

## Gonorrhoea: A Moving Target

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### ABSTRACT

*Gonorrhoea remains a major concern throughout the world because of its persistent prevalence and substantial morbidity, attributing largely to the remarkable adaptive ability of *Neisseria gonorrhoeae* to enhance survival and transmission through changes in clinical features and antimicrobial resistance patterns. Escalating quinolone resistance in Hong Kong had prompted a search for an alternative first line treatment. Ceftriaxone, a new, orally active, third generation cephalosporin was recently shown to be an effective and well tolerated treatment. However, as antibiotic resistance continues to develop and spread, finding a new effective antimicrobial treatment may only mean a short term measure, with the anticipation of gradual selection for resistant strains after increasing usage. The ultimate goal of developing an effective vaccine would hopefully be achieved in the near future.*

**Keywords:** Gonorrhoea, Ceftriaxone, Quinolone, PPNG

### INTRODUCTION

Gonorrhoea is a disease recognized since antiquity. Despite our better understanding of the disease, advances in antimicrobial therapy and improved health education, it remains a major health and social concern throughout the world. As a target, gonorrhoea is certainly not stationary. This is attributed to the remarkable adaptive power of the causative organism, *Neisseria gonorrhoeae*, to continually evolve mechanisms to evade treatment.

### HISTORICAL MILESTONES<sup>1</sup>

The clinical syndrome of gonorrhoea was first described in *Leviticus 15* of the Old Testament. The

causative organism, *N. gonorrhoeae*, was observed in urethral smears in 1879 and successfully cultured *in vitro* in 1882. Before effective antimicrobial agents were developed, the treatments for gonorrhoea were largely mechanical. These included the passage of urethral sounds and low-pressure irrigation with detergents or antiseptics. The usually quoted, but rarely seen, complications of gonorrhoea such as ascending infections or strictures were probably results of these treatments rather than the disease itself.

In the mid-1930's, sulphonamide was the first effective antimicrobial therapy against *N. gonorrhoeae*. Resistance developed rapidly, rendering it unsuitable for gonococcal treatment in less than 10 years. The penicillin era starting in the early 1940's provided an effective anti-gonococcal agent for the next 25 years. This was followed by the emergence of chromosomally mediated resistance *N. gonorrhoeae* (CMRNG) in late 1950's, and penicillinase producing *N. gonorrhoeae* (PPNG) in 1976.<sup>2</sup> Report of plasmid mediated tetracycline resistant *N. gonorrhoeae* (TRNG) was published in 1985.<sup>3</sup> In the same year, the quinolones were recommended as alternative first line therapy. However, in the early 1990's, escalating quinolone resistance was reported worldwide.

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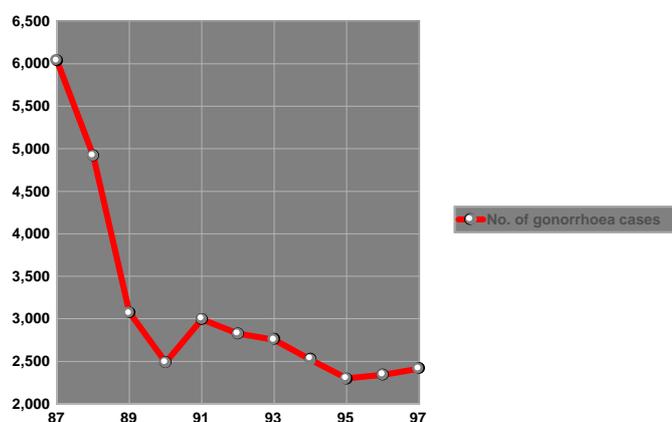
Hong Kong

## EPIDEMIOLOGY

The World Health Organization (WHO) recently estimated the number of new cases of gonorrhoea worldwide to be 62 million annually.<sup>4</sup> In the US, the number of cases reported to the Centers for Disease Control (CDC) annually sharply decreased by 70% between 1982 and 1996.<sup>5</sup> However, it is still the most frequently reported infectious disease.

