Need for treatment of gonorrhea to be effective against *Chlamydia trachomatis*

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WR BOWIE, J AST, L SIBAU, C SHAW, HD JONES, WA BLACK. Need for treatment of gonorrhea to be effective against Chlamydia trachomatis. Can J Infect Dis 1993;4(6):347-351. Men and women with gonorrhea or contact to gonorrhea are frequently co-infected with *Chlamydia trachomatis*. To assess the importance of using treatment regimens active against both *Neisseria gonorrhoeae* and *C trachomatis*, tetracycline 500 mg orally four times daily for five days, with activity against both organisms, was compared with ceftriaxone, 250 mg once intramuscularly, with activity against only *N gonorrhoeae*. *N gonorrhoeae* microbiological failure occurred in six of 148 patients (4%) on tetracycline and zero of 85 on ceftriaxone. Microbiological failure for *C trachomatis* occurred in zero of 27 on tetracycline and 10 of 12 (83%) on ceftriaxone (P<0.001). In addition, 14 others on ceftriaxone had *C trachomatis* first isolated after treatment. When all types of microbiologialc and clinical failures are included, outcome was significantly better on tetracycline (P<0.001). Optimal treatment of patients with gonorrhea must include regimens with activity against both *C trachomatis* and *N gonorrhoeae*.

Key Words: *Ceftriaxone, Chlamydia trachomatis, Gonorrhea, Neisseria gonorrhoeae, Tetracycline*

De la nécessité d'un traitement efficace contre la gonorrhée dans l'infection à *Chlamydia trachomatis*

RÉSUMÉ: Les hommes et les femmes atteints de gonorrhée ou exposés à cette maladie sont fréquemment infectés à la fois par *Chlamydia trachomatis*. Pour mesurer l'importance de recourir à des schémas thérapeutiques efficaces tant contre *Neisseria gonorrhoeae* que contre *C trachomatis*, la tétracycline 500 mg par voie orale quatre fois par jour durant cinq jours, active contre les deux organismes, a été comparée avec la ceftriaxone 250 mg une fois par voie intramusculaire, active contre *N gonorrhoeae*. Un échec thérapeutique a été constaté contre *N gonorrhoeae* chez six des 148 patients (4 %) traités avec tétracycline et chez aucun des 85 patients à qui l'on administrait la ceftriaxone. L'échec thérapeutique contre *C trachomatis* ne s'est produit chez aucun des 27 patients prenant de la tétracycline, et s'est produit chez 10 des 12 patients sous ceftriaxone (83 %) (P<0,001). De plus, chez 14 autres patients sous ceftriaxone, on avait d'abord isolé *C trachomatis* après le traitement. Lorsque tous les types d'échecs thérapeutiques microbiologiques et cliniques ont été inclus, le résultat s'est révélé nettement meilleur avec la tétracycline (P<0,001). Le traitement optimal des patients atteints de gonorrhée doit inclure des schémas thérapeutiques qui soient efficaces à la fois contre *C trachomatis* et *N gonorrhoeae*.

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ALTHOUGH THE OVERALL FREQUENCY OF GONOCOCCAL infections in Canada is decreasing, the prevalence of isolates resistant to penicillins and tetracyclines is increasing (1,2). This has resulted in the need for treatment with alternative antimicrobials active against *Neisseria gonorrhoeae* as is reflected in the 1988 Canadian guidelines as well as both recent and older American guidelines (3-5). These guidelines have also stressed the importance of treating gonococcal infection with regimens active against both *N gonorrhoeae* and *Chlamydia trachomatis*. Among patients with gonorrhea or contact to gonorrhea, approximately 20 to 30% of heterosexual men and 40 to 50% of women (6) are co-infected with *C trachomatis*, and focusing treatment only on *N gonorrhoeae* often fails to manage adequately the whole patient. Single dose regimens usually fail to eradicate *C trachomatis* and leave patients at risk not only for more trivial problems like post gonococcal urethritis and post gonococcal proctitis, but also more significant sequelae like endometritis and salpingitis (7,8).

Recent Canadian data indicate that treatment for gonorrhea directed against both *N gonorrhoeae* and *C trachomatis* is still not being used regularly (2). A study conducted in Vancouver from 1982 to 1984 clearly showed the importance of treating both infections in patients with gonorrhea. It also demonstrated the usefulness of ceftriaxone, which has emerged as a mainstay of treatment for *N gonorrhoeae*. At the time the study was performed, penicillinase-producing *N gonorrhoeae* (PPNG) were infrequent, but chromosomally mediated resistance to *N gonorrhoeae* (CMRNG) was more frequent (9). High level tetracycline resistance was not documented in British Columbia (or anywhere in Canada) until 1986 (10).

