium* have not changed substantially. The detection rates of *M. genitalium* in European studies were higher than those in Japan;[7,10] it remains unclear why the prevalence of *M. genitalium* might have a regional difference.

Diagnosis for urethritis with *M. genitalium*

Male urethritis shows symptoms of discharge from the urethral meatus and urethral pain; in addition, it is important to detect increases in WBC counts in the urethral smear, urinary sediments or uncentrifuged urine. As the criterion for urethritis, counts of ≥5 polymorphonuclear leukocytes per high-power field (×1000) in the urethral smear by Gram stain are generally used.[35–40,45–47] Furthermore, counts of ≥5 WBC per high-power field (×400) in the urinary sediment of FVU[41,43–45] or counts of ≥10 WBC/μL in uncentrifuged FVU[44,48] are also used in clinical situations.

M. genitalium is closely related to symptomatic NGU; *M. genitalium* has been detected more frequently from specimens of men with symptomatic NGU than specimens of men without symptoms. Furthermore, *M. genitalium* is related to persistent or recurrent NGU after treatment of male urethritis by tetracyclines,[51,52] fluoroquinolones[37,53] or azithromycin.[54] The severities of discharge or the urethral pain by *M. genitalium*-infection were varied, and the clinical features of *M. genitalium*-related urethritis are indistinguishable from those of chlamydial NGU. The urethritis with *M. genitalium* cannot be diagnosed by symptoms only.

For detection of *M. genitalium*, the FVU or the urethral swab specimens are used for nucleic acid amplification tests as described in Table 1. Generally, FVU specimens are available as a painless method in Japan. In the Japanese literature, the amplicons for PCR to detect *M. genitalium* were portions of 16S *r*RNA or adhesion gene.[35–41,43–48]

Antimicrobial susceptibility of *M. genitalium*

Because it is still difficult to isolate of *M. genitalium* from clinical specimens, the antimicrobial susceptibility of *M. genitalium* is extremely limited. Earlier reports showed that *M. genitalium* strains were sensitive to tetracyclines, macrolides and fluoroquinolones; however, it has become clear that there are some differences among the responses to these types of antimicrobials. Table 2 shows the antimicrobial susceptibilities of 23 *M. genitalium* strains.[55] Among the 10 tested antimicrobials, macrolides showed the strongest activity against *M. genitalium*. However, the MIC of azithromycin and clarithromycin against one strain were ≥250 μg/mL and 128 μg/mL, respectively. This strain was evidently a macrolide-resistant strain, which signals a considerable problem, as this resistant strain has emerged and is spreading worldwide, as described later. Among the fluoroquinolones, there were large differences among the seven tested agents; sitafloxacin and moxifloxacin showed strong activity. The MIC of tetracyclines, such as minocycline, doxycycline and tetracycline, were not substantially lower; two strains had a higher MIC against tetracycline.

Clinical studies and antimicrobial resistance

Tetracyclines and macrolides

In earlier studies, the tetracyclines and the macrolides were tested, and their efficacies in the treatment of urethritis with *M. genitalium* were compared. In Gambini's report, the microbiological efficacies of doxycycline 200 mg/day for 7 days and azithromycin 1 g stat were 94.3% and 82.4%, respectively.[56] However, two more recent studies showed that the efficacy of doxycycline against *M. genitalium* was inferior to that of azithromycin.[57,58] The *M. genitalium* eradication rates for doxycycline 200 mg/day for 7 days at the urethra were found to be 45.2% and 30.8%, despite relatively good *in vitro* MIC of doxycycline in most *M. genitalium* strains.[55]

Clinical studies using azithromycin showed good results, with an eradication rate of *M. genitalium* of almost 100% before Bradshaw's report.[59] Bradshaw *et al.* carried out an open-label clinical study in Australia, and used azithromycin 1 g stat on 34 male patients with *M. genitalium*, among whom *M. genitalium* persisted in nine. Three patients were treated with additional azithromycin 1 g for three more attempts, but all of the trials failed. Finally, *M. genitalium* was treated by moxifloxacin 400 mg/day for 10 days. The urethral swab specimens of these patients were sent to Jensen's laboratory in Denmark and newer, high-level, macrolide-resistant *M. genitalium* strains were isolated.[15] Seven macrolide-resistant strains were isolated from Australia or Scandinavia. This macrolide-resistance was found to be related to genetic mutations on region V of the 23S *r*RNA gene, a similar type of mutation to that observed in macrolide-resistant *Mycoplasma pneumonia* strains.[60,61]

As aforementioned, small numbers of macrolide-resistant *M. genitalium* strains have actually been isolated and cultured. However, it became clear that mutations of the 23S

Table 1 Prevalence of *Mycoplasma genitalium* and *Chlamydia trachomatis* among male patients with urethritis in Japanese studies

