公務出國或赴大陸地區報告提要

出國或赴大陸地區報告名稱：參加 2015 年歐洲臨床微生物學和傳染病學會

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內容摘要：
一、 出國目的:
歐洲臨床微生物學和傳染病學會(European Society of Clinical Microbiology and Infectious Diseases, 以下簡稱ESCMID)自1990年起每年定期舉辦學術會議，讓歐洲各個國家學者們可以分享研究的成果以及相互討論。此次與會亦是希望能借發表研究報告的機會與國外學者相互學習，加強國內感染疾病的研 究。

二、 過程:
於 會 議 期 間 ( 4 / 2 5 ~ 4 / 2 8 ) 每 天 早 上 進 行 與 專 家 會 面 ，可 向 專 家 發 問 ，他 們 會 親 自 回 答 問 題，尤其是臨床上實際面對的問題，他們會盡他們所能回答；今年特別加強指導抗生素給藥方式，內容包含廣泛 ：感染控制、實驗室檢查、抗生素治療、疫苗研發、抗生素抗藥性、公共衛生。今年特別強調電子壁 報，每天均有不同的專家針對細菌及真菌不同的主題發表。我的壁報展示在2015/4/26下午的泌尿生殖 和性傳播感染時段發表。

三、 心得及建議:
今年參加歐洲臨床微生物學和傳染病學會年會的專家學者特別多，大約超過1萬多人；除了歐洲各國學者，美洲、亞洲、非洲學者也不少。每天早上參加與專家會面時，可向專家發問臨床上實際面 對的問題。他們會盡他們所能回答，就像師傅和學徒，師傅教導，徒弟功力可立刻加倍。建議本院應 該分配更多的同事組隊參加ECCMID，以學習更多新科技發展。
附件一、照片：

圖一：和壁報於會場合影
Changes in the six most common sequence types of *Neisseria gonorrhoeae*, including ST4378, identified by surveillance of antimicrobial resistance in northern Taiwan from 2006 to 2013

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**KEYWORDS**
antimicrobial resistance; gonorrhea; homosexuals; *Neisseria gonorrhoeae*-multi Antigen Sequence Typing; sequence types

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**Background:** There has been no longitudinal study of drug susceptibility in *Neisseria gonorrhoeae* in Taiwan since 2006.

**Methods:** We collected 1090 gonococcal isolates from Taipei City Hospital, Taiwan from April 2006 to August 2013. We used a disk diffusion assay to determine the susceptibility to five antibiotics and an E-test to determine the minimum inhibitory concentrations for cefixime and ceftriaxone in isolates with resistance. *Neisseria gonorrhoeae*-multi Antigen Sequence Typing and DNA sequencing of the *por* and *tbpB* genes were used to identify sequence types.

**Results:** Among the 1090 isolates, the resistances to penicillin, ciprofloxacin, cefpodoxime, cefixime, and ceftriaxone were 61.01%, 83.39%, 9.63%, 6.70%, and 2.39%, respectively. The highest minimum inhibitory concentrations of cefixime and ceftriaxone were 0.19 mg/L and 0.50 mg/L, respectively. There were 327 sequence types. The four most common sequence types in homosexuals were ST4378, ST359, ST4654, and ST547; the two most common sequence types in heterosexuals were ST421 and ST419. Each of these sequence types had more than 25
Gonorrhea is a sexually transmitted infection caused by Neisseria gonorrhoeae. Along with chlamydia, syphilis, and trichomoniasis, gonorrhea is among the most common sexually transmitted infections and is a significant public health problem worldwide. Research in the late 1990s indicated that gonorrhea and genital ulcer diseases can increase the spread of sexually transmitted HIV. Recent research has continued to focus on the role of gonorrhea in the spread of HIV. In particular, a study in 2005 indicated that the rate of HIV transmission in patients with gonorrhea can be up to five times greater than in those without gonorrhea.

Gonorrhea can also increase the risk of developing other acute infections and complications. An effective treatment for gonorrhea is urgently needed, but treatment options are diminishing because N. gonorrhoeae has developed resistance to several commonly used antimicrobial drugs, such as the sulfonamides, penicillin, tetracyclines, and quinolones.

