

Simple algorithms for the management of genital ulcers: evaluation in a primary health care centre in Kigali, Rwanda

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A cross-sectional study was conducted among 395 patients presenting with genital ulcers at a primary health care centre in Kigali, Rwanda. Using clinical data and the results of a rapid plasma reagin (RPR) test, we simulated the diagnostic outcome of two simple WHO flowcharts for the management of genital ulcers. These outcomes and a clinical diagnosis were then compared with the laboratory diagnosis based on culture for genital herpes and Haemophilus ducreyi and serology for syphilis.

The prevalence of HIV infection was high (73%) but there was no difference between HIV-positive and HIV-negative patients in the clinical presentation and etiology of genital ulcer disease. The proportion of correctly managed chancroid and/or syphilis cases was 99% using a syndromic approach, 82.1% using a hierarchical algorithm including an RPR test, and 38.3% with a clinical diagnosis.

In situations where no laboratory support is available, a simple syndromic approach is preferable to the clinical approach for the management of genital ulcer. If an RPR test can be included in the diagnostic strategy, patients with a reactive RPR test should be treated for both syphilis and chancroid infection.

Introduction

Prompt diagnosis and treatment of genital ulcer disease (GUD) is important not only to reduce morbidity but also to slow down the spread of human immunodeficiency virus (HIV) (1). In developing countries, where laboratory facilities are scarce, etiological diagnosis of GUD is usually based on clinical criteria only. However, even before the HIV era, it was reported that this approach was not very accurate, even if performed by experienced clinicians (2, 3). To assure prompt and effective treatment of patients with sexually transmitted diseases (STDs) at the primary health care level, WHO has developed simple flowcharts (4), including two designed for the management of GUD.

In Rwanda, which has a population of around 7 million, about 5000 cases of primary syphilis are

reported annually to the health authorities, other causes of GUD are reported only sporadically or not at all. In the Centre Médico Social de Bilyogo in Kigali in 1985, the proportions of chancroid, syphilis and genital herpes diagnosed among patients with GUD were 18%, 28%, and 19%, respectively; 59% of these patients were infected with HIV-1 (5).

The first objective of this study was to assess the proportion of genital herpes, syphilis, and chancroid in patients with and without HIV infection who presented with GUD at a primary health care centre in Kigali. The second, was to compare three simple methods for the management of GUD (two WHO algorithms (flowcharts) and a clinical approach) to determine which approach would result in the largest proportion of patients with chancroid and/or syphilis receiving the correct treatment.

Patients and methods

Data collection

During 1990–92, on three working days each week, all consecutive men and women presenting with genital ulcers at the Centre Médico Social de Bilyogo in Kigali were included in the study. This primary health care centre serves the lower socioeconomic levels and is situated in a part of the city where prostitution is widespread.

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Demographic and clinical information about the patients were obtained in a standard interview. All patients underwent a physical examination of the external genitalia and the inguinal region before specimens for laboratory analysis were taken; each patient was diagnosed clinically by a physician (JB) before the laboratory results were known. The following criteria were used: invasive ulcers were considered as chancroid; noninvasive ulcers, as primary syphilis; and genital herpes was diagnosed if vesicles were present, or if there was a history of recurrences, or the ulcers were superficial (erosions). Pain and purulence were not used as diagnostic criteria. If the clinical picture did not correspond to one of these criteria, the diagnosis remained undetermined. No attempts were made to identify clinically other causes of GUD or mixed infections. All patients were requested to return for clinical and microbiological evaluation on days 7, 14, 21 and 28 after the initial visit.

