

The Clinical Diagnosis of Genital Ulcer Disease in Men

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We report the sensitivity and specificity of physical examination findings for diagnosing primary syphilis, chancroid, and genital herpes. The physical features of genital ulcers in 446 men were measured in accordance with a quantitative scale. Two hundred-twenty of these men had an established, single microbiological diagnosis. Forty-five (20%) had primary syphilis, 118 (54%) had chancroid, and 57 (26%) had genital herpes. There was considerable overlap in the clinical presentation of these three diseases. The classic clinical sign complex attributed to primary syphilis (painless, indurated, clean-based ulcers) was only 31% sensitive but 98% specific. The classic presentation of a chancroid ulcer (a deep, undermined, purulent ulcer) was only 34% sensitive but 94% specific. The classic description of genital herpes ulcers (multiple, shallow, tender ulcers) was only 35% sensitive but 94% specific. Inguinal lymph node findings did not contribute significantly to clinical diagnostic accuracy. These data indicate that the clinical diagnosis of genital ulcer disease can be made with reasonable certainty only for a minority of patients. Rapid, sensitive, and specific diagnostic tests for syphilis, chancroid, and genital herpes are needed.

The treatment of patients with genital ulcer disease (GUD) is often based on clinical diagnosis. Reliance on this method is necessitated by the lack of rapid diagnostic tests in many clinics and by the insensitivity of such tests when they are available. Darkfield microscopy for the detection of *Treponema pallidum* in primary syphilis lesions has a sensitivity that ranges between 70% and 95%, depending on the expertise of the technician [1]. The results of gram staining to detect *Haemophilus ducreyi* in chancroid lesions may be misleading because the ulcers are frequently colonized with multiple organisms [2, 3]. Tzanck smears for identifying multinucleate giant cells in genital herpes lesions have a sensitivity of ~50% [4]. Thus, even under optimal clinic conditions, many cases of GUD are treated empirically on the basis of the appearance of the ulcers; accordingly, clinicians who see patients with sexually transmitted diseases should be aware of the likely etiologies of genital ulceration and understand the clinical manifestations of this condition.

See editorial response by Ronald on pages 299–300.

Genital herpes is the most common sexually transmitted GUD in North America, followed by primary syphilis and chancroid [5, 6]. The typical appearances of primary syphilis,

chancroid, and genital herpes are well described in medical texts. A syphilitic chancre is usually described as “a painless, clean-based, indurated ulcer” [7]. A chancroid lesion is usually described as “a sharply circumscribed, somewhat ragged, and undermined painful ulcer,” the base of which “may be covered with a grayish necrotic exudate” [7]. The manifestations of genital herpes are known to be highly variable [8]. However, this disease is usually described as a group of vesicles that quickly ulcerate, resulting in multiple, shallow, painful ulcers.

While these clinical descriptions are considered classic, several authors have noted that it is difficult to correctly diagnose GUD on the basis of clinical criteria alone [9]. Dangor et al. [10] found an overall “accuracy” of 68% for clinical diagnoses among men with genital ulcers treated at a sexually transmitted disease clinic in Carletonville, South Africa. However, the accuracy was highly variable, ranging from 80% in cases of chancroid to 22% in cases of genital herpes [10]. In Durban, South Africa, O’Farrell et al. [11] found that the accuracy of a clinical diagnosis differed for men and women with genital ulcers. Overall, however, its accuracy was low for syphilis, chancroid, and genital herpes [11]. In both of these studies, accuracy was defined as the percentage of clinical diagnoses that were correct (as confirmed by a microbiological diagnosis). Therefore, while these studies demonstrated the difficulty inherent in making an accurate clinical diagnosis of GUD, the outcomes were dependent on the unquantifiable skill of the clinicians working in the study clinics, and the results may not be generalizable.

During a recent outbreak of chancroid in New Orleans, we studied the clinical diagnosis of GUD from a different perspective. The physical features of genital ulcers were measured in accordance with quantitative scales. The objective of the study was to test the sensitivity and specificity of specific clinical signs for syphilis, chancroid, and genital herpes. The rationale for this approach was to remove, to the greatest

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Informed consent was obtained from the patients, and the guidelines of the U.S. Department of Health and Human Services were followed in the conduct of this research.

