

Review Article

Urogenital *Neisseria gonorrhoeae* infection: the problem of antibiotic resistance and treatment failure

泌尿生殖系統淋病雙球菌感染：抗生素抗藥性和治療失敗的問題

CFY Siu 蕭鳳兒 and CK Kwan 關志強

Gonococcal infection is one of the commonly encountered sexually transmitted diseases. The emergence of antibiotic resistance has remained a challenge for a few decades. The third generation cephalosporins are now the first-line therapy in many regions, however, the reduction of the susceptibility to cephalosporins is likely to emerge and spread. The article summarizes the contemporary treatment recommendations, the current problem of treatment failure with cephalosporins and the report of local data.

淋球菌感染是其中一種常見的性傳染病，其抗生素抗藥性的出現是這數十年間的一大挑戰。第三代頭孢菌素是現今很多地區的第一線治療，但淋球菌對其藥物敏感度的下降，將會有很大的機會發生及散播。本文章將概述當代的治療建議、頭孢菌素現今的治療失敗問題及本地數據報告等。

Keywords: Antibiotic resistance, cephalosporins, *Neisseria gonorrhoeae*, treatment failure

關鍵詞： 抗生素抗藥性，頭孢菌素，淋病雙球菌，治療失敗

Introduction

Neisseria gonorrhoeae is a Gram-negative diplococcus that commonly infects the mucous membrane lined by columnar or cuboidal and

non-cornified epithelial cells. Therefore, it can cause cervicitis, urethritis, proctitis, pelvic inflammatory disease, pharyngitis and conjunctivitis. Chronic pelvic pain, ectopic pregnancy, infertility, stillbirths, prematurity, low birth weight in infants and increased susceptibility to HIV infection are possible sequelae.

Social Hygiene Service, Department of Health, Hong Kong

CFY Siu, FHKAM(Medicine)
CK Kwan, FHKAM(Medicine)

Correspondence to: Dr. CFY Siu

Fanling Integrated Treatment Centre, 6/F, Fanling Health Centre, 2 Pik Fung Road, Fanling, New Territories

Multiple antibiotics had been used for treatment of *N. gonorrhoeae* in the past 60 years. Sulphonamides, penicillins, tetracyclines and fluoroquinolones were the treatment options in the past but are no longer efficacious now. Newer treatment regimes employing relatively newer and more effective drugs including third generation

cephalosporins like cefixime and ceftriaxone, spectinomycin and new generation of macrolides such as azithromycin are more commonly used nowadays. However, we still continue to face the balance between the emerging challenge to maintain antimicrobial effectiveness and gonorrhoea control.

Historical perspective on antimicrobial resistance and treatment recommendations

It was recommended that the ideal antibiotic treatment for gonorrhoea should be a single-dose of antibiotic therapy that will cure a minimum of 95% or more of cases.¹ The Centres for Disease Control and Prevention (CDC) in United States and the World Health Organization (WHO) recommend a change in the treatment regimen when the prevalence of antimicrobial resistance exceeds 5% for a specific antibiotic, while taking into account the prevalence of gonorrhoea in the community, the cost of diagnostic and treatment regimens, and the availability of antimicrobial susceptibility data.² An accepted definition of gonococcal treatment efficacy requires a cure rate of over 95% with a lower boundary of the 95% confidence interval (CI) of at least 90%. More stringent criteria have been proposed that require that the lower boundary of the 95% CI be at least 95%.²

As the gonococcus has developed resistance to antimicrobials including sulphonamides, penicillins, tetracyclines and fluoroquinolones,³ third-generation cephalosporins are now the first-line therapy for gonorrhoea in some regions. CDC recommends ceftriaxone or cefixime plus azithromycin or doxycycline for treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum (Figure 1).⁴

Among the centres in the WHO Western Pacific Region, most recommend ceftriaxone and cefixime for treating gonococcal urethritis.⁵ Cephalosporins are not recommended in only three jurisdictions

(Figure 2). A single oral dose of 400 mg cefixime is often recommended among most regions of West Pacific Regions but the dosage and the administrative route of ceftriaxone regimens ranges between 125 mg to 1 gm and varies from the intravenous and intramuscular route. In Hong Kong, oral ceftibuten is used because cefixime is not available in Social Hygiene Service and injectable cefodizime is recommended in Japan as an alternative for ceftriaxone (Figure 2).⁵ Current knowledge suggests that treatment with ceftriaxone in higher doses may decrease the impact of the circulation of "cephalosporin-resistant" gonococci in West Pacific Region.⁵

