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NEISSERIA GONORRHOEAE WITH DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN IN BRITISH COLUMBIA: AN IMPORTED PHENOMENON

Introduction

According to current interpretive criteria, *Neisseria gonorrhoeae* isolates with ciprofloxacin minimum inhibitory concentrations (MICs) of ≤ 0.06 µg/mL are considered susceptible[1]. Intermediate and resistant MIC breakpoints have not yet been established but isolates of *N. gonorrhoeae* with ciprofloxacin MICs of 0.05 to 0.25 µg/mL have been associated with apparent treatment failure with a regimen of a single 250 mg dose[2,3]. A report from Australia has also documented a strain with a ciprofloxacin MIC of 1.0 µg/mL that failed to respond to treatment with 500 mg of ciprofloxacin[4]. In Canada, as early as 1989, six penicillinase-producing *N. gonorrhoeae* (PPNG) isolates submitted to the National Laboratory for Sexually Transmitted Disease, Laboratory Centre for Disease Control, showed decreased susceptibility to fluoroquinolones. These isolates exhibited ciprofloxacin MICs of 0.25 to 0.5 µg/mL and were all recovered from male patients infected outside the country[5].

Antimicrobial Susceptibility Testing

The Provincial Laboratory at the British Columbia Centre for Disease Control began ciprofloxacin agar dilution susceptibility testing of gonococcal isolates in May 1992. Of 1,074 isolates tested between 1 May, 1992 and 5 April, 1995, 38 (3.5%) had ciprofloxacin MICs ≥ 0.125 µg/mL. The percentage of gonococci with decreased susceptibility to ciprofloxacin showed an increase from 1.0% of isolates tested in 1992 to 9.8% of isolates tested from 1 January to 5 April, 1995 (Table 1). Five of the 38 isolates were PPNG and 28 had penicillin or tetracycline MICs ≥ 2.0 µg/mL and were considered to be chromosomally-mediated resistant *N. gonorrhoeae* (CMRNG). Eighteen isolates came from women and 20 from men.

Table 1
Neisseria gonorrhoeae isolates with decreased susceptibility to ciprofloxacin, British Columbia, May 1992 to April 1995

Year tested	Total tested	Number of isolates with MICs (µg/mL) of						Total (%)*
		0.125	0.25	0.5	1.0	8.0	32.0	
1992	300		2		1			3 (1.0)
1993	343	1	3	6				10 (2.9)
1994	312			12	1	1		14 (4.4)
1995	112	2	4	2	2		1	11 (9.8)
TOTAL	**1,074**	**3**	**9**	**20**	**4**	**1**	**1**	**38 (3.5)**

* % of total isolates tested.

Case Investigation

From 1 January, 1994, to 1 April, 1995, investigation was conducted on all isolates with MICs ≥ 0.25 µg/mL. Of 23 such isolates, 19 had their origin overseas, 17 from Asia. Eleven were directly acquired: six from China, one from Hong Kong, two from the Philippines, one from an unspecified Asian location, and one from an unspecified overseas location. Eight others came from women whose only recent sexual contact was with a husband or male lover who had recently had sex overseas: three in China, three in Hong Kong, one in Vietnam, and one from an unspecified overseas location. For the remaining four cases, overseas origin

remains possible. One was a contact with U.S. navy personnel, one Chinese immigrant had only had contact with her travelling husband who was treated as a contact but not tested. For one man, contact with "an unidentified hitch hiker" was cited and for one person, no contact information was provided.

Discussion

The drug of choice for uncomplicated gonococcal infection in British Columbia is cefixime. To date, there has been no significant development of resistance to third generation cephalosporins, such as cefixime and ceftriaxone, in this jurisdiction. Accordingly, none of the discussed cases are known to have resulted in treatment failure. As predicted by many, development of decreased susceptibility to fluoroquinolones by *N. gonorrhoeae* has not taken long to manifest itself. To date, all evidence suggests that strains identified in B.C. with ciprofloxacin MICs ≥ 0.125 µg/mL have been largely imported from Southeast Asia. This is of particular relevance to other provinces and states that use fluoroquinolones as drugs of choice for the treatment of gonorrhea. Since decreased susceptibility to fluoroquinolones in this part of Canada does not appear to be a major endemic phenomenon, other jurisdictions should be concerned about fluoroquinolone treatment if they share similar immigration and tourism patterns with B.C. In B.C., cefixime or ceftriaxone will continue to be recommended as drugs of first choice for the treatment of *N. gonorrhoeae*. Fluoroquinolones remain a viable alternative for persons with immediate hypersensitivity reaction to penicillin where domestic acquisition of gonorrhea has occurred or for isolates with documented fluoroquinolone susceptibility. Ciprofloxacin is not recommended for imported cases, and where it is used in such a setting, a test of cure is strongly recommended.