Author	Study period	Patients Diagnosis for urethritis	Specimens Method for detecting *M. genitalium*	Prevalence % (*n*)		Others
				M. genitalium	*C. trachomatis*	
Deguchi[35]		114 with NGU ≥5 WBC/hpf (×1000) of urethral smear	Urethral swab, PCR for MgPa	14.9 (17)	–	
Maeda[36]	1995–1997	76 with NGU ≥5 WBC/hpf (×1000) of urethral smear	Urethral swab, PCR for MgPa	13.2 (10)	55.2 (42)	
Maeda[37]	1999–2000	72 with NGU ≥5 WBC/hpf (×1000) of urethral smear	FVU, PCR for 16S rRNA	17.1(13)	45.9 (34)	Clinical study by levofloxacin
Yoshida[38]	1999–2000	93 with NGU ≥5 WBC/hpf (×1000) of urethral smear	FVU, PCR-microtiter hybridization assay	15.1 (14)	50.5 (47)	
Maeda[39]	1999–2002	153 with NGU ≥5 WBC/hpf (×1000) of urethral smear or ≥15 WBC hpf of urinary sediments of FVU	FVU, PCR-microtiter hybridization assay	17.0 (26)	47.4 (73)	
Yokoi[40]	1999–2005	104 with post-GU ≥5 WBC/hpf (×1000) of urethral smear	FVU, PCR-microtiter hybridisation assay	9.6 (10)	49.0 (51)	*M. genitalium* was detected from 3.8% of GU
Takahashi[41]	2004	42 with NGU ≥5 WBC hpf of urinary sediments	FVU, PCR-microtiter hybridization assay	7.1 (3)	38.1 (16)	Clinical study by azithromycin
Shimada[42]	2006–2008	308 specimens from patients with urethritis	Stocked FVU	18.8 (58)	–	Retrospective study for stocked specimens
Takahashi[43]	2009–2010	87 with NGU ≥5 WBC hpf of urinary sediments	FVU, PCR-microtiter hybridization assay	4.6 (4)	21.8 (19)	Clinical study by levofloxacin
Hamasuna[44]	2008	135 with NGU ≥5 WBC hpf of urinary sediments or ≥10 WBC/1 μL of FVU	FVU, real-time PCR for adhesion gene, PCR for 16S rRNA gene	13.3 (18)	32.6 (44)	Clinical study by gatifloxacin
Hagiwara[45]	2004–2007	194 with NGU ≥5 WBC/hpf (×1000) of urethral smear or ≥15 WBC hpf of urinary sediments of FVU	FVU, PCR-microtiter hybridization assay	20.1 (39)	–	Clinical study by azithromycin
Shigehara[46]	2008–2010	176 with urethritis including GU ≥5 WBC/hpf of urethral swabs	Liquid-based samples, PCR for adhesion protein gene	18.2 (32)	25.6 (45)	Specimens were collected by rubbing the distal urethra
Kawaguchi[47]	2009–2010	121 with NGU ≥5 WBC/hpf of urethral swabs	Liquid-based urine samples, PCR for adhesion protein gene	15.7 (19)	19.0 (23)	
Ito[48]	2009–2011	89 with NGU ≥10 WBC/1 μL of FVU	FVU, PCR-microtiter hybridization assay	15.7 (14)	49.4 (44)	Clinical study using sitafloxacin

Table 2 Antimicrobial MIC distribution for 23 *Mycoplasm genitalium* strains

Antibacterial agent	MIC† (μg/mL)															
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	≥16	MIC50	MIC90
Azithromycin	22													1	0.001	0.002
Clarithromycin	9	9	4											1	0.004	0.008
Doxycycline						7	7	7	1		1				0.125	0.25
Minocycline					3	8	9	3							0.125	0.25
Tetracycline						3	11	5	2		1			1	0.125	0.5
Norfloxacin										2	1	2	3	15	32	64
Ciprofloxacin						1	1	1	3	1	3	10	3		4	8
Levofloxacin							1	5	1	11	5				1	2
Gatifloxacin					2	3	5	11	2						0.25	0.5
Moxifloxacin				1	5	11	5	1							0.06	0.125
Sitafloxacin			2	2	5	6	7	1							0.06	0.125

†MIC were measured using the broth-dilution method.

*r*RNA gene and the failure of azithromycin treatment regimens were closely related. Therefore, if mutations of the 23S *r*RNA gene are found in the *M. genitalium* genome obtained from the urine or urethral swab specimens, we can say that patients were infected by macrolide-resistant *M. genitalium*, although these genotypes were not detected in all specimens from patients who showed azithromycin treatment failure. Macrolide-resistance in *M. genitalium* seems to be spreading worldwide, and has been reported in Scandinavian countries,[15] France,[62] Australia,[59,63] New Zealand,[64] Greenland[65] and Japan.[66] In Australia, 27.2% of pretreatment specimens showed mutations related to macrolide-resistance.[63] In Greenland, these mutations were detected from all tested specimens of *M. genitalium*.[65] In Japan, Ito *et al.* showed that the same mutations were found in four urine specimens from seven patients with azithromycin treatment failure.[66] Importantly, it was discovered that the use of azithromycin, in particular at 1 g stat, had the potential to induce mutations on the 23S *r*RNA gene, as some reports indicated that the mutations on 23S *r*RNA were found in post-treatment specimens that had no mutations present in pretreatment.[15,67] In the recent randomized control trial of treatment of NGU by azithromycin or doxycycline regimen, the efficacy of azithromycin showed some decline from the 1990s.[68] However, azithromycin is still effective and can constitute a first-line treatment for NGU arising from both *M. genitalium* and *C. trachomatis*. In addition, azithromycin 2 g stat is acceptable for use in urethritis or cervicitis in Japan; therefore, evidence on the treatment of NGU will continue to build over the years.