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extent possible, the inherent variability in the diagnostic accuracy of different clinicians working in environments with different incidences of disease. Our hypothesis was consistent with findings in the published literature and with our own clinical experience, i.e., that the clinical diagnosis of GUD lacks sensitivity and specificity.

Methods

Study patients. The present study was conducted at the City of New Orleans Health Department Sexually Transmitted Disease (STD) Clinic between August 1990 and February 1992. Men who were ≥ 18 years of age and had clinically diagnosed GUD (without obvious herpetic vesicles) were eligible for inclusion. A genital ulcer was defined as a lesion on the skin surface of the penis, scrotum, or perianal region from which the epithelium had been denuded. For this study, only men with an ulcer from which exudate could be obtained for diagnostic tests were included. Therefore, patients whose ulcers were dry and crusted or had reepithelialized were not eligible.

Patients who did not have an established microbiological diagnosis were excluded from the analysis because the sensitivity and specificity of clinical signs of known causes of GUD were being tested. Patients with two microbiologically defined diseases were also excluded.

Interview and clinical evaluation. Informed consent was obtained from the patients, and the confidentiality of all information was assured. Patients were interviewed by a study nurse. A standard interview form was used to collect demographic data as well as data about the history of the ulcer, any recent use of systemic or topical medications, use of alcohol, use of illicit drugs, and the patient's sexual history. Following the interview, a study nurse conducted a careful clinical examination. The study nurse quantified and documented the number of ulcers as well as their size, depth, location, degree of induration, and tenderness; characteristics of the bases and borders of the ulcers were also noted. Objective criteria for the quantitative assessment of these characteristics were standardized by the investigators who worked with the study nurses during the initiation of the study.

The largest ulcer present was measured along its major and minor axes. These dimensions were averaged to give a diameter that was used as an approximation of ulcer size. An ulcer was considered 1+ deep if only the epithelium was denuded, 2+ deep if the lesion appeared to involve the subcutaneous tissue, and 3+ deep if it obviously extended into the subcutaneous tissue (figure 1). Induration of an ulcer was graded 0 if the borders of the ulcer had the consistency of normal tissue, 1+ if the borders were firmer than normal tissue, 2+ if the borders and surrounding tissue had a rubbery consistency, and 3+ if the lesion was very firm.

Tenderness was graded 1+ if the patient reported pain upon palpation but displayed no involuntary pain reaction, 2+ if there was an involuntary pain reaction upon palpation, and 3+

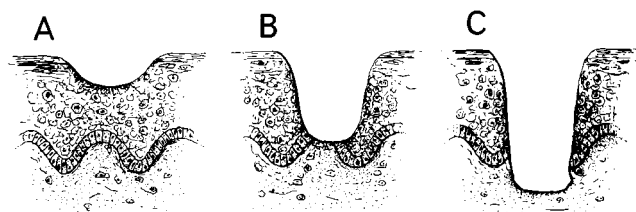


Figure 1. Ulcer depth in patients with genital ulcer disease. Ulcer depth was graded as (A) shallow (1+) if only the epithelium was denuded; (B) moderately deep (2+) if the lesion appeared to involve the subcutaneous tissue; or (C) deep (3+) if it obviously extended into the subcutaneous tissue.

if pain was severe enough to make examination difficult. The lesion was considered painless if the patient both reported no pain and had no visible pain reaction upon palpation.

Purulence of the ulcer base was graded as 0 if there was no purulent material present, 1+ if $<30\%$ of the ulcer base was covered by purulent material, 2+ if $30\%–70\%$ of the ulcer base was covered by purulent material, and 3+ if $>70\%$ was purulent. Undermining of the border was graded as present if any part of the lesion invaded beneath the border of normal tissue (figure 2). The number and location of inguinal lymph nodes were also documented. Lymph node size was assessed by measuring the diameter of the largest node or node masses in two directions and averaging these measurements for the estimation of ulcer size. Tenderness and fluctuance of lymph nodes were recorded as present or absent.

Microbiological evaluation. Darkfield microscopy and rapid plasma reagin testing were performed by clinic personnel in accordance with standard protocols. Serum was also submitted to the Louisiana State Health Department Diagnostic Laboratory (New Orleans) for the VDRL (Venereal Disease Research Laboratories) test. For purposes of this study, a primary case of syphilis was defined as positive findings on darkfield examination and negative cultures for *H. ducreyi* and herpes simplex virus. Exudate was obtained by vigorously rubbing the base of the lesion with a Dacron swab. This material was inoculated onto two media (described below) for culture of *H. ducreyi*. A second swab specimen was obtained in a similar fashion, and this specimen was placed directly into viral transport media, refrigerated, and, within 3 hours, inoculated onto human laryngeal carcinoma A549 and human fetal lung diploid fibroblast (Bartels, Issaquah, WA) cell lines for culture of herpes simplex virus.

