Extragenital Infection with Sexually Transmitted Pathogens

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Abstract: The significant characteristics of STDs are as follows: (1) no spontaneous eradication without medical treatment; (2) an asymptomatic infectious source; and (3) lethal complications arising after a protracted post-infection period. The incidence of extra genital STD infections increases with increased extra genital contact during sex. Both Neisseria gonorrhea and Chlamydia trachomatis infect the pharynx, since the columnar epithelium of the urethra and cervix is similar to that of the pharynx. Because Japanese are a homogenously well-educated, cautious people, the number of cases of gonorrhea has dropped by approximately one-fifth after a large media AIDS campaign conducted in 1985. However, the ratio of ‘male gonococcal urethritis contracted via the female pharynx’ among total male gonococcal urethritis cases simultaneously increased up to approximately 50%. This trend is due to the fact that fellatio without vaginal intercourse is commercially available in Japan. At present some 30% of both gonococcal male urethritis and female cervicitis cases also have gonococcal pharyngitis. The significant characteristics of gonococcal pharyngitis are (1) a lack of symptoms; (2) difficulty in detecting the gonococcus; and (3) difficulty in eradicating the gonococcus. Regarding (1), patients tend to have no subjective symptoms, e.g. discharge, pain on swallowing, and no redness or discharge can be observed on clinical examinations. Regarding characteristic (2), due to the large number of normal flora in the pharynx, false negative reactions by culture isolation and false positive reactions by Amplicor PCR are frequent in pharyngeal specimens. Regarding (3), after eradicating gonococcus from the urethra and cervix by chemotherapy, the same strain can still be isolated from the pharynx of the same patient.

Key words: Gonococcal pharyngitis; Quinolone-resistant gonococci; Cephem-resistant gonococci; Amplicor PCR

Prevalence of Sexually Transmitted Diseases (STDs) Worldwide

Thanks to the development of antimicrobial agents and vaccines, the control of infectious diseases, which had formerly ranked first among the leading causes of death, became possible during the latter half of the twentieth century.
Nevertheless, because no vaccines have been developed to inoculate against STDs, and the proportion of infected patients who transmit STDs with subjective symptoms and also seek treatment is low, STDs remain the most poorly controlled of all infectious diseases.

According to information published by the WHO in 1995, 335 million people have STDs that are treatable by chemotherapy and these diseases include gonorrhea, chlamydial infection, syphilis, and trichomoniasis, while the number of infected people including asymptomatic individuals with infections such as herpes simplex virus, human papilloma virus or HIV infection may amount to several billion. In the same year, the World Bank announced that the number of individuals with STDs including AIDS in the 15–49-year-old age group ranked second among all disorders in developing countries, while in the US, 12 million people were reported to be suffering STDs that are treatable with chemotherapy, while 2 million teenagers had STDs.

HIV can be transmitted in circulating blood by blood contact through anal intercourse, shared needle use for intravenous drug use (IDU) narcotics, and so forth. The importance and degree of prevalence vary considerably depending on the geographical location and socioeconomic conditions. Clarification of these issues has revealed the prevalence and causes of STDs, which vary with race and social settings, and are also related to societal trends as well as of some aspects of human society such as homosexuality and narcotics abuse which are normally concealed from public notice.

Current estimates indicate the cumulative number of HIV cases in the United States to be approximately 780,000 in 2000; with the number of infected patients notified during the 1981–1992, 1993–1995, and 1996–2000 periods each accounting for approximately one third of the total. Eighty percent of all AIDS cases are male, 61% are blacks and Hispanics, and 85% are people aged between 20–49 years. Reportedly, 46% of cases are homosexual or bisexual men (men who have sex with men = MSM), 25% are intravenous narcotics abusers, and 10% have contracted the infection via heterosexual intercourse. In Africa, in contrast, the male: female ratio of cases is 1:1, with an infection rate of as high as 8.8% for the 15–49-year-old age group. AIDS mortality has already resulted in a decrease in the mean life expectancy in this region. This characteristic prevalence of HIV infection is largely attributable to a social environment that encourages multiple sexual partners and a high STD infection rate. The infection rate for the 15–49-year-old age group has been reported to be 0.7% in India, 82% for intravenous drug abusers and 6% for prostitutes in China, and 2.1% for adults in the Caribbean Islands. HIV infection has the highest mortality rate in Africa and ranks fourth worldwide.