In Hong Kong, 2412 new cases of gonorrhoea were diagnosed in the Government Sexually Transmitted Disease (STD) clinics in 1997, accounting for 12% of the total new STD diagnoses.<sup>6</sup> It is now the third commonest STD, trailing non-specific genital infection and genital wart. Analysis of annual incidence of gonorrhoea over a 10-years period, from 1988 to 1997, revealed a declining trend which was sharp in the first 3 years, and steady off at the latter half (Figure 1).

Possible explanations for this decrease in incidence of gonorrhoea included efficacious antimicrobial therapy, readily available treatment (free and confidential in Government STD clinics in Hong Kong), active and vigorous contact tracing with epidemiological treatment, appropriate counseling and health education, and behavioral modification secondary to the HIV epidemic. With all these positive factors operating, one would expect further reduction even to the point of complete eradication. Obviously, such was not the case. The gonococcus managed to enhance survival and



**Figure 1: Trend of annual incidence of gonorrhoea in Government STD clinics in Hong Kong**

transmission through changes in presenting clinical features and patterns of antimicrobial resistance.

## CLINICAL FEATURES

In the older medical textbook, the dysuric symptoms of gonococcal urethritis were described with phrases like 'passing broken glass', 'passing red hot needles', and 'red hot poker in the pipe'. These suggested a significant degree of severity in dysuria, which were rarely encountered nowadays.

Sherrard and Barlow reviewed 1749 episodes of gonorrhoea in 1382 men from 1990 to 1992.<sup>7</sup> Urethral discharge was the most common symptom (81.9%), followed by dysuria (52.8%). The classical symptoms of discharge with dysuria occurred in only 48.1% of cases. In no case was severe burning discomfort reported.

Symptom was absent in 10.2% of cases. This latter result was highly significant as it was well known that gonorrhoea and other STD usually were transmitted by patients with asymptomatic infections or who had symptoms that they ignored or discounted. This led to the concept of 'core transmitters' who played an important role in maintaining substantial prevalence of infection in any individual community, which underlay the importance of taking active steps to trace contacts for epidemiological treatment.

The average time from development of symptoms to presentation at clinic was 6.2 days, which had significantly increased from Lodin's finding of 1.8 days in 1938 and 3.5 days in 1955.<sup>8</sup> This again reflected a gradual lessening of severity of symptoms, so that patients could bear a little longer before they seek medical help.

Lodin documented an increase in the incubation period from 4.9 days in 1932 to 6.1 days in 1955.<sup>8</sup> Progressive lengthening of incubation period was further demonstrated by Schofield (6.2 days in 1978)<sup>9</sup> and Sherrard (7.9 days in 1989, and 8.3 days in 1990-92).<sup>8,10</sup>

All in all, these evidences suggested that with effective treatment, the organism had evolved to produce fewer and milder symptoms with a longer incubation period. These changes enhanced the chance of transmission of infection and survival of the organism.

## ANTIMICROBIAL SUSCEPTIBILITY

Gonococci are inherently quite sensitive to antimicrobial agents, in contrast to other Gram-negative organisms. However, selective pressure for the evolution of resistant strain is an inevitable consequence of prolonged usage of any single antibiotic as first line treatment. This is further aided by excessive and/or inappropriate prescribing pattern, especially in areas where antibiotic therapy is not closely regulated.

There are two types of antimicrobial resistance in *N. gonorrhoeae*, namely chromosomally mediated, and plasmid mediated.