The two culture media used to isolate *H. ducreyi* were heart infusion agar (Difco Laboratories, Detroit) with 5% defibrinated rabbit blood (Becton Dickinson Microbiology Systems, Cockeysville, MD) and GC II agar base (Becton Dickinson) with 1% bovine hemoglobin. Both media were supplemented with 1% isovitalex (Becton Dickinson), 5% fetal bovine serum (Whittaker MA Bioproducts, Walkersville, MD), and 3 $\mu\text{g}/\text{mL}$ of vancomycin. Both culture media were incubated at

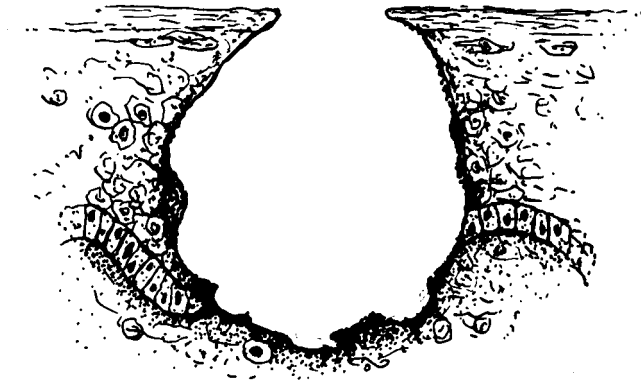


Figure 2. Border undermining of ulcers (invasion of any part of the ulcer beneath the border of normal tissue) in patients with genital ulcer disease.

33°C in a humidified 6% CO₂ atmosphere. The plates were held for 7 days before being reported as negative.

Small, waxy, yellow colonies that appeared typical of *H. ducreyi* were subcultured to chocolate II agar (Becton Dickinson) for further evaluation. Identification was made by means of gram staining and testing for the production of oxidase, catalase, alkaline phosphatase, and nitrate reductase and by performing the porphyrin test.

Treatment. Standard treatment for primary syphilis in the clinic was 4.8 million units of benzathine penicillin G divided into two intramuscular doses given 1 week apart. Patients who were allergic to penicillin were treated with 100 mg of oral doxycycline given twice daily for 14 days. Standard treatment for suspected chancroid was a single 250-mg dose of ceftriaxone given intramuscularly in the deltoid muscle. Some patients with suspected chancroid were enrolled in a treatment trial [12], in which case they were randomized to receive either intramuscular ceftriaxone or a single 1.0-g dose of oral azithromycin. Patients were not treated for genital herpes unless the culture for herpes simplex virus was positive and treatment was deemed necessary by an investigator when the patient returned for follow-up.

Statistical analysis. Data were analyzed with the assistance of the SAS System (SAS, Carey, NC) computer program. Odds ratios, confidence intervals, and *P* values were calculated with use of this program. The sensitivity of clinical findings for each disease was defined as the number of disease cases that had a specific or constellation of specific findings (true positives) divided by the total number of laboratory-confirmed disease cases (true positives plus false negatives). The specificity of clinical findings for each disease was defined as the number of patients without laboratory evidence of the disease who also did not have a specific or constellation of specific clinical findings (true negatives) divided by the total number of patients without laboratory evidence of the disease (true negatives plus false positives). The positive predictive value of a clinical finding for a disease was defined as the number of laboratory-

confirmed disease cases that had the clinical finding of interest (true positives) divided by the total number of patients who had those findings (true positives plus false positives).

Results

Patient population. A total of 446 patients were evaluated. One hundred eighty-two patients (41%) had ulcers that were negative on darkfield examination and culture negative for both *H. ducreyi* and herpes simplex virus. These patients were excluded from the analysis because no definitive diagnosis could be established. Seven patients (1.6%) with positive darkfield examinations who had a clinical diagnosis of secondary syphilis were also excluded.