In Hong Kong, penicillin had been the mainstay of treatment for gonococcal urethritis till 1985. Afterwards, it was replaced by ofloxacin due to penicillin resistance. A single oral dose of ceftibuten 400 mg succeeded ofloxacin since 1997 and now become the standard first-line therapy in Social Hygiene Service of Hong Kong.⁶ However, the rate of ceftibuten resistance has been rising recently, Social Hygiene Service is now switching to ceftriaxone as the first-line treatment.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

OR, IF NOT AN OPTION

Cefixime 400 mg orally in a single dose

OR

Single-dose injectable cephalosporin regimens

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Figure 1. CDC regimens for uncomplicated gonococcal infections of the cervix, urethra and rectum.⁴

Failure of treatment with extended-spectrum cephalosporins in gonorrhoea

Treatment failure following therapy with oral third-generation cephalosporins (cefixime and ceftibuten) has been reported, but not with the injectable cephalosporin preparations (ceftriaxone)¹ until a paper published in July 2011, Japan has isolated the first strain of *N. gonorrhoeae* with high level resistance to ceftriaxone.⁷

Treatment failure with oral cephalosporin was first reported in Japan in 2001.⁸ Well-documented treatment failures with cefixime and ceftibuten were recorded in several studies in Japan and Hong Kong respectively.^{8,9} The number of

treatment failures with oral cefixime in Japan was so significant that it is now no longer recommended as a treatment option in that country.¹ In Japan, intravenous ceftriaxone is now recommended as the first-line treatment of gonococcal infections. Resistance is rarely encountered for spectinomycin and ceftriaxone,¹⁰ but the problem of resistance to oral third-generation cephalosporins has emerged and spread in Asia, Australia and elsewhere.³

The problem of antimicrobial resistance of gonococci is not only limited in West Pacific Region, but also has spread to Europe. The European surveillance of antimicrobial resistance in gonococci found that the rate of resistance to ciprofloxacin were as high as 42 to 52% across Europe.¹¹ High-level resistance to tetracyclines and

Country	Ceftriaxone	Cefixime (oral)	Other Cephalosporin
Australia	250mg IM	Not available	Not used
Cambodia	Not used	400mg	No
China	250mg IM proprietary 1gm IM generic	Not used	Not used
Japan	1 gm IV	Not recommended	1gm cefodizime IV
Laos	250mg IM	400mg	Not used
Malaysia	250mg IM	Registered, but not used	
New Zealand	250mg IM	Not used	Not used
Philippines	125mg IM	400mg	Not used
Singapore	250mg IM generic	Rarely used 400mg	Not used
Vanuatu	Rarely used, 2 nd line treatment 250mg IM	Not used	Not used
Vietnam	250mg IM	400mg	Not used

IM, intramuscular; IV intravenous administration.

No cephalosporin recommended for the treatment of gonorrhoea in 3 jurisdictions: Fiji, New Caledonia and Papua New Guinea

Figure 2. Oral and injectable third-generation cephalosporins recommended as standard treatment regimens for gonorrhoea in the WHO Western Pacific Region.⁵

penicillins remained relatively constant at 16% and 12% respectively.¹¹ Although resistance to ceftriaxone was not demonstrated, an upward shifting in the minimal inhibitory concentration (MIC) was identified. In 2004, around 55% of gonococci isolates demonstrated the ceftriaxone MIC ≤ 0.002 mg/L. Only around 12% of the isolates demonstrated the MIC ≤ 0.002 mg/L in 2008.¹¹ None of the isolates were resistant to spectinomycin.¹¹

Another study done in Sweden showed there was an in-vitro decreased susceptibility and increased resistance to the extended-spectrum cephalosporins. 9.1% of gonococci isolates had in-vitro resistance to the cefixime and 0.3% with resistance to ceftriaxone.¹² Eight per cent were resistant to ampicillin and 91% to ciprofloxacin, but no spectinomycin resistance was identified.¹²

The above data suggest ciprofloxacin, penicillins and tetracyclines are no longer effective in treating gonococcal infection whereas, the upward shifting ceftriaxone MIC level suggests that close monitoring is essential. Spectinomycin seems to be a very effective treatment for gonococci, however, availability is the main problem for its use because most of countries do not have spectinomycin. Although rare, spectinomycin resistance is still possible.

Is Azithromycin a drug of choice for gonococcal urethritis?

