

Original Article

Co-infection rate of chlamydial urethritis in patients with gonorrhoea in Hong Kong

香港衣原體尿道炎在淋病患者的共同感染率

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Background: Both gonorrhoea and chlamydia urethritis present with dysuria and discharge. It is difficult to differentiate by history and clinical examination alone. Empirical treatment may induce drug resistance whereas complications and the spread of infections may be increased if treatment is started only after the availability of gonococcal culture and chlamydia polymerase chain reaction (PCR) results that take around few weeks. A study to determine the co-infection rate will help to streamline the treatment strategy. **Objectives:** The objectives are to determine (1) the co-infection rate of chlamydia among patients with gonorrhoea and (2) their independent risk factors. **Methods:** All available patients' records who attended the Social Hygiene Clinics of the Department of Health, Hong Kong with urogenital (urethral/cervical) smear done during July 2005 to June 2008 were reviewed. For patients having positive *N. gonorrhoeae* cultures, concomitant chlamydia PCR results were reviewed to determine the co-infection rate. **Results:** The chlamydia co-infection rate with gonorrhoea was 22.2% (95% CI=20.7%-23.7%) in which female, younger age (≤ 25 years) and lack of condom use were the independent risk factors of co-infection. **Conclusions:** Using a simple and cost-effective diagnostic tool of Gram stain and microscopy together with the knowledge of the co-infection rate of chlamydia among gonorrhoea patients in this retrospective study, empirical treatment should be considered to cover both gonococcal and chlamydial urethritis particularly in high-risk groups such as female patients, young age groups and those not using a condom.

背景：淋病和衣原體尿道炎都會出現排尿困難和尿道分泌物，這是很難從病歷和臨床檢查去區分的。憑經驗治療可能會增加耐藥性，但淋球菌培養和衣原體聚合酶鏈反應結果大約需時幾個星期，若證實後才開始治療可能會增加併發症和傳播感染的風險。研究以確定共同的感染率可能有助於簡化治療的策略。**目標：**目標是去確定（一）衣原體在淋病患者的共感染率和（二）他們的獨立風險因素。**方法：**將所有在 2005 年 7 月至 2008 年 6 月到社會衛生科診所求診而可用的病人病歷及有做泌尿生殖系統（尿道/宮頸）抹片檢查的，進行了審查。對於那些淋病菌培養顯示陽性結果的記錄，伴隨有衣原體聚合酶鏈反應結果進行了審查，以確定其共同感染率。**結果：**衣原體與淋病的共同感染率為 22.2%（95% CI=20.7%-23.7%），其中女性，年輕（ ≤ 25 歲），而不使用安全

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套的，都是共同感染的獨立危險因素。**結論：**使用一個簡單的和具成本效益的診斷工具如革蘭氏染色和顯微鏡及這項回顧性研究中淋病患者和衣原體的共同感染率的知識，在特別高風險的群體，如女性患者，年輕人和那些不使用避孕套的，都是值得考慮給予憑經驗性治療去覆蓋淋球菌和衣原體尿道炎。

Keywords: Chlamydial urethritis, co-infection rate, gonorrhoea

關鍵詞：衣原體尿道炎，共同感染率，淋病

Introduction

Urethritis refers to an inflammation of the anterior urethra and is one of the commonest sexually transmitted infections (STIs) in Hong Kong. It gives rise to not only symptoms that require treatment but also leads to serious complications such as pelvic inflammatory disease, epididymo-orchitis, urethral stricture, prostatitis and even infertility if not treated properly. It can be broadly classified into gonococcal urethritis (GC) and non-gonococcal urethritis (NGU). Non-specific genital infection (NSGI) is the more preferred term in females as the vagina and cervix are the common sites for genital infections in addition to the urethra.