The World Health Organization estimated in 1999 that approximately 340 million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis occur every year and that most new cases occur in developing countries, including Southeast Asia, sub-Saharan Africa, Latin America, and the Caribbean. The diagnosis and treatment of gonorrhea can be problematic because N. gonorrhoeae is difficult to culture and has developed resistance to many oral antibiotics. This has led to the inadequate control of gonorrhea in many parts of the world.

Surveillance of antimicrobial resistance in N. gonorrhoeae can help to identify new resistant strains and changes in the pattern of resistance, ultimately assisting in disease control. Current treatment guidelines recommend the use of single-dose injectable or oral third-generation cephalosporin (ceftriaxone or cefixime). The emergence and spread of ceftriaxone-resistant and multidrug-resistant N. gonorrhoeae strains is a worrying trend, indicating the need for careful monitoring and investigation. Thus clinical laboratories must remain alert for the early detection of resistant strains so they can implement more appropriate control strategies. The treatment strategy and prevention of gonorrhea require regular review and revision.

The Gonococcal Resistance to Antimicrobials Surveillance Program of the Health Protection Agency reported in 2010 that 17.4% of N. gonorrhoeae isolates in the UK had cefixime minimum inhibitory concentration (MIC) values of ≥0.125 mg/L and that 6.3% of isolates had cefixime MIC values ≥0.25 mg/L. Thus the Health Protection Agency announced that cefixime was no longer a suitable first-line treatment for gonorrhea as the percentage of N. gonorrhoeae isolates with a cefixime MIC ≥0.25 mg/L has exceeded 5%.

There were 2265 cases of gonorrhea in Taiwan in 2010 and the annual incidence was 9.79 per 100,000 population, higher than in 2009 (9.26 per 100,000) and the highest reported incidence since 2006. In addition, disk diffusion tests indicated that 9% of gonococci were resistant to cefixime in 2003, but that resistance to cefixime and cefodoxime (another third-generation cephalosporin) were 16.4% and 21.2%, respectively, during 2006–2007. In 2006, a new surveillance program, the Gonococci-National Isolate Collection for Epidemiology (G-NICE), began the collection of gonococcal isolates from hospitals and clinics to monitor changes in drug resistance and the molecular epidemiology of gonococci in Taiwan. The G-NICE presented data for 2009 and 2010 in the Taiwan Epidemiology Bulletin of 2010 and 2011. However, there has been no longitudinal study of gonococcal resistance following the establishment of G-NICE in 2006.

The results presented here provide the most recent information on the emergence and transmission of drug-resistant gonococci in high-risk sexual networks in Taiwan.

Materials and methods

Collection of gonococcal isolates

We collected 1111 gonococcal isolates at our Kun-Ming Branch of Taipei City Hospital, Taiwan from April 2006 to August 2013. Our Kun-Ming Branch is a specialized clinic for sexually transmitted diseases in Taipei City. Twelve isolates had incomplete data and nine isolates could not be cultured for definitive identification. Thus 1090 isolates were used for analysis.

According to the Taiwan Centers for Disease Control (CDC) annual report, there were about 1500 confirmed cases of gonorrhea per year in Taiwan after 2003 and about 500 of these cases were from Taipei City (23% of all cases in Taiwan). Our hospital in Taipei City collected about 80–200 isolates of gonorrhea each year from 2006 to 2012.
Culture conditions

Gonococcal isolates were inoculated on chocolate agar and incubated at 37°C for 16–18 hours. Fresh colonies were added to Mueller-Hinton solutions and the turbidity was adjusted to 0.5–0.6 McFarland standards with a nephelometer (BD Diagnostic Systems, Franklin Lakes, NJ, USA).

Tests for drug susceptibility

The antimicrobial susceptibilities to penicillin, ciprofloxacin, cefixime, cefpodoxime, and ceftriaxone were analyzed using the disk diffusion method. Isolates that exhibited resistance to cefixime or ceftriaxone by this assay were further evaluated by the Epsilometer test (E-test) for the determination of MIC values. Drug susceptibility was determined by the size of the inhibition zone using the BIOMIC V3 assay (Giles Scientific, Santa Barbara, CA, USA). The results were interpreted according to the Clinical and Laboratory Standards Institute guidelines for N. gonorrhoeae.12 Isolates with MICs of ≤0.25 mg/L were considered susceptible.