Azithromycin is an azalide derived from the macrolide class of antibiotics. It has better tissue penetration, absorption and broader spectrum compared to erythromycin. It is commonly used to treat non-gonococcal urethritis (NGU). Previously, a single dose of azithromycin 2 gm given orally was found to have promising results in treating gonococcal urethritis.¹³ In a more recent study done in Israel, 95% of pharyngeal gonorrhoea in female sex workers was eradicated by 2 gm single oral dose of azithromycin.¹⁴ However, high level resistance to azithromycin

developed rapidly.^{15,16} As a result of this, azithromycin is no longer recommended as the sole agent in treating the gonorrhoea.¹⁷

Resistance mechanisms associated with altered cephalosporin, azithromycin and spectinomycin susceptibility

Extended spectrum cephalosporins (cefixime or ceftriaxone) is now the mainstay of treatment for gonorrhoea and the problem of treatment failure or resistant strains of *N. gonorrhoeae* may emerge and spread.

The mechanism of resistance to oral third generation cephalosporins seems to be associated with a mosaic penicillin-binding protein in addition to other chromosomal mutations previously found to confer resistance to beta-lactam antimicrobials.³

N. gonorrhoeae has three penicillin-binding proteins (PBPs), PBPs1, 2 and 3. PBP1 and 2 are the major targets of beta-lactam antibiotics. PBP2 has a 10-fold greater affinity for penicillin than PBP1.¹⁸ The amino acid sequences of pen A gene, penicillin binding protein 2 in *N. gonorrhoeae* strains are of two types: pen A mosaic and non-mosaic strains.¹⁹ In the mosaic type, the acquisition of pen A mosaic allele alters the pen A gene that encodes the PBP 2. By alteration of PBP 2, it can reduce its affinity of penicillins as well as the cephalosporins leading to resistance and decreased susceptibility.¹²

A study noted that in the pen A mosaic strain, some regions in the transpeptidase- encoding domain in pen A were similar to those of *Neisseria perflava/sicca*, *Neisseria cinerea*, *Neisseria flavescens*, *Neisseria polysaccharea*, and *Neisseria meningitides*.¹⁹ These findings suggest that the pathogens might have evolved by gene transformation between resistant *Neisseria spp.* and the original susceptible gonococci attributable to the existence of wide spread commercial oral sex.²⁰

In the pen A non-mosaic allele type of resistance, an alteration of a single amino-acid at A501 of the pen A gene causes the decrease in susceptibility of cephalosporins.¹²

Furthermore, mutations in the promoter or repressor gene *mtr* cause over-expression of the *mtrCDE* efflux pump system that promotes the export of the cephalosporins from the cell, further decreasing the susceptibility to cephalosporins. Also, the alteration of amino-acid G101 and A102 in *por B1b* gene results in decreasing permeability of the cephalosporins at the outer cell membrane of *N. gonorrhoeae* inducing a further drop in susceptibility to cephalosporins.¹²

As mentioned above, Japan has isolated the first *N. gonorrhoeae* strain (H041 or new NG-MAST ST4220) that is highly resistant to the extended-spectrum cephalosporins (ESC) – ceftriaxone. It was isolated from the pharynx of a female commercial sex worker in Kyoto Japan and displayed a MIC of ceftriaxone of 2 µg/ml.⁷ It has a very high level of resistance. The sequencing of ESC resistance determinants showed that H041 possessed a unique pen A mosaic allele (pen A_{H041}) and other previously described *mtrR*, pen B and pon A1 resistance determinants. No new *pilQ* mutations were found.⁷ Therefore, the only new resistance determinant for causing such high level of ESC MIC was pen A_{H041}. This pen A_{H041} was highly similar to previous pen A mosaic allele that had been correlated with cefixime treatment resistance in Japan.⁷ Also, by using the Multilocus Sequence Typing (MLST), H041 seems to represent a subclone of previously described MLST ST7376 cefixime resistance *N. gonorrhoeae* found in Japan.⁷ This clone has caused cefixime treatment failure and seems to have further evolved and developed resistance to ceftriaxone.⁷

There are two proposed mechanisms for accounting the development of azithromycin resistance in *N. gonorrhoeae*. The first one is through modification of the ribosomal attachment sites. The azithromycin is targeted at the 23S ribosomal RNA. By altering this target, it can

induce resistance. This targeted 23S ribosomal RNA can be altered by methylation and genetic mutation. The mutations associated with the peptidyl-transferase loop of domain V of 23S ribosomal RNA have been found in association with high levels of azithromycin resistance.²¹ The second mechanism is through the efflux systems. The *N. gonorrhoeae* *mtr* gene encodes the efflux pump that actively exports the macrolides out from the cell. This mechanism also contributes to the chromosomal resistance to the penicillins, tetracyclines, quinolones and cephalosporins.²¹