Fluoroquinolones

The first clinical trial that used fluoroquinolone for urethritis with *M. genitalium* was carried out in Japan.[37] Levofloxacin 100 mg, three times/day for 7 days were tested, but the microbiological efficacy was just 36.4%. Furthermore, three other clinical studies were carried out in Japan that used regimens of levofloxacin,[43] gatifloxacin[44] or sitafloxacin[48] (Table 3). In Europe and Australia, two studies on regimens of moxifloxacin or ofloxacin were carried out.[59,69] We can extrapolate important information from these studies on the microbiological efficacies of fluoroquinolones and MIC.[44] The microbiological efficacies of levofloxacin, gatifloxacin, moxifloxacin and sitafloxacin were 33–60%, 83.3%, 100% and 100%, respectively, and the MIC90 of these agents were 2 μg/mL. 0.5 μg/mL, 0.125 μg/mL and 0.125 μg/mL, respectively. Considering the tissue level of fluoroquinolone, the optimal activity against *M. genitalium* might be at an MIC90 of 0.125 μg/mL. As the use of moxifloxacin is limited to only respiratory infections in Japan, sitafloxacin is the recommended fluoroquinolone for *M. genitalium* infection; however, further research on this agent is required.

Fluoroquinolone-resistance is known to exist in Gram-negative bacterial species and mutations in the gyrase genes, as *gyrA* and *parC* are known to be closely related to resistance. Deguchi *et al.* showed mutations on *gyrA* and *parC* genes from purified *M. genitalium* DNA obtained from urine specimens that had shown treatment failure with levofloxacin 100 mg, three times/day for 7 days.[70] They also detected mutations on the *gyrA*, *gyrB*, *parC* and *parE* genes of *M. genitalium* DNA from pretreated urine specimens.[42,71] In our past study on gatifloxacin, genetic mutations on *gyrA* or *parC* of *M. genitalium* were detected and linked to the efficacy of fluoroquinolone.[72] Of the 18 patients in the present study, *M. genitalium* remained in the specimens of three patients. Mutations on the *gyrA* or *parC* genes were found in the *M. genitalium* DNA of these three patients after treatment. No mutations on the *gyrA* gene of three *M. genitalium* DNA samples from pretreatment specimens were

Table 3 Clinical studies for treatment of urethritis with *Mycoplasma genitalium* by fluoroquinolones

Author Country	Year	Regimens for treatment	Microbiological efficacies† % (numbers of patients with treatment success/numbers of enrolled patients)	Comments
Maeda[37] Japan	2001	Levofloxacin 100 mg × 3/day, 7 days	36.4% (4/11)	
Bradshaw[59] Australia	2006	Second or third line treatment Moxifloxacin 400 mg × 1/day, 10 days	100% (9/9)	Moxifloxacin was used for patients with treatment failure by azithromycin regimens
Jernberg[69] Norway	2008	First line treatment		Ofloxacin or moxifloxacin was used for patients with treatment failure by azithromycin regimens
		Ofloxacin 200 mg × 2/day, 10 days	44.4% (4/9)	
		Moxifloxacin 400 mg/day, 7 days	100% (3/3)	
		Second or third line treatment		
		Ofloxacin 200 mg × 2/day, 10 days	58.3% (21/36)	
		Moxifloxacin 400 mg/day, 7 days	100% (24/24)	
Takahashi[43] Japan	2011	Levofloxacin 500 mg/day 7 days	60% (3/5)	
Hamasuna[44] Japan	2011	Gatifloxacin 200 mg × 2/day, 7 days	83.3% (15/18)	
Ito[48] Japan	2012	Sitafloxacin 100 mg × 2/day, 7 days	100% (11/11)	

†Microbiological efficacies showed the eradication rates of *Mycoplasma genitalium* after treatment by nucleic acid amplification tests.

found; thus, the mutations on the *gyrA* gene were thought to be selected for or induced by treatment. Regarding *parC*, mutations were found on *M. genitalium* DNA from two pretreatment specimens, but different mutations were found in the *M. genitalium* DNA from one of the post-treatment specimens. These data showed the presence of fluoroquinolone-resistant *M. genitalium* in Japan, but future studies are necessary to understand the mechanisms for the fluoroquinolone-resistance of *M. genitalium in vivo* and *in vitro*.

Treatment strategies for urethritis with *M. genitalium*

For NGU, macrolides and tetracycline are recommended in the guidelines of many countries.[2–5] However, tetracyclines are less effective against *M. genitalium*. Azithromycin regimens including 1 g stat or 2 g stat are now recommended, but if the azithromycin regimens fail, we must consider the use of fluoroquinolone, such as sitafloxacin, in Japan. The most important issues include the acceptance of *M. genitalium* examinations by the national insurance system in Japan and the individual treatment of *C. trachomatis* and *M. genitalium* in the not-too-distant future.

Conflict of interest

None declared.

References

1 Bradshaw CS, Tabrizi SN, Read TR *et al.* Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. *J. Infect. Dis.* 2006; **193**: 336–45.

2 Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm. Rep.* 2010; **59** (RR-12): 1–110.