Chromosomal mediated resistance to penicillin results from additive effects of mutations at independent chromosomal DNA loci. Three well-studied examples of these loci are *penA*, *mtr* and *penB*.<sup>11</sup> Mutations at the *penA* loci results in alteration of penicillin binding protein 2, hence reducing its affinity for penicillin. The *mtr* locus actively removes the antibiotic from the cell by an efflux system. The *penB* locus encodes for outer membrane porins of bacteria, when mutated, will impede penetration of beta-lactam antibiotics. These processes prevent the accumulation of the antibiotic at its site of action. This type of resistance is characterized by slow progressive increase in antimicrobial resistance, i.e. increase in MIC, and its slow spread. Gonococci with this form of resistance have been designated chromosomally mediated resistant *N. gonorrhoeae* (CMRNG). Antimicrobials affected by this type of resistance include penicillin, tetracycline, erythromycin, spectinomycin, fluoro-quinolones and cephalosporins.

Plasmid-mediated resistance arises through the acquisition of plasmid. A plasmid is an extra-chromosomal cyclic double-stranded DNA molecules which replicates independently of the chromosomes. It can encode for different functions including antibiotic resistance (R plasmid), and conjugation (F plasmid). Production of penicillinase is mediated by R plasmid. This causes enzymatic deactivation of penicillin. R plasmids are transferred from one cell to another by conjugation mediated by the F plasmid. This type of resistance results in high level resistance and spreads rapidly. Antimicrobials affected by this include penicillin, tetracycline and early generation cephalosporin.

## Penicillin

Penicillin was highly effective in treating gonorrhoea when introduced in the early 1940's. With time, a gradual increase in prevalence and extent of resistance were noted. This was chromosomally mediated and required dosage increment with the later addition of probenecid to accommodate for the increasing MIC. However, even consistent efforts to use high doses could not prevent the emergence of resistant strains.

Plasmid-mediated resistance to penicillin was first documented in 1976.<sup>2</sup> Spread of PPNG are now reported worldwide. A recent survey by WHO's Gonococcal Antimicrobial Surveillance Programme (GASP) examined 8421 isolates of *N. gonorrhoeae* collected from 17 centres in the Western Pacific Region in 1996.<sup>12</sup> PPNG were present in 16 out of 17 centres. Notably, the proportion of PPNG in Vietnam has increased from 55% in 1992 to 97.5% in 1996. High levels of penicillin resistance were also recorded in Korea (90%), China (82.1%) and Cambodia (79%) and Brunei (78%). In Philippines and Taiwan, more than 50% of isolated strains of *N. gonorrhoeae* were PPNG.<sup>13,14</sup>

In Hong Kong, the percentage of penicillin resistant strains (PPNG and CMRNG inclusive) ranged from 66.6% to 77.9% in the period 1992-1996. Of interest was the significant decrease in prevalence of PPNG in Hong Kong from over 30% in the late 80's to an average of 5.9% in the period 1994 to 1997 (Figure 2). Kam and colleagues noted the association of this rapid decline of PPNG with the emergence of quinolone-resistant *N. gonorrhoeae* after extensive and prolonged use of 4-fluoroquinolones. They reported this

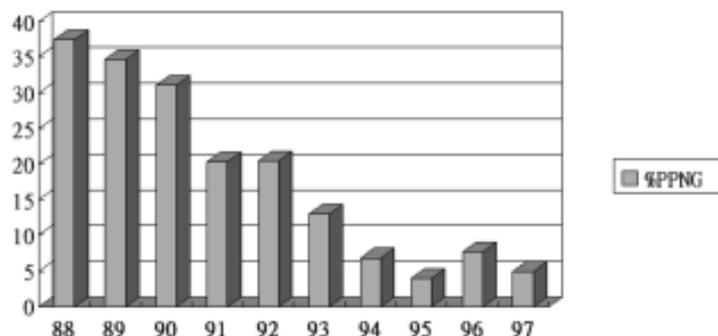


Figure 2: Trend of PPNG in Hong Kong

as the plasmid-curing effect of 4-fluoroquinolones.<sup>15</sup> Such phenomenon had been well demonstrated in early *in vitro* studies using enterobacteria. Possible mechanisms included loss of the conjugative plasmids preventing the maintenance of a high PPNG prevalence, or the inhibition of plasmid conjugation by 4-fluoroquinolones. However, despite this decline in PPNG, the proportion of penicillin resistant strains remained high. The majority of which were presumably chromosomally mediated.