There are fewer cases of HIV infection in Japan and the Republic of Korea, and cases attributable to unheated blood products still account for approximately half of all reported cases in Japan. However, as is the case of syphilis, HIV as an STD cannot be eradicated. The treatment of AIDS reportedly costs 100 million yen per annum per patient when covered by national health insurance in Japan; hence the effective control of HIV infection is an urgent task.

STDs are contagious diseases, and each STD patient has a contact who serves as the source of infection and one or more contacts to whom the infection may have been transmitted. STDs are often asymptomatic, and such individuals thus spread the infection without being aware that they are infected. Treatment of the patient alone does not suffice to control STDs, and it is essential to pursue the source of infection and sexual partner(s) and to undertake epidemiological treatment. In the U.S.A. and Europe these duties are undertaken by free STD clinics.

To date, no medical care system for STDs has been developed in Japan despite the volume of antimicrobial agents used in this country being virtually equivalent to one third of total output worldwide, owing in part to the peculiarities of
EXTRAGENITAL STD

The nationwide universal health insurance system. The control of STDs in the country is thus not based on epidemiological treatment upon correct diagnosis but on “untargeted mass-dose antimicrobial medication”. Even control of condyloma acuminatum and syphilis has generally been achieved via these measures. In Japan, the chlamydial infection rate for young females remains at approximately 5% despite the fact that annual consumption of even a single new quinolone antibiotic is almost “sufficient to cure chlamydial infection in 3.8 million patients”. This high infection rate has remained constant since 1985 when the diagnosis of chlamydial infection became possible. It is thus considered ineffective to reduce the prevalence of chlamydial infection using the above method. While extragenital infections with sexually transmitted pathogens such as HIV and syphilis are not uncommon, I would like to review the situation regarding gonorrhea where asymptomatic pharyngeal infection constitutes the source of infection in a majority of cases.

**Gonococcal or Chlamydial Pharyngeal Infection**

Gonococci and *Chlamydia trachomatis* (CT) normally infect the columnar epithelium of the male urethra and female uterine cervix but also cause an infection in the conjunctiva, pharynx and rectum, the surfaces of which are lined with a similar quality of epithelium. A conjunctival infection with gonococci and CT in newborns caused by birth canal infections have long been known as neonatal acute purulent conjunctivitis and neonatal inclusion conjunctivitis. Meningococci, which are gram-negative cocci similar to gonococci, are occasionally isolated from the throat even in the absence of...
any lesions.

In the 1980s, changes in the pattern of sexual behavior and the consequent popularity of fellatio, generated an increase in the number of cases of gonococcal urethritis (GU) infected from the pharynx (Fig. 1). Current gonococci are isolated from the pharynx in approximately half of all GU cases and from around 30% of gonococcal genital infections (Table 1). Gonococci isolated from the pharynx are smaller in quantity than those isolated from the urethra or cervix. Possibly due to the smaller quantity of inoculated organisms at the time of infection, GU infected from the pharynx has a slightly extended incubation period and slightly milder systemic inflammatory symptoms, including lower leukocyte counts and milder CRP than GU infected from the cervix (Table 2).

Points at issue of pharyngeal gonococcal

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Table 1 (A) Rates of Chlamydial Detection from the Pharynx and Rectum in Patients with Genital Chlamydial Infection

<table>
<thead>
<tr>
<th></th>
<th>Pharynx</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2/51</td>
<td>0/12</td>
</tr>
<tr>
<td>Female</td>
<td>4/38</td>
<td>24/25</td>
</tr>
</tbody>
</table>

Table 1 (B) Rates of Gonococcal Detection from the Pharynx and Rectum in Patients with Genital Gonococcal Infection

<table>
<thead>
<tr>
<th></th>
<th>Pharynx</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5/17</td>
<td>0/15</td>
</tr>
<tr>
<td>Female</td>
<td>5/15</td>
<td>7/15</td>
</tr>
</tbody>
</table>

Table 2 Differences in the Clinical Findings of Gonococcal Urethritis by Site of Source of Infection