Laboratory procedures

Haemophilus ducreyi was isolated by inoculating a swab specimen from the ulcer directly onto two selective media. The first medium consisted of Mueller–Hinton agar base 2 (BioMérieux, Marcy l’Etoile, France) supplemented with 1% Iso Vitalex (BBL Microbiology Systems, Cockeysville, MD, USA), 5% fetal calf serum (Gibco, Paisley, Scotland), 1% haemoglobin (Difco, Detroit, MI, USA) and 3 µg/ml vancomycin. The second medium had a gonococcal agar base (GC-Agar, Difco, Detroit, MI, USA) and the same supplements as the first. Isolates were identified on the basis of typical colony morphology and Gram-stain results. Specimens for isolation of herpes simplex virus (HSV) were obtained with a nontoxic cotton swab which was transported in Hank’s balanced salt solution to the Institute of Tropical Medicine, Antwerp, Belgium, where HSV was detected by its cytopathic effect on a monolayer of Vero cells. Specimens were taken for cultures of *H. ducreyi* and HSV at 1-week intervals until complete healing of the ulcer.

For the diagnosis of syphilis, both the rapid plasma reagin (RPR) test (Becton Dickinson, Baltimore, MD, USA) and the *Treponema pallidum* haemagglutination assay (TPHA: Fujirebio, Tokyo, Japan) were performed on day 0 and on day 14 for patients who presented within 7 days of ulcer onset. Darkfield microscopy was carried out on the first 86 patients who reported not having used antibiotics before consultation, but we abandoned this subsequently since no positive cases were found.

Antibodies to HIV-1 were detected in sera collected on day 0 using enzyme-linked immunosorbent

assay (ELISA) (Vironostika HIV-mixt, Organon Teknika, Oss, Netherlands). Positive reactions were confirmed by line immunoassay (LIA) (INNO-LIA HIV1/HIV2 Antibody, Innogenetics, Zwijndrecht, Belgium). Supplementary testing using Western blot (Du Pont, Wilmington, DE, USA) was performed if the LIA results were indeterminate. The TPHA, LIA, and Western blot tests were carried out at the Institute of Tropical Medicine, Antwerp, Belgium.

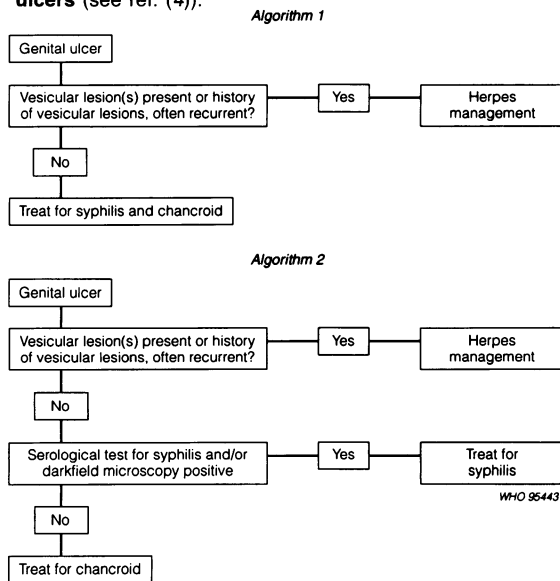
Etiological diagnosis

Isolation of *H. ducreyi* and HSV was used for the diagnosis of chancroid and genital herpes, respectively. Active syphilis was considered when the RPR test had a titre of ≥1:2 and was confirmed by a positive TPHA result (titre ≥1:80) on day 0 or day 14.

Sensitivity of the diagnostic models

The two algorithms for GUD management recommended by WHO are shown in Fig. 1 (4). Algorithm 1 is a syndromic approach for use in settings without any laboratory support; algorithm 2 is hierarchical and is intended for locations where an RPR test or darkfield microscopy can be performed. For each patient the diagnostic outcome of the algorithms was simulated using data obtained from interview, clinical examination, and the results of an RPR test. The clinical diagnosis made on day 0 by the physician was readily available. The sensitivity

Fig. 1. WHO flowcharts for the management of genital ulcers (see ref. (4)).



of each approach (defined as the proportion of proven infection identified by applying each model) was calculated separately for genital herpes, syphilis, and chancroid.

