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Evaluation of the Abbott LCx Ligase Chain Reaction Assay for Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in Urine and Genital Swab Specimens from a Sexually Transmitted Disease Clinic Population

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The Abbott LCx ligase chain reaction (LCR) assay for the simultaneous detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* was evaluated by using swab and urine specimens from 562 patients. *C. trachomatis* results by LCR were compared to those by the Gen-Probe PACE 2 assay, whereas *N. gonorrhoeae* results by LCR were compared to those by culture. The Gen-Probe and LCR assays were performed according to the manufacturers' instructions. Gram-negative diplococci growing on modified Thayer-Martin medium were confirmed as *N. gonorrhoeae* by the GonoGen II assay. Supplemental data analysis was performed by major outer membrane protein PCR for *C. trachomatis* and probes for pilin gene detection for *N. gonorrhoeae*. A true-positive result for each pathogen was defined as a positive result for all three or two of three assays. Overall agreement among the six assays was 94.8%. *C. trachomatis* prevalence was 16.2%; *N. gonorrhoeae* prevalence was 5.5%. The overall sensitivity and specificity, respectively, for each test (after supplemental data analysis) were as follows: for *C. trachomatis*, Gen-Probe, 65.9 and 100%; LCR on urine, 90.1 and 100%; LCR on swab specimens, 96.7 and 100%; and for *N. gonorrhoeae*, culture, 80.6 and 100%; LCR on urine, 93.5 and 99.8%; and LCR on swab specimens, 96.8 and 100%. For women, the *N. gonorrhoeae* culture was very insensitive compared to its performance in men (58.3 versus 94.7%, respectively). For *C. trachomatis*, the Gen-Probe assay's sensitivity was lower for men than for women (62.3 versus 71.1%, respectively). The sensitivity for *C. trachomatis* detection by LCR on urethral and cervical swab specimens was 96.2 and 97.4% for men and women, respectively. For men, swab results were slightly better than urine results for both pathogens (sensitivity for *C. trachomatis* in swab and urine specimens, 96.2 and 92.5%, respectively; sensitivity for *N. gonorrhoeae* in swab and urine specimens, 100 and 94.7%, respectively), while for women, cervical swabs were superior in sensitivity to urine samples for detecting *C. trachomatis* (swab, 97.4%; urine, 81.6%) and equivalent for *N. gonorrhoeae* (swab, 92.3%; urine, 91.6%). The LCx LCR appears to be both sensitive and specific for the detection of *C. trachomatis* and *N. gonorrhoeae* when performed on urine or genital swab samples. Swab samples had better sensitivity than urine samples for the detection of both pathogens.

Chlamydia trachomatis is one of the major causes of sexually transmitted diseases (STDs) worldwide. Many of the infections are asymptomatic yet lead to severe sequelae, especially in women, who may develop pelvic inflammatory disease and infertility. Accurate diagnosis of those infected is essential for effective treatment and control strategies (3).

While *Neisseria gonorrhoeae* is less prevalent than *C. trachomatis*, STD clinics continue to report rates of 327 cases/100,000 men and 229 cases/100,000 women annually in the United States (4). As many as 40% of men and 30 to 50% of women with gonococcal disease are coinfected with *C. trachomatis* (3). Laboratory tests designed to detect both pathogens may be advantageous to clinics that have active screening programs. In addition, tests that allow screening using urine samples (as opposed to urethral swabs) tend to be more successful among adolescent males, who are at a high risk of infection. Amplification tests, as opposed to enzyme immunoassay (EIA) and culture, were found to be more cost-effective, as reported in a recent paper on screening asymptomatic women for *C. trachomatis* infections (10).

The present study evaluated the performance of the Abbott LCx ligase chain reaction (LCR) for the detection of *C. trachomatis* and *N. gonorrhoeae* in genitourinary samples from men and women attending an STD clinic.

MATERIALS AND METHODS

Patient selection. Over a period of 3 months, 600 consecutive patients attending the Salt Lake City-County STD clinic were evaluated. Patients ranged in age from 14 to 57 years. Clinical histories obtained from all patients included the following information: gender, year of birth, presence of symptoms and signs, recent exposure to an STD, treatment, and risk history (number of sexual partners, change in sexual partners, and previous positive test for *C. trachomatis* or *N. gonorrhoeae*). Patients were not included in the study if they were currently on treatment or had completed treatment for *C. trachomatis* or *N. gonorrhoeae* within the 2 weeks prior to evaluation.