Extraction of gonococcus DNA

DNA was extracted with the MasterPure Yeast DNA Purification Kit (Epicentre Biotechnologies, Madison, WI, USA). Gonococcal isolates were cultured on chocolate agar at 37°C for 16–18 hours. The bacteria were then inoculated into 100 μL of phosphate-buffered saline and mixed with 250 μL of a cell lysis solution. After the addition of 150 μL of a protein precipitation solution, the mixture was vortexed for 10 s and centrifuged (12,000×g, 10 minutes). To facilitate DNA precipitation, 500 μL of 100% isopropanol was added to the supernatant. The precipitated DNA was rinsed with 70% alcohol and 100 μL of a hydration solution was added to dissolve the extracted DNA. The concentration of the extracted DNA was determined by spectrophotometry at 260 nm. The DNA was stored at −20°C prior to further study.

Neisseria gonorrhoeae-multi Antigen Sequence Typing

The Neisseria gonorrhoeae-multi Antigen Sequence Typing (NG-MAST) molecular typing of gonococcal isolates was conducted by sequencing the internal fragments of two highly polymorphic loci, por and tbpB.13 The por gene (750 bp) was amplified by the polymerase chain reaction (PCR) using the forward primer 5'-CAA GAA GAC GAC TTC GGC AA-3' and the reverse primer 5'-CCG ACA ACC ACT TGG T-3'. The tbpB gene (600 bp) was amplified by PCR using the forward primer 5'-CGT TGT CGG CCG GGC AAC-3' and the reverse primer 5'-TTT ATC GGT GCC GCG CTC GCC TCG-3'. The PCR conditions have been reported previously.14 The DNA sequences of isolated gonococci were analyzed using BioNumerics Version 5.0 (Applied Maths NV, Sint-Martens-Latem, Belgium). The sequence data of each por and tbpB gene were uploaded to the NG-MAST website (www.ng-mast.net) to obtain the allele number and the sequence type (ST).

Statistical analysis

We use the Chi-square test to assess the relationships between STs and the clinical characteristics of the infected patients, including sexual orientation, HIV status, and syphilis status; p = 0.001 was considered statistically significant (Table 1). SAS Version 9.03 (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analysis.

Results

Drug resistance

In our study, the annual numbers of gonorrhea isolates from 2006 to 2013 were as follows: 74 (2006), 134 (2007), 107 (2008), 120 (2009), 167 (2010), 197 (2011), 179 (2012), and 112 (2013).

We initially tested the drug susceptibility of all 1090 bacterial isolates by the disc diffusion assay. The results indicated that 61.01% of isolates were resistant to penicillin, 83.39% were resistant to ciprofloxacin, 9.63% were resistant to cefpodoxime, 6.70% were resistant to cefixime, and 2.39% were resistant to ceftriaxone. The E-test results for the resistant strains showed that the ceftriaxone MICs of all the tested isolates were ≤0.50 mg/L (range 0.016–0.50 mg/L); the cefixime MICs were 0.125 mg/L in 14 isolates and 0.19 mg/L in three isolates; and the other 109 tested isolates had decreased susceptibility to ceftriaxone (MIC ≥0.125 mg/L, range 0.125–0.50 mg/L). The MIC90 values of ceftriaxone and cefixime were 0.047 mg/L and 0.032 mg/L, respectively, and the MIC90 values of ceftriaxone and cefixime were 0.25 mg/L and 0.094 mg/L, respectively.