Chlamydia trachomatis has been well established as a pathogen of NGU/NSGI ranging from 15% to 60%,¹⁻⁵ followed by *Ureaplasma urealyticum*,^{6,7} and *Mycoplasma genitalium*.⁸ Herpes simplex virus, *Neisseria meningitides* and *Candida* species are rarely reported.¹ Moreover, no organism can be detected in approximately 20-30% NGU/NSGI patients (Table 1).¹

The Social Hygiene Service is responsible for treating STIs in the public sector in Hong Kong. A significant amount of new Social Hygiene Clinic attendees have urethritis. During the years from 2005 to 2008, NGU/NSGI was the most common STI among the new cases attending Social Hygiene Clinics in Hong Kong, while GC was ranked the third (Table 2).⁹

Both gonorrhoea and chlamydia infection can present with urethral or vaginal discharge and

dysuria. In the Social Hygiene Clinics, the diagnosis of gonococcal urethritis is reached by demonstrating the presence of polymorphs with Gram-negative intracellular diplococci in urethral/cervical smear. This procedure takes less than ten minutes by experienced nursing staff. The specimen is also sent to Public Health Laboratory Centre (PHLC) in Hong Kong for confirmation by culture in modified Thayer-Martin medium.

For chlamydia urethritis, the smear is sent to PHLC for polymerase chain reaction (PCR) and the result is available after two to three weeks. Treatment for chlamydia infection is usually given only when the results of chlamydia PCR from PHLC are positive. This time lapse compounded by patients defaulting follow-up may lead to delay or missed treatment. For cases of gonorrhoea who are co-infected with chlamydia, this may lead to complications as well as enhancing the spread of chlamydial infection, posing a public health concern.

Table 1. Aetiology of NGU/NSGI

Infectious organisms	Proportion (%)
<i>Chlamydia trachomatis</i>	15-60% ¹⁻⁵
<i>Ureaplasma urealyticum</i>	10-40% ⁶⁻⁷
<i>Mycoplasma genitalium</i>	14-33% ⁸
<i>Trichomonas vaginalis</i>	1-17% ¹
<i>Candida</i> species, herpes simplex virus, bacterial vaginosis, <i>Neisseria meningitides</i> and others	<10% ¹
No organisms identified	20-30% ¹

NGU: non-gonococcal urethritis; NSGI: non-specific genital infection

Table 2. The number and percentage of new cases of NGU/NSGI and GC in relation to new STI diagnoses in Social Hygiene Clinics in Hong Kong

Year	2005	2006	2007	2008
NGU/NSGI	9298 (50.4%)	8314 (50.1%)	6761 (47.3%)	6518 (47.0%)
GC	1748 (9.5%)	1595 (9.6%)	1481 (10.4%)	1423 (10.3%)
Total new diagnoses	18,436	16,588	14,305	13,867

NGU: non-gonococcal urethritis; NSGI: non-specific genital infection; GC: gonococcal urethritis; STI: sexually transmitted infection

The aims of this study are to reveal the chlamydia co-infection rate among patients with gonorrhoea and any associated risk factors in Hong Kong.

Methodology

Definition of *Neisseria gonorrhoeae* infection

The preliminary diagnosis of gonococcal urethritis was made when Gram-negative intracellular diplococci were found on microscopy and the definitive diagnosis of gonococcal urethritis was confirmed when the urethral smear in male patients and urethral or cervical smears in female patients showed a positive culture in the modified Thayer-Martin medium culture plate which was kept in a carbon dioxide-enriched environment for 48 hours before transport.

Definition of chlamydia trachomatis infection

The nucleic acid amplification test, Amplicor[®], was used in the Social Hygiene Clinics for detecting chlamydia urogenital infection. The diagnosis was confirmed if chlamydia PCR by Amplicor[®] test was positive from the urethral smear in male patients and cervical smears in female patients.

Patients and data sources – inclusions and exclusions

The study period was from July 2005 to June 2008 and was performed in all the eight Social Hygiene Clinics. All available records with a positive culture of *N. gonorrhoeae* were reviewed for chlamydial co-infection. Patients were excluded from the study if the chlamydia PCR was not simultaneously performed with the *N. gonorrhoeae* culture.

Statistical analysis

The data were entered and stored by using SPSS version 15 in Window. The co-infection rate of chlamydia among patients with gonococcal urethritis patients was calculated. Univariate analysis for the individual risk factors was performed with Pearson's Chi-square test or Fisher's Exact test, whichever was suitable for nominal variable and an independent *t* test was used for comparing continuous variable. Independent risk factors for co-infection of chlamydia among gonococcal urethritis patients were evaluated by using the multivariate logistic regression model. The odds ratio of the independent risks factors was also calculated if applicable. A *p* value <0.05% was determined statistically significant.

