Acute Primary *Chlamydia trachomatis* Infection in Male Adolescents After Their First Sexual Contact

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**Background:** *Chlamydia trachomatis* infection occurs primarily among young sexually active persons. Few studies have evaluated the kinetics of markers of infection in male adolescents after their first sexual contact.

**Design:** Primary *C* *trachomatis* infection in 4 young male adolescents after their first sexual contact was diagnosed by polymerase chain reaction and antigen detection in sequential first voiding urine and urethral specimens, respectively. Serial serum samples were assessed for the presence of specific IgA and IgG antibodies.

**Results:** Both polymerase chain reaction and antigen detection correctly identified all cases of primary *C* *trachomatis* infection. The polymerase chain reaction method was, however, an earlier marker of infection. Three patients were seronegative at presentation. Two of these subsequently seroconverted to either IgA or IgG, while the third remains seronegative. The time interval from onset of symptoms to seroconversion ranged from 10 to 25 days.

**Conclusions:** Although polymerase chain reaction and antigen and serologic detection have previously been described in primary *C* *trachomatis* infection, this report documents the variability of these markers during the first phase of infection in non–sexually active young male adolescents. *C* *trachomatis* can be acquired by male adolescents after their first sexual contact; however, there is a prolonged period when the patient is seronegative, yet infections can occur.


**C** *Hlamydia trachomatis* infections occur primarily among sexually active persons. Infections are associated with many clinical syndromes, ranging from urethritis, proctitis, and epididymitis in men to cervicitis, salpingitis, cystitis, ectopic pregnancy, infertility, and pelvic inflammatory disease in women. In infants born to infected mothers, conjunctivitis and pneumonia may be present. Unfortunately, symptoms are often mild or absent among infected men and women, creating a large reservoir of infected persons who spread the infection to new sexual partners. Widespread screening, therefore, has been recommended for persons at increased risk; ie, those who are young, sexually active, and who have new or multiple sexual partners. Diagnosis is made either by isolation of the pathogen or by a nonculture method, such as direct fluorescent antibody (DFA), antigen (Ag) detection, DNA probe, or DNA amplification technique confirmed by either a second culture or a nonculture test method. *C* *trachomatis* infection is highly prevalent in young sexually active adolescents. The acute nature of this clinical syndrome in young males without previous sexual experience, and its relation to nonculture diagnostic methods and serologic testing have, however, not been addressed previously. We therefore undertook an investigation of extensive laboratory markers in sequential urine, urethral, and serum samples obtained from 4 male adolescents attending a sexually transmitted disease (STD) clinic for *C* *trachomatis* infection subsequent to their first sexual contact. We used the polymerase chain reaction (PCR), Ag detection, and serologic detection methods.

**RESULTS**

Four young males without previous sexual experience were available for continued evaluation. All presented to the STD clinic with genital symptoms. None had a previous history of *C* *trachomatis* infection and...
PATIENTS AND METHODS

PATIENT REPORTS

Patient 1

A 15-year-old healthy male adolescent developed urethral discharge and dysuria 5 days before he was seen in the STD clinic. On the second day of his illness tender inguinal lymph nodes were noted. His first ever-sexual contact was 17 days previously, with a female partner, and was unprotected. The patient had never been tested for chlamydial infection and denied previous urethral symptoms. His physical examination was remarkable except for a profuse yellow urethral discharge and tender inguinal lymph nodes. The symptoms gradually resolved after 2 weeks of oral therapy with 100 mg of doxycycline twice daily. The patient remained asymptomatic in the ensuing 6 months.

Patient 2

A 14-year-old healthy male adolescent noted pain in his right testicle approximately 2 weeks before evaluation. He was not sexually active until 3 weeks prior to the onset of his symptoms. He had never suffered from urethral symptoms or discharge. His physical examination was remarkable for a right tender and swollen epididymis without testicular involvement. His symptoms gradually improved after administration of 2 weeks of 100 mg of oral doxycycline twice daily. He remained asymptomatic after 8 months of follow-up.

Patient 3

A healthy 15-year-old male adolescent developed urethritis without urethral discharge approximately 10 days before his first presentation to the STD clinic. His first sexual contact occurred 2 weeks before the onset of his illness and was unprotected. His illness resolved completely over the ensuing 2 weeks following treatment with 500 mg of azithromycin daily for 3 days. He remained asymptomatic after 6 months of follow-up.

Patient 4

Patient 4 was a 16-year-old male adolescent that developed a white creamy urethral discharge and dysuria 3 days before he presented to the STD clinic. In addition, he reported bilateral inguinal pain. He had his first sexual contact 26 days prior to his illness with a female partner and was unprotected. He was treated with 1000 mg of azithromycin for one day with gradual resolution of his symptoms.