Simulated management of chancroid and/or syphilis

Patients were considered as correctly managed if they received the appropriate treatment for chancroid and/or syphilis by applying the diagnostic strategies. In the clinical approach, only the clinically identified infections were treated. An alternative clinical approach was simulated in which clinically undetermined ulcers were treated for syphilis and chancroid (clinical diagnosis + syndromic approach). Treatment for more than one infection (e.g., treatment for chancroid and syphilis) was considered correct provided the proven infection was treated. Overtreatment for syphilis was calculated as the proportion of patients not seroreactive for syphilis among all patients treated for syphilis.

Statistical analysis

The data were analysed using Epi-Info, version 5 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). For comparison of proportions, Yates' corrected χ^2 and two-tailed Fisher's exact tests were used.

Results

Clinical data and etiology of genital ulcers

Table 1 summarizes the clinical and etiological data from all 395 patients and compares the data for HIV-infected (HIV+) and HIV-negative (HIV-) patients. The prevalence of HIV infection was high; 67% (166/247) of men and 83% (123/148) of women. A significantly higher proportion of HIV-infected patients reported a history of genital ulcers (40.1% versus 15.1%, $P < 0.001$). There was no significant difference between the two groups in the delay between ulcer onset and consultation; more than one-third of the patients presented within a week, but 20.8% had waited more than 4 weeks before attending the health centre. Self-medication before consultation was very common; 28.4% of HIV+ and 30.2% of HIV- patients reported antibiotic use.

Invasive ulcers were somewhat less frequent among HIV+ than HIV- patients (32.9% versus 43.4%; $P = 0.07$), but this difference disappeared after stratification by sex (data not shown). HIV+ patients also had fewer inguinal buboes than HIV- patients, although after stratification the difference was only significant among men (9% versus 18.5%;

$P = 0.05$). All the other clinical signs were similar for HIV+ and HIV- patients.

HSV was equally common among HIV+ and HIV- patients. *H. ducreyi*, alone or in combination with HSV or a reactive syphilis serology, was the most commonly identified etiology, causing 29.1% of the ulcerations. Chancroid or a mixed infection (chancroid + another etiology) was diagnosed in 27.7% of HIV+ and 33% of HIV- patients ($P = 0.36$).

Among the 118 patients with a reactive RPR test on the first visit, 109 (92.4%) also had a reactive TPHA result. Only one of the 57 patients whose ulcer onset was ≤ 7 days previously seroconverted in the RPR test and TPHA. A reactive syphilis serology was significantly more commonly observed for HIV+ than HIV- patients (89/289 (30.8%) versus 21/106 (19.8%); $P = 0.03$). The RPR test and TPHA results were reactive among 25.3% of HIV+ and 17.3% of HIV- men ($P = 0.21$); and among 38.2% of HIV+ and 28% of HIV- women ($P = 0.46$).

Sensitivity of the models for diagnosis

The sensitivity of the three diagnostic models for each etiology is shown in Table 2.

Of the 89 patients who had a positive culture for herpes, only four (4.5%) presented with vesicles and no patient reported a history of vesicles. The clinical approach, which considered not only vesicles but all superficial ulcers as herpes, identified 43 (48.3%) of the 89 cases.

In the simulated application of WHO algorithm 1, all 387 patients without vesicles were treated for both syphilis and chancroid. Of these patients, 108 had a reactive syphilis serology on day 0 and/or on day 14. Two syphilis cases were missed, since these patients also had vesicles. The 115 patients with proven chancroid infection all received treatment for syphilis and chancroid, corresponding to 100% sensitivity of algorithm 1 for chancroid.

In the simulated application of the hierarchical algorithm which includes an RPR test (algorithm 2), three syphilis cases were missed, including two patients with reactive syphilis tests who had vesicles and another patient who seroconverted (RPR test) during follow-up. Only 83 patients who had a non-reactive RPR test on day 0 were managed as chancroid. At 72.2%, the sensitivity for chancroid with algorithm 2 was lower than with algorithm 1.