Specimen collection and processing. Prior to the study, the standard of practice in the STD clinic was to collect cervical and urethral swab specimens from women and men, respectively. For a diagnosis of *N. gonorrhoeae*, the swab was cultured on modified Thayer-Martin (MTM) medium, which was incubated at an on-site laboratory. A Gen-Probe swab specimen was collected for *C. trachomatis*

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TABLE 1. Summary of algorithm for supplemental testing of specimens[a]

Pathogen	Gen-Probe or culture[b]	LCR performed on:		Total no. of specimens
		Urine	Swab specimen	
C. trachomatis	Pos	Neg	Neg	0
	Neg	Pos	Neg	3
	Neg	Neg	Pos	9
N. gonorrhoeae	Pos	Neg	Neg	0
	Neg	Pos	Neg	2
	Neg	Neg	Pos	1

[a] Any single assay positive (Pos) for either *N. gonorrhoeae* or *C. trachomatis* was sent for supplemental testing. Neg, negative.
[b] *C. trachomatis* and *N. gonorrhoeae* specimens were assayed by the Gen-Probe test and culture, respectively.

diagnosis and was tested off-site at the Bureau of Epidemiology and Laboratory Services, Utah Department of Health, several miles from the clinic. During the study, specimens were collected from women in the following fashion. The larger swab in the LCx STD assay collection kit was used to clear away the cervical mucus. The smaller swab was used to collect the endocervical specimen. The LCx swab was used to inoculate the MTM medium for *N. gonorrhoeae* culture. After inoculation of the MTM medium, the swab was returned to the LCx transport tube. A Gen-Probe cervical collection swab was used to collect specimens from females for *C. trachomatis* testing. After careful collection of the swab samples, 15 to 20 ml of first-voided urine (FVU) was subsequently collected in a plastic preservative-free sterile collection cup.

For men, the smaller LCx swab was used to collect a urethral specimen. This same swab was likewise used to inoculate the MTM medium for *N. gonorrhoeae* culture. The Gen-Probe collection swabs from males were obtained for comparative *C. trachomatis* testing, followed by the 15 to 20 ml of FVU collected as specified above.

LCR swab specimens were transported to the Associated Regional and University Pathologists laboratories at room temperature and were stored at 2 to 8°C until processed. All samples were processed within 5 days of collection. Urine specimens were immediately refrigerated and were transported and stored at 2 to 8°C. Gen-Probe swabs were transported at room temperature and were stored at 2 to 8°C until tested. All specimens were tested within 7 days of collection.

Gen-Probe PACE 2 assay. The PACE 2 assay was performed according to the manufacturer's instructions. After arrival in the laboratory, each transport tube was vortexed and the swab was removed. Hybridization and separation reagents were added, and the appropriate incubation steps were performed. The tubes were placed on a magnetic separation base for 20 min at room temperature. The supernatant was decanted, and wash solution was added. After resuspension of the pellets, the tubes were placed in a LEADER Luminometer. Results were calculated based on the difference between the response (in relative light units) of the specimen and the mean response of the negative reference. Samples with results of >2,000 relative light units were retested and reported as high positives. Samples with results of 2,000 relative light units down to the positive cutoff were defined as low positives. These samples were confirmed by the Gen-Probe probe competition assay (PCA). Negative samples with results ranging from the cutoff to 30% below the cutoff were defined as high negatives (HN). All HN were tested by PCA. HN that were confirmed by PCA were reported as inconclusive, and the subject was required to submit another sample.

Abbott LCR. The LCx LCR uses oligonucleotide pairs to hybridize target sequences of the cryptic plasmid of *C. trachomatis* and the *opa* gene of *N. gonorrhoeae*. The tests were performed according to the manufacturer's specifications. Cervical and urethral swab specimens were heated at 97°C for 15 min and cooled, and the swabs were expressed and discarded. One hundred microliters of the remaining fluid was added to a tube containing 100 μl of the LCR mixture. Amplification was performed for 40 cycles of incubation for 1 s at 93°C, 1 s at 59°C, and 1 min 10 s at 62°C. One hundred microliters of the amplified product was transferred to a reaction cell, which was placed in the analyzer for detection by microparticle EIA. Two positive controls, two negative controls, and two calibrators were included in each run.