Eight patients (1.8%) had dual infections and were also excluded from the analysis; cultures for both *H. ducreyi* and herpes simplex virus were positive for two; darkfield examinations and cultures for *H. ducreyi* were positive for three; and darkfield examinations and cultures for herpes simplex virus were positive for three. Twenty-nine patients (6.5%) whose cultures were positive for *H. ducreyi* (25 patients) or herpes simplex virus (4) also had serological tests positive for syphilis (even though the darkfield examination was negative). These patients were also excluded from the analysis to ensure that no dually infected patients were included, since the results of darkfield examinations could have been false negative in an unknown percentage of these cases.

A known single microbiological etiology of GUD was determined for 220 patients (49%). Forty-five (20%) of these patients had primary syphilis, 57 (26%) had genital herpes, and 118 (54%) had chancroid. There was no significant difference in terms of race between the three groups (overall, 97% were African American). In addition, there were no significant differences in educational level or employment status between the three groups. Patients with genital herpes were significantly younger (mean age, 26.1 years) than were patients with chancroid (mean age, 30.1 years) or those with primary syphilis (mean age, 31.6 years) ($P \leq .015$).

There was no significant difference in the duration of ulcers between patients with genital herpes, syphilis, or chancroid; nor was there a significant difference in the duration of ulcers between these three groups and those for whom no microbiological diagnosis was made. Five percent of patients with primary syphilis reported the use of systemic antibiotics during the 2 weeks before presentation at the clinic, whereas 25% of patients with chancroid, 23% of those with genital herpes, and 29% of those for whom no microbiological diagnosis was established reported the use of antibiotics ($P < .02$). However, there was no difference in the use of topical agents between any of the groups. There was no significant difference in the rates of prior episodes of GUD between the three groups. Only 9% of the patients with genital herpes had had a previous diagnosis of genital herpes simplex virus infection.

Clinical findings in patients with GUD. The results of the clinical examinations of ulcers and lymph nodes are summarized in table 1. It is noteworthy that patients with genital herpes were more likely to be uncircumcised than were patients with chancroid (81% vs. 64%, respectively; OR = 2.3; 95% CI = 1.1–5.0). When individual clinical signs were compared, there were statistically significant differences between the ulcers of chancroid, genital herpes, and primary syphilis. However, despite the statistical significance of these differences, there was considerable overlap between the three groups.

The percentage of patients with palpable inguinal lymph nodes was >50% in each group, although patients with primary syphilis were more likely to have adenopathy than were patients with genital herpes ($P = .012$; OR = 3.1; 95% CI = 1.3–7.7). Among those patients who had palpable inguinal adenopathy, there was no difference in the level of pain reported ($\geq 1+$ tenderness). However, none of the patients with syphilis, 5% of the patients with genital herpes, and 10% of the patients with chancroid had $\geq 2+$ tenderness (visible withdrawal from palpation). Patients with chancroid were more likely than those with genital herpes to have large lymph nodes. The number of patients with inguinal buboes who presented to this clinic was low, preventing any meaningful analysis of this finding.

Sensitivity, specificity, and positive predictive value of clinical findings for the diagnosis of primary syphilis. The sensitivity and specificity of clinical signs of syphilis are shown in table 2. No single clinical finding had both a high degree of sensitivity and a high degree of specificity. A 3+ induration was the single most specific sign, but it had a low sensitivity. Purulence of $\leq 1+$ was the most sensitive finding. If all three findings were present simultaneously (the classic description

Table 2. Sensitivity and specificity of selected clinical signs of syphilis.

Clinical signs	Sensitivity (%)	Specificity (%)
Ulcer induration, 3+	47	95
Tenderness, $\leq 1+$	67	58
Purulence, $\leq 1+$	82	53
Classic primary syphilis (all three signs present)	31	98

of a syphilitic chancre), then a diagnosis of genital herpes or chancroid could be ruled out with 98% specificity. However, this classic constellation of signs was seen in only 14 of the 45 patients who had a darkfield-positive primary syphilis lesion (31% sensitivity).

Four of the 118 patients with chancroid and none of the 57 patients with genital herpes presented with the classic triad of signs of syphilis. Therefore, in the population studied, the positive predictive value of a painless, indurated, clean-based ulcer for the diagnosis of primary syphilis was 78%.