The sensitivity of the clinical diagnosis was 18.2% for syphilis and 64.3% for chancroid.

Simulated management of chancroid and/or syphilis

Table 3 compares the numbers of patients correctly treated for chancroid, syphilis, and mixed infection

Table 1: Clinical data and etiological diagnosis for patients with genital ulcer disease (GUD), in Kigali, Rwanda, by human immunodeficiency virus (HIV) infection status

Patients with genital ulcers	All patients (n = 395)	HIV+ve (n = 289)	No. of HIV–ve (n = 106)	P
No. of men/women	247/148	166/123	81/25	—
History of GUD	132 (33.4) ^a	116 (40.1)	16 (15.1)	<0.001
<i>Ulcer onset:</i>				
≤7 days	150 (38.0)	106 (36.7)	44 (41.5)	0.45
8–14 days	101 (25.6)	73 (25.3)	28 (26.4)	0.92
15 days to 4 weeks	60 (15.2)	45 (15.6)	15 (14.2)	0.85
≥4 weeks	82 (20.8)	64 (22.1)	18 (17.0)	0.33
Unknown	2 (0.5)	1 (0.3)	1 (0.9)	0.46
Antibiotic use before consultation	114 (28.9)	82 (28.4)	32 (30.2)	0.82
Loss to follow-up on day 7	92 (24.8)	74 (25.6)	24 (22.6)	0.45
<i>Clinical signs</i>				
Vesicles	8 (1.9)	6 (2.1)	2 (1.9)	1.00
Superficial ulcers	122 (30.9)	95 (32.9)	27 (25.5)	0.20
Noninvasive ulcers	51 (12.9)	35 (12.1)	16 (15.1)	0.54
Invasive ulcers	141 (35.7)	95 (32.9)	46 (43.4)	0.07
Undetermined	73 (18.5)	58 (20.1)	15 (14.2)	0.23
Buboes	36 (9.1)	20 (6.9)	16 (15.1)	0.02
<i>Laboratory diagnosis^b</i>				
<i>Single infections:</i>				
HSV	72 (18.2)	48 (16.6)	24 (22.6)	0.22
<i>H. ducreyi</i>	79 (20.0)	48 (16.6)	31 (29.2)	0.008
Syphilis ^c	72 (18.2)	53 (18.3)	19 (17.9)	0.96
<i>Mixed infections:</i>				
HSV + <i>H. ducreyi</i>	7 (1.7)	5 (1.7)	2 (1.9)	1.00
HSV + syphilis	9 (2.3)	9 (3.1)	0	0.12
<i>H. ducreyi</i> + syphilis	28 (7.1)	26 (9.0)	2 (1.9)	0.03
HSV + <i>H. ducreyi</i> + syphilis	1 (0.2)	1 (0.3)	0	
Undetermined	127 (32.2)	99 (34.3)	28 (26.4)	0.17

^a Figures in parentheses are percentages.

^b HSV = herpes simplex virus; *H. ducreyi* = *Haemophilus ducreyi*.

^c Reactive RPR test and positive TPHA result.

(chancroid and syphilis) in the simulated application of the different diagnostic models. For chancroid and/or syphilis, 99% of the patients were correctly treated under algorithm 1, 82.1% under algorithm 2 and 38.3% under the clinical approach. None of the mixed infections, which represented 14.8% of all patients with chancroid and/or syphilis were treated by applying algorithm 2 or the clinical approach. With the alternative approach, treating all clinically undetermined cases for chancroid and syphilis, 5/29 (17.2%) mixed infections were treated. By means of this strategy the proportion of correctly treated patients with chancroid and/or syphilis increased to

58.7%. The proportion of overtreatment of syphilis was 72.1% (279/387) using algorithm 1, 7.8% (9/116) using algorithm 2, and 60.8% (31/51) using the clinical approach.