Fig. 1 shows the susceptibility of the isolates to the five different antibiotics annual from 2006 to 2013. Ceftriaxone susceptibility remained the highest and nearly 100% of isolates were susceptible to this drug in most years, although the susceptibility dropped in 2010 (91.02%) and 2013 (92.86%). The isolates had similar changes in susceptibility to cefixime and cefpodoxime over the study period, with minima in 2007 (79.85% and 74.63%) and maxima in 2013 (100% for both). Penicillin and ciprofloxacin susceptibilities were low throughout the study period. Penicillin susceptibility was 0% in 2007, 2008, and 2009 and ciprofloxacin susceptibility ranged from 20.36% (2010) to 2.68% (2013). Previous studies of gonorrhea in Taiwan have reported similar resistance patterns for these two antibiotics.15,16

NG-MAST STs of isolates

Fig. 2 shows the antibiotic susceptibility of the 27 most common STs during the study period. Among the 1090 isolates, there were 327 STs. There was one isolate each for 212 STs, two isolates each for 35 STs, and three to 58 isolates each for the other 80 STs. Twenty-seven STs (ST4378, ST421, ST359, ST419, ST4654, ST547, ST225, ST7784, ST2992, new, ST2253, ST1614, ST2178, ST2180, ST2175, ST5809, ST835, ST2194, ST3680, ST5232, ST4919, ST2179, ST3684, ST5877, ST4988, ST2422, and ST3081) accounted...
for >50% of the total. The six most common STs (ST4378, ST421, ST359, ST419, ST4654, ST547) each had >25 isolates. The most common sequence type in our study was ST4378 and it accounted for 5.32% (58 isolates) of the total (Fig. 2).

Of the STs shown in Fig. 2, 0–25% of the isolates were susceptible to penicillin. For ciprofloxacin, the percentage of susceptibility in most STs was 0–33%, but this was 89.8% in ST359 and 62.07% in ST547. Most STs were susceptible to cefixime and ceftriaxone, but four STs had low susceptibility to cefixime (ST2253, 26.32%; ST2180, 37.50%; ST835, 42.86%; and ST3680, 64.29%) and two STs had low susceptibility to ceftriaxone (ST2253, 73.68%; ST3680, 71.43%). Notably, ST2253 and ST3680 had a high resistance to cefixime and ceftriaxone. Most STs were susceptible to cefpodoxime (range 78.57–100%), but three of 16 isolates of ST2180 (18.75%), three of 14 isolates of ST385 (21.43%), and three of 19 isolates of ST2253 (15.79%) had low susceptibilities to cefpodoxime.

**Antibiotic susceptibility patterns of drug-resistant gonococci**

Based on the results of the disc diffusion assays, we classified the 1090 isolates into six drug susceptibility patterns, with Type 1 having the lowest susceptibility and Type 6 having the highest susceptibility. The antibiotic susceptibility patterns were further simplified into three groups: those with low (Types 1 and 2), intermediate (Types 3 and 4), and high (Types 5 and 6) susceptibility.

Most isolates of the 21 most common STs had intermediate to low resistance to ceftriaxone, cefixime, and cefpodoxime. Some isolates of ST4378, ST2253, ST2180, ST385, ST419, and ST2194 showed high susceptibility (Fig. 3). Isolates of most STs were susceptible to cefixime and ceftriaxone, but only ST2253, ST2180, ST385, and ST3680 showed higher resistance to these two drugs (Figs. 2 and 3).

Finally, we examined the distribution of different STs in homosexuals and heterosexuals (Fig. 4). The results indicated that ST4378, ST359, ST4654, ST547, ST2992, ST2253, ST1614, and ST5232 were mainly from male homosexual patients, but ST421, ST419, ST225, ST2175, ST2194, and ST2178 were mainly from heterosexual patients. There were distinctly different susceptibility patterns in these two groups. Heterosexual patients (with ST421, ST419, ST225, ST2175, and ST2194) mostly had gonococci with medium resistance (Types 3 or 4), but homosexual patients...
Figure 2. Percentage of susceptible isolates among the 27 most common gonorrhea sequence types from 2006 to 2013.
had isolates with either low (Types 1 or 2) or very high (Type 6) susceptibility.

There were 58 isolates with ST4378. The ceftriaxone MICs of these 58 isolates ranged from <0.016 mg/L to 0.19 mg/L; those <0.25 mg/L were considered susceptible. The cefixime MICs of these isolates ranged from <0.016 mg/L to 0.094 mg/L and <0.25 mg/L were considered susceptible.

