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Comparison of Digene Hybrid Capture 2 and Conventional Culture for Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in Cervical Specimens

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Digene's Hybrid Capture 2 (HC2) CT/GC, CT-ID, and GC-ID DNA tests were evaluated by comparison to traditional culture methods for detecting *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in 669 cervical specimens from high-risk female populations attending two sexually transmitted disease clinics. For detection of either or both infections, the HC2 CT/GC test algorithm had 93.8% sensitivity and 95.9% specificity compared to those of culture. After resolution of discrepant results by direct fluorescent-antibody (DFA) staining or PCR assay, the relative sensitivity and specificity of the HC2 CT/GC test algorithm increased to 94.8 and 99.8%, while the values for culture were 83.6% (McNemar's *P* value, 0.0062) and 100%, respectively. For detection of the individual pathogens, the relative sensitivities for the HC2 CT-ID and GC-ID tests were 97.2 and 92.2% and the specificities were greater than 99% compared to culture adjucated by DFA staining and PCR. Test performance varied at the two clinics: the HC2 CT/GC algorithm, CT-ID, and GC-ID tests had significantly higher sensitivities (McNemar's *P* value, <0.05) than that of culture for the population at one clinic as well as for the combined populations. At the other clinic, the HC2 tests performed as well as culture.

Chlamydia trachomatis and *Neisseria gonorrhoeae* infections are a worldwide public health problem with a combined estimated incidence of over 75 million cases. They contribute to ongoing epidemics of infertility and ectopic pregnancy and lead to billions of dollars in direct and indirect health care costs (15, 20, 21). Treatments for both *C. trachomatis* and *N. gonorrhoeae* are effective and relatively inexpensive. Early detection followed by proper treatment is the key to slowing and preventing the spread of these common sexually transmitted diseases. Routine laboratory screening of sexually active, asymptomatic individuals at high risk for infection has been recommended (3, 16).

Until recently, conventional culture was considered the "gold standard" for the detection of both *C. trachomatis* and *N. gonorrhoeae*. Culture has been recognized as a relatively sensitive and highly specific diagnostic test; however, it is a labor-intensive, time-consuming, and technique-dependent method. Potential shortcomings that can have substantial impacts on culture results include culture techniques that differ from site to site and variations in patient population, specimen handling, storage and transport conditions, and media used for culture (2, 9). For performance evaluation of newer, highly sensitive tests, use of an "expanded gold standard" based on an adjudicated culture result has been used increasingly as the standard against which new tests are evaluated (2, 10, 18). Many studies have shown that culture has limited sensitivity, varying from 37.5 to 93% for chlamydiae (1, 5, 12) and 57.7 to 96.5% for gonococci (4, 5, 8, 14). It is generally recognized that culture detects less than 100% of all patient infections.

Digene Corporation (Gaithersburg, Md.) has developed the Hybrid Capture 2 (HC2) CT/GC, CT-ID, and GC-ID DNA tests, which use a signal amplification-based chemiluminescence method for the qualitative detection of *C. trachomatis* and *N. gonorrhoeae* in clinical specimens. In this study, we compared the performance of Digene's HC2 CT/GC algorithm with those of traditional culture methods for detecting *C. trachomatis* and *N. gonorrhoeae* infections in cervical specimens obtained from two high-risk female populations.

Clinical specimens. After informed consent was obtained, specimens were collected from high-risk female populations attending the sexually transmitted disease clinics at the Jefferson County Department of Health (Birmingham, Ala., site) and the Baltimore City Health Department (Baltimore, Md., site). Three cervical specimens were collected from each patient. The first specimen was a swab for gonococcal culture. The second and third specimens were a swab for chlamydial cell culture and a cervical brush specimen for Digene's HC2 tests, with the order of collection of the second and third specimens alternated between patients. Swab specimens were cultured for chlamydiae and gonococci at each site. Cervical brush specimens were shipped to Digene for blinded HC2 CT/GC testing. The study protocol was approved by institutional review boards at the University of Alabama at Birmingham and the Johns Hopkins University in Baltimore, Md.