The objective of our study was to evaluate in a Canadian centre three treatment regimens for patients with gonorrhea in terms of the total clinical and microbiological outcome, rather than just the microbiological outcome for *N gonorrhoeae*. Results are presented for tetracycline 500 mg orally four times daily for five days (as a regimen which at that time was likely to be active against both *N gonorrhoeae* and *C trachomatis*), and for ceftriaxone 250 mg intramuscularly (a regimen likely to be totally active against *N gonorrhoeae* but without activity against *C trachomatis* [11]).

METHODS

Study participants were drawn from consecutive men and women who presented to the Vancouver Sexually Transmitted Disease Clinic in the Provincial Health Building from June 1982 to June 1984 with gonorrhea or a history of contact to gonorrhea. Patients were eligible for the study if they were willing to cooperate with follow-up, were not allergic to antimicrobials used in the study, were not pregnant, had not missed their last period, and had not taken antimicrobials in the preceding two weeks.

A standard sexual history and genital examination were performed. Urethral specimens from heterosexual men, and urethral and rectal specimens from homosexual or bisexual men, were obtained for culture for *N gonorrhoeae and C trachomatis*. Cervical, urethral, and rectal cultures for *N gonorrhoeae* and cervical and urethral cultures for *C trachomatis* were obtained from all women, and rectal cultures for *C trachomatis* were obtained from the last 53 women. Pharyngeal cultures for *N gonorrhoeae* were obtained if indicated. The swab for taking *C trachomatis* urethral specimens from men was inserted 3 to 4 cm. Endourethral specimens from men, and vaginal swabs from women, were obtained for culture for *Ureaplasma urealyticum*. After obtaining urethral specimens, the first 10 mL of urine were obtained from men to detect trichomonads and to quantitate pyuria. Serum was obtained from all individuals for syphilis serology.

Patients with specimens showing Gram-negative intracellular diplococci on initial smears, those whose cultures were known to be positive for *N gonorrhoeae*, or those with a history of known or possible contact to a patient with gonorrhea were then randomized to receive treatment according to a computer-generated randomization schedule. The regimens were: oral tetracycline 500 mg qid for five days; oral trimethoprim-sulfamethoxazole (TMP-SMX) nine tablets (720 mg/3600 mg) once daily for three days; and ceftriaxone 250 mg given intramuscularly with 2 mL of 1% xylocaine without adrenaline. Ceftriaxone was included in the randomization schedule after it was approved for use by the Health Protection Branch in January 1993. Treatment was not blinded. Since TMP-SMX is no longer considered a therapeutic option for treatment of gonorrhea, the results with TMP-SMX are not provided here.

An attempt was made to see all treated individuals five to seven days after cessation of treatment. Those whose initial cultures were positive for either *N gonorrhoeae* or *C trachomatis* were requested to return two, four, and six weeks after cessation of treatment. Men were requested to return for follow-up evaluations without having voided for four or more hours. With the exception of the syphilis serology, all studies performed initially were repeated on each follow-up visit. Where possible, patients were re-treated only under the following conditions: follow-up diagnostic tests were positive; symptomatic proctitis was present; or there was persistent or recurrent urethritis associated with all three of: symptoms, urethral discharge, and increased numbers of polymorphonuclear leukocytes on smear or in the first voided urine.

Laboratory diagnosis was by standard methods (12-14). On smear, the significant number of polymorphonuclear leukocytes was defined as a mean of four or more per field in five 1000x oil fields in a Gram stain of the urethral smear. In urine, the significant number was defined as 15 or more polymorphonuclear leuko-

TABLE 1
Initial isolation of *N gonorrhoeae, C trachomatis* and *U urealyticum* according to sexual preference

		Number (%)						
Sex	Sexual preference	Total	C+N+	C–N+	C+N–	C–N–	U+	(%) C+N+/N+
Female	Heterosexual	109	34 (31)	42 (39)	11 (10)	22 (20)	101 (93)	44
Male	Heterosexual	222	39 (18)	171 (77)	2 (1)	10 (5)	70 (32)	19
Male	Bisexual	44	3 (7)	34 (77)	–	7 (16)	11 (25)	8
Male	Homosexual	146	14 (10)	112 (77)	2 (1)	18 (12)	37 (25)	11

C+N+ C trachomatis *and* N gonorrhoeae *both identified; C–N+ Only* N gonorrhoeae *identified; C+N– Only* C trachomatis *identified; C–N– Neither* C trachomatis *nor N gonorrhoeae identified;* U+ U urealyticum *isolated*

cytes in two or more of five random 400x fields in the sediment of the first voided urine (15).