Discussion

The study confirmed a very high rate of HIV infection among patients with genital ulcers in Kigali. No difference in GUD etiology was demonstrated between HIV+ and HIV– patients. Our findings showed that GUD patients would more frequently be cor-

Table 2: Sensitivity of three diagnostic models (two WHO algorithms and a clinical approach) for the diagnosis of genital herpes, syphilis and chancroid, Kigali, Rwanda

Etiology	Diagnostic model:		
	Algorithm 1	Algorithm 2	Clinical
<i>Herpes</i> (n = 89)			
No. of diagnoses (total) ^a	8	8	130
No. confirmed by culture	4	4	43
Sensitivity	4.5%	4.5%	48.3%
<i>Syphilis</i> (n = 110)			
No. of diagnoses (total) ^a	387	116	51
No. RPR +ve and TPHA +ve ^b	108	107	20
Sensitivity	98.2%	97.3%	18.2%
<i>Chancroid</i> (n = 115)			
No. of diagnoses (total) ^a	387	271	141
No. confirmed by culture	115	83	74
Sensitivity	100%	72.2%	64.3%

^a No. of patients treated for the corresponding etiology according to the model.

^b No. of patients with a reactive rapid plasma reagin (RPR) test and *Treponema pallidum* haemagglutination assay (TPHA).

rectly managed using a simple syndromic approach than by a hierarchical procedure that includes an RPR test.

The high prevalence of HIV among GUD patients found in the study (73.2%) is comparable with data from some other African cities such as Lilongwe, Malawi (62.4%) (6) and Lusaka, Zambia (54%) (7). It should be noted that such high prevalences were already present in Kigali in 1986 among women with GUD (77%), at which time 43% of the men with GUD were HIV+ (5). These proportions provide a strong case for focusing behaviour-change education and condom promotion on patients with genital ulcers.

The clinical presentation of genital ulcers was similar among HIV+ and HIV- patients, except for a lower frequency of inguinal buboes among HIV+

men. A lower frequency of inguinal buboes was also found among patients with chancroid in Zimbabwe and could be caused by the absence of functioning T lymphocytes in the inguinal lymph nodes of HIV+ individuals (8). Lymphatic drainage is less superficial in women than in men, and this could explain the differences between the sexes that we found here. HIV infection did not affect the relative frequency of genital herpes and chancroid. Among a group of female commercial sex workers in Abidjan, Côte d'Ivoire, those who were HIV- had significantly more ulcers (9), but the relative frequencies of genital herpes and chancroid in HIV+ and HIV- women were similar to those in the present study. The proportion of ulcers with undetermined etiology in Kigali was also similar to that in the present study (35.7% in 1986 (5) and 32.2% in 1992).

Table 3: Number of patients with proven infection of chancroid and/or syphilis correctly managed by the three diagnostic models

	Syphilis	Chancroid	Syphilis and chancroid	Total
No. of infected patients	81	86	29	196
<i>No. of such patients correctly managed by:</i>				
Algorithm 1	79 (97.5) ^a	86 (100)	29 (100)	194 (99.0)
Algorithm 2	78 (96.3)	83 (96.5)	0 (0)	161 (82.1)
Clinical diagnosis	18 (22.2)	57 (66.3)	0 (0)	75 (38.3)
Clinical diagnosis + syndromic approach ^b	41 (50.6)	69 (80.2)	5 (17.2)	115 (58.7)

^a Figures in parentheses are percentages.

^b Patients treated according to clinical diagnosis and all patients with indeterminate clinical diagnosis would have received treatment for both chancroid and syphilis.