PATIENT POPULATION

From September 1995 through July 1997, young adolescent males attending Bnai Zion Medical Center Sexually Transmitted Disease Clinic (Haifa, Israel) were prospectively enrolled. Our aim was to detect a new chlamydial infection in adolescent males after their first sexual experience. After informed consent was obtained, a questionnaire addressing sexual behavior and symptoms suggesting a STD was administered. The questionnaire asked about STD history, consistent condom use, and whether the patient had multiple or new sexual partners within the previous 90 days. All patients underwent a physical examination and collection of urethral specimens. A presumptive diagnosis of chlamydia urethritis in males was made if there was a history of urethral discharge or dysuria and 4 or more polymorphonuclear leukocytes per oil immersion field of a Gram-stained urethral smear or pyuria noted in urinalysis and no gram-negative diplococci. All adolescent males who attended the STD clinic were routinely screened for chlamydia by PCR or urethral symptoms (Roche Molecular Systems, Branchburg, NJ). Eleven male adolescents reported their first sexual contact with a partner in the previous month. Six of them had symptoms, while 5 reported contact with someone with a possible STD as a reason for their visit. Other STDs that were evaluated included new episodes of gonorrhea, syphilis, trichomoniasis, seroconversion to human immunodeficiency virus, herpes simplex type 2, and hepatitis B virus. Following the patient's baseline visit, subsequent specimens were obtained whenever the patient returned to the clinic for therapy after the diagnosis has been made, or for a follow-up visit because of the presence of symptoms. Four adolescents were available for continuous laboratory testing, while the rest were lost to follow-up. Written informed consent was obtained from all patients and the institutional review board approved this study.

LABORATORY PROCEDURES

Urethral and urine specimens for chlamydia testing were refrigerated at 4°C immediately after collection for 96 hours until processed according to the manufacturer's instructions. A separate set of urethral swabs for Neisseria gonorrhoeae, Ureaplasma urealyticum, and Trichomonas vaginalis was obtained and processed immediately.

Chlamydia Ag test (DAKO; IDEA, United Kingdom) was obtained following a prostate massage by inserting a narrow-shafted, dacron-tipped swab 2 to 3 cm into the urethra. The swab was placed into a chlamydia transport vial containing sucrose-phosphate buffer, 10% fetal bovine serum, and antibiotics.

Polymerase chain reaction–polymerase chain reaction analysis was performed by a commercial, rapid, nonradioactive assay (Roche Molecular Systems, Branchburg, NJ) from first voiding urine specimens according to the manufacturer's instructions.

Serology-sequential blood samples for determination of antibodies to C. trachomatis were obtained from all patients. The presence of specific antibodies against C. trachomatis was assessed by an enzyme immunoassay with 2 commercial kits (Sero CT; Savoy Diagnostics, Yavne, Israel) a peptide-based enzyme-linked immunosorbent assay (ImmunoComb; Organics, Yavne, Israel). All serum samples were examined for IgA and IgG antibodies.

The patient reference standard was the following: patients who had 2 or more positive Ag or PCR tests were considered truly infected. Laboratory values for PCR, Ag, and serologic detection methods are presented in the Table. Selective media (Thayer Martin selective media; Hy labs, Rehovot, Israel) was used for N. gonorrhoeae culture. Urealyticum was isolated by selective media (Mycostant Fasten, Signes, France). T. vaginalis was detected by wet mount and syphilis by rapid plasma reagin and Treponema pallidum hemagglutination serologic testing (BioKit, Barcelona, Spain).
no other STD was demonstrated. All patients were correctly diagnosed for Chlamydia trachomatis infection by PCR and Ag detection. Chlamydia trachomatis was positive by PCR at least twice in all patients both at presentation and several days later when antibiotic treatment was introduced. Three patients became PCR negative after treatment, and patient 4 remained PCR positive 7 days after antibiotic treatment was started.

Chlamydia PCR was an earlier marker of infection compared with Ag detection in 2 patients. Chlamydia Ag was detected in only 50% of the PCR-positive specimens. Seroconversion to C trachomatis was documented by enzyme immunoassay in 3 of the 4 patients on the basis of the development and subsequent increase in specific antibodies in the serum (Table). There were no major differences between the 2 serologic kits in the IgA and IgG signal/cutoff values. Patient 3 seroconverted to IgA-specific and IgG-specific antibodies. Seroconversion was noted for IgG only in patient 1 and for IgA only in patient 2. Patient 4 had no detectable C trachomatis antibodies for 120 days after onset of his symptoms. On presentation at the STD clinic, 3 patients were seronegative for C trachomatis. They subsequently developed antibodies to C trachomatis 10 to 25 days after onset of their symptoms.