Culture procedure. For gonococcal culture, modified Thayer-Martin medium was inoculated at each collection site and immediately incubated in a CO_2 environment at 35 to 37°C for up to 48 h (72 h over a weekend). Plates were examined for growth and colony morphology at 18 to 24 h and at 48 h if no

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growth was present. Suspicious colonies were Gram stained and tested for cytochrome *c* oxidase. The identifications of all oxidase-positive, gram-negative colonies were confirmed using commercially available fluorescein-conjugated antibodies specific for *N. gonorrhoeae*. For chlamydial cell culture, specimens were tested as described previously (6).

Study procedure for Digene HC2 tests. All HC2 testing was performed by technicians blinded to the results of the other tests. Specimens for the HC2 tests were collected into Digene specimen transport medium. All specimens were examined first by using the HC2 CT/GC test according to the manufacturer's instructions and as described previously (6, 17). After data analysis, all CT/GC test-positive specimens, all specimens showing discrepancies between CT/GC test and culture results, all specimens with results within 30% of the CT/GC cutoff, and an equal number of negative specimens were retested by using both the CT-ID and GC-ID tests to identify the specific organism(s) present in each specimen. For the HC2 CT/GC testing algorithm, specimens that tested positive by the CT/GC test and whose results were then confirmed (or identified) by the CT-ID and/or the GC-ID test were considered positive for the specific organisms identified.

PCR. A 75-μl aliquot of denatured specimen was transferred from each selected specimen to a new tube for phenol extraction and was then subjected to ethanol precipitation by using a previously validated procedure (13). The DNA pellet in each tube was then resuspended in 50 μl of Tris-EDTA. Two aliquots (1 and 5 μl) from each specimen were taken and processed for PCR amplification in a total reaction volume of 50 μl. PCR products were analyzed by the SHARP Signal System (Digene Corporation). In addition to the specimens showing discrepant results, an equal number of randomly chosen negative specimens were also tested as the PCR assay control.

Discrepant analysis. Discrepant results for specimens tested by the HC2 tests and culture were adjudicated by a direct fluorescent-antibody (DFA) stain assay (for chlamydia) at the original testing sites and by an in-house PCR test for both *C. trachomatis* and *N. gonorrhoeae* in denatured HC2 specimens. A conservative approach was chosen for adjudicated data analysis. Culture-positive specimens were always scored as positive regardless of the results from other tests. Chlamydia-culture-negative and HC2 CT/GC algorithm-positive specimens confirmed by DFA assay were considered positive. In addition, HC2 CT/GC algorithm-positive specimens were also considered true positives if they were confirmed by PCR adjudication.

McNemar's paired test was used for statistical evaluation, and a P value of <0.05 was considered statistically significant.

Among a total of 669 clinical specimens evaluated, 113 (17%) were culture and DFA positive, with 59 (9%) positive for *C. trachomatis* (58 culture positive, 1 DFA positive) and 72 (11%) positive for *N. gonorrhoeae*. Eighteen of these 113 specimens were positive for both organisms. Of the 112 culture-positive specimens, the HC2 CT/GC test algorithm detected 105 and found 23 positive specimens that were not detected by culture. Based on the adjudicated results, the relative sensitivity and specificity for the HC2 CT/GC algorithm were 94.8 and 99.8%, respectively, whereas culture had a significantly lower relative sensitivity (83.6%; P value = 0.0093) and 100% specificity (by definition). The HC2 CT-ID and GC-ID tests had 97.2 and 92.2% relative sensitivities, respectively (Table 1). In contrast, the relative sensitivities for culture were 80.6% for *C. trachomatis* and 80.0% for *N. gonorrhoeae*. Employing the HC2 CT/GC test algorithm, the CT-ID and GC-ID tests had greater than 99% specificities (99.2 and 99.8%, respectively), which were comparable to the 100% specificity for culture. While the performances of the HC2 CT/GC, CT-ID, and GC-ID tests were similar when compared to adjudicated results, there was a substantial difference in test performance between the two sites when HC2 test performance was compared to culture test results obtained at the two clinics (Table 2).