Although spectinomycin resistance is rare, it can be due to a mutation targeted at 16S rRNA by a cytosine to thymine transition at position 1192. Similar spectinomycin resistance can be also found in *Escherichia coli*.²²

The local data

The mainstay of treatment for uncomplicated gonococcal infection in Hong Kong is oral ceftibuten. Figure 3 summarizes the current treatment options for gonococcal infections in the Social Hygiene Service.^{4,6,17,23}

Ceftibuten is an orally active, third-generation cephalosporin. A single dose of 400mg oral ceftibuten should be effective for the treatment of gonorrhoea.⁶ In treatment of uncomplicated gonococcal urethritis in men, the overall cure rate was 98.2% in a local study done in year 1996-1997.⁶

In a more recent local study published at 2008, the clinical treatment failure rate of oral ceftibuten treatment in government sexually transmitted disease (STD) clinics was 3.7% (45 cases out of 1228) between October 2006 and August 2007,⁹ and was still within the 5% figure of acceptable resistance level. It was concluded that ceftibuten resistance may contribute to the empirical treatment failure of gonorrhoea caused by strains harbouring the mosaic pen A gene, which confers reduced susceptibility to oral extended-spectrum

Urogenital GC/ Anal GC	- Ceftriaxone 250mg IMI x 1 dose/OR -Ceftibuten 400mg po x 1 dose (test of cure after treatment is strongly recommended) /OR - Spectinomycin 2gm IMI x 1 dose
Oropharyngeal GC	- Ceftriaxone 250mg IMI x 1 dose
Epididymo-orchitis GC	- Ceftriaxone 250mg IMI x 1 dose + doxycycline 100mg bd po x 10-14 days
GC in pregnancy/ breastfeeding	-same as urogenital/ anal GC
Children/ Infants (uncomplicated)	-same as adult (>45kg) -Ceftriaxone 125mg IMI x 1 dose (< or =45kg)
GC Ophthalmia	-Ceftriaxone 25-50mg/kg IMI/ IVI x 1 dose (neonate: max 125mg) -Ceftriaxone 1gm IMI x 1 dose (adult)

Figure 3. Gonorrhoea (GC) treatment regimens in Hong Kong Social Hygiene Service.

cephalosporins. By using *N. gonorrhoeae* Multi-antigen Sequence Typing (NG-MAST), most of the strains belonged to ST 835.⁹ This implies a significant public health concern to prevent the spread of this extended spectrum of cephalosporins resistant strain.

Screening for such resistance in the routine clinical laboratory may be undertaken by the disk diffusion test with 30- μ g ceftibuten disks. A MIC of ≥ 8 mg/litre and a disk diffusion zone size of ≤ 27 mm would suggest resistance, whereas respective values of ≤ 1 mg/liter and ≥ 30 mm would likely indicate susceptibility.⁹ It was suggested that when in a clinical laboratory setting where ceftibuten MIC testing is not practicable, the disk diffusion test using 30- μ g ceftibuten disks would give an indication of likely ceftibuten resistance.⁹

However, the case of ceftibuten treatment failure rate has been increasing since April 2011. According the figure given by the Public Health

Laboratory Centre and Social Hygiene Service in Hong Kong, the incidence of isolates with reduced susceptibility to ceftibuten had been increasing from 2.6% in January 2011 to 8.4% in April 2011 and even to 20% in August 2011. The figure decreased slightly to 12% in September 2011. Therefore, the first-line treatment of gonorrhoea in Social Hygiene Service has been changed from ceftibuten to ceftriaxone and also ceftriaxone has been recommended as the antibiotic of choice for empirical treatment of gonorrhoea by community-based doctors.²⁴

Preventive strategy

Surveillance for resistance, primary screening (such as for sexually active women at risk or sexually active men-who-have-sex-with-men), secondary screening for sexual partners and gonorrhoea treatment are the four main principles for gonorrhoea prevention and control.² With the

emergence of adaptive organisms and antimicrobial resistance, timely prevention and control programs for STDs are essential.²

Conclusion

The reduction of the susceptibility of *N. gonorrhoeae* strains to oral extended-spectrum cephalosporins is likely to emerge and spread. Vigilant monitoring of resistance strains with implementation of control and preventive strategies will be the key in controlling its further dissemination.

