Validity and cost-effectiveness of the Gonozyme test in the diagnosis of gonorrhea

Original Research

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Although bacterial culture is considered to provide the most definitive diagnosis of gonorrhea, it has limitations when specimens must be transported long distances. A study was carried out to evaluate the validity and cost-effectiveness of an alternative method of diagnosing gonorrhea, the Gonozyme test, a commercially available enzyme immunoassay. Urogenital specimens from 100 men and 100 women with symptoms suggestive of or a history of exposure to gonorrhea were tested for the presence of *Neisseria gonorrhoeae* by means of bacterial culture and for gonococcal antigen with the Gonozyme test. The specimens from the men were also examined by means of microscopy of Gram-stained smears. The sensitivity and specificity of the Gonozyme test with reference to culture results were 95.6% and 97.4% respectively in the men and 84.2% and 98.7% in the women. The predictive value of a positive result was 91.6% in the men and 94.1% in the women, and the predictive value of a negative result 98.6% in the men and 96.3% in the women. The cost-effectiveness of the Gonozyme test was higher than that of bacterial culture in this population, which had a high prevalence rate of gonorrhea (23% in the men and 19% in the women). The Gonozyme test would be an adequate alternative to culture for the diagnosis of gonorrhea and contact tracing in areas far from diagnostic laboratories.

Le diagnostic ferme de blennorragie se fait par la culture. Mais celle-ci est problématique lorsque les échantillons doivent être expédiés loin. On étudie ici la fiabilité et la rentabilité du diagnostic par le Gonozyme, épreuve du commerce fondée sur l'immunodosage enzymatique d'un antigène. On compare les résultats de la recherche de *Neisseria gonorrhoeae* à la culture et de l'antigène gonococcique au Gonozyme, à partir de prélèvements génito-urinaires sur 100 hommes et 100 femmes chez qui les symptômes ou la notion d'un contact font soupçonner une blennorragie. Pour les hommes on fait aussi un frottis coloré au Gram. En prenant comme critère le résultat de la culture, le Gonozyme donne une sensibilité de 95,6% chez les hommes et 84,2% chez les femmes, une spécificité de 97,4% chez les premiers et 98,7% chez les secondes. Le pouvoir de prédiction d'un résultat positif est de 91,6% chez les hommes et 94,1% chez les femmes, celui d'un résultat négatif 98,6% chez les uns et 96,3% chez les autres. Dans cette population, où la morbidité de la blennorragie est élevée (23% chez les hommes, 19% chez les femmes), le Gonozyme est plus rentable que la culture. Il pourrait la remplacer avantageusement pour le diagnostic de la blennorragie et la recherche des contages dans les régions éloignées des laboratoires.

Sexually transmitted diseases accounted for 69% of all notified diseases in Canada in 1982; 96% were caused by *Neisseria gonorrhoeae*.[1] The reported incidence of gonorrhea is higher in regions with lower population densities; the highest rate is in the Northwest Territories.[1]

The problem of providing adequate laboratory facilities in remote areas in Canada is well recognized. Recent improvements in transport systems and selective culture media for the isolation of *N. gonorrhoeae* are of limited value in these areas, as was shown in a recent study conducted at the University of Saskatchewan.[2] The results of microscopy of Gram-stained smears of urethral swabs collected from 100 consecutive men with urethritis

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were compared with the results of culture of the swabs in a laboratory 250 km away. The swabs were transported to the laboratory inoculated onto Transgrow medium (Provincial Laboratory, Regina). Only 51% of the swabs that showed intracellular gram-negative diplococci in the smears gave positive results when cultured.

These limitations to the diagnosis of gonorrhea when specimens must be transported long distances before culture may be overcome by the use of methods other than culture. Two such methods have recently been described: a genetic transformation test[3,4] and an enzyme immunoassay.[5] These tests do not require living organisms and can detect gonococcal antigen in the specimen up to 5 days after collection. The commercially available enzyme immunoassay, the Gonozyme test (Abbott Laboratories, North Chicago, Illinois), is now available in Canada. We carried out a study to evaluate the validity and cost-effectiveness of this test as an alternative method for diagnosing gonorrhea.

Materials and methods

Urogenital specimens were collected from 100 men and 100 women who consecutively attended the Public Health Clinic, University Hospital, Saskatoon, from August 1984 to January 1985. All had symptoms suggestive of or a history of exposure to gonorrhea. The specimens were examined in the Clinical Microbiology Department for the presence of *N. gonorrhoeae* by means of microscopy, bacterial culture and the Gonozyme test.

