Published in final edited form as:
Sex Transm Dis. 2009 August ; 36(8): 498–500. doi:10.1097/OLQ.0b013e3181a4d147.

Early Repeat *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections Among Heterosexual Men

Patricia J. Kissinger, PHD[*], **Kathleen Reilly, MPH**[*], **Stephanie N. Taylor, MD**[†], **Jami S. Leichliter, PHD**[‡], **Susan Rosenthal, PHD**[§], and **David H. Martin, MD**[†]

[*]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana

[†]Department of Medicine, Louisiana State University, Baton Rouge, Louisiana

[‡]Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

[§]Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas

Chlamydia trachomatis (CT) and neisseria gonorrhoeae (GC) are the 2 most common sexually transmitted infections in the United States.[1] Among women, repeated infections with CT and GC are associated with serious reproductive outcomes such as pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, and infertility.[2-6] Because men often spontaneously clear infection[7,8] and do not have the same adverse outcomes as women, less attention has been paid to repeated infections among men. However, the burden of repeat infections among men is high. The average repeat infection rates of CT and GC among men (11% and 7%)[9] are close to those reported among women (10.7% and 3.6%).[10] Repeatedly infected men are reservoirs of infection for women,[11,12] thus preventing repeat infections among men is an important public health measure. Understanding whether these repeat infections result from reexposure to a baseline partner, infection from a new partner, or treatment failure is important in understanding the most effective interventions.

Centers for Disease Control and Prevention (CDC) suggests expedited partner treatment (EPT) or the provision of medication or prescriptions for index persons to deliver to their sex partners if there is concern that their partner will not seek care.[13] The basic assumption of this approach is that most repeat infections are due to reexposure and treating the source of exposure will reduce the repeat infection. Although the efficacy of EPT for preventing repeat infections among men has been demonstrated in several studies, repeat infection rates among men given EPT remain high (10%–14%).[14,15] This suggests that, among men, some of the repeat infections may be due to factors other than reexposure and that rescreening in addition to the provision of EPT may be needed.

As an additional prevention measure among women, the CDC strongly encourages rescreening of women 3 months posttreatment. Suggestions for men are more nebulous. The CDC states that there is a lack of evidence to support rescreening among men.[16] The purpose of this article is to examine the possible origin of infection among heterosexual men who rescreen positive for CT and/or GC.

Correspondence: Patricia J. Kissinger, PhD, Department of Epidemiology, Tulane University School of Public Health and Tropic Medicine, SL-18, 1440 Canal St, New Orleans, LA 70012. kissing@tulane.edu..

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

METHODS

The study sample consisted of a subset of men who were recruited for a randomized controlled trial of patient-delivered partner treatment for EPT. The methods of the randomized controlled trial have been described elsewhere.[17] Briefly, inclusion criteria for the study were: men attending a public STD clinic in New Orleans, LA between December 2001 and March 2004, were 16 years of age or older, had at least one female sex partner in the last 60 days, and were diagnosed and treated for urethritis based on microscopy. To be included in this subset analysis, study participants had to have a positive test for CT or GC at baseline and to have been retested at 1-month follow-up.

At baseline, the diagnosis of urethritis was made via microscopic examination of a urethral smear stained with a solution of 20% gentian violet and 80% methylene blue. Men were diagnosed with gonococcal urethritis if intracellular diplococci were noted in a stained urethral smear. Nongonococcal urethritis (NGU) was diagnosed if an average of ≥5 white blood cells per oil immersion field were present in the absence of intracellular diplococci. A urethral swab was obtained and tested for CT and GC using the Gen-Probe Pace 2 test (Gen-Probe Inc. San Diego, CA). Index men diagnosed with NGU were treated with 1 g of azithromycin or doxycycline 100 mg twice daily for 7 days. Index men diagnosed with GU were treated with cefixime 400 mg (before removal from the market in 2002) or ciprofloxacin 500 mg (after 2002), or ceftriaxone 250 mg intramuscularly and azithromycin 1 g. Consumption of the first dose of medication by the index men was directly observed by clinic nurses. By design, one-third of the men were randomized to give medication to deliver to their sex partners (i.e., 1 g azithromycin for NGU and 1 g azithromycin plus 400 mg cefixime or 500 mg ciprofloxin for GU).

Patients were asked to return 4 weeks after the initial clinic visit (with a window of 3–8 weeks)[18] for a follow-up interview and to provide a urine sample (per protocol) or urethral swab (if the humans refused urine testing or came to the clinic for a nonstudy visit) for STD testing. Testing of urine specimens was conducted with the strand-displacement amplification method (BD ProbeTec assay, Becton Dickinson Inc. Sparks, MD).

Men were interviewed by study staff or underwent audio and computer-assisted self interview, depending on preference. Interviews included questions about sexual activity for each partner identified on the baseline survey and about any new partners acquired in the follow-up period. Sexual reexposure was assessed for each baseline partner by asking: “Since we last saw you on [date], how many times did you have vaginal sex with [partner named on baseline].” Exposure to a new partner was ascertained by the question “did you have sex with any new partners since we saw you on [date].” Data were summarized over partner categories to: reexposure only, exposure to new partner only, reexposure and new partner, or no exposure. χ^2 test and Fisher Exact tests, when appropriate, were conducted using SAS 9.1 (Cary, NC).