<table>
<thead>
<tr>
<th>Age of patient (mean)</th>
<th>Gonococcal urethritis infected from the cervix ($n = 135$)</th>
<th>Gonococcal urethritis infected from the pharynx ($n = 51$)</th>
<th>Chlamydial urethritis ($n = 175$)</th>
<th>Gonococcal cervicitis ($n = 27$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period (mean)</td>
<td>27.2 years</td>
<td>30.8 years</td>
<td>29.7 years</td>
<td>23.2 years</td>
</tr>
<tr>
<td>Urethral discharge</td>
<td>Profuse</td>
<td>Rather profuse</td>
<td>Scant</td>
<td>—</td>
</tr>
<tr>
<td>Leukocytes in urine sediment (mean)</td>
<td>$\geq 50$/HPF</td>
<td>$\geq 30$/HPF</td>
<td>3 to $\leq 20$/HPF</td>
<td>Variable</td>
</tr>
<tr>
<td>Peripheral blood leukocytes (mean)</td>
<td>$9,500 \pm 2,300$</td>
<td>$7,900 \pm 1,500$</td>
<td>$6,300 \pm 1,900$</td>
<td>$5,500 \pm 1,300$</td>
</tr>
<tr>
<td>% cases with CRP&gt;0.5</td>
<td>28.6%</td>
<td>11.1%</td>
<td>0%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Estimated number of organisms per swab</td>
<td>$2 \times 10^3$</td>
<td>$7 \times 10^4$</td>
<td>$5 \times 10^4$</td>
<td>$3 \times 10^4$</td>
</tr>
<tr>
<td>Quantity of organism in post-urination collected semen</td>
<td>Frequently $\geq 10^3$/mL</td>
<td>Frequently $\geq 10^3$/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semen</th>
<th>WBC</th>
<th>Granulocytes (mean)</th>
<th>Lymphocytes</th>
<th>CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15,000</td>
<td>10,000</td>
<td>2,900</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>2,200</td>
<td>1,800</td>
<td>400</td>
<td>20</td>
</tr>
</tbody>
</table>

* Inflammatory symptoms are milder in chlamydial urethritis than in gonococcal urethritis (GU).
* The incubation period is longer, the CRP-positive rate is lower and the quantity of organisms at the infected site is smaller in GU infected from the female pharynx than in GU infected from the uterine cervix.
Fig. 2 False positive reactions with pharyngeal or rectal swab specimens negative for gonococci or chlamydiads as tested by a non-culture detection assay for these pathogens. The non-culture detection assay is remarkably useful for the diagnosis of STDs; however, results of the assay are reported merely in terms of a positive or negative reaction, no isolates can be obtained and there is no means of reassessing the data. The assay may also give false positive results with pharyngeal and rectal swab specimens containing indigenous contaminants. An amplicor PCR assay is a highly sensitive detection test but produces false positive reactions with 10% or more of pharyngeal swab specimens which are later proven to be gonococcus-free.
infection include: (1) a lack of subjective symptoms, which thus constitute a source of infection over a long period of time, (2) difficulty in diagnosis, and (3) difficulty in attaining gonococcal eradication. Regarding point (1), gonococci are detected at this site of infection in 30% of male and female patients, respectively, but such patients usually have no clinical manifestations of inflammation such as a sore throat and redness and the infection tends to remain undetected unless such patients are specifically examined for the pathogen. Regarding point (2), gonococcal culture isolation cannot be achieved without using selective media for *Neisseria gonorrhoeae* since pharyngeal swabs also contain an abundant normal flora. Amplified polymerase chain reaction (PCR) assay, a nucleic-acid amplification test, is highly sensitive for detecting this organism, thus allowing for easier detection from the pharynx even when the gonococci are not abundant. However, the pharynx is indigenously inhabited by nonpathogenic *Neisseria spp.*, cross reactions which cause false positive reactions in nearly 10% of all cases examined (Fig. 2). As for (3), gonococci of the same strain may persist in the pharynx of the same individual even after the gonococci are eradicated from the urethra or uterine cervix by antimicrobial chemotherapy. It follows that pharyngeal gonococci are less liable to be eradicated by chemotherapy than the organisms infecting the urethra or uterine cervix. GU is an infection seen in healthy subjects without any associated local compromising factors, and the clinical response to chemotherapy does not vary among patients. In such cases, the breakpoint coincides with the minimum inhibitory concentration (MIC) for gonococci, which are eradicated without exception upon exposure to plasma drug concentrations above the MIC level over a period of 6–8 hours (Fig. 3). Failures have been encountered in chemotherapy for pharyngeal infection using spectinomycin (SPCM) and various other antimicrobial agents; accordingly, it is essential to confirm eradication after the completion of treatment.