After the urine samples were mixed, 1 ml was removed and centrifuged for 15 min at 13,000 × *g*. The resulting pellet was resuspended in 1 ml of resuspension buffer, heated, cooled, and tested by LCR as described above.

***N. gonorrhoeae* culture.** Cervical and urethral specimens inoculated onto MTM medium were transported immediately to the on-site laboratory. Plates were incubated at 35°C for 48 h in a humidified CO_2 incubator. Oxidase-positive, gram-negative diplococci were confirmed as *N. gonorrhoeae* by the GonoGen II membrane immunoassay monoclonal antibody test (Becton Dickinson Microbiology Systems, Cockeysville, Md.).

Definition of true positives. A true-positive result was defined as follows: (i) for *C. trachomatis*, positive results by the Gen-Probe assay, LCR using urine, and LCR using a swab specimen; (ii) for *N. gonorrhoeae*, positive results by culture, LCR using urine, and LCR using a swab specimen; (iii) positive results by two of three assays for either of the two diseases; or (iv) a positive result by a single assay alone, which was confirmed by supplemental testing performed by Abbott Laboratories.

Supplemental testing. Probes specific for the pilin and protein 1 genes were used to confirm *N. gonorrhoeae* results (14). Probes specific for the major outer membrane protein gene were used to confirm *C. trachomatis* results (9) (Table 1).

Data analysis. Sensitivity, specificity, and positive and negative predictive values were calculated for each assay after inclusion of supplemental data. Statistical significance was determined by chi-square analysis.

RESULTS

Results from 562 patients, 283 men and 279 women, were available for analysis. Thirty-eight patients were excluded for the following reasons: insufficient specimen for supplemental data analysis ($n = 3$); mislabeled specimens ($n = 2$); incomplete specimen collection ($n = 8$); and specimens that did not reach the reference laboratory for LCR testing ($n = 25$). The overall prevalence of *C. trachomatis* was 16.2% (18.7% for men and 13.6% for women). For *N. gonorrhoeae*, the overall prevalence was 5.5% (6.7% for men and 4.3% for women). A total of 449 samples were negative by all tests, and three patients tested positive for both pathogens by all six methods performed. Five men and three women had confirmed dual infections. The overall agreement among the tests was 94.8%. All data are summarized in Table 2.

***C. trachomatis* testing.** The LCR test was compared to the Gen-Probe assay because the latter was the standard assay in use at the time of the study. Before the supplemental data analysis, there were 79 patients who met the definition of a true-positive case. Sixty of these patients were *C. trachomatis* positive by the Gen-Probe test, and all 79 were positive by both the LCR swab and LCR FVU assays, for overall sensitivities of 75.9, 100, and 100% and specificities of 100, 98.1, and 99.4%,

TABLE 2. Summary of assay sensitivity and specificity[a]

Pathogen	Total no. of samples tested	Total no. of positive samples	Assay	Sensitivity (%)						Specificity (%)					
				Before supplemental data analysis			After supplemental data analysis			Before supplemental data analysis			After supplemental data analysis		
				Overall	M	F	Overall	M	F	Overall	M	F	Overall	M	F
C. trachomatis	562	91	Gen-Probe	75.9	70.2	84.4	65.9	62.3	71.1	100	100	100	100	100	100
			LCx (swab specimen)	100	100	100	96.7	96.2	97.4	98.1	98.3	97.9	100	100	100
			LCx (urine specimen)	100	100	100	90.1	92.5	86.8	99.4	99.1	99.6	100	100	100
N. gonorrhoeae	562	31	Culture	86.2	100	63.6	80.6	94.7	58.3	100	100	100	100	100	100
			LCx (swab specimen)	100	99.6	100	96.8	100	91.7	99.6	99.6	100	100	100	100
			LCx (urine specimen)	96.6	100	90.1	93.5	94.7	91.7	99.6	99.6	99.6	99.8	99.6	100

[a] M, male; F, female.

respectively (Table 2). After the addition of the supplemental data, 91 patients, 53 men and 38 women, had confirmed *C. trachomatis* infections. The Gen-Probe assay was positive for 60 patients, the LCR swab assay was positive for 88 patients, and the LCR FVU assay was positive for 82 patients, for overall sensitivities of 65.9, 96.7, and 90.1%, respectively, and specificities of 100% (for all three tests) (Table 2). The LCR swab and LCR FVU assays were statistically more sensitive than the Gen-Probe test for the detection of *C. trachomatis* infection ($P < 0.001$ and $P = 0.005$, respectively).