RESULTS

At baseline, 921 men were diagnosed with urethritis via microscopy and of these, 692 (75.1%) tested positive for CT and/or GC. Of the CT/GC positive men,198 (28.6%) were retested. Those who were retested were similar to those who were not in terms of demographics (age, race, education), baseline risk behavior (having more than one sex partner, having given partners money or drugs for sex, binge drinking, street drug use), and having baseline symptoms, and or participation in the EPT trial arm.

Of the baseline 198, 4 men were rescreened before 3 weeks, 12 men were inappropriately treated based on microscopy, and 4 men did not have treatment information documented and

were removed from the analysis. The median time to rescreen for men included (n = 178) in the analysis was 43 days (range: 21–90 days). Baseline results for the 178 included were: CT only (n = 53), GC only (n = 110), and both CT and GC (n = 15).

The retest positive rate was 51/178 (28.7%). Of the 51 who retested positive, 76.5% had the same organism and 23.5% had a different organism than baseline. The rate of reinfection was highest for CT (25/68, 36.8%) compared with GC (20/125, 16.0%) $P < 0.001$, Table 1.

Sexual exposure among the men who had repeat infections (n = 39) was: reexposure to baseline partner 38.1%, new partner only 11.9%, baseline and new partner 4.7%, and no sexual exposure 45.3%. Although the rate of reinfection among men with CT was significantly higher than for men with GC, there was no difference in reexposure histories between men with recurrent CT and those with recurrent GC (Table 1).

DISCUSSION

Our study found high rates of rescreen positives (28.7%) among heterosexual men testing positive for CT and/or GC. Most of these infections were with the same organisms (76.5%) as found at baseline and nearly half (48.6%) of the men who had these reinfections admitted to sexual reexposure. This suggests that the many of these infections were truly repeat infections (i.e., originating from reexposure to an untreated or inadequately treated partner). However, if the number of infections with new organisms (n = 12) are added to the numbers who denied sexual reexposure (n = 19), then 60.5% of these rescreen positives were not repeat infections, suggesting that many infections would not have been prevented by the provision of EPT and rescreening may also be needed.

The proportion of men who rescreened positive for the same organism yet denied sexual exposure (45.3%) was higher than expected. This could have resulted either from inaccurate reporting by the index humans or treatment failure. We attempted to improve the validity or responses by using audio and computer-assisted self-administered survey[19] but inaccurate reporting cannot be ruled out. Genotyping in addition to sexual histories would have improved our ability to correctly classify repeat versus new infection.[20]

The higher rate of repeat infection among men with CT compared with men with GC was surprising. Treatment failure rates should have been low as CT infection has been shown to be highly susceptible to azithromycin[21-23] and GC resistance to ciprofloxacin was low in Louisiana when this study was carried out.[24] However, since sexual exposure was similar between the CT and GC groups, the possibility of increased treatment failures among the CT cases has to be considered. Our data in addition to that from a small randomized trial demonstrating high persistent and/or recurrence rates in the azithromycin treated group[25] suggest that the efficacy of azithromycin may need to be readdressed.

Though there are limitations to this study, several important points are raised. CT and GC rescreening among heterosexual men yields high infection rates. Although much of the rescreen positive rate was driven by reinfection, treatment failure and new infections were also contributors. These data suggest that rescreening among men, in addition to the provision of EPT, could be a useful public health strategy. Future studies utilizing highly discriminatory genotyping methods and strategies to increase male rescreening rates are needed to confirm these findings.

Acknowledgments

Supported by grants from Centers for Disease Control and Prevention Cooperative Agreement R30/CCR619146 and NIH grant U19 AI061972.