CT is frequently detected in the pharynx of patients with a chlamydial conjunctival infection, whereas complications by pharyngeal chlamydial infection is less frequent among patients with urethral or cervical infection with this pathogen, as compared to gonococcal infections. The main problem implicit in gonococcal pharyngeal infection is its resistance to chemotherapy. The eradication of gonococci in GU can be accomplished with single-dose therapy with SPCM (2 g) in 100% of cases while that of pharyngeal gonococci occurs in no more than
half the cases treated. In Japan, furthermore, gonococci which are resistant to cephems have been rapidly increasing since 2000, in addition to the rapid increase in new quinolone-resistant gonococci encountered in the 1990s; it is now becoming increasingly difficult to eradicate pharyngeal gonococci. The following section pertains to the problem of increasing gonococcal drug resistance.

**Increasing Gonococcal Resistance to All Antimicrobial Agents**

According to the experience gained at the JRC Medical Center, treatment failure of GU during the 1976–1999 period was limited to one case, the first in Japan, in which treatment failed to eradicate an SPCM-resistant organism; one case of infection with penicillinase-producing *N. gonorrhoeae* (PPNG) previously treated with ABPC without success for 4 weeks at another institution, and cases of gonococcal pharyngeal infection. It was assumed that the succession of newly developed oral antimicrobial agents such as CEX, CCL, CFIX, PPA, NFLX, and OFLX, as well as single-dose therapy with intramuscular SPCM (2 g) and single-dose therapy with intravenous CTRX (1 g), would all be effective in the treatment of GU.

From 1989, failure to achieve eradication with new quinolones occurred, and the isolation of OFLX-resistant organisms with MICs of $\geq 1 \mu g/ml$ increased to as much as 30% in 2000. The growing resistance to cephems has failed to attract much attention since the efficacy of SPCM, CTRX, and CFIX has been retained, however, such resistance has been increasing progressively for a long period of time. In 2000, cases of failure in treatment with CFIX appeared. Increased resistance was also evident with such drugs as CTRX, CFIX, and CDZM against which the increase in gonococcal resistance had been rather modest among the cephems. In 2001, the highest MIC for CFIX against clinical isolates exceeded the attained plasma concentration (Fig. 4).

For extensively used antimicrobial agents, the increased frequency of resistant organisms among gonococcal clinical isolates is known to accelerate if the MIC exceeds the attained plasma concentration. In Japan, there has been no further increase in the MICs of PCG and ABPC against gonococci despite the rapid increase in isolates resistant to new quinolone or cephems in the 1990s. PCG and ABPC use decreased before the advent of PPNG in Japan. In fact, a decrease, rather than a progressive
increase, in the MICs of these antimicrobial agents, which are not much used in Japan, has been noted (Fig. 4), thus indicating the possibility of back mutation in gonococcal chromosomal resistance.

SPCM-resistant gonococcal strains have existed for many decades, and the MIC for this antibiotic increases substantially via one-point gene mutations, yet the frequency with which such resistant strains has been isolated has not increased. The reason for this seems to be that few organisms survive after exposure to SPCM because eradication of infectant gonococci occurs following single-dose therapy with this antibiotic. The superiority of single-dose therapy is obvious even from these experiences. SPCM therapy is not effective in the treatment of chlamydial infection. The MICs of the new quinolones that were frequently prescribed in Japan against gonococci have increased rapidly. With these new quinolones, even parenteral administration yields plasma concentrations that are not appreciably different from those noted after oral administration; hence these new drugs have already become ineffective against gonococci. A considerable percentage of cephem-resistant strains have manifested an increased resistance to multiple classes of drugs, including the new quinolones. CTRX has an exceptionally long plasma elimination half-life as a cephem antibiotic and its MIC is approximately 0.25μg/ml against those gonococcal isolates obtained in 2000. Single-dose therapy with this cephem antibiotic will continue to be valid for some time before its MIC exceeds the level of approximately 20μg/ml. Somewhat illogically, however, its use in the treatment of gonococcal infection and urethritis is still not covered by the national health insurance system in Japan.

The MIC for gonococci of oral CFIX has been increasing and is now approaching the plasma concentration attained with a single 100-mg oral dose approved for insurance coverage. As a result, a failure in therapy has occurred. The Centers for Disease Control (CDC) in the United States recommend single-dose therapy with oral CFIX at 400mg. It is merely a matter of time before a failure to achieve eradication occurs even with this dosage regimen. Under the national universal health insurance system in Japan, resistant gonococci that cannot be eradicated with usual doses of virtually all oral antimicrobial drugs have already emerged and SPCM is now not sufficiently effective against pharyngeal gonococci. In the treatment of gonorrhea, there can be no supreme manual for accomplishing a 100% eradication of the pathogen; thus the timely selection of drugs that are appropriate for the MICs of the infecting organisms in individual cases is required.11)

REFERENCES
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