Table 2 also summarizes the data for men and women before and after supplemental data were included. For men, the chlamydia results prior to addition of supplemental data were similar to the overall values. The Gen-Probe sensitivity before and after the addition of supplemental data was 70.2 and 62.3%, respectively. Likewise, the LCR swab and LCR urine assay data were statistically superior to the Gen-Probe data for detection of *C. trachomatis*, with sensitivities of 96.2 and 92.5%, respectively ($P < 0.001$ and $P = 0.05$, respectively).

There were 20 men with confirmed true-positive chlamydia infection after the inclusion of supplemental data who tested negative for *C. trachomatis* by the Gen-Probe assay. Clinical data were available for all of these individuals, and the data were categorized into four areas: symptoms, signs, history of exposure, and other Centers for Disease Control and Prevention-defined risk factors (3, 4). Only one patient denied any symptoms, exposure history, or risk factors and had a negative physical examination. This patient tested positive for *C. trachomatis* by both the LCR swab and FVU assays. More than half (80%) of the patients had positive findings for at least two of the four categories listed above. Nine patients had recently acquired a new sexual partner, and nine patients had exposure to an individual with a confirmed *C. trachomatis* or *N. gonorrhoeae* infection.

For the women, the performance of the Gen-Probe assay was slightly better than its performance in men, both before and after the inclusion of supplemental data, with sensitivities of 84.4 and 71.1%, respectively. The LCR swab was equal in its performance in men and women after the inclusion of supplemental data and was clearly superior to the Gen-Probe assay (sensitivity, 97.4%; $P = 0.05$). The LCR FVU results for women, while superior to those for the Gen-Probe cervical swab, were less sensitive than those for men, with sensitivities 86.8 and 92.5%, respectively. Clinical data were available for 10 of the 11 Gen-Probe-negative patients confirmed as positive. There were no patients who were negative for any of the four categories mentioned above. Seven of the patients had at least two positive findings for *C. trachomatis*, and three patients had exposure to a partner known to be infected with *C. trachomatis*. Seven women had acquired a new sexual partner within 3 months of presentation.

***N. gonorrhoeae* testing.** LCR swab and urine results were compared to those by culture; culture was the standard practice at the clinic at the time of the study. Before the supplemental data, there were 29 specimens that met the definition of a true positive. Culture was positive for 25 patients, the LCR swab assay was positive for 29 patients, and the LCR urine assay was positive for 28 patients, for overall sensitivities of 86.2, 100, and 96.6% and specificities of 100, 99.6, and 96.6%, respectively (Table 2).

After supplemental data analysis, 31 patients, 12 women and 19 men, had confirmed *N. gonorrhoeae* infections. The subsequent sensitivities and specificities for culture, LCR swab assay, and LCR urine assay after the addition of the supplemental data were as follows: 80.6 and 100%, 96.8 and 100%, and 93.5 and 99.8%, respectively. The LCR tests identified seven additional *N. gonorrhoeae*-positive patients missed by culture. However, these results are not statistically significant ($P = 0.25$).

The separate data for men and women are also included in Table 2. For men, all of the methods used had high sensitivity and specificity both before and after supplemental data analysis. The LCR performed the best, with a 100% sensitivity. The single patient who had a positive test by the LCR swab assay had only symptoms of urethritis but no discharge and had been exposed to a new sexual partner with another STD in the previous 90 days. In one totally asymptomatic patient with no risk factors or history of exposure, the FVU tested positive by LCR while all other assays were negative, including the supplemental assays. This test was the only false-positive result during the study.