**Discussion**

The number of gonorrhea isolates in our study increased from 2006 to 2012. The increasing rate (about 20% each year) was higher than the mean rate (about 0.4% each year) of our population increase in the past 10 years in Taiwan. This means that the increase in cases of gonorrhea was not only due to a natural increase in the population. The incidence rate of gonorrhea was much lower than those of neighboring Asian countries (the annual incidence of *Neisseria gonorrhoeae* in Southeast Asia in 2008 for men was 37.0 per 1000 population and 16.2 per 1000 population for women). Therefore our incidence rate of gonorrhea might be underestimated.

After the establishment of the Taiwan CDC on July 1, 1999, there were increasing numbers of reported sexually transmitted diseases, including syphilis and gonorrhea. Prior to the establishment of the Taiwan CDC, most patients with sexually transmitted diseases sought help from local medical doctors or bought medicine for themselves at pharmacies. Taiwanese citizens have become more educated in recent years and now visit large hospitals for the treatment of severe diseases. These large hospitals are required by the Communicable Disease Prevention Act 2007 to report to the Taiwan CDC as soon as possible. Therefore we can now identify more cases of the disease; in the past, no-one knew about patients with sexually transmitted diseases.

However, the number of isolates in 2013 was much lower than in other years as our data was only collected up to August 2013. We did not have the complete data for the whole of 2013. The results of the G-NICE program indicated a similar trend to our study in that the number of gonorrhea isolates...
isolates in Taiwan increased by 19% from 2009 (519 isolates) to 2010 (644 isolates). The proportion of isolates reported to the CDC also increased from 24.3% (519 isolates, 2137 cases) in 2009 to 28.4% (644 isolates, 2265 cases) in 2010.10 This may indicate that there are an increased number of cases of gonorrhea in Taiwan, more patients seeking medical treatment, or more clinicians reporting cases to the Taiwan CDC. The results of our disk diffusion tests showed that a high proportion of N. gonorrhoeae isolates were resistant to penicillin (97.07%) and ciprofloxacin (87.88%). Susceptibility to ceftriaxone remained the highest and nearly 100% of isolates were susceptible to this drug. According to the Clinical and Laboratory Standards Institute standards, isolates with cefixime and ceftriaxone MICs of \( \leq 0.25 \) mg/L are considered as susceptible. In the G-NICE 2010 program, only one isolate had a ceftriaxone MIC of 0.125 mg/L and no isolate had ceftriaxone MIC >0.25 mg/L; there were 28 isolates (4.35%) with cefixime MICs of \( \geq 0.125 \) mg/L and five isolates (0.78%) had MICs of \( \geq 0.25 \) mg/L.

In our study, none of the N. gonorrhoeae isolates had cefixime MICs of \( \geq 0.25 \) mg/L and the maximum MICs of cefixime and ceftriaxone remained the same in 2009 and 2010 (0.125 mg/L and 0.38 mg/L, respectively). Our results also showed that the highest MICs of cefixime and ceftriaxone were 0.19 mg/L and 0.50 mg/L, respectively. Nearly all these isolates were susceptible based on the Clinical and Laboratory Standards Institute standards (MIC <0.25 mg/L), although the \( M_{\text{MIC}} \) values of cefixime and ceftriaxone (0.25 mg/L and 0.094 mg/L, respectively) in our study were both higher than that reported by the G-NICE study in 2009 (0.064 mg/L for both) and 2010 (cefixime, 0.19 mg/L; ceftriaxone, 0.064 mg/L).9,10 Thus we still recommend oral cefixime and injectable ceftriaxone as first-line drug treatments for gonococcal infections in Taiwan. Our results indicated that gonorrhea isolates had an increasing susceptibility to cefixime and cefpodoxime from 2007 to 2012, possibly because of improving antibiotic stewardship and control in Taiwan.13,19,20 Patients carrying the same ST may belong to the same transmission network. Thus ST421 and ST419 remained the most common STs in 2009 and 2010 (from G-NICE data); these were the second and fourth most common STs in our study, respectively, and were most common in heterosexual patients. These STs peaked in 2010. ST4378 was the most common ST in our study (58 isolates) and there was only one isolate of ST1407. ST4378 is closely related to the globally successful ST1407, which is notorious for its resistance to cefixime and ceftriaxone. In fact, the porB sequence of ST4378 and ST1407 differed by only one nucleotide.21 This emerging ST might have been introduced to Taiwan via homosexual patients and circulated in a high-risk sexual network thereafter. This is an alarming result. We must have more careful follow up to patients with gonorrhea with ST4378 to ensure that they receive the correct antibiotic treatment and to prevent further spread of the infection. Fortunately, all the isolates with ST4378 in our study were sensitive to cefixime and ceftriaxone. Continuous collaborative surveillance at the global level is very important.