Results

Demographic data and sexual behaviour

There were a total of 68,709 microscopic examinations done for gonorrhoea during the three-year study period in all the Social Hygiene Clinics of Hong Kong. Three thousand two hundred and twenty-one (5.7%) smears were found to have positive culture for *N. gonorrhoeae*. In addition, 1,156 patients' records were excluded from the study as the chlamydia PCR were not done simultaneously with the *N. gonorrhoeae* culture. Finally, 2,765 patients' records were reviewed and analysed. The mean age of patients was 38.1 years, ranging from 13 to 91 years and 2,440 (88.2%) patients were male while 325 (11.8%) were female. The mean age for male patients was 38.6 years and the mean age for female patients was 34.6 years.

Heterosexual behaviour was practised by 99.4% of the patients, followed by homosexual practice (0.5%) and bisexual practice (0.1%). In seventy-one patients' records, the sexual behaviour was not documented. Concerning the sexual partners of male patients, most of them were female commercial sex workers (90.9%), followed by girlfriends (6.8%), wives (1.6%) and boyfriends for those who were homosexual or bisexual (0.6%). The sexual partners of female patients were as follows: boyfriend 48.6%; husband 41.0%; male commercial sex worker or "one-night-stand" 9.8%. The sexual partners were not disclosed in 78 records.

Co-infection rate of chlamydia trachomatis in patients with gonorrhoea

A total of 2,765 patients' records that were confirmed with gonococcal urethritis by positive culture were reviewed and analysed. In 22.2% (95% CI=20.7%-23.7%) of the patients, there was concomitant chlamydia and gonococcal infection. The co-infection rate was 20.5% and 35.7% for male and female patients respectively. The Pearson's chi-square test was used to compare the difference which was found to be statistically significant ($p < 0.001$). The crude odds ratio was 2.16 (95% CI=1.69-2.77). The results suggested that female patients had a higher chance of co-infection with chlamydia and gonorrhoea (Table 3).

Risk factors for co-infection

Apart from the gender difference, we also investigated any other risk factors associated with co-infection. Younger patients were more often co-infected with gonorrhoea and chlamydia. The mean age of patients with gonorrhoea with and without chlamydial co-infection was 36.6 years and 38.6 years respectively. The difference was statistically significant ($p = 0.003$) and the mean difference was -1.98 (95% CI=-3.29 to -0.66).

When we classified the study population into the younger age group (age less than or equal to 25 years) and older age group (age greater than 25 years), we found that the younger age group with gonococcal urethritis were more likely to have co-infection with chlamydia. The percentage of patients in the younger and older age group having chlamydia co-infection with gonorrhoea was 28.6% and 20.3% respectively. The difference was compared by Pearson's chi-square test and found to be statistically significant ($p < 0.001$). The crude odds ratio was 1.57 (95% CI=1.29-1.92). Therefore, the younger age group had more co-infection of chlamydia among patients with gonorrhoea (Table 4).

Condom use is a recognised factor in the prevention of the spread of sexually transmitted infections. In this study, we also noted that unprotected sexual intercourse increased the chance of co-infection with gonorrhoea and chlamydia. Among these patients, 461 patients did not use condoms whereas 109 patients did. The difference was statistically significant ($p = 0.008$). The crude odds ratio was 1.37 (95% CI=1.09-1.73) (Table 5).

Independent risk factors for co-infection of chlamydia and gonococcal urethritis were evaluated by using the multivariate logistic regression model. It supported the findings that female sex, young age group with age less than or equal to 25 years and not using condom during coitus were the independent risk factors for co-infection of gonorrhoea and chlamydia. The adjusted odds ratios for female sex, young age group (≤ 25 years) and not using condom was 2.04 (95% CI=1.57-2.64), 1.49 (95% CI=1.21-1.84) and 1.35 (95% CI=1.07-1.71) respectively. Table 6 is the overall summary.