At the Birmingham site, 8.6% (41 of 477) of the specimens were culture positive for *C. trachomatis* and 12.6% (60 of 477) were positive for *N. gonorrhoeae*, with 18 specimens positive for both (3.8%). All 477 specimens were tested by the HC2 CT/GC test, and 252 specimens were tested by both the CT-ID and GC-ID tests using an expanded application of the CT/GC test algorithm (Table 2). The HC2 CT/GC test algorithm was able to detect 78 of 83 culture-positive specimens and found 8 positive specimens that were not detected by culture, thus exhibiting a relative sensitivity of 94.0% (78 of 83 specimens) and a specificity of 98.0% (386 of 394 specimens). After discrepant results for specimens from culture and the HC2 tests were resolved by DFA staining and PCR assay, all eight of the culture-negative and HC2-positive specimens were confirmed to be positive. Thus, the HC2 CT/GC test algorithm had a relative sensitivity of 94.5% (86 of 91 specimens), whereas the value for culture was 91.2% (83 of 91 specimens).

At the Baltimore site, culture positivity for *C. trachomatis* was 7.8% (15 of 192 specimens). The culture positivity for gonococci was 6.3% (12 of 192 specimens) with no double infections detected. All 192 specimens were tested by the HC2 CT/GC test, and 115 specimens were examined by both the CT-ID and GC-ID tests. Initial results comparing the HC2 test to culture revealed that the sensitivity and specificity of the HC2 CT/GC test algorithm were 93.1% (27 of 29 specimens) and 90.8% (148 of 163 specimens), respectively (Table 2). The positive predictive value was 64.3% (27 of 42 specimens), which is much lower than that at the Birmingham site (90.7%). The HC2 CT/GC test algorithm did not detect two culture-positive specimens but did detect 15 positive specimens that were scored negative by culture. Of those 15 culture-negative and HC2-positive specimens, 1 was scored positive by DFA staining and 13 were scored positive by PCR assay. Both specimens that tested positive by culture and negative by the HC2 test were also negative by PCR assay. Thus, following adjudication, the relative sensitivity and specificity of the HC2 CT/GC test algorithm improved to 95.3% (41 of 43 specimens) and 99.3% (148 of 149 specimens), respectively. The positive predictive value also improved significantly from 64.3 to 97.6% (41 of 42), whereas the negative predictive value was not affected by adjudication. In comparison, the relative sensitivity and specificity for culture were 67.4% (29 of 43) and 100% (149 of 149), respectively. The relative sensitivities of culture and the HC2 CT/GC test algorithm were significantly different (P value, 0.0036) at the Baltimore site.

In this study, all clinical specimens were tested by both culture and the HC2 tests, but not every specimen was tested by DFA staining and/or PCR assay. It is possible that some true positives may not have been detected by either culture or the HC2 test.

TABLE 1. Comparison of HC2 CT-ID and GC-ID test algorithm performance to culture and DFA and PCR adjudicated results