3 BASHH. 2007 UK national guideline on the management of non-gonococcal urethritis. [Cited 1 Dec 2008.] Available from URL: http://www.bashh.org/guidelines

4 Australia National Guidelines for sexually transmissible infections. 2008. [Cited 28 Dec 2012.] Available from URL: http://www.mshc.org.au/Portals/6/NMGFSTI.pdf

5 Kamidono S, Onodera S, Kishimoto S. Guideline for diagnosis adn tretment for sexually transmitted infections, 2011. *Jpn. J. Sex. Transm. Infect.* 2011; **22** (1 Suppl) 1–163 (in Japanese).

6 Taylor-Robinson D, Tully JG, Furr PM, Cole RM, Rose DL, Hanna NF. Urogenital mycoplasma infection of man: a review with observations on a recently discovered mycoplasmas. *Isr. J. Med. Sci.* 1981; **17**: 524–30.

7 Taylor-Robinson D, Jensen JS. Mycoplasma genitalium: from Chrysalis to multicolored butterfly. *Clin. Microbiol. Rev.* 2011; **24**: 498–514.

8 Tully JG, Whitcomb RF, Clark HF, Williamson DL. Pathogenic mycoplasmas: cultivation and vertebrate pathogenicity of a new spiroplasma. *Science* 1977; **195**: 892–4.

9 Tully JG, Taylor-Robinson D, Cole RM, Rose DL. A newly discovered mycoplasma in the human urogenital tract. *Lancet* 1981; **1**: 1288–91.
10 Jensen JS. Mycoplasma genitalium infections. *Dan. Med. Bull.* 2006; **53**: 1–27.
11 Samra Z, Borin M, Bukowsky Y, Lipshitz Y, Sompolinsky D. Non-occurrence of Mycoplasma genitalium in clinical specimens. *Eur. J. Clin. Microbiol. Infect. Dis.* 1988; **7**: 49–51.
12 Jensen JS, Hansen HT, Lind K. Isolation of Mycoplasma genitalium strains from the male urethra. *J. Clin. Microbiol.* 1996; **34**: 286–91.
13 Hamasuna R, Osada Y, Jensen JS. Antibiotic susceptibility testing of *Mycoplasma genitalium* by TaqMan 5′ nuclease real-time PCR. *Antimicrob. Agents Chemother.* 2005; **49**: 4993–8.
14 Hamasuna R, Osada Y, Jensen JS. Isolation of Mycoplasma genitalium from first-void urine specimens by coculture with Vero cells. *J. Clin. Microbiol.* 2007; **45**: 847–50.
15 Jensen JS, Bradshaw CS, Tabrizi SN, Fairley CK, Hamasuna R. Azithromycin treatment failure in Mycoplasma genitalium-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. *Clin. Infect. Dis.* 2008; **47**: 1546–53.
16 Fraser CM, Gocayne JD, White O *et al.* The minimal gene complement of Mycoplasma genitalium. *Science* 1995; **270**: 397–403.
17 Gibson DG, Benders GA, Andrews-Pfannkoch C *et al.* Complete chemical synthesis, assembly, and cloning of a Mycoplasma genitalium genome. *Science* 2008; **319**: 1215–20.
18 Taylor-Robinson D. The role of mycoplasmas in non-gonococcal urethritis: a review. *Yale J. Biol. Med.* 1983; **56**: 537–43.
19 Tully JG, Taylor-Robinson D, Rose DL, Furr PM, Graham CE, Barile MF. Urogenital challenge of primate species with Mycoplasma genitalium and characteristics of infection induced in chimpanzees. *J. Infect. Dis.* 1986; **153**: 1046–54.
20 Hjorth SV, Bjornelius E, Lidbrink P *et al.* Sequence-based typing of Mycoplasma genitalium reveals sexual transmission. *J. Clin. Microbiol.* 2006; **44**: 2078–83.
21 Hamasuna R, Tsukino H. Urethritis. In: Naber KG, Schaeffer AJ, Heyns CF, Matsumoto T, Shoskes DA, Bjerklund-Johansen TE (eds). *Urological Infection, Edition 2010.* European Association of Urology, Stockholm, 2010; 777–829.
22 Manhart LE, Broad JM, Golden MR. Mycoplasma genitalium: should we treat and how? *Clin. Infect. Dis.* 2011; **53** (Suppl 3): S129–42.
23 McGowin CL, Anderson-Smits C. Mycoplasma genitalium: an emerging cause of sexually transmitted disease in women. *PLoS Pathog.* 2011; **7**: e1001324.
24 Eickhoff JH, Frimodt-Moller N, Walter S, Frimodt-Moller C. A double-blind, randomized, controlled multicentre study to compare the efficacy of ciprofloxacin with pivampicillin as oral therapy for epididymitis in men over 40 years of age. *BJU Int.* 1999; **84**: 827–34.
25 Ito S, Tsuchiya T, Yasuda M, Yokoi S, Nakano M, Deguchi T. Prevalence of genital mycoplasmas and ureaplasmas in men younger than 40 years-of-age with acute epididymitis. *Int. J. Urol.* 2012; **19**: 234–8.
26 Krieger JN, Riley DE, Roberts MC, Berger RE. Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. *J. Clin. Microbiol.* 1996; **34**: 3120–8.
27 Mandar R, Raukas E, Turk S, Korrovits P, Punab M. Mycoplasmas in semen of chronic prostatitis patients. *Scand. J. Urol. Nephrol.* 2005; **39**: 479–82.
28 Horner PJ, Taylor-Robinson D. Association of Mycoplasma genitalium with balanoposthitis in men with non-gonococcal urethritis. *Sex. Transm. Infect.* 2011; **87**: 38–40.
29 Taylor-Robinson D, Jensen JS, Svenstrup H, Stacey CM. Difficulties experienced in defining the microbial cause of pelvic inflammatory disease. *Int. J. STD AIDS* 2012; **23**: 18–24.
30 Lawton BA, Rose SB, Bromhead C, Gaitanos LA, MacDonald EJ, Lund KA. High prevalence of Mycoplasma genitalium in women presenting for termination of pregnancy. *Contraception* 2008; **77**: 294–8.
31 Bjartling C, Osser S, Persson K. The association between Mycoplasma genitalium and pelvic inflammatory disease after termination of pregnancy. *BJOG* 2010; **117**: 361–4.
32 Anagrius C, Lore B, Jensen JS. Mycoplasma genitalium: prevalence, clinical significance, and transmission. *Sex. Transm. Infect.* 2005; **81**: 458–62.
33 Hitti J, Garcia P, Totten P, Paul K, Astete S, Holmes KK. Correlates of cervical Mycoplasma genitalium and risk of preterm birth among Peruvian women. *Sex. Transm. Dis.* 2010; **37**: 81–5.
34 Manhart LE, Kay N. Mycoplasma genitalium: is It a Sexually Transmitted Pathogen? *Curr. Infect. Dis. Rep.* 2010; **12**: 306–13.
35 Deguchi T, Komeda H, Yasuda M *et al.* Mycoplasma genitalium in non-gonococcal urethritis. *Int. J. STD AIDS* 1995; **6**: 144–5.
36 Maeda S, Tamaki M, Nakano M, Uno M, Deguchi T, Kawada Y. Detection of Mycoplasma genitalium in patients with urethritis. *J. Urol.* 1998; **159**: 405–7.
37 Maeda SI, Tamaki M, Kojima K *et al.* Association of Mycoplasma genitalium persistence in the urethra with recurrence of nongonococcal urethritis. *Sex. Transm. Dis.* 2001; **28**: 472–6.
38 Yoshida T, Maeda S, Deguchi T, Ishiko H. Phylogeny-based rapid identification of mycoplasmas and ureaplasmas from urethritis patients. *J. Clin. Microbiol.* 2002; **40**: 105–10.
39 Maeda S, Deguchi T, Ishiko H *et al.* Detection of Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma parvum (biovar 1) and Ureaplasma urealyticum (biovar 2) in patients with non-gonococcal urethritis using polymerase chain reaction-microtiter plate hybridization. *Int. J. Urol.* 2004; **11**: 750–4.