Sensitivity, specificity, and positive predictive value of clinical findings for the diagnosis of chancroid. The sensitivity and specificity of the clinical signs of chancroid are shown in table 3. Again, no single clinical finding had both a high degree of sensitivity and a high degree of specificity. The presence of an undermined lesion border was the most sensitive single sign for chancroid. If all three findings were present simultaneously (the classic description of a chancroid ulcer), then a diagnosis of primary syphilis or genital herpes could be ruled out with 94% specificity. However, if all three signs were required to

Table 1. Clinical findings in patients with genital ulcer disease.

Finding	No. of patients with chancroid positive for the finding/total no. of patients with chancroid (%)	No. of patients with primary syphilis positive for the finding/total no. of patients with primary syphilis (%)	No. of patients with genital herpes positive for the finding/total no. of patients with genital herpes (%)
Uncircumcised*	75/117 (64)	32/45 (71)	46/57 (81)
Painless ulcer	14/118 (12)	18/45 (40)	6/57 (11)
Ulcer depth, $\geq 2+^{*†}$	107/116 (92)	26/39 (67)	23/57 (40)
Undermined lesion border [‡]	100/118 (85)	15/45 (33)	18/57 (32)
Three or more lesions ^{*†}	40/115 (35)	17/44 (39)	32/51 (63)
Induration size, 3+ ^{†‡}	8/117 (7)	21/45 (47)	0
Purulence, $\geq 2+^{*†}$	75/117 (64)	8/44 (18)	17/57 (30)
Average ulcer diameter, ≥ 10 mm ^{*†‡§}	27/118 (23)	21/45 (47)	5/57 (9)
Palpable lymph nodes [†]	82/116 (71)	36/45 (80)	32/57 (56)
Lymph node tenderness, $\geq 1+$	42/82 (51)	13/36 (36)	16/32 (50)
Mean ulcer diameter, ≥ 4 cm ^{*§}	21/82 (26)	5/36 (14)	2/32 (6)
Fluctuant lymph nodes	1/82 (1)	0/36	1/32 (3)

* $P < .05$ for comparison of patients with chancroid and those with genital herpes.

† $P < .05$ for comparison of patients with primary syphilis and those with genital herpes.

‡ $P < .05$ for comparison of patients with chancroid and those with primary syphilis.

§ Mean diameter of largest lesion or largest lymph node.

Table 3. Sensitivity and specificity of selected clinical signs of chancroid.

Clinical signs	Sensitivity (%)	Selectivity (%)
Undermined lesion border	85	68
Tenderness, $\geq 2+$	57	52
Purulence, $\geq 2+$	64	75
Classic chancroid (all three signs present)	34	94

make the diagnosis of chancroid, then most cases would be missed. This classic constellation of signs had a sensitivity of only 34% (40 of 118 cases).

Two of the 45 patients with primary syphilis and four of the 57 patients with genital herpes presented with the classic triad of signs of chancroid. Therefore, the positive predictive value of a painful, undermined, purulent ulcer for chancroid in the study population was 87%.

Sensitivity, specificity, and positive predictive value of clinical findings for the diagnosis of genital herpes. Seventeen percent of the patients with genital herpes reported that their ulcer(s) began as a "blister" or "group of blisters." The sensitivity and specificity of clinical signs present at the time of examination are shown in table 4. No single examination finding had a high degree of sensitivity for diagnosing genital herpes. The presence of ulcers with only 1+ depth had the highest specificity (88%). Only 20 of the 57 patients with culture-positive genital herpes had multiple (at least three), shallow, tender ulcers (35% sensitivity). However, if this constellation of signs was present, then the diagnosis of primary syphilis or chancroid could be ruled out with 94% specificity.

Seven of the 45 patients with primary syphilis and two of the 118 patients with chancroid also had multiple, tender, shallow ulcers. Therefore, the positive predictive value of this constellation of signs for genital herpes in this study population was 69%.

Discussion

GUD has been an important public health problem in the United States for several reasons. First, the incidence of syphilis and chancroid rose sharply in the mid 1980s. While the overall incidences of these diseases have declined in the 1990s, localized chancroid epidemics continue to be reported, and the incidence of syphilis remains high among the urban underclass and, more generally, in the southeastern United States [13]. Second, it has been clear for some time that genital ulceration facilitates transmission of HIV [14, 15]. Finally, it has been demonstrated that the timely diagnosis and treatment of sexually transmitted diseases can reduce the incidence of HIV infection [16]. Therefore, the appropriate management of GUD can benefit the community.