Site, test, and comparison	% Sensitivity	95% CI[e]	% Specificity	% PPV[f]	% NPV[f]
1 (Birmingham)[a]					
CT-ID					
HC2 vs. culture	97.6 (40/41)	0.871–0.999	97.5 (425/436)	78.4 (40/51)	99.8 (425/426)
HC2 vs. adjudicated	98.0 (48/49)	0.892–0.999	99.3 (425/428)	94.1 (48/51)	99.8 (425/426)
Culture vs. adjudicated	83.7 (41/49)	0.703–0.927	100 (428/428)	100 (41/41)	98.2 (428/436)
GC-ID					
HC2 vs. culture	90.0 (54/60)	0.795–0.962	98.1 (409/417)	87.1 (54/62)	98.6 (409/415)
HC2 vs. adjudicated	91.0 (61/67)	0.815–0.966	99.8 (409/410)	98.4 (61/62)	98.6 (409/415)
Culture vs. adjudicated	89.6 (60/67)	0.797–0.957	100 (410/410)	100 (60/60)	98.3 (410/417)
2 (Baltimore)[b]					
CT-ID					
HC2 vs. culture	94.1 (16/17)	0.713–0.999	95.4 (167/175)	66.7 (16/24)	99.4 (167/168)
HC2 vs. adjudicated	95.7 (22/23)	0.781–0.999	98.8 (167/169)	91.7 (22/24)	99.4 (167/168)
Culture vs. adjudicated	73.9 (17/23)	0.516–0.898	100 (169/169)	100 (17/17)	96.6 (169/175)
GC-ID					
HC2 vs. culture	91.7 (11/12)	0.615–0.998	93.9 (169/180)	50.0 (11/22)	99.4 (169/170)
HC2 vs. adjudicated	95.7 (22/23)	0.781–0.999	100 (169/169)	100 (22/22)	99.4 (169/170)
Culture vs. adjudicated	52.2 (12/23)	0.306–0.732	100 (169/169)	100 (12/12)	93.9 (169/180)
Combined					
CT-ID					
HC2 vs. culture[c]	96.6 (56/58)	0.881–0.996	96.9 (592/611)	74.7 (56/75)	99.7 (592/594)
HC2 vs. adjudicated	97.2 (70/72)	0.903–0.997	99.2 (592/597)	93.3 (70/75)	99.7 (592/594)
Culture vs. adjudicated	80.6 (58/72)	0.695–0.889	100 (597/597)	100 (58/58)	97.7 (597/611)
GC-ID					
HC2 vs. culture[d]	90.3 (65/72)	0.810–0.960	96.8 (578/597)	77.4 (65/84)	98.8 (578/585)
HC2 vs. adjudicated	92.2 (83/90)	0.846–0.968	99.8 (578/579)	98.8 (83/84)	98.8 (578/585)
Culture vs. adjudicated	80.0 (72/90)	0.703–0.877	100 (579/579)	100 (72/72)	97.0 (579/597)

[a] A total of 252 specimens were examined by both the CT-ID and GC-ID tests. The data analyses were based on the algorithm results and 477 specimens tested by the CT/GC kit.
[b] A total of 115 clinical specimens were tested by both CT-ID and GC-ID kits for this site, and 192 specimens were tested by the CT/GC kit.
[c] McNemar's two-sided P value is 0.0005.
[d] McNemar's two-sided P value is 0.0310.
[e] Confidence intervals (CI) were calculated by the binomial method.
[f] PPV, positive predictive value; NPV, negative predictive value.

Therefore, we used "relative" sensitivity and specificity to compare the results of culture and the HC2 tests to adjudicated results. Nonetheless, we found that Digene's HC2 CT/GC test algorithm had significantly higher relative sensitivity than culture (94.8 versus 83.6%, respectively; $P = 0.0062$) and very good specificity (99.8%) relative to that of culture. These results are similar to those of a recently reported multicenter evaluation by Schachter et al. (17) and are consistent with the demonstrated higher sensitivity of molecular signal- or target amplification-based technologies. Since positive culture results were always considered positive, the specificity of culture was 100% by definition. Using this criterion, only 1 false positive by the HC2 CT/GC test algorithm was found among the 669 specimens tested. Our data also suggest that the sensitivity and specificity of the HC2 CT/GC tests are comparable to those described for other sensitive methods, such as PCR- and ligase chain reaction-based tests (4, 7, 8, 18, 19).

The CT-ID test was slightly more sensitive in detecting chlamydiae than the GC-ID test was in detecting gonococci. One explanation for these results could be that the HC2 test specimens may have contained very low levels of *N. gonorrhoeae*, since the first swab was always collected for gonococcal culture, followed by alternate collection of chlamydial culture swabs and HC2 test brushes. As a result, specimens collected for the HC2 tests may have contained fewer organisms than the specimens obtained for gonococcal culture. The performance of the HC2 tests was more reproducible from site to site than was that of culture.