Analysis of outcome: Five types of failure were defined: persistence or recurrence of *N gonorrhoeae* or *C trachomatis* in patients from whom these organisms were initially detected; new isolation of *C trachomatis* in patients from whom it was not initially detected; persistent urethritis in men where there was minimal or no response to treatment but cultures were negative for *N gonorrhoeae* and *C trachomatis* soon after treatment; post gonococcal urethritis in men, 14 or more days after treatment (increased number of polymorphonuclear leukocytes plus symptoms of urethritis, plus urethral discharge, but excluding those with positive cultures for *C trachomatis*); and post gonococcal proctitis (rectal symptoms and an increased number of polymorphonuclear leukocytes on rectal smears, but negative cultures for *N gonorrhoeae* and *C trachomatis*) 14 or more days post treatment.

For patients who initially had positive cultures for *N gonorrhoeae* or *C trachomatis*, and had positive cultures after treatment, it was considered to be a definite microbiological failure when patients denied having sexual intercourse, had sexual intercourse but used a condom, or had sexual intercourse only with a partner who was known to be treated adequately. Additionally for *N gonorrhoeae*, to be considered a microbiological failure, the in vitro susceptibility of the isolate at the time of failure was similar to the initial isolate.

Fisher's exact test (fewer than 60 patients) (16) or χ^2 analysis with Yates' correction (more than 60 patients) (17) were used for statistical comparisons.

The protocol was approved by the Human Subjects Review Committee of the University of British Columbia. All patients gave written informed consent.

RESULTS

Initial isolation results: A total of 109 women and 412 men were enrolled in the study. The number of patients identified initially with *C trachomatis, N gonorrhoeae*, and *U urealyticum* are shown according to sex and sexual preference in Table 1. All *C trachomatis* isolates from heterosexual and bisexual men were from the urethra, while nine of 16 (56%) isolates from homosexual men were from the rectum. Overall rates of detection of *C trachomatis* were not significantly different between men with different sexual preferences, although urethral *C trachomatis* infection was significantly less frequent in homosexual compared with heterosexual men ($P<0.001$). Eighteen women had positive cultures for *C trachomatis* from both the cervix and urethra, 23 from the cervix alone, two from the urethra alone, and two from the cervix, urethra, and rectum. *U urealyticum* was isolated from 18 of 56 men (32%) with *N gonorrhoeae* and *C trachomatis*; 79 of 317 men (25%) with *N gonorrhoeae* alone; three of four men with *C trachomatis* alone; and 18 of 35 men (51%) with neither *N gonorrhoeae* nor *C trachomatis* (not shown in Table 1). The difference in overall rates of isolation of *U urealyticum* between men with *N gonorrhoeae* alone and men with neither *N gonorrhoeae* nor *C trachomatis* was statistically significant ($P<0.025$).

Microbiological outcome for *N gonorrhoeae* treatment: There were no statistically significant differences between treatment groups with respect to age, sex, sexual preference, or initial microbiology. Unless stopped because of side effects, patients were thought to have taken their medications (according to patient diaries and questioning). In total, 387 of the 449 individuals (86.2%) initially shown to have *N gonorrhoeae* made one or more follow-up visits, six or more days after cessation of treatment. Rates of follow-up were similar on both regimens. All women were cured (27 on tetracycline, eight on ceftriaxone). The treatment results for *N gonorrhoeae* in men are shown in Table 2 for all who were culture positive initially and were followed six or more days after cessation of treatment. For men, ceftriaxone always succeeded (58 urethra, 21 rectal, and two pharyngeal infections), and tetracycline succeeded in 142 of 148 men (with failures in two of 109 urethral, four of 15 rectal, and zero of seven pharyngeal infections).

Microbiological outcome for *C trachomatis* infections: Of the 105 individuals with *C trachomatis* infection diagnosed initially, 83 (79%) made one or more follow-up visits 20 or more days after cessation of treatment. The microbiological treatment results for *C trachomatis* are shown in Table 2 for all men initially infected with *C trachomatis* and followed 21 or more days after cessation of treatment. Definite microbiologi-

TABLE 2
Overall outcome in men with *N gonorrhoeae* infection according to treatment regimens, excluding re-exposed failures

Outcome	Regimen	
	Tetracycline n=121	Ceftriaxone n=77
Microbiological failure		
N gonorrhoeae	6/121 (5%)	0/77
C trachomatis	0/16	8/10 (80%)*
Additional *C trachomatis* positive	0/105	12/67 (18%)*
Persistent urethritis	0	1 (1%)
Post gonococcal urethritis	2 (2%)	2 (3%)
Post gonococcal proctitis	0	1 (1%)
Total poor outcome	8 (7%)	24 (31%)*

* *P<0.001*

cal failure occurred in no patients on tetracycline (11 women and 16 men) and 83% on ceftriaxone (two of two women and eight of 10 men) (P<0.001). Furthermore, an additional 13 individuals who received ceftriaxone and had negative cultures for *C trachomatis* initially had positive cultures for *C trachomatis* at the first follow-up visit. One other patient who received ceftriaxone developed positive cultures for *C trachomatis* at the second follow-up after treatment.