### Tetracycline

As was the case with penicillin, gonococcal resistance to tetracycline was shown by a slow gradual increases in MIC in the early years which was chromosomally mediated. In 1985, high level plasmid-mediated resistance to tetracycline was first reported.<sup>3</sup> TRNG was present in 11 of 13 centres in the 1996 GASP report. Consistently high proportion of isolates with this form of resistance was reported in Singapore (74%) and Malaysia (76%).<sup>12</sup> This is no longer recommended for treating gonorrhoea because of the necessity of multi-dose regimen and the unacceptable level of resistance worldwide.

### Spectinomycin

Spectinomycin was developed and marketed with only one indication: treatment of infection caused by *N. gonorrhoeae*. It is safe to use in pregnancy. However it is relatively expensive and has inadequate efficacy against pharyngeal gonorrhoea.

Resistance to spectinomycin was first described in 1973. Outbreaks of infection with spectinomycin-resistant gonococci had been reported in Korea and UK, when spectinomycin was used as primary treatment. This resistance was high level and occurred as a single step mutation, affecting binding of the antibiotic to the ribosome.<sup>16</sup> It was unstable and reverted once its use was discontinued. Spectinomycin resistance was consistently seen only in China and Papua New Guinea, but only in low numbers.<sup>12</sup> Ye reported 5.3 % of resistant strains in a survey done on gonococcal strains from 6 cities in China during the period 1987-1992.<sup>17</sup> In Hong Kong, it is used mainly as a second line treatment. Resistance is rare and sporadic.

### Cephalosporins

$\beta$ -lactamase stable cephalosporins is highly effective in the treatment of gonorrhoea with both plasmid and chromosomally mediated resistance. Ceftriaxone, with its very high intrinsic potency, lack of resistant strains and long half life, has remained highly efficacious as single-dose therapy for gonorrhoea, and even as treatment of pharyngeal infections. In previous studies, the efficacy of ceftriaxone consistently exceeded 96%,<sup>19,31,32</sup> making it a standard benchmark regimen in the evaluation of new therapeutic agents. It has become the drug of choice in the current CDC recommendations.<sup>18</sup> The drawbacks of this agent include the cost and the necessity of intramuscular administration.

Cefixime, an oral third-generation cephalosporin, showed clinical activity equivalent to that of ceftriaxone - 96% and 98% cure after a single 400mg or 800mg dose respectively.<sup>19</sup> The greater ease and patient acceptance of oral therapy may well favour such an agent. However it is not currently available in Hong Kong.

In the 1996 GASP report, no resistance to ceftriaxone was evident among the 5287 strains tested by 13 centres.<sup>12</sup> The potential problem with cephalosporins is that very widespread use could conceivably accelerate the process of selecting less and less  $\beta$ -lactam-susceptible strains. Similar situation in the past might occur: CMRNG increased slowly in incidence over the decades during which penicillin was the drug of choice for gonorrhoea.

### Quinolones

Fluoroquinolones were popular therapeutic agents against PPNG during the mid-80's. Ofloxacin had been the first line treatment for uncomplicated gonorrhoea in the Government STD clinics in Hong Kong since 1985. The initial dosages used were 400 and 600mg for male and female patients respectively. There were only 1% of resistant strain then. This was followed by the emergence and establishment of quinolone-resistant strains accounting for 14.59% in 1994; 12.44% in 1995; 21.71% in 1996; and 35.8% in 1997. (Data of Social Hygiene Service, Department of Health, Hong Kong). This escalating bacterial resistant pattern was also

observed and reported in other countries, including Japan,<sup>20</sup> Australia<sup>21</sup> and US.<sup>22</sup>

According to GASP, low-level resistance to quinolones, detected in three of eight Western Pacific countries in 1992, was detected in 12 of 13 centers in 1994. High-level quinolone resistance was documented in two of eight centers in 1992 and 7 of 13 centers in 1994.<sup>23</sup> There was little further change in 1996. Latest figures showed that in 1996,<sup>12</sup> the highest proportion of resistant isolates was seen in the Philippines (66%), and Cambodia (53%). The proportion of 'less sensitive' strains was particularly high in China (69.4%), Hong Kong (55.2%) and the Republic of Korea (38%).