Discussion

Urethritis is the commonest presentation among patients attending the Social Hygiene Clinics in

the public sector in Hong Kong. In the present study, the overall co-infection rate of chlamydial urethritis among patients with gonorrhoea was 22.2%. When the co-infection rate analysis was disaggregated by gender, it was 35.7% in females and 20.5% in males. The percentage of female patients with co-infection of gonorrhoea and chlamydia was significantly higher than male patients in this study which is comparable to other studies.¹⁰⁻¹⁴ In a United Kingdom (UK) study done in Newcastle,¹⁰ the co-infection rate in females was 36.6% and was only 8% in males. In another UK study done in Glasgow, the co-infection rate was 48% in females and 22% in males.¹¹ A London study revealed that the co-infection of chlamydia

in female gonococcal urethritis patients was 38.5% and it was 24.2% in the male patients.¹² In a similar study, the overall prevalence of chlamydia co-infection among patients with gonorrhoea was shown to be 10.7%. However, the co-infection rate was found to be much higher in females (41.4%) than in males (3.3%).¹³ In a United States (US) study,¹⁴ the co-infection rate in females and males were 42% and 20% respectively which was similar to our study.

Although the percentage of co-infection among different studies was not the same, most of them reported a similar rate of about 30% to 48% in females and 10% to 25% in males. This implies

Table 3. Co-infection rate of chlamydia in patients with gonorrhoea

	CT +ve*	CT -ve	Total no. of patients (%)
No. of female patients (%)	116 (35.7%)	209 (64.3%)	325 (100%)
No. of male patients (%)	499 (20.5%)	1941 (79.5%)	2440 (100%)
Total	615 (22.2%)	2150 (78.8%)	2765 (100%)

*(χ^2 test: $p < 0.001$ /OR=2.16, 95% CI=1.69-2.77)

Table 4. Relationship between younger patients and co-infection of GC & CT

	CT +ve*	CT -ve	Total no. of patients (%)
No. of patients (Age ≤ 25) (%)	186 (28.6%)	465 (71.4%)	651 (100%)
No. of patients (Age > 25) (%)	429 (20.3%)	1685 (79.7%)	2114 (100%)
Total	615 (22.2%)	2150 (78.8%)	2765 (100%)

*(χ^2 test: $p < 0.001$ /OR=1.57, 95% CI=1.29-1.92)

Table 5. Relationship between condom usage and co-infection of GC & CT

	CT +ve*	CT -ve	Total no. of patients (%)
No. of patients not using condom (%)	461 (24.6%)	1411 (75.4%)	1872 (100%)
No. of patients using condom (%)	109 (19.2%)	458 (80.8%)	567 (100%)
Total	570 (23.4%)	1869 (76.6%)	2439 (100%)

*(χ^2 test: $p = 0.008$ /OR=1.37, 95% CI=1.09-1.73)

Table 6. Independent risk factors for co-infection of CT in GC patients

	% Co-infection (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Female sex	35.7% (30.5%-40.9%)	2.16 (1.69-2.77)	2.04 (1.57-2.64)
Age ≤ 25	28.6% (25.1%-32.1%)	1.57 (1.29-1.92)	1.49 (1.21-1.84)
Not using condom	24.6% (22.6%-26.6%)	1.37 (1.09-1.73)	1.35 (1.07-1.71)

that female patients with gonorrhoea were much more likely to be co-infected with chlamydia in the urogenital tract than males. The figures quoted in other studies are comparable with this study (Table 7).

More studies reported that the co-infection rate of chlamydia in women infected with gonorrhoea was relatively high, although their male partners were not studied. Moreover, these studies showed that different clinical settings might have different co-infection rates. In Asia, a study done in a general hospital in Singapore showed that the co-infection of chlamydia in women with gonorrhoea was 27%.¹⁵ One study done for women who had STI screening in an urban area emergency department in New York showed that the co-infection rate was 16%.¹⁶ A similar finding of a co-infection rate of 13.6% in female patients was noted in a study done in an emergency department at Oakland.¹⁷

Another study done in the family planning clinics showed that the co-infection rate in females was 39.1%.¹⁸ The percentage of cases of co-infection was much higher in venereology clinics

which could be up to 52% in a New Zealand study.¹⁹ This is probably due to the difference in the characteristic of attendees; patients attending venereology clinics are more likely to have STIs. Therefore, the incidence of co-infection is higher in the venereology clinics (Table 8).