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ISOLATES OF *NEISSERIA GONORRHOEAE* IN ONTARIO SHOWING CHROMOSOMALLY-MEDIATED RESISTANCE TO PENICILLIN COMBINED WITH PLASMID-MEDIATED RESISTANCE TO TETRACYCLINE

Introduction

High-level tetracycline-resistant isolates of *Neisseria gonorrhoeae* (TRNG) were first reported in the United States in 1985[1]. Since that time TRNG strains from various parts of the world have been described[2]. The first report of TRNG isolates in Canada was made in 1986 by Shaw and colleagues in British Columbia[3]; more recently TRNG strains, which were also penicillinase-producing (PPNG/TRNG), have been investigated[4]. Both the TRNG and PPNG/TRNG isolates had similar minimal inhibitory concentration (MIC) ranges to tetracycline (16.0 to 32.0 mg/L); moreover, the penicillin MIC range of TRNG strains, which were non-PPNG, was 0.063 to 0.25 mg/L, i.e., moderately susceptible[4]. These findings were similar to other reports of TRNG isolates that were non-PPNG[1,5,6]. Resistance to penicillin in non-PPNG isolates occurs through a variety of chromosomal mutations, each producing small increments in resistance[7]. *N. gonorrhoeae* isolates that show chromosomally-mediated resistance (CMRNG) to penicillin have a MIC ≥ 2.0 mg/L.

In a recent article[8] we reported that the total number of TRNG isolates in Ontario had increased steadily each year since 1990. In addition, the percentage of CMRNG isolates in 1994 had risen compared to previous years. Between January and September, 1994, TRNG strains with MIC values > 32 mg/L have been isolated in our laboratory at the Ontario Ministry of Health in Toronto. These isolates were investigated for plasmid profiles, MICs and hybridization with the *tet M* probe[9].

Methods

Antimicrobial susceptibility testing was performed using an agar dilution technique. GC agar base (Difco) enriched with 1.5% lysed horse blood and 1% Kellogg's supplement was used for all antimicrobial agents. The inoculum was prepared and plates inoculated as outlined in the National Committee of Clinical Laboratory Standards (NCCLS) Document M7-A3, Vol. 13, No. 25[10]. The concentrations of antimicrobial agents tested were as follows: two-fold dilutions of penicillin and tetracycline from 0.06 mg/L to 16.0 mg/L, and 0.25 mg/L to 1,024 mg/L, respectively; erythromycin, 1.0 mg/L; cefixime, 0.25 mg/L; ceftriaxone, 0.25 mg/L; ciprofloxacin, 0.03 mg/L; spectinomycin 16.0 and 32.0 mg/L. MICs were defined as the lowest concentration of antibiotic that inhibited growth. The plasmid content of all isolates was determined using the method of Portnoy and White as outlined by Crosa and Falkow[11]. Hybridization of isolates with the *tet M* probe was done as described[9].

Results and Discussion

Three different resistant phenotypes were detected. One set of isolates of *N. gonorrhoeae* had combined high-level resistance to tetracycline and chromosomally-mediated resistance to penicillin (TRNG/CMRNG). The MIC value for tetracycline among all the CMRNG/TRNG isolates was 128 mg/L; for penicillin, the values ranged from 2.0 mg/L to 4.0 mg/L. The second group of isolates was non-PPNG/TRNG with penicillin MIC values ranging from 0.12 mg/L to 0.5 mg/L (moderately susceptible) and tetracycline MIC values ranging from 64 mg/L to 256 mg/L. The other group

of strains was PPNG/TRNG, which had tetracycline MIC values of 64 mg/L.

A total of 48 strains of CMRNG/TRNG had been isolated as of November, 1994, representing 50.5% of all CMRNG strains. Eight of 710 non-PPNG, non-CMRNG/TRNG isolates (1.1%) and 3/119 PPNG/TRNG isolates (2.6%) had tetracycline MIC values > 32 mg/L. All 59 isolates were sensitive to erythromycin, cefixime, ceftriaxone, ciprofloxacin, and spectinomycin (MICS ≤ 1,0, ≤ 0.25, ≤ 0.25, ≤ 0.03, and ≤ 16 mg/L, respectively). The number of CMRNG/TRNG cases among the different age groups is listed in Table 1. The majority of isolates came from the 14 to 25-year age group; this was also true for the TRNGs. The three isolates of PPNG/TRNG were found in the 20 to 31-year age group. The majority of CMRNG/TRNG isolates, 26/48 (54.2%), were recovered from male patients; a high percentage of PPNG/TRNG isolates (66.7%) was also from males. The results from TRNG strains were different, however: 5/8 (62.5%) were from female patients. The geographic location of the 48 CMRNG/TRNG isolates is shown in Table 2. The London, Mississauga, Brampton area had the highest incidence (rate) with 28/48 (58.3%), followed by the Toronto area with 12/48 (25%). Fewer isolates were recovered in other areas. Strains from Windsor accounted for 6/8 (75%) of the TRNGs with MIC > 32 mg/L; 2/3 (66.7%) of the PPNG/TRNGs were from the Brampton area.