In women, *N. gonorrhoeae* culture had a very low sensitivity both before and after supplemental data analysis, 63.6 and 58.3%, respectively. The performance of LCR on swabs was equivalent to that on FVU (91.7% sensitivity). Five women with confirmed infection tested negative by culture. Two of the five women were symptomatic and had mucopurulent cervicitis on examination. Two other women had symptoms and had a history of exposure to documented *N. gonorrhoeae* from a new sexual partner within the previous 90 days. Only one patient had no symptoms, signs, or exposure history, but she did admit to a new sexual partner within the previous 3 months. This patient tested positive for *N. gonorrhoeae* by both the cervical swab and the FVU assay.

DISCUSSION

There are numerous studies in the literature comparing LCR to culture and other nonculture methods for the detection of both chlamydia and gonorrhea in asymptomatic and symptomatic males and females by using FVU and/or swabs. When detection of *C. trachomatis* by LCR using FVU from women alone was compared to cervical- and/or urethral-specimen culture, the overall sensitivities and specificities, respectively, in three studies (1, 11, 12) were found to be as follows: for LCR on FVU, 88 to 94% and 99.9 to 100%, and for cervical culture, 56 to 74% and 100%. Results of cervical swab specimens tested by LCR and culture for *C. trachomatis* in a multicenter study by Schachter et al. (13) revealed sensitivities of 94 and 65%, respectively.

In a multicenter study (5) evaluating men alone, LCR performed on urethral swabs had a sensitivity of 93% in a group of asymptomatic males, whereas culture was only 73% sensitive. LCR performed on FVU also revealed similar results, with a reported sensitivity of 96%. The performance of LCR was slightly better in the symptomatic group who had LCR performed on urethral swabs (98% sensitivity). Deguchi et al. (8) compared LCR and EIA performed on urine samples from a group of men with symptomatic urethritis. The sensitivity results were as follows: LCR, 94%; Chlamydiazyme (Abbott Laboratories, Abbott Park, Ill.), 82%; and IDEIA (Novo BioLabs, Ltd., Cambridge, United Kingdom), 94%. In the same group of patients, the urethral culture was 85% sensitive. de Barbeyrac et al. (7) found that LCR had slightly better sensitivity than PCR, but both assays had very high specificities.

Less is published on the performance of LCR in the diagnosis of gonococcal infections. Ching et al. (6) found that LCR performed better than culture when testing urethral swabs in men and cervical swabs in women. In a study of FVU from women attending an STD clinic (14), LCR gave essentially the same performance as cervical culture, both with sensitivities of 95 to 96%. Finally, a recent report by Buimer et al. (2), looking at combination testing in men and women attending an STD

clinic, demonstrated better LCR performance with swabs than with FVU. LCR, however, was more sensitive on both types of specimens than culture for detecting gonorrhea in men. For women, LCR on cervical swabs had a sensitivity of 95%, whereas LCR on FVU and cervical culture demonstrated a sensitivity of only 50%. This study also looked at results of chlamydia detection by LCR on swabs and urine from the same group of patients. Results were similar to those reported in studies, and it is noteworthy that LCR swab results were more sensitive than LCR FVU results in men and women.

This study is one of the few to evaluate the LCR assay using urine and swab specimens from men and women for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Our data are similar to those reported in the literature for populations with a high prevalence of infection. Results may differ for non-STD clinic populations. LCR was more sensitive than the Gen-Probe assay for the detection of *C. trachomatis*, detecting 31 additional *C. trachomatis*-positive patients. The majority of these patients had symptoms or risk factors compatible with an STD. For both *C. trachomatis* and *N. gonorrhoeae* in men and *C. trachomatis* in women, LCR swab results were more sensitive than those obtained with FVU. The discrepancy between the swab and the FVU data was less for men with chlamydia than for women with chlamydia. For women, the urethra may not have been involved in those patients who had early infection. For women with gonorrhea, however, FVU and cervical-swab LCR tests were equivalent in performance (91.7% sensitivity), in contrast to the widely disparate results of the study by Buimer et al. (2). While FVU has some distinct advantages with respect to screening targeted high risk groups, such as adolescents and prisoners, among others, we do not recommend replacement of the pelvic examination and collection of cervical swab specimens with FVU as the diagnostic approach for women at risk for STDs.

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