There are several reasons to explain why females are more susceptible to co-infection. Firstly, asymptomatic gonococcal and chlamydial infections are more common in women than in men. In the present study, less than 1% (19/2440) of gonococcal infected male patients were asymptomatic whereas 27.86% (90/323) of female patients were asymptomatic. As the infection is asymptomatic, it will remain undetected and untreated and will result in dual infection if another STI is acquired. Secondly, STI pathogens that produce a discharge or reside in genital secretions like gonococci and chlamydia are generally more efficiently transmitted from male-to-female than via the female-to-male route.^{20,21} It may be partly due to a more extended contact with the pathogens after sexual exposure among women with infected male partners than among men with infected female partners. If the male

Table 7. Summary of published studies on the co-infection rate of GC & CT

Articles	Female - co-infection rate	Male - co-infection rate
Present study	35.7%	20.5%
Watson ¹⁰	36.6%	8.0%
Hijazi et al ¹¹	48.0%	20.0%
Creighton et al ¹²	38.5%	24.2%
Dragovic et al ¹³	41.4%	3.3%
Lyss et al ¹⁴	42.0%	20.0%

Table 8. Summary of co-infection rate of CT & GC in different clinical settings

Articles	Clinical settings	CT & GC co-infection rate (female)
Lim et al ¹⁵	General Hospital	27.0%
Wiest et al ¹⁶	Emergency Department	16.0%
Levitt et al ¹⁷	Emergency Department	13.6%
Gershman and Barrow ¹⁸	Family Planning Clinic	39.1%
Willmott et al ¹⁹	Venereology Clinic	52.0%
Present study	Venereology Clinic	35.7%

partner has the STI pathogens, infected semen is deposited and remains in the vagina after intercourse. In contrast, if the female partner is infected, the male's exposure to the pathogen is largely limited to the duration of coitus. Lastly, iron which is rich in menstruation blood may promote the growth of gonococci.

Our study also found that younger age was an independent risk factor associated with a higher rate of co-infection with gonococci and chlamydia which is comparable with other studies.¹¹⁻¹³ Similarly, a UK study reviewed that age less than 25 years was the predictive risk factor of co-infection.²² There are several reasons why the younger age or adolescence are at higher risk for being co-infected with gonorrhoea and chlamydia. First of all, young people are more likely to engage in high-risk sexual practices. They are more likely to have unprotected intercourse and engage in substance abuse.²³ Furthermore, they may less frequently seek health care counselling.²⁴ Adolescents are also likely to have more sexual partners and networks than older patients.²⁵ All these high-risk sexual behaviours increase their susceptibility of co-infection with gonorrhoea and chlamydia.

Secondly, biological changes, particularly in adolescent females, also increase the risk of having co-infection. During puberty, oestrogen exposure causes the vaginal lining to thicken and be replaced by squamous epithelium. Although cervical columnar epithelium in young women eventually recedes completely and is replaced by squamous epithelium, the replacement is gradual and extends into early adulthood. Therefore some columnar epithelium may persist at the cervix which is referred to as ectopy. This ectopy in young women significantly increases their vulnerability to STIs.²⁶

Last but not least, not using a condom is an independent risk factor for co-infection. It is well known that condom as a barrier effectively decreases the infection rate of STIs. In our study,

not using condoms significantly increased the risk of co-infection with gonorrhoea and chlamydia. It is mainly due to the contact of mucosal surface of genitalia during coitus. Therefore, condom usage can prevent the genital mucosal contact and so decreases the opportunity of bacterial entry. In other words, condom usage decreases the co-infection rate of chlamydia in patients with gonorrhoea.

Conclusion

Gonorrhoea and chlamydial urethritis commonly present with dysuria and discharge. It is difficult to differentiate between them by history and clinical examination alone. The overall co-infection rate of gonorrhoea and chlamydia in this study was 22.2%. While the co-infection rate was 35.7% for females, it was only 20.5% for males. Thus, females were at a higher risk of co-infection with gonorrhoea and chlamydia. Furthermore, age less than 25 years and not using condom were also found to be independent risk factors for co-infection. It is worthwhile considering empirical treatment to cover both gonococcal and chlamydial urethritis in high-risk groups including female patients, young age and those who do not use condoms.

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