Clinical outcome in women: One woman who had received ceftriaxone developed adnexal tenderness at follow-up. She had positive cultures for *C trachomatis* at follow-up.

Outcome in men initially infected with *N gonorrhoeae*: There was a poor outcome in 7% of men on tetracycline and 31% of men on ceftriaxone (P<0.001) (Table 2). If microbiological or clinical failures that arose in men who may have been reinfected are included, the rates of failure rose to 12 of 123 on tetracycline (10%) and 30 of 77 on ceftriaxone (39%) (P<0.001).

Side effects: Information about side effects was obtained from a daily diary filled in by the patient and by questioning. Patients were not specifically asked about a list of side effects. In 181 tetracycline and 90 ceftriaxone courses, side effects of any kind were noted in 49% and 43%, respectively. All were minor except for two individuals on tetracycline who stopped treatment because of side effects. Abdominal symptoms were most frequent on tetracycline (38%) and local discomfort on ceftriaxone (32%).

DISCUSSION

This study clearly shows that for best management of individuals with gonorrhea or contact to gonorrhea, treatment regimens must be active in vivo against not only *N gonorrhoeae*, but also *C trachomatis* and, to a lesser extent, *U urealyticum*.

When this study was initiated, the suggested tetracycline regimen for treatment of gonorrhea had been 500 mg four times daily for five days. We continued the regimen since our results were more than satisfactory for all but rectal gonorrhea in men. However, we concur with the currently recommended seven day regimen. It should again be stressed that tetracyclines alone would no longer be expected to have similar efficacy against infection with *N gonorrhoeae* because of increasing resistance, but the need for combination therapy remains. Despite studies such as this one, and the existence of Canadian and American guidelines strongly promoting the use of combination treatment in patients with proven or suspect gonococcal infection (3-5), combination treatments are not being used routinely in Canada (2). A large cross-Canada study that, if anything, would have been biased towards obtaining data from centres more likely to use recommended regimens, still reported frequent therapy directed only against *N gonorrhoeae* (2). Typically the portion of therapy for *N gonorrhoeae* was a penicillin. Penicillins are not the most appropriate choice in many parts of Canada (1,2,18). Ceftriaxone is the currently recommended choice in these areas. In our study, as in others (11), ceftriaxone was highly effective against *N gonorrhoeae*.

In addition to the conclusion that use of regimens that eradicate both *N gonorrhoeae* and *C trachomatis* are clinically desirable, there are also practical reasons for choosing a regimen with activity against both pathogens, and against *U urealyticum* if feasible. Three reasons are very important. First, diagnostic facilities for *C trachomatis* that provide rapid results are not available to all practitioners. Diagnosis of gonorrhea or history of contact to gonorrhea indicates a significant likelihood of the presence of *C trachomatis*, as has been shown again in this study. Second, as was seen in this study, concurrent *C trachomatis* infection may not be detected at the time of initial evaluation, even using cultures. Many of our culture-positive patients were initially recognized at the first follow-up visit. This presumably is related to the slower replication of *C trachomatis* compared with *N gonorrhoeae*, resulting in a longer interval after exposure before the *C trachomatis* replicates sufficiently to be recognized in diagnostic tests. Finally, diagnosis of *C trachomatis* infection at follow-up by clinical criteria can be exceedingly difficult. Thus, many men with *C trachomatis* lack an increase in the number of polymorphonuclear leukocytes in urethral material. Only three of 25 men who had positive urethral cultures for *C trachomatis* at follow-up had increased polymorphonuclear leukocytes plus symptoms plus urethral discharge at the first follow-up visit with a positive culture for *C trachomatis*. Nevertheless, increased polymorphonuclear leukocytes at follow-up were frequent in men without *C trachomatis* or *N gonorrhoeae* being detected (data not shown). For all these reasons, initial use of a regimen with activity against both *N gonorrhoeae* and *C trachomatis* has practical advantages. Some might argue that it

might not be necessary for homosexual men since the rate of urethral *C trachomatis* infection is usually less in homosexual men with gonorrhea, as was found in this and other studies (6). Nevertheless, because 6% of the homosexual men in this study had rectal *C trachomatis* infection, the overall prevalence of *C trachomatis* in homosexual men with gonorrhea was not significantly different from heterosexual men.

Thus there are numerous reasons why treatment of gonorrhea should include a regimen with complete in vivo activity against both *N gonorrhoeae* and *C trachomatis*. The choice of regimens will vary with time, but the need for dual activity will not.

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