**COMMENT**

Our patients presented with clinical and laboratory findings consistent with primary C trachomatis infection following their first sexual experience. The reason for the varied presentations of acute C trachomatis infection is unknown, but it is likely to involve several factors, including the immune response of the host and the quantity, virulence, or tropism of the infecting bacterial strains. Chlamydial infections are highly prevalent in young, sexually active adolescents. More than half of all high school students in the United States have had sexual intercourse by age 18 years.² Having multiple sexual partners or a new sexual partner has been shown to predict chlamydial infection.⁸,⁹ Our study, in which all males reported that they were not sexually active prior to their infection, confirmed previous findings that having a new sex partner was associated with an increased chance of chlamydial infection.⁸,⁹ None of the patients used condoms, indicating another increased risk not only for chlamydial infections, but also for other STDs. This was not demonstrated in our study, because none of our patients had other STDs. Nevertheless, it is prudent to perform a broad evaluation for STDs in a symptomatic adolescent with proven chlamydial infection.

Chlamydia trachomatis was readily detectable by PCR in all first voiding urine specimens on presentation at the clinic. C trachomatis PCR was positive prior to Ag detection in 2 patients, suggesting that it is an earlier and more sensitive marker of infection.¹⁰,¹¹ Nucleic acid amplification assays, because of their high sensitivity, can be used for routine screening of noninvasive specimens such as urine. With sexually active teens practicing high-risk behavior, frequent testing is ideal and offers multiple opportunities for education and counseling by the health care worker. All of our young males were symptomatic. However, only 4 of 11 eligible males were available for our prospective cohort study requiring repeated swabs and venipunctures. It would be more informative if completely asymptomatic males who first had intercourse less than a month earlier were also tested to determine if asymptomatic boys acquired chlamydial infection.

Our study did not address numerous issues, such as how sexually active adolescents should be screened and whether adolescents with repeated infection are more likely to be asymptomatic compared with those with a primary infection. Nevertheless, because of the high prevalence and the frequently asymptomatic nature of chlamydial infections, a targeted screening program in adolescents may have great potential to reduce the morbidity of sequelae such as pelvic inflammatory disease and neonatal chlamydial infections.

The presence of C trachomatis DNA in patient 1 after 7 days of therapy does not necessarily indicate treatment failure. There is likely to be an interval following initiation of therapy during which nucleic acid detection test will remain positive. This is thought to be a result of the antibiotic therapy, in which chlamydial or
organisms are initially killed, but residual chlamydial Ag and nucleic acid remain at the site of infection and are not cleared by the immune system for some time after therapy is completed. Using doxycycline therapy, this interval has been reported to persist for up to 3 weeks after completion of treatment.12,13

Serologic tests are not considered to be useful in the diagnosis of acute C trachomatis infections of the genital tract in men.4,15 Indeed, 3 of our patients were seronegative for C trachomatis at presentation, and 1 of them (patient 4) did not mount a serologic response. This patient had been infected previously by Chlamydia pneumonia (he had high specific titers for C pneumonia). It is possible that the presence of IgG to C pneumonia generated an amnestic response to his most recent exposure to C trachomatis.

The kinetics of the development of the C trachomatis–specific antibody response was not similar in all 4 patients. The time to seroconversion ranged from 9 to 25 days following initiation of symptoms. Only patient 3 demonstrated the classic serologic response of IgA preceding the IgG response against C trachomatis.16 In contrast, patients 1 and 2 demonstrated a selective seroconversion of either IgG or IgA. Therefore, the absence of antichlamydial antibodies in a single serum specimen could not reliably exclude the presence of an acute genital infection in our male patients. Sequential sera for both IgA and IgG antibodies may improve the sensitivity of these methods.

Positive PCR for C trachomatis with negative serologic test results may suggest an acute infection in adolescent males after their first sexual experience. Infection may be possible for a period of more than 120 days. Chlamydial infections are highly prevalent in young adolescents. Because more are asymptomatic and the consequences of such infections can be so severe as to cause pelvic inflammatory disease, ectopic pregnancy, and infertility, active screening is strongly recommended by the Centers for Disease Control and Prevention. Prevention and control of C trachomatis may be enhanced by urine amplification assays that are cost-effective and that can be used frequently throughout the adolescent years, when teenagers are at most risk of becoming infected.17

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REFERENCES

17. Howell MR, Quinn TC, Brathwaite W, Gaydos CA. Urine based amplification vs two non-amplified techniques for identification of Chlamydia trachomatis. cost effectiveness under three screening alternatives in a low prevalence population in women [abstract]. In: Proceedings of the third meeting of the European Society for Chlamydial Research; March 20, 1996; Bologna, Italy.