High-level transmissible tetracycline resistance in *N. gonorrhoeae* has been associated with a 25.2 megadalton (Md) plasmid that carries the streptococcal *tet M* determinant[1]. Recent studies have shown that the *tet M* resistance gene can be found on two types of conjugative plasmids, the American and the Dutch type, named after the country in which the strains were first isolated[12]. All of the 59 isolates in this study carried the 2.6 Md cryptic plasmid and a 25.2 Md conjugative plasmid, similar in size to the *tet M* plasmid usually found in isolates demonstrating high-level resistance to tetracycline[1,4]. Hybridization with the oligoprobe specific for *tet M*[9] was successful with all isolates. The PPNG isolates carried a 3.05 Md β-lactamase-encoding (Toronto-type)[13] plasmid in addition to the 2.6 Md and 25.2 Md plasmids.

Table 1
Incidence of CMRNG/TRNG, PPNG/TRNG, and TRNG cases with tetracycline MIC > 32 mg/L, by age, Ontario, January to September 1994

	Number of Isolates		
Age (Years)	CMRNG/TRNG	PPNG/TRNG	TRNG
14-19	13	0	3
20-25	15	1	4
26-31	4	2	0
31-45	7	0	1
Unknown	9	0	0
TOTAL	**48**	**3**	**8**

Table 2
Origin of cases of *Neisseria gonorrhoeae* with tetracycline MICs > 32 mg/L

	Number of Cases		
Origin	CMRNG/ TRNG[a]	TRNG[b]	PPNG/TRNG[c]
London	13	0	0
Mississauga	9	0	0
Brampton	6	1	2
Toronto	12	1	0
York/North York	4	0	0
Don Mills	2	0	0
Scarborough	1	0	0
St. Catharines	1	0	0
Windsor	0	6	0
Willowdale	0	0	1

[a] penicillin MIC 2.0 to 4.0 mg/L (CMRNG)
[b] penicillin MIC 0.5 mg/L (penicillin, moderately susceptible)
[c] penicillin MIC ≥ 16.0 mg/L (PPNG)

High-level transmissible tetracycline resistance in *N. gonorrhoeae* has been associated with a 25.2 megadalton (Md) plasmid that carries the streptococcal *tet M* determinant[1]. Recent studies have shown that the *tet M* resistance gene can be found on two types of conjugative plasmids, the American and the Dutch type, named after the country in which the strains were first isolated[12]. All of the 59 isolates in this study carried the 2.6 Md cryptic plasmid and a 25.2 Md conjugative plasmid, similar in size to the *tet M* plasmid usually found in isolates demonstrating high-level resistance to tetracycline[1,4]. Hybridization with the oligoprobe specific for *tet M*[9] was successful with all isolates. The PPNG isolates carried a 3.05 Md β-lactamase-encoding (Toronto-type)[13] plasmid in addition to the 2.6 Md and 25.2 Md plasmids.

Strains of *N. gonorrhoeae* that exhibit a high level of resistance to tetracycline with MICs of 64 mg/L have been reported in the United States[1], and more recently, Van Dyck and Associates[14] described one strain from Central Africa with a tetracycline MIC of 128 mg/L. This isolate was PPNG/TRNG with a β-lactamase plasmid (African type) of 3.2 Md in size and a *tet M* 25.2 Md plasmid. The 25.2 Md plasmid, seen in the CMRNG/ TRNG isolates which are becoming established in Ontario, is the *tet M* plasmid with worldwide distribution among isolates of *N. gonorrhoeae*[2]. That *tet M* determinant is capable of transposition to resident plasmids and dissemination to a new class of resistant *N. gonorrhoeae* is not surprising.