40 Yokoi S, Maeda S, Kubota Y *et al.* The role of Mycoplasma genitalium and Ureaplasma urealyticum biovar 2 in postgonococcal urethritis. *Clin. Infect. Dis.* 2007; **45**: 866–71.
41 Takahashi S, Matsukawa M, Kurimura Y *et al.* Clinical efficacy of azithromycin for male nongonococcal urethritis. *J. Infect. Chemother.* 2008; **14**: 409–12.
42 Shimada Y, Deguchi T, Nakane K *et al.* Emergence of clinical strains of Mycoplasma genitalium harbouring alterations in ParC associated with fluoroquinolone resistance. *Int. J. Antimicrob. Agents* 2010; **36**: 255–8.
43 Takahashi S, Ichihara K, Hashimoto J *et al.* Clinical efficacy of levofloxacin 500 mg once daily for 7 days for patients with non-gonococcal urethritis. *J. Infect. Chemother.* 2011; **17**: 392–6.
44 Hamasuna R, Takahashi S, Kiyota H *et al.* Effect of gatifloxacin against Mycoplasma genitalium-related urethritis: an open clinical trial. *Sex. Transm. Infect.* 2011; **87**: 389–90.
45 Hagiwara N, Yasuda M, Maeda S, Deguchi T. In vitro activity of azithromycin against Mycoplasma genitalium and its efficacy in the treatment of male Mycoplasma genitalium-positive nongonococcal urethritis. *J. Infect. Chemother.* 2011; **17**: 821–4.
46 Shigehara K, Kawaguchi S, Sasagawa T *et al.* Prevalence of genital Mycoplasma, Ureaplasma, Gardnerella, and human papillomavirus in Japanese men with urethritis, and risk factors for detection of urethral human papillomavirus infection. *J. Infect. Chemother.* 2011; **17**: 487–92.
47 Kawaguchi S, Shigehara K, Sasagawa T *et al.* Liquid-based urine cytology as a tool for detection of human papillomavirus, Mycoplasma spp., and Ureaplasma spp. in men. *J. Clin. Microbiol.* 2012; **50**: 401–6.
48 Ito S, Yasuda M, Seike K *et al.* Clinical and microbiological outcomes in treatment of men with non-gonococcal urethritis with a 100-mg twice-daily dose regimen of sitafloxacin. *J. Infect. Chemother.* 2012; **18**: 414–18.
49 Yoshida T, Deguchi T, Ito M, Maeda S, Tamaki M, Ishiko H. Quantitative detection of Mycoplasma genitalium from first-pass urine of men with urethritis and asymptomatic men by real-time PCR. *J. Clin. Microbiol.* 2002; **40**: 1451–5.
50 Yoshida T, Maeda S, Deguchi T, Miyazawa T, Ishiko H. Rapid detection of Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma parvum, and Ureaplasma urealyticum organisms in genitourinary samples by PCR-microtiter plate hybridization assay. *J. Clin. Microbiol.* 2003; **41**: 1850–5.
51 Horner P, Thomas B, Gilroy CB, Egger M, Taylor-Robinson D. Role of Mycoplasma genitalium and Ureaplasma urealyticum in acute and chronic nongonococcal urethritis. *Clin. Infect. Dis.* 2001; **32**: 995–1003.
52 Falk L, Fredlund H, Jensen JS. Tetracycline treatment does not eradicate Mycoplasma genitalium. *Sex. Transm. Infect.* 2003; **79**: 318–19.
53 Deguchi T, Yoshida T, Yokoi S *et al.* Longitudinal quantitative detection by real-time PCR of Mycoplasma genitalium in first-pass urine of men with recurrent nongonococcal urethritis. *J. Clin. Microbiol.* 2002; **40**: 3854–6.
54 Bradshaw CS, Chen MY, Fairley CK. Persistence of Mycoplasma genitalium following azithromycin therapy. *PLoS One* 2008; **3**: e3618.
55 Hamasuna R, Jensen JS, Osada Y. Antimicrobial susceptibilities of Mycoplasma genitalium strains examined by broth dilution and quantitative PCR. *Antimicrob. Agents Chemother.* 2009; **53**: 4938–9.
56 Gambini D, Decleva I, Lupica L, Ghislanzoni M, Cusini M, Alessi E. Mycoplasma genitalium in males with nongonococcal urethritis: prevalence and clinical efficacy of eradication. *Sex. Transm. Dis.* 2000; **27**: 226–9.
57 Mena LA, Mroczkowski TF, Nsuami M, Martin DH. A randomized comparison of azithromycin and doxycycline for the treatment of Mycoplasma genitalium-positive urethritis in men. *Clin. Infect. Dis.* 2009; **48**: 1649–54.
58 Schwebke JR, Rompalo A, Taylor S *et al.* Re-evaluating the treatment of nongonococcal urethritis: emphasizing emerging pathogens – a randomized clinical trial. *Clin. Infect. Dis.* 2011; **52**: 163–70.
59 Bradshaw CS, Jensen JS, Tabrizi SN *et al.* Azithromycin failure in Mycoplasma genitalium urethritis. *Emerg. Infect. Dis.* 2006; **12**: 1149–52.
60 Morozumi M, Hasegawa K, Chiba N *et al.* Application of PCR for Mycoplasma pneumoniae detection in children with community-acquired pneumonia. *J. Infect. Chemother.* 2004; **10**: 274–9.
61 Lucier TS, Heitzman K, Liu SK, Hu PC. Transition mutations in the 23S rRNA of erythromycin-resistant isolates of Mycoplasma pneumoniae. *Antimicrob. Agents Chemother.* 1995; **39**: 2770–3.
62 Chrisment D, Charron A, Cazanave C, Pereyre S, Bebear C. Detection of macrolide resistance in Mycoplasma genitalium in France. *J. Antimicrob. Chemother.* 2012; **67**: 2598–601.
63 Twin J, Jensen JS, Bradshaw CS *et al.* Transmission and selection of macrolide resistant Mycoplasma genitalium infections detected by rapid high resolution melt analysis. *PLoS One* 2012; **7**: e35593.
64 Yew HS, Anderson T, Coughlan E, Werno A. Induced macrolide resistance in Mycoplasma genitalium isolates from patients with recurrent nongonococcal urethritis. *J. Clin. Microbiol.* 2011; **49**: 1695–6.
65 Gesink DC, Mulvad G, Montgomery-Andersen R *et al.* Mycoplasma genitalium presence, resistance and epidemiology in Greenland. *Int. J. Circumpolar Health* 2012; **71**: 1–8.
66 Ito S, Shimada Y, Yamaguchi Y *et al.* Selection of Mycoplasma genitalium strains harbouring macrolide resistance-associated 23S rRNA mutations by treatment with a single 1 g dose of azithromycin. *Sex. Transm. Infect.* 2011; **87**: 412–14.