Microscopy

A smear prepared from the urethral swab obtained for culture from the men was stained with Gram's method. The result was considered positive if intracellular gram-negative diplococci were seen on microscopy.

Bacterial culture

Endocervical and urethral swabs in the women and urethral swabs in the men were collected for culture. The swabs were immediately inoculated onto Modified Martin–Lewis Media Pill-pocket Plates (PML Laboratories, Richmond, BC) and placed in an environmental bag with a carbon-dioxide-generating tablet. The plates were incubated overnight at 35°C in the clinic. The next morning they were transported to the laboratory and incubated at 35°C in 5% carbon dioxide. The plates were examined after 18 to 24 hours of incubation and again after 48 hours. Colonies that were oxidase-positive and showed typical Gram-stain morphologic features and that were catalase-positive when tested with the Superoxol 1-second test (Fischer Scientific, Edmonton) were further identified by means of coagglutination with the Phadebact Gonococcus Test (Pharmacia Diagnostics, Uppsala, Sweden). Strains that gave positive results were presumed to be *N. gonorrhoeae*. Their identification was further confirmed by means of sugar fermentation reactions.

Gonozyme test

Endocervical specimens from the women and urethral specimens from the men were collected with specially designed swabs (STD-EZE for women and STD-PEN for men) supplied by the manufacturer. The swabs were transported to the laboratory and refrigerated at 4°C until tested; all specimens were tested within 5 days of collection. The test was performed according to the manufacturer's instructions. Briefly, antigen was eluted from the swab by shaking after the addition of 1 mL of specimen dilution buffer; 200 μL of the elution was then added to a specially treated bead that adsorbs any gonococcal antigen present. The bead was incubated with rabbit antigonococcal antibody, then with a conjugate of goat antirabbit antibody and horseradish peroxidase, and finally with peroxidase substrate. The bead was washed with deionized water before each new reagent was added. A positive result is suggested by the development of a yellow-orange colour after addition of the final reagent. Absorbance values were read on a spectrophotometer (Quantum II Dual Wavelength Analyzer, Abbott Laboratories) at 492 nm. If the optical density reading was equal to or greater than the cutoff value, the result was considered positive.

Results

Men

Microscopy, culture and the Gonozyme test gave positive results in 22, 23 and 24 of the 100 specimens respectively (Table I). One specimen that gave a positive result when cultured gave negative results in the Gonozyme test (optical density reading of 0.039) and on microscopy. Two specimens that gave positive results in the Gono-

Table I—Comparison of results of bacterial culture and microscopy with those of the Gonozyme test in the detection of *Neisseria gonorrhoeae* in urethral specimens from 100 men

Gonozyme test result	Result; no. of specimens			
	Culture		Microscopy	
	Positive	Negative	Positive	Negative
Positive (n = 24)	22	2	22	2
Negative (n = 76)	1	75	0	76

zyme test (optical density readings of 0.508 and more than 2.000) gave negative results when cultured; the first also gave a negative result on microscopy. All specimens that gave positive results on microscopy also gave positive results in the Gonozyme test, but one gave a negative result when cultured.

When the culture result was used as the standard of reference, the Gonozyme test had a sensitivity of 95.6% and a specificity of 97.4%. The predictive value of a positive result was 91.6% and of a negative result 98.6%.

The predictive values were calculated for various optical density values. The maximum predictive value of a positive result, 95.4%, was obtained at an optical density of 0.600. At this same optical density the predictive value of a negative result was 97.4% (Fig. 1).