Our results demonstrated that the relative sensitivities of culture varied between the Birmingham and Baltimore sites: 91.2% (83 of 91 specimens) versus 67.4% (29 of 43) for *C. trachomatis* and *N. gonorrhoeae* combined, 83.7% (41 of 49) versus 73.9% (17 of 23) for *C. trachomatis*, and 89.6% (60 of 67) versus 52.2% (12 of 23) for *N. gonorrhoeae*. The relative sensitivities for the Baltimore site were similar to those obtained in previous studies of molecular amplification tests at this site (5, 11). The differences observed between the two sites could be caused by many factors, including variations in sample populations, specimen collection methods, storage and transport conditions, and culture techniques. The results from our studies emphasize the advantage that a routine molecular method such as the HC2 test can have over culture in terms of sensitivity and reproducibility from different sites.

In conclusion, the HC2 CT/GC DNA test is a reliable and rapid method for detection of *C. trachomatis* and *N. gonor-*

TABLE 2. Comparison of HC2 CT/GC algorithm performance to culture and DFA and PCR adjudicated results

Site and comparison	% Sensitivity	95% CI[f]	% Specificity	% PPV	% NPV
1 (Birmingham)[a]					
HC2 vs. culture[b]	94.0 (78/83)	0.865–0.980	98.0 (386/394)	90.7 (78/86)	98.7 (386/391)
HC2 vs. adjudicated	94.5 (86/91)	0.876–0.982	100 (386/386)	100 (86/86)	98.7 (386/391)
Culture vs. adjudicated	91.2 (83/91)	0.834–0.961	100 (386/386)	100 (83/83)	98.0 (386/394)
2 (Baltimore)[c]					
HC2 vs. culture[d]	93.1 (27/29)	0.772–0.992	90.8 (148/163)	64.3 (27/42)	98.7 (148/150)
HC2 vs. adjudicated	95.3 (41/43)	0.842–0.994	99.3 (148/149)	97.6 (41/42)	98.7 (148/150)
Culture vs. adjudicated	67.4 (29/43)	0.515–0.809	100 (149/149)	100 (29/29)	91.4 (149/163)
Combined					
HC2 vs. culture[e]	93.8 (105/112)	0.876–0.975	95.9 (534/557)	82.0 (105/128)	98.7 (534/541)
HC2 vs. adjudicated	94.8 (127/134)	0.895–0.979	99.8 (534/535)	99.2 (127/128)	98.7 (534/541)
Culture vs. adjudicated	83.6 (112/134)	0.762–0.894	100 (535/535)	100 (112/112)	96.1 (535/557)

[a] A total of 483 specimens were received from the Birmingham site, and 6 of them were excluded from the data analysis due to inadequate specimen volume. Of these, one tested positive by culture for *N. gonorrhoeae* and one was positive for both *C. trachomatis* and *N. gonorrhoeae* by culture. For both CT-ID and GC-ID tests, 252 specimens were examined.
[b] McNemar's two-sided *P* value is 0.5791.
[c] A total of 201 specimens were received from the Baltimore site and 9 of them were excluded. Of these, 2 had inadequate specimen volume, 6 specimens did not have culture results for either *C. trachomatis* or *N. gonorrhoeae* available, and 1 specimen had toxic chlamydia culture result. For this site, 115 clinical specimens were tested by both CT-ID and GC-ID kits. One specimen was culture negative but DFA stain positive.
[d] McNemar's two-sided *P* value is 0.0036.
[e] McNemar's two-sided *P* value is 0.0062.
[f] CI, confidence intervals.

rhoeae simultaneously from a single specimen and is ideal for screening in low-prevalence populations. The HC2 CT-ID and GC-ID tests can be used either as follow-up tests to the HC2 CT/GC test for identifying the specific pathogens or as stand-alone tests for direct screening for *C. trachomatis* or *N. gonorrhoeae*. The HC2 CT/GC DNA tests can be easily adapted in a routine laboratory setting as a screening and diagnostic tool because of their sensitivity, accuracy, high throughput, and ease of use. In addition, HC2 test specimens can be stored at room temperature for up to 2 weeks and transported without refrigeration. The same specimen collected for the HC2 CT/GC tests can also be used to detect human papillomavirus, the leading cause of cervical cancer, thus expanding the possibilities for screening.

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