67 Chrisment D, Charron A, Cazanave C, Pereyre S, Bebear C. Detection of macrolide resistance in Mycoplasma genitalium in France. *J. Antimicrob. Chemother.* 2012; **67**: 2598–2601. doi:10.1093/jac/dks263.
68 Manhart LE, Gillespie CW, Lowens MS *et al.* Standard Treatment Regimens for Nongonococcal Urethritis Have Similar but Declining Cure Rates: a Randomized Controlled Trial. *Clin. Infect. Dis.* 2013; **56**: 934–42.
69 Jernberg E, Moghaddam A, Moi H. Azithromycin and moxifloxacin for microbiological cure of Mycoplasma genitalium infection: an open study. *Int. J. STD AIDS* 2008; **19**: 676–9.
70 Deguchi T, Maeda S, Tamaki M *et al.* Analysis of the gyrA and parC genes of Mycoplasma genitalium detected in first-pass urine of men with non-gonococcal urethritis before and after fluoroquinolone treatment. *J. Antimicrob. Chemother.* 2001; **48**: 742–4.
71 Shimada Y, Deguchi T, Yamaguchi Y *et al.* gyrB and parE mutations in urinary Mycoplasma genitalium DNA from men with non-gonococcal urethritis. *Int. J. Antimicrob. Agents* 2010; **36**: 477–8.
72 Hamasuna R, Takahashi S, Matsumoto M, Sho T, Matsumoto T (eds). Mutations on gyrA or parC genes of Mycoplasma genitalium and efficacies of treatment with fluoroquinolone against M. genitalium urethritis. 19th International Society for STD Research; 2011; Quebeck, Canada.