Three mechanisms of fluoroquinolone resistance had been reported: the development of mutations in the DNA gyrase subunit A (GyrA) encoded by the *gyrA* gene, mutations in the DNA topoisomerase IV encoded by the *parC* gene, and reduced quinolone accumulation in the cells by an active efflux system across the inner membrane.<sup>24</sup>

In 1994, within the Government STD clinics in Hong Kong, dosage for treatment of male gonococcal urethritis was increased to 600mg in order to accommodate for the climbing MIC. However, the relentless progression of this resistance pattern continued and the quinolone group of antibiotics was given up altogether as first line treatment in 1998 in Hong Kong.

## Azithromycin

Azithromycin, a new azalide antibiotic, is derived from the macrolide erythromycin. It has improved oral absorption, and rapidly achieves a high and prolonged intracellular levels. Single dose therapy is effective against genital infection caused by *Chlamydia trachomatis*. Its clinical efficacy in treating uncomplicated gonorrhoea was examined recently. Single-dose treatment with 2gm orally gave a cure rate of 98.9%.<sup>25</sup> It proved highly effective against pharyngeal infection and all co-infections of *C. trachomatis* were cured. This is especially valuable since concomitant gonococcal and chlamydial genital infections occur in 20-60% of patients presenting with gonorrhoea. Gastrointestinal side-effects were common (35%), but were generally mild. The main disadvantage is the expensive cost which will inhibit its routine use.

## IDEAL ANTIMICROBIAL AGENT FOR FIRST LINE TREATMENT OF UNCOMPLICATED GONORRHOEA

The escalating rates of gonococcal resistance to quinolone in Hong Kong have prompted a search for an alternative first-line antimicrobial agent for use in treating uncomplicated gonococcal urethritis.

An ideal drug should have several desirable characteristics. It must have excellent activity against all gonococcal strains circulating in that particular community, as indicated by a low MIC *in vitro*. The minimal criterion of clinical efficacy is that treatment should be expected to eradicate >95% of uncomplicated anogenital gonorrhoea. Its pharmacokinetic properties should render single dose regimen feasible, so that treatment can be given under direct supervision and question of non-compliance eliminated. The serum and tissue concentration of antibiotic should substantially exceed the MIC (minimally 3 x MIC for 8 hours) in order to reduce the potential for selection of resistant strains. Oral preparation is preferable to injections. The latter has associated problems of inconvenience, pain and discomfort at injection site, and risk of needle stick injury. Good safety profile is also important. Other desirable properties should include safety in women who are pregnant, or breast-feeding; efficacy against pharyngeal gonorrhoea; efficacy against concomitant *C. trachomatis* genital infection; and low cost.

## CEFTIBUTEN

Ceftibuten is an orally active, third generation cephalosporin with potent in-vitro activity against both  $\beta$ -lactamase positive and negative strains of *N. gonorrhoeae*. The minimum inhibitory concentrations for 90% of strains (MIC<sub>90</sub>) is 0.03mg/l.<sup>26</sup> Its pharmacokinetic properties, including 75-90% oral bioavailability,<sup>27</sup> average peak plasma concentrations of 14-19mg/l,<sup>28</sup> elimination half life of 2-3 hours,<sup>27</sup> and stability with  $\beta$ -lactamase,<sup>29</sup> suggested that single oral dose of ceftibuten should be effective for treatment of gonorrhoea. Currently, this is not a listed indication of ceftibuten.