REFERENCES

1. Xia M, Whittington WL, Holmes KK, et al. Pulsed-field gel electrophoresis for genomic analysis of *Neisseria gonorrhoeae*. J Infect Dis. 1995; 171:455–458. [PubMed: 7844389]
2. Hillis SD, Wasserheit JN. Screening for chlamydia–a key to the prevention of pelvic inflammatory disease [comment]. N Engl J Med. 1996; 334:1399–1401. [PubMed: 8614429]
3. Westrom LV. Sexually transmitted diseases and infertility. Sex Transm Dis. 1994; 21(suppl 2):S32–S37. [PubMed: 8042113]
4. Westrom L. Effect of pelvic inflammatory disease on fertility. Venereology. 1995; 8:219–222. [PubMed: 12291198]
5. Lan J, van den Brule AJ, Hemrika DJ, et al. *Chlamydia trachomatis* and ectopic pregnancy: Retrospective analysis of salpingectomy specimens, endometrial biopsies, and cervical smears. J Clin Pathol. 1995; 48:815–819. [PubMed: 7490313]
6. Pearlman MD, McNeeley SG. A review of the microbiology, immunology, and clinical implications of *Chlamydia trachomatis* infections. Obstet Gynecol Surv. 1992; 47:448–461. [PubMed: 1620525]
7. Parks KS, Dixon PB, Richey CM, et al. Spontaneous clearance of *Chlamydia trachomatis* infection in untreated patients. Sex Transm Dis. 1997; 24:229–235. [PubMed: 9101635]
8. Joyner JL, Douglas JM Jr, Foster M, et al. Persistence of *Chlamydia trachomatis* infection detected by polymerase chain reaction in untreated patients. Sex Transm Dis. 2002; 29:196–200. [PubMed: 11912459]
9. Fung M, Scott KC, Kent CK, et al. Chlamydia and Gonorrhea Re-infection among Males: A Systematic Review of Data to Evaluate the Need for Re- testing. Sex Transm Infect. 2007; 83:304–309. [PubMed: 17166889]
10. Peterman TA, Tian LH, Metcalf CA, et al. High incidence of new sexually transmitted infections in the year following a sexually transmitted infection: a case for rescreening [summary for patients in Ann Intern Med 2006; 145:144; PMID: 17043335]. Ann Intern Med. 2006; 145:564–572. [PubMed: 17043338]
11. Gunn RA, Fitzgerald S, Aral SO. Sexually transmitted disease clinic clients at risk for subsequent gonorrhea and chlamydia infections: possible "core" transmitters. Sex Transm Dis. 2000; 27:343–349. [PubMed: 10907910]
12. Ellen JM, Gaydos C, Chung SE, et al. Sex partner selection, social networks, and repeat sexually transmitted infections in young men: a preliminary report. Sex Transm Dis. 2006; 33:18–21. [PubMed: 16385217]
13. Centers for Disease Control P. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006 [erratum appears in MMWR Recomm Rep 2006; 55:997.]. MMWR Recomm Rep. 2006; 55(RR-11):1–94. [PubMed: 16888612]
14. Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection [comment]. N Engl J Med. 2005; 352:676–685. [PubMed: 15716561]
15. Kissinger P, Mohammed H, Richardson-Alston G, et al. Patient-delivered partner treatment for male urethritis: a randomized, controlled trial. Clin Infect Dis. 2005; 41:623–629. [see comment]. [PubMed: 16080084]
16. Centers for Disease Control and Prevention Male Chlamydia Screening Consultation–Meeting Report. Meeting Report; Atlanta, GA. March 28–29; 2006. May 22, 2007 http://www.cdc.gov/std/chlamydia/ChlamydiaScreening-males.pdf
17. Kissinger P, Mohammed H, Richardson-Alston G, et al. Patient-delivered partner treatment for male urethritis: A randomized controlled trial. Clin Infect Dis. 2005; 41:623–629. [PubMed: 16080084]
18. Brunham RC, Plummer FA. A general model of sexually transmitted disease epidemiology and its implications for control. Med Clin North Am. 1990; 74:1339–1352. [PubMed: 2246943]
19. Kissinger P, Rice J, Farley T, et al. Application of computer-assisted interviews to sexual behavior research. Am J Epidemiol. 1999; 149:950–954. [PubMed: 10342804]

20. Pedersen LN, Podenphant L, Moller JK. Highly discriminative genotyping of *Chlamydia trachomatis* using ompl and a set of variable number tandem repeats. Clin Microbiol Infect. 2008; 14:644–652. [PubMed: 18558936]
21. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: A meta-analysis of randomized clinical trials. Sex Transm Dis. 2002; 29:497–502. [PubMed: 12218839]
22. Tobin JM, Harindra V, Mani R. Which treatment for genital tract *Chlamydia trachomatis* infection? Int J STD AIDS. 2004; 15:737–739. [PubMed: 15537459]
23. Wang SA, Papp JR, Stamm WE, et al. Evaluation of antimicrobial resistance and treatment failures for Chlamydia trachomatis: a meeting report. J Infect Dis. 2005; 191:917–923. [PubMed: 15717267]
24. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis. 1995; 20(suppl 1):S47–S65. [PubMed: 7795109]
25. Stamm WE, Batteiger BE, McCormack WM, et al. A randomized, double-blind study comparing single-dose rifalazil with single-dose azithromycin for the empirical treatment of nongonococcal urethritis in men. Sex Transm Dis. 2007; 34:545–552. [PubMed: 17297383]

TABLE 1

Sexual Behavior of Those Rescreening Positive for the Same Organism

	CT	GC
Rescreened positive with same organism *	25/68 (36.8%) †	20/125 (16.0%)
Sex with baseline partner(s) only	11/25 (44.0%)	7/18 (38.9%) ‡
Sex with new partner(s) only	3/25 (12.0%)	2/18 (11.1%) ‡
Sex with baseline partner and new partner	2/25 (8.0%)	0/18 (0.0%) ‡
Denied sex	9/25 (36.0%)	9/18 (50.0%) ‡

* The denominators include 15 men coinfected with CT and GC infection at baseline.

† $P < 0.01$.

‡ Sexual behavior missing for 2 men with GC.