Our analysis of changes in STs over time indicated that ST4378, ST359, and ST4654, which are most common in heterosexual patients, appeared after 2009. By contrast, ST547 was also common in homosexual patients, but decreased from 2006 to 2009 (Fig. 5A). This might be because these different STs are from different homosexual sources. Again, this trend should be followed in the coming years and further molecular biological evaluation might be helpful.

ST547 decreased from 2006 to 2009, but ST359 has increased since 2009 (Fig. 5A). ST547 and ST359 were most common in homosexual patients and had similar susceptibility patterns (low resistance). The G-NICE data indicated that ST547 was not among the 13 most common STs in 2009. However, a study by Wong et al22 in 2006 indicated that ST547 was the most common ST in Taiwan and that ST359 was not among the eight most common STs. Therefore it appears that ST359 might have replaced ST547 in Taiwan (Fig. 5A). The low resistance of ST547 might be related to its decrease from 2006 to 2009. It might imply that ST547 could be easily controlled by antibiotics and not cause any further epidemics. The introduction and upsurge of ST359 might be due to its link with other countries, in particular the UK. Moreover, ST547, ST359, and ST225 are three of the seven major genotypes in men who have sex with men in the UK.23 In our study, ST225 was very different and was most common in heterosexuals, increasing from 2006 to 2009, but disappearing after 2012 (Fig. 5B). This trend should be followed in the coming years; the clinical implications of this change require further evaluation. In 2010 there was a maximum number of patients with gonorrhea at our institution, both homosexuals and heterosexuals. Changes in sexual 

Figure 5. (A) Changes in the four most common gonorrhea sequence types among homosexual men from 2006 to 2013. (B) Changes in the three most common gonorrhea sequence types among heterosexuals from 2006 to 2013.
behavior, including more sex parties without the use of condoms may have contributed to this peak.

Previous studies have reported that ST359 and ST547 were two of the seven major genotypes in men who have sex with men in the UK. These results should be considered in the determination of the most appropriate antimicrobial treatment for patients with gonorrhea. At present, we suggest the treatment of gonorrhea with oral cefixime or intramuscular ceftriaxone as a first-line treatment. For homosexual patients with gonorrhea, drug resistance must be considered and an adequate dose and frequency of antimicrobial treatment should be given.

We further analyzed the 21 most prevalent STs in patients of different sexual orientation, with or without HIV, and with or without syphilis (Table 2). ST4378, ST359, ST4654, and ST547 were the most common in homosexual patients and ST421 and ST419 were the most common in heterosexual patients ($p < 0.001$). However, the presence of HIV and syphilis were unrelated to any STs, although our sample sizes were too small for meaningful analysis. In 2009, Bernstein et al. reported a similar result.

There were some limitations in our study. Our isolates were only collected from symptomatic patients. Thus, we cannot make any inferences about the epidemiology of non-genital $N. gonorrhoeae$ infections or asymptomatic urogenital infections. Although our sample size (1090 isolates) was not very small, 212 of the 327 types of STs (64.8%) contained only one isolate. Meaningful analysis of these 212 STs is difficult. Future analysis of more isolates would allow a more complete evaluation of the relationship between different STs and comorbid diseases.

Oral cefixime or ceftriaxone injections remained the first-line drugs for the treatment of gonorrhea from 2006 to 2013 in Taiwan because gonorrhea isolates had low MICs for these two drugs. The abrupt emergence of ST4378 (closely related to the notorious ST1407) since 2009 is a cause for alarm. Changes in sexual behavior without the use of condoms may have contributed to the peak in cases of gonorrhea in 2010. Further molecular epidemiological investigations are crucial.

Conflicts of interest

All authors declare no conflicts of interest.

References

Changes in sequence types of *Neisseria gonorrhoeae*


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