The MIC of a drug for a strain can be influenced by a number of factors. Ikeda[15] reported an interaction between plasmid-mediated and chromosomal resistance resulting in a 32-fold to 128-fold increase in MIC of ampicillin for strains of *N. gonorrhoeae*. Single mutational events may also alter the response of these organisms to a variety of antimicrobial agents[16]. Some of these mutations act together to produce increases in resistance that are additive. The combined effects of three genes, *tet*, *penB* and *mtr* can produce a 16-fold increase in tetracycline MICs[17]. More

than 12 classes of tetracycline resistance determinants have been distinguished in Gram-negative and Gram-positive bacteria[18]. Recently[19] it has been shown that in some species the presence of more than one resistance determinant can contribute, in an additive way, to the degree of resistance to tetracycline. MICs were increased two-fold in strains harboring two resistance determinants. Although this has not yet been shown in *N. gonorrhoeae*, further studies are being conducted in our laboratory on this new class of TRNG to determine whether such a situation exists. Tetracycline as therapy for gonorrhea is no longer recommended.

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Editorial Comment

The 1995 Update (available in fall 1995) of the *Canadian Guidelines for the Prevention, Diagnosis, Management and Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults* recommends one of the third generation cephalosporins, **ceftriaxone (125 mg IM in a single dose)** OR **cefixime (400 mg orally in a single dose)**, OR one of the fluoroquinolones, **ciprofloxicin (500 mg orally in a single dose)** OR **ofloxicin (400 mg orally in a single dose)**, as preferred therapy for uncomplicated gonococcal infection in adolescents and adults. These therapies are recommended because of the increased prevalence of gonoccocal isolates which are resistant to penicillin and tetracycline. **Spectinomycin (2 g IM in a single dose)** is recommended as an alternative therapy. Ampicillin/amoxicillin is no longer recommended as an alternative therapy as it was in the 1992 edition. All treatment regimens for gonorrhea should be followed by an antimicrobial effective against *Chlamydia trachomatis*, either **doxycycline 100 mg orally x 2/day for 7 days, or tetracycline 500 mg orally x 4/day for 7 days, or azithromycin 1 g orally in a single dose (azithromycin is not recommended for non-gonococcal/non-chlamydial urethritis or cervicitis).**

Resistance to currently recommended therapies is expected to develop just as resistance developed to penicillins and tetracyclines. Resistance to fluoroquinolones has been reported in Southeast Asia, notably the Philippines, which supports the findings of the report by Patrick et al. Increasing resistance to fluoroquinilones, such as ciprofloxicin, will eventually raise questions as to their utility in the long-term. The increase in the prevalence of tetracycline resistant gonococcal isolates raises issues concerning treatment: dual therapy, with an agent effective against penicillin-resistant and tetracycline-resistant gonorrhea followed by an antimicrobial effective against chlamydia is the treatment regimen recommended (see above).

Erratum

PERTUSSIS IN QUEBEC: ONGOING EPIDEMIC SINCE THE LATE 1980s, VOL. 21-5, PAGE 45

The first reference of the editorial comment to this article on page 48 was cited incorrectly. The reference should be as follows:

1. National Advisory Committee on Immunization, Advisory Committee on Epidemiology and the Canadian Paediatric Society. *Statement on management of persons exposed to pertussis and pertussis outbreak control*. CCDR 1994;20:193-99.

Announcements

2ND NATIONAL CANADIAN CONFERENCE ON IMMUNIZATION

8 - 11 December, 1996
Toronto, Ontario

The Laboratory Centre for Disease Control has begun the planning and organizing of its 2nd National Canadian Conference on Immunization. The last conference, *Immunization in the 90s: Challenges and Solutions*, was held in Quebec City, 5 - 7 October, 1994. The 2nd Conference will be increased to four days and will be held at the Royal York Hotel in Toronto. Current plans include an expanded exhibition area and additional time for peer-reviewed oral and poster presentations. Requests for further information, or to be placed on the conference information mailing list, should be faxed to Mr. Chuck Schouwerwou, Conference and Committee Coordinator, at (613) 998-6413, or submitted in writing to the Childhood Immunization Division, Laboratory Centre for Disease Control, P.L. # 0603E1, Tunney's Pasture, Ottawa, Ontario K1A 0L2.

7th CONFERENCE ON THE HEALTH OF INTERNATIONAL TRAVELLERS

2-3 November, 1995
Montreal, Quebec

This 7th conference on international travel medicine organized by the Montreal-Centre Public Health Department will be held on 2 and 3 November, 1995, at the Inter-Continental Hotel, 360 Saint-Antoine St. West, Montreal, Quebec. Topics will include malaria prevention, immunization against hepatitis A, water disinfection, controversies surrounding immunization and clinical problems.

For more information please contact **Guylaine Brunet, Clinique Santé-Voyage, Direction de la Santé publique de Montréal-Centre, 3700 rue Berri, Montréal (Québec) H2L 4G9, telephone: (514) 845-3187 or by FAX: (514) 845-6757**.

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