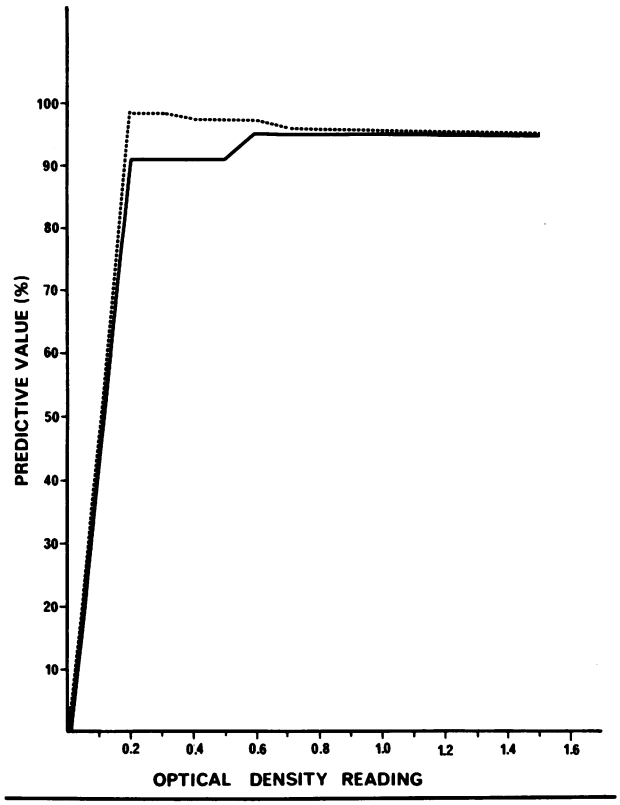

Fig. 1—Predictive value of Gonozyme test in men at prevalence rate of gonorrhea of 23%, according to optical density reading. Dashed line is predictive value of negative result; solid line is predictive value of positive result.

Table II—Comparison of results of bacterial culture with those of the Gonozyme test in the detection of *N. gonorrhoeae* in urogenital specimens from 100 women

	Culture result; no. of specimens	
Gonozyme test result	Positive	Negative
Positive (n = 17)	16	1
Negative (n = 83)	3	80

Women

Culture gave positive results in 19 of the 100 specimens; 16 of the 19 also gave positive results in the Gonozyme test (Table II). The optical density readings of the three specimens that gave negative results in the Gonozyme test were 0.050, 0.135 and 0.080. In the first two, *N. gonorrhoeae* was isolated from the urethral swab only and was present in small numbers. The Gonozyme test gave positive results in 17 specimens, of which 1 (optical density reading of 0.250) gave a negative result when cultured.

When the culture result was used as the standard of reference, the sensitivity of the Gonozyme test was 84.2% and the specificity 98.7%. The predictive value of a positive result was 94.1% and of a negative result 96.3%. When the predictive values were calculated at various optical density values, the maximum predictive value of a positive result was 100% at an optical density of 0.300; the predictive value of a negative result at this optical density was 95.2% (Fig. 2).

Cost

The cost of the Gonozyme test was $6.64, of which $4.40 was for materials and $2.24 was for

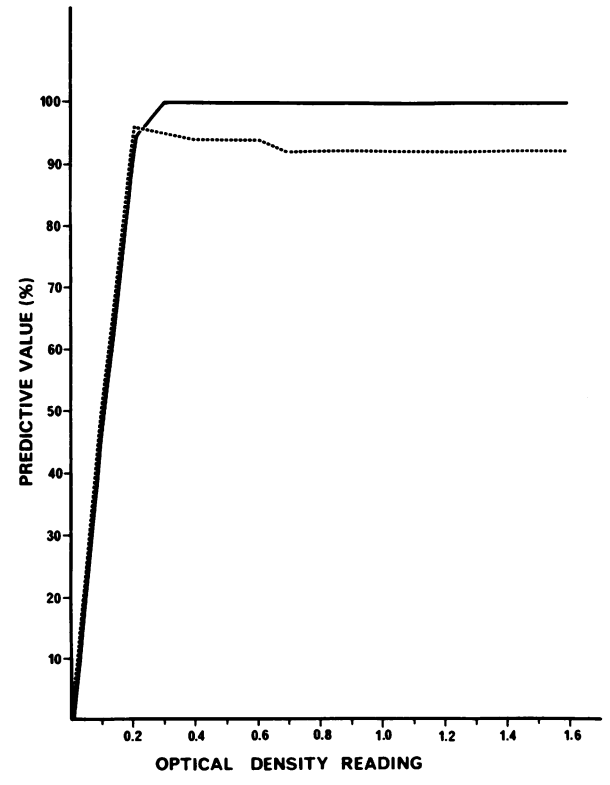

Fig. 2—Predictive value of Gonozyme test in women at prevalence rate of gonorrhea of 19%, according to optical density reading. Dashed line is predictive value of negative result; solid line is predictive value of positive result.

laboratory time (seven work units at $0.32 per unit).

The cost of bacterial culture was calculated for screening culture and for full identification of specimens that gave positive results in screening. The cost of screening culture was $4.71 ($0.55 for materials and $4.16 for laboratory time [13 work units]). The cost of full identification was $15.82 ($6.86 for materials and $8.96 for laboratory time [28 work units]).

The cost of direct Gram-staining was $2.60.

The cost of the Gonozyme test and of culture was calculated at various prevalence rates of gonorrhea. As shown in Table III, the cost of culture increased with increasing prevalence, as each positive result in screening required full identification to be done.