The data presented above indicate that the classic clinical presentations of primary syphilis, chancroid, and genital herpes are insensitive tools for the diagnosis of sexually transmitted GUD. However, when these findings are present, they are highly specific.

Investigators have previously focused on this issue by using "diagnostic accuracy" [10, 11] or "sensitivity of presumptive clinical diagnoses" [17] as measures. These measures are dependent on the skill of the clinician and are thus influenced by factors including previous experience, knowledge of epidemiological risk factors, and disease prevalence. Therefore, the accuracy of a clinical diagnosis may be highly variable in different clinics. For example, in a study from a primary care clinic in Nairobi conducted by Ndinya-Achola et al. [17], the sensitivity of a clinical diagnosis of chancroid was found to be high (91%). However, this high sensitivity was due to the high degree of suspicion for chancroid in this clinic. As a result, the specificity for this clinical diagnosis was low (24%). Because of this variability, we believe that our data provide a better estimate of the accuracy of the clinical diagnosis of GUD than do those from previous studies.

The results of this study may be useful to clinicians in a variety of settings. Certain individual signs, such as a clean-based ulcer in cases of primary syphilis and undermined lesion borders in cases of chancroid, had good sensitivity (82% and 85%, respectively). Likewise, 3+ induration in ulcers of primary syphilis and shallow ulceration in cases of genital herpes had good specificity (95% and 88%, respectively). These individual signs may more often be helpful to clinicians than are the constellations of findings deemed classic in cases of primary syphilis, chancroid, and genital herpes.

The positive predictive value of the clinical findings depended on the relative prevalence of the three major causes of GUD in our study population. As a disease becomes more prevalent in a population, the likelihood that a positive test result (or a constellation of clinical findings) truly indicates the presence of that disease increases. Chancroid was the most prevalent disease in our study sample. Therefore, it follows that the positive predictive value of classic physical findings was highest for chancroid (87%). If the prevalence of disease in a population is low, then a greater percentage of positive tests are likely to be false positives, and the positive predictive value will decrease. In a community with very few cases of

Table 4. Sensitivity and specificity of selected clinical signs of genital herpes.

Clinical signs	Sensitivity (%)	Specificity (%)
Three or more lesions	63	64
Lesion depth, 1+	60	88
Tenderness, 2+	60	50
Classic genital herpes (all three signs present)	35	94

chancroid, the positive predictive value of classic findings for chancroid might be quite low.

These data underscore the unreliability of surveillance for chancroid in the United States. In 1990, Schulte et al. [18] surveyed 115 STD clinics located in 32 states and in Puerto Rico. Only 16 (14%) of the 115 clinics could perform cultures for isolation of *H. ducreyi*. These investigators concluded that chancroid was probably significantly underreported. However, as our data suggest, there is great potential for overreporting as well. We applied the 1990 Centers for Disease Control (CDC) case definition of probable chancroid to our study population (as it would be applied in 58% of clinics because, according to Schulte et al., these clinics lack the capability to diagnose herpes simplex virus infection). The case definition is as follows: the presence of at least one painful genital ulcer and (1) no evidence of syphilis on the basis of darkfield examination and serology and (2) the presence of lesions not typical for genital herpes. We found that 86% of our chancroid cases met the CDC case definition.

At the same time, however, 56% of our culture-positive herpes cases also met that case definition. It is clear that surveillance for chancroid based on clinical case definitions in the absence of objective laboratory data is unreliable. During the early 1990s, it was our experience in the New Orleans STD Clinic that most patients for whom darkfield examinations were negative and who did not have obvious herpetic vesicles were given a clinical diagnosis of chancroid.

Only one patient with chancroid in this series presented with an inguinal bubo. It has been estimated that 20%–40% of patients with chancroid typically present with fluctuant inguinal adenopathy [19]. In New Orleans, men with buboes most often presented to a hospital emergency department. This circumstance minimized the usefulness of this finding as a specific indicator of chancroid in our study. On the basis of the literature, as well as our experience with emergency department cases [20], we believe that a fluctuant inguinal-node mass in a patient with a genital ulcer is highly specific for chancroid. Lymphogranuloma venereum causes fluctuant inguinal-node masses, but the genital ulcer is usually absent. It is of interest that one patient with genital herpes also presented with fluctuant inguinal adenopathy, a finding that is infrequently reported. This patient may have had a dual infection, and the culture for *H. ducreyi* was false negative.