References

1. Tapsall JW. Neisseria gonorrhoeae and emerging resistance to extended spectrum cephalosporins. *Curr Opin Infect Dis* 2009;22:87-91.
2. Workowski KA, Berman SM, Douglas JM, Jr. Emerging antimicrobial resistance in Neisseria gonorrhoeae: urgent need to strengthen prevention strategies. *Ann Intern Med* 2008;148:606-13.
3. Barry PM, Klausner JD. The use of cephalosporins for gonorrhea: the impending problem of resistance. *Expert Opin Pharmacother* 2009;10:555-77.
4. Centres for disease control and prevention. Sexually transmitted diseases treatment guidelines 2010. Gonorrhoea MMWR 2010 (www.cdc.gov/std/treatment/).
5. Tapsall JW. Implications of current recommendations for third-generation cephalosporin use in the WHO Western Pacific Region following the emergence of multiresistant gonococci. *Sex Transm Infect* 2009;85:256-8.
6. Chong LY, Cheung WM, Leung CS, Yu CW, Chan LY. Clinical evaluation of ceftibuten in gonorrhea. A pilot study in Hong Kong. *Sex Transm Dis* 1998;25:464-7.
7. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is Neisseria gonorrhoeae initiating a future era of untreatable gonorrhoea? Detailed characterization of the first strain with high-level resistance to ceftriaxone. *Antimicrob Agents Chemother* 2011;55:3538-45.
8. Akasaka S, Muratani T, Yamada Y, Inatomi H, Takahashi K, Matsumoto T. Emergence of cephem - and aztreonam-high-resistant Neisseria gonorrhoeae that does not produce beta-lactamase. *J Infect Chemother* 2001;7:49-50.
9. Lo JY, Ho KM, Leung AO, et al. Ceftibuten resistance and treatment failure of Neisseria gonorrhoeae infection. *Antimicrob Agents Chemother* 2008;52:3564-7.
10. Deguchi T, Yasuda M, Maeda S. Lack of nationwide surveillance of antimicrobial resistance of Neisseria gonorrhoeae in Japan. *Ann Intern Med* 2008;149:363-4.
11. Cole MJ, Chisholm SA, Hoffmann S, Stary A, Lowndes CM, Ison CA. European surveillance of antimicrobial resistance in Neisseria gonorrhoeae. *Sex Transm Infect* 2010;86:427-32.
12. Golparian D, Hellmark B, Fredlund H, Unemo M. Emergence, spread and characteristics of Neisseria gonorrhoeae isolates with in vitro decreased susceptibility and resistance to extended-spectrum cephalosporins in Sweden. *Sex Transm Infect* 2010;86:454-60.
13. Handsfield HH, Dalu ZA, Martin DH, Douglas JM, Jr., McCarty JM, Schlossberg D. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. *Sex Transm Dis* 1994;21:107-11.
14. Dan M, Poch F, Amitai Z, Gefen D, Shohat T. Pharyngeal Gonorrhea in female sex workers: Response to a single 2-g dose of azithromycin. *Sex Transm Dis* 2006;33:512-5.
15. Tapsall JW, Shultz TR, Limnios EA, Donovan B, Lum G, Mulhall BP. Failure of azithromycin therapy in gonorrhea and discorrelation with laboratory test parameters. *Sex Transm Dis* 1998;25:505-8.
16. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant Neisseria gonorrhoeae following treatment with azithromycin. *Int J STD AIDS* 1997;8:299-302.
17. Bignell C. 2009 European (IUSTI/WHO) guideline on the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS* 2009;20:453-7.
18. Lindberg R, Fredlund H, Nicholas R, Unemo M. Neisseria gonorrhoeae isolates with reduced susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. *Antimicrob Agents Chemother* 2007;51:2117-22.
19. Osaka K, Takakura T, Narukawa K, et al. Analysis of amino acid sequences of penicillin-binding protein 2 in clinical isolates of Neisseria gonorrhoeae with reduced susceptibility to cefixime and ceftriaxone. *J Infect Chemother* 2008;14:195-203.
20. Ameyama S, Onodera S, Takahata M, et al. Mosaic-like structure of penicillin-binding protein 2 Gene (penA) in clinical isolates of Neisseria gonorrhoeae with reduced susceptibility to cefixime. *Antimicrob Agents Chemother* 2002;46:3744-9.
21. Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. *Sex Transm Infect* 2010;86:422-6.
22. Galimand M, Gerbaud G, Courvalin P. Spectinomycin resistance in Neisseria spp. due to mutations in 16S rRNA. *Antimicrob Agents Chemother* 2000;44:1365-6.
23. Bignell C, FitzGerald M. UK National guideline for management of gonorrhoea in adults 2011. *Int J STD AIDS* 2011;22:541-7.
24. Ho KM, Lo YCJ. Recent increase in ceftibuten resistant in GC. *Communicable Disease Watch*. 2011;8:86-7. (www.chp.gov.hk/files/pdf/cdw_v8_21.pdf)