性感染症

065 クラミジア感染症

濵砂良一*

1 概念・病因

クラミジア感染症は *Chlamydia trachomatis* による感染症である。*C. trachomatis* は偏性細胞内寄生体であり，特殊な生活環を持つ。細胞外では，感染性を持つ基本小体（elementary body：EB）という球体の形態をとる（核とリボゾームを充満した細胞質を有する）。EB が宿主細胞に感染すると，網様体（reticular body：RB）という形に変わる。RB は核，細胞質の区別のない構造で，二分裂を繰り返しながら増殖し，宿主の細部質内に封入体を形成する。感染後，20～24 時間後に成熟すると，EB に変わり細胞を破って細胞外に出る。

C. trachomatis は性感染症（sexually transmitted infection：STI）から最も高い頻度で分離される病原体である。性器クラミジア感染症として，男性では主に尿道炎と精巣上体炎を，女性では子宮頸管炎と骨盤内炎症性疾患（pelvic inflammatory diseases：PID）の病態を示す。男性尿道炎患者の 30～40%より分離され，女性では STI の 60～70%を性器クラミジア感染症が占める。また，淋菌感染症の約 20%に *C. trachomatis* が合併感染する[1,2]。

淋菌感染症同様，性器以外の *C. trachomatis* 感染例が増加している。オーラルセックスにより，男女の咽頭から *C. trachomatis* が検出される[3]。慢性扁桃炎や咽頭炎で治療に反応しないものから分離されることもある。またアナルセックスにより直腸炎を起こす。*C. trachomatis* 感染妊婦より新生児が産道感染すると，新生児クラミジア肺炎や新生児結膜炎が起こる。感染母体から生まれた新生児のクラミジア肺炎の発症率は 3～20%といわれる。このほか，わが国では稀であるが，鼠径リンパ肉芽腫症を引き起こすことがある。外陰部の丘疹が潰瘍化し，さらに鼠径部リンパ節が有痛性に大きく腫大し，自壊し排膿する。性器クラミジア感染症の分泌物による眼の汚染により，成人型封入体結膜炎を発症することがある。結膜の充血，眼脂，眼瞼腫脹を主訴とし，眼瞼結膜に濾胞を形成する。

C. trachomatis は，性的活動期にある男女から高い頻度で検出されることが知られている。Imai ら[4]の検討では，症状を有しない性交経験のある女子学生の 9.5%，男子学生の 8.7%より *C. trachomatis* が検出された。

2 診断のポイント

男性の尿道炎のうち，*C. trachomatis* が検出されるものをクラミジア性尿道炎と呼ぶ。感染機会後，1～3 週間で排膿（尿道分泌物），尿道痛といった尿道炎症状を呈する。淋菌性尿道炎と比較すると，発症は比較的緩徐で，症状は軽微なものが多い。尿道分泌物は漿液性で，少量から中等量である。尿道不快感や，尿道掻痒感から，無症候に近い症例も多い。クラミジア性尿道炎の 5%程度に精巣上体炎を合併する。性的活動期の年齢の精巣上体炎では，まずクラミジア性を疑う。ほかの細菌による精巣上体炎と比較すると，陰嚢内容の腫脹は軽度で，発熱の程度も低いことが多い。

女性では感染機会後，1～3 週間で子宮頸管炎を起こす。主たる症状は帯下の増加，不正出血などであるが，半数以上の症例では自覚症状を感じな

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表 1　わが国で使用できるクラミジア検出法

製品名（販売会社）	検出法	検体〔最少検出感度〕
アプティマ™ Combo2 クラミジア/ゴノレア（富士レビオ）	遺伝子増幅法 Transcription mediated amplification（TMA）法	男性：初尿*1，尿道分泌物（尿道スワブ） 女性：子宮頸管スワブ 男女：咽頭スワブ 〔1 IFU/アッセイ〕
BD プローブテック ET クラミジア・トラコマティス ナイセリア・ゴノレア（日本ベクトン・ディッキンソン）	遺伝子増幅法 Strand displacement amplification（SDA）法	男性：初尿*1，尿道分泌物（尿道スワブ） 女性：子宮頸管スワブ 男女：咽頭スワブ 〔1 IFU/アッセイ〕
アキュージーン® m-CT/NG（アボット・ジャパン）	遺伝子増幅法 Real-time PCR 法	男性：初尿*1，尿道分泌物（尿道スワブ） 女性：子宮頸管スワブ 〔1 IFU/アッセイ〕
淋菌，クラミジア・トラコマティス/リアルタイム PCR（ロッシュ・ダイアグノスティックス）	遺伝子増幅法 Real-time PCR 法	男性：初尿*1 女性：子宮頸管スワブ 男女：咽頭検体（うがい液）*2 〔1 IFU/アッセイ〕
イデイア PCE クラミジア®（協和メディックス）	酵素抗体法	男性：初尿*1，尿道分泌物（尿道スワブ） 女性：子宮頸管スワブ 〔20 IFU/アッセイ〕
クリアビュークラミジア® アーリアメディカル ラピッドエスピー®クラミジア（DS ファーマバイオメディカル）	免疫クロマトグラフィー法	男性：初尿*1 女性：子宮頸管スワブ 〔1,000EB/ml（クリアビュー）〕 〔80 EB/アッセイ（ラピッドエスピー）〕
ヒタザイム®クラミジア（日立化成）	抗体測定（IgA，IgG）	血液