Discussion

Bacterial culture is considered to provide the most definitive diagnosis of gonorrhea and is the current "gold standard" against which all other methods are assessed. While this method is very specific, its sensitivity ranges from 40% to 90%. Reported limiting factors are inhibition of *N. gonorrhoeae* by vancomycin hydrochloride in selective media, poor specimen collection and inadequate proficiency in isolation and identification.[6] In addition, recovery through culture is often jeopardized by the transport system used and time taken in transporting the specimen to a diagnostic laboratory.[7] For the presumptive diagnosis of gonorrhea the presence of intracellular gram-negative diplococci in a smear of urethral discharge is sensitive and specific in symptomatic males but not in females, in whom the sensitivity may be as low as 55%.[8]

Alternative methods for diagnosing gonorrhea, in particular the Gonozyme test, have been assessed.[5,9-12] These methods have shown high sensitivity and specificity, and results similar to ours in men have been reported.[5,9,10] Although one specimen from one of our male patients gave a positive result when cultured but a negative result in the Gonozyme test and on microscopy, culture yielded a small number of organisms. Of the two specimens from men that gave positive results in the Gonozyme test and negative results when cultured, one had an optical density greater than 2.000 and gave a positive result on microscopy; it could have represented a vancomycin-sensitive strain of *N. gonorrhoeae*. The second, which had an optical density of 0.508, gave a negative result on microscopy as well; this could have been due to faulty sampling technique, or the Gonozyme test may have given a false-positive result.

Table III—Cost of bacterial culture and of the Gonozyme test at various prevalence rates of gonorrhea

Prevalence rate, %	Cost of 100 tests, $; test	
	Culture	Gonozyme test
25	748.75	664.00
20	693.20	664.00
15	637.65	664.00
10	582.10	664.00
5	526.55	664.00
2	493.22	664.00

In the women, we found that the Gonozyme test had a sensitivity of 84.2%, similar to that found by other investigators,[5,10] and a specificity of 98.7%, higher than that previously found.[11] In two of the three specimens that gave negative results in the Gonozyme test, the endocervical swabs gave a negative result when cultured, but a scanty growth of *N. gonorrhoeae* was obtained from the urethral swabs. If the Gonozyme test results are compared with those of endocervical swab culture only, the Gonozyme test has a sensitivity of 94.1%. This raises the question of whether endocervical and urethral swabs should be collected for the Gonozyme test in females. As shown in Fig. 2, increasing the cutoff optical density value for a positive result had little effect on the predictive values.

Although we found Gram-staining alone to be the least expensive method for diagnosing gonorrhea in symptomatic men with urethritis, when we compared the cost of bacterial culture, including identification, with that of the Gonozyme test, we found the latter to be less expensive in areas with high prevalence rates of gonorrhea. In addition, the Gonozyme test gives a more reliable diagnosis than culture when specimens must be transported from remote areas to diagnostic laboratories.

Conclusions

The Gonozyme test is an adequate alternative to bacterial culture in areas with a low population density, particularly those far from laboratory facilities. This is especially so in females because of the low sensitivity of Gram-staining for the presumptive diagnosis of gonorrhea. However, the Gonozyme test has several drawbacks, including its inability to assess the antibiotic sensitivity of *N. gonorrhoeae*, its current limitation for use with urogenital specimens only and its lack of established value as a test of cure. Nevertheless, the reduced sensitivity of culture after transportation of specimens to laboratories from remote areas as well as the potential for eradicating gonorrhea from relatively isolated populations by means of intense treatment and contact tracing make the use of methods other than culture, including the Gonozyme test, attractive in areas of Canada with a low population density.

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large size of his infarction the patient drifted into cardiogenic shock and died 2 weeks later.

Comments

The first cardiac pacemakers were external and paced the heart through skin electrodes.[1] However, with the advent of implantable pacemakers, transcutaneous pacing rapidly became obsolete. Recently transcutaneous pacing has been resurrected and has been shown to be useful in the immediate management of severe bradycardia.[2-5] This case report illustrates a new use of transcutaneous pacing — for terminating ventricular tachycardia.

Transvenous rapid ventricular pacing has been shown to be useful in terminating sustained ventricular tachycardia,[6,7] but even synchronous pacing can accelerate the tachycardia or induce ventricular fibrillation.[8,9] The pacemaker we used is a fixed-rate device that has no sensing capability and hence might be more arrhythmogenic. A further limitation might be difficulty in capturing the heart at higher pacing rates.

Further testing of the safety of this method of terminating ventricular tachycardia is warranted in view of both its ease of use and the possible risk of accelerating tachyarrhythmias and inducing ventricular fibrillation.

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