An additional observation of some interest is that men with genital herpes were more likely to be uncircumcised than were men with chancroid (81% vs. 64%, respectively; $P < .05$). It is generally believed that the presence of a foreskin is a risk factor for chancroid. Our data suggest the possibility that the same is true for a first episode of genital herpes in populations such as ours. There are other possible explanations for this observation in addition to the possibility of increased susceptibility to genital herpes. For example, uncircumcised men may have more-severe manifestations of genital herpes than do circumcised men. Further study of this issue would be of interest.

One limitation of the present study is the fact that it was restricted to men. This might be particularly important if the manifestations of GUD differ systematically between men and women. O'Farrell et al. [11] found that GUD was more accurately diagnosed in women than in men. However, in a study of the clinical diagnosis of GUD in Kenyan women, the investigators found that there was considerable overlap between the clinical features of syphilitic and chancroidal ulcers [21]. Furthermore, the same investigators found that the most sensitive clinical findings for chancroid in women were tenderness, purulence, and ulcer depth and undermining; these findings are similar to the findings presented herein. Overall, there are few data suggesting that the objective manifestations of primary syphilis, genital herpes, and chancroid differ substantially between men and women. While a study, similar to the present study, that includes women would be useful, we are currently of the opinion that physical examination is as insensitive for diagnosing GUD in women as it is in men.

Another potential limitation to our study is that the exact prevalence of HIV infection among the study sample is not known. The clinical appearance of genital ulcers may be altered by immunosuppression, which would affect the generalizability of the results of a study such as ours. However, the overall rate of HIV seropositivity among all patients seen in our clinic is 2%–3% currently, and the rate of HIV infection among 140 patients from this clinic who were enrolled in a chancroid treatment trial [12] was 3%. Therefore, it is doubtful that HIV infection had a significant effect on the appearance of our patients' ulcers.

A final limitation of our study is the fact that it included a low number of patients with genital herpes. This number is probably not representative of the true prevalence of symptomatic genital herpes among patients seen in this clinic. The manifestations of genital herpes are highly variable, and many patients do not present with true genital ulceration [8]. For patients who present with (or have a history of) vesicular lesions, genital herpes can be diagnosed with a reasonable degree of specificity. However, the objective of the present study was to determine the utility of physical examination in those cases of herpetic GUD that might be confused with primary syphilis or chancroid. Therefore, we restricted the study to that subset of patients with genital herpes who presented with ulcers alone.

The performance of additional diagnostic tests might have allowed the inclusion of more patients in the analysis and could possibly have changed the results. For example, the use of multiplex PCR to detect DNA from the three pathogens causing GUD might have established a diagnosis for some of the patients who were excluded because of negative darkfield examinations and cultures. If the infections in a significant number of patients with culture-negative, shallow ulcers had been diagnosed as genital herpes in this manner, the sensitivity of this finding might have been increased.

The degree of overlap in physical findings among patients with all three causes of GUD indicates that what are usually

thought of as "atypical" presentations may actually be the norm. This has been noted in the past for patients with primary syphilis [22]. Since GUD is difficult to diagnose on clinical grounds, most patients with GUD are treated empirically according to the principles of syndromic management. Patients are treated for infection due to the most likely etiologic organisms on the basis of the local epidemiological situation. In cases of GUD that are not obviously herpetic (vesicles are not reported by the patient and are not found on physical examination), treatment would consist of that for primary syphilis alone, or treatment for both syphilis and chancroid in areas where chancroid is endemic. On the basis of our observations of the diagnostic specificity for the classic clinical triads, it would probably be reasonable to withhold such therapy for patients who have three or more shallow, painful ulcers.

The syndromic approach to GUD will remain the standard until rapid, sensitive diagnostic tools are developed. Current diagnostic tests are relatively insensitive; in our study, a definitive microbiological diagnosis was established for only 59% of all patients with GUD. PCR has proven to be very sensitive for the diagnosis of primary syphilis, chancroid, and genital herpes [23]. However, it is unlikely that PCR can be adapted for use in rapid diagnosis. Furthermore, the cost of this technology is unknown. Given that the appropriate management of GUD can reduce the incidence of HIV infection in a community and that the classic physical examination findings of GUD have a low sensitivity in the diagnosis of GUD, the development of inexpensive, rapid, and sensitive diagnostic tests is an endeavor worthy of additional research.

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