*1排尿後，1 時間以上を経過した初尿を採取。
*2滅菌生理食塩水を 15〜20 ml 口に含み，10〜20 秒間うがいをしたものを検体とする。

いといわれている。*C. trachomatis* は子宮頸管から子宮付属器，腹腔内へ侵入する。子宮付属器炎（卵管炎，卵巣炎），PID を起こし，発熱，下腹部痛，腹部疝痛などの症状を呈する。肝周囲炎を起こすこともある。卵管炎の後遺症として，卵管内腔の狭小化より，卵管性不妊の原因となる。

クラミジア感染症の診断は *C. trachomatis* の検出による。*C. trachomatis* の分離，培養は極めて困難であるため，検出には核酸増幅法，酵素抗体法や免疫クロマトグラフィー法を用いる[1]。また，PID などで腹腔内に感染があるが，子宮頸管から *C. trachomatis* が検出されない場合，抗体検査法も用いられる。わが国では 4 種類の核酸増幅法が使用できる（**表 1**）が，その診断までに数日間かかる。このため，受診日に診断可能な酵素抗体法や免疫クロマトグラフィー法が用いられることがあるが，核酸増幅法と比較して，その感度は劣る。男性尿道炎では初尿，子宮頸管ではスワブ，また咽頭検体を検査する。

3 治　療

C. trachomatis 感染症に対する治療薬は，マクロライド系，テトラサイクリン系抗菌薬が第一選択薬となる[1,2,5]（**表 2**）。マクロライドの中でも azithromycin 1 g および 2 g 徐放製剤は単回での治療が可能である。また，ニューキノロン系抗菌薬も症例により選択可能である。テトラサイクリン，ニューキノロンでは 7 日間の投与が必要となる。セックスパートナーの治療，患児の両親の治療も積極的に行う。*C. trachomatis* の上記，マクロライド，テトラサイクリン，ニューキノロンに対する耐性株の報告はあるが，世界的にその蔓延は認められない。

4 ここがポイント

わが国の保険システム上，原則としてクラミジ

表 2　性器クラミジア感染症に対する推奨治療薬

・アジスロマイシン（ジスロマック®）1 g　経口　単回投与
・アジスロマイシン（ジスロマック SR®）2 g　徐放製剤　経口　単回投与
・クラリスロマイシン（クラリス®，クラリシッド®）1 回 200 mg　2 回/日　経口　7 日間
・ミノサイクリン（ミノマイ®）1 回 100 mg　2 回/日　経口　7 日間
・ドキシサイクリン（ビブラマイシン®）1 回 100 mg　2 回/日　経口　7 日間
・レボフロキサシン（クラビット®）1 回 500 mg　1 回/日　経口　7 日間
・トスフロキサシン（オゼックス®，トスキサシン®）1 回 150 mg　2 回/日　経口　7 日間
・シタフロキサシン（グレースビット®）1 回 100 mg　2 回/日　経口　7 日間

（三鴨廣繁，他：日性感染症会誌 **22**（1 Suppl.）：60-64，2011[1]より引用）

ア検査の結果を確認したうえで，治療を開始する。パートナーの治療は積極的に行うべきだが，プライバシーの問題などを考慮する必要がある。

文献

1) 三鴨廣繁，高橋　聡，野口昌良，他：性器クラミジア感染症．性感染症診断・治療ガイドライン 2011．日性感染症会誌 **22**（1 Suppl.）：60-64，2011
2) Workowski KA and Berman S：Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep **59**（RR-12）：1-110, 2010
3) Hamasuna R, Takahashi S, Uehara S, et al：Should urologists care for the pharyngeal infection of Neisseria gonorrhoeae or Chlamydia trachomatis when we treat male urethritis? J Infect Chemother **18**：410-413, 2012
4) Imai H, Nakao H, Shinohara H, et al：Population-based study of asymptomatic infection with Chlamydia trachomatis among female and male students. Int J STD AIDS **21**：362-366, 2010
5) Lau CY and Qureshi AK：Azithromycin versus doxycycline for genital chlamydial infections：a meta-analysis of randomized clinical trials. Sex Transm Dis **29**：497-502, 2002

Antimicrobial Agents and Chemotherapy

Antimicrobial Resistance and Molecular Typing of Neisseria gonorrhoeae Isolates in Kyoto and Osaka, Japan, 2010 to 2012: Intensified Surveillance after Identification of the First Strain (H041) with High-Level Ceftriaxone Resistance

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