An open, prospective, non-comparative, multicentre pilot study with aim to evaluate the efficacy, tolerability, and safety of an single oral dose of 400mg

Ceftibuten in the treatment of uncomplicated gonococcal urethritis in male has recently been completed in the Government Social Hygiene Service in Hong Kong.<sup>30</sup> The overall cure rate was 98.2% (110 of 112 evaluable cases). Adverse events, occurring in 4.5 % of cases, were mild and short-lived. No significant changes in blood parameters were noted.

The authors concluded that single oral dose of 400mg ceftibuten was both an effective and well tolerated treatment for uncomplicated gonococcal urethritis in the male. However, these results should be confirmed by further comparative studies and ongoing audit of effectiveness in routine clinical practice. Its efficacy in treating genital gonorrhoea in the female patients, and infection in other anatomic sites, such as the pharynx and the rectum, would also need to be studied.

**Learning points:**

***Single oral dose of 400mg Ceftibuten is an effective and well tolerated treatment for uncomplicated gonococcal urethritis in male.***

## VACCINE

As antibiotic resistance continues to develop and spread, development of an effective vaccine must remain a target. Vaccines could offer long lasting and efficient solution aiming at containment of the disease to the point at which, it no longer constitutes a public health problem.

The interaction of gonococci with human mucosal cells is mediated mainly by components of the outer membrane, which contains several classes of proteins and lipo-oligosaccharide (LOS). Any protective immune response is likely to be primarily directed against these components, which act as candidates for vaccine development.

Pili are cilia-like projections lining the outer membrane of the gonococcus. They mediate attachment to various epithelial cells and interfere with neutrophil phagocytosis. Single antigenic gonococcal pilus vaccine has shown partial protection against homologous strain

in animal studies. However, no protection could be demonstrated against heterologous strain in human volunteers in large, randomized, placebo-controlled, double blind efficacy trial.<sup>33</sup> This is due to extensive pilus antigenic variation, and the problem may be surmounted by a polyvalent vaccine.

Protein I (PI) is the major outer membrane protein of the gonococcus, forming anion-selective transmembrane channels (porins) that permit the exchange of hydrophilic molecules through the outer membrane. It is stably expressed with no antigenic variation. Infection with one type of PI serovar has been shown to have reduced likelihood of recurrent infection with a strain with the same type of porin protein. However, there is still a need to define the epitopes on PI which induce protective immunity. Recently, strains of recombinant *Salmonella typhimurium* that expressed gonococcal PI has been cloned.<sup>34</sup> This may permit further investigation of the potential of an oral vaccine using this *S. typhimurium* expressed PI.

Other potential vaccine candidates currently under investigations include LOS, protein II, outer membrane transferrin and lactoferrin.

An ultimate vaccine candidate for gonococcus should show minimal or no antigenic variation, and contains one or a few epitopes that are conserved and that targets for protective antibodies. PI is the most promising candidate for vaccine development at this stage.

## CONCLUSION

*N. gonorrhoeae* is a versatile and successful pathogen of humans and continues to evolve mechanisms to evade our attempts at eradication with antimicrobial agents. Finding a new effective antimicrobial treatment may only mean a short term measure, with the anticipation of gradual selection for resistant strains after increasing usage. Before the advent of an effective vaccine, treatment will rely upon sensible use of existing effective antimicrobial agents. Use of currently available effective treatments on a rotational basis may delay the emergence of resistant strains. Continuous surveillance of gonococcal antibiotic susceptibility patterns at global, regional, and national levels, is critically important. This can predict the outcome of therapy, detect the

emergence of resistant strains and monitor the drifts in susceptibility to the treatment of choice; thereby ensuring that limited resources are used in the best possible way.

Finally, as we approach the next millennium, can we look to the better containment of the disease, or will it still be a target on the move?

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