Studies on the etiology of GUD remain problematic because of constraints of the gold standard laboratory techniques. Laboratory confirmation of chancroid by culture is highly specific but the sensitivity is poor (10), i.e., when a culture for *H. ducreyi* is negative, there are two possibilities: either the genital ulcer is not a chancroid or the culture gives a false-negative result. Use of culture as the gold standard for genital herpes has the same constraint (11), especially when the samples are transported over a long distance. The value of a reactive RPR test and TPHA in diagnosing "a syphilitic ulcer" is equivocal, particularly for populations with a high background prevalence of reactive syphilis serology such as STD patients. Persistently reactive RPR serology after treatment of syphilis has been documented. In one study, only 44% of the patients with late latent syphilis became seronegative within 5 years of treatment (12); however, as only one patient seroconverted (RPR and TPHA results), the sensitivity of syphilis serology was very high in our study.

From the public health perspective, it is more important that the diagnostic approach to GUD has a high sensitivity than a high specificity; the lower the sensitivity, the more infected individuals will remain untreated, resulting in complications and the risk of secondary infections, including HIV. Other studies have generally focused on the accuracy of a clinical diagnosis for genital ulcers (13, 14).

Both chancroid and syphilis can readily be treated with the antibiotics widely available in developing countries. In the present study, the simpler syndromic approach resulted in the highest proportion of correctly treated chancroid and/or syphilis cases. If no laboratory tests are available, this approach is preferable to that of clinical diagnosis. Even an alternative strategy, in which we treated clinically undetermined ulcers for syphilis and chancroid, resulted in more missed infections than the syndromic approach used in WHO algorithm 1. It should also be emphasized that, in the present study, clinical diagnosis was made by a physician, which is not always the case in developing countries.

An algorithm that includes an RPR test should only be considered in locations with adequate laboratory facilities and where the results of the test can be made available within a reasonable period of time. Although the inclusion of an RPR test in a hierarchical model may lead to missed chancroid cases, it may also lower the level of overtreatment for syphilis; in the present study, such an approach reduced overtreatment from 72.1% (algorithm 1) to 7.7% (algorithm 2). Unnecessary treatment of patients and their contacts for syphilis would therefore be reduced. Alternatively all patients with a reactive RPR test could be treated for both syphilis and chancroid,

nonreactive patients being treated only for chancroid. RPR tests are also useful screening methods for pregnant women and other STD patients.

Vesicles as a typical sign of genital herpes are rarely seen at clinics in developing countries, where patients often present late in the course of the disease. However, underdiagnosis of genital herpes is a minor problem, since adequate treatment is not available or is too expensive for routine use in many settings. In addition, 70% of patients who had genital herpes in the present study were cured within 2 weeks, without any specific treatment and irrespective of their HIV status (15).

In conclusion, in locations where syphilis and chancroid rank among the major causes of GUD and where no laboratory support is available, a simple syndromic management is superior to a clinical approach and should result in more cases being cured. If an RPR test is readily available, patients whose tests are positive should be treated for both syphilis and chancroid since mixed infections are common. This approach should result in more effective case management of GUD.

Résumé

Algorithmes simples pour la prise en charge des ulcères génitaux: évaluation dans un centre de soins de santé primaires à Kigali, Rwanda

Pour assurer un traitement rapide et efficace des patients atteints de maladies sexuellement transmissibles au niveau des soins de santé primaires, l'OMS a élaboré des diagrammes simples, dont deux pour la prise en charge des ulcères génitaux. La présente étude avait pour objectifs d'évaluer la proportion d'herpès génital, de syphilis et de chancre mou chez des patients infectés par le VIH ou non, dans un centre de soins de santé primaires de Kigali (Rwanda), et de comparer les approches de la prise en charge des ulcères génitaux, y compris celles qui utilisent les diagrammes de l'OMS.

L'étude transversale a été réalisée chez 395 patients consultant un centre de soins de santé pour des ulcères génitaux. Les renseignements démographiques et cliniques ont été recueillis lors d'un entretien type, et tous les malades ont subi un examen physique. Les techniques de laboratoire utilisées pour rechercher l'étiologie des ulcères génitaux étaient la culture du virus de l'herpès et de *Haemophilus ducreyi*, le test rapide

des réagines plasmatiques (RPR) et l'épreuve d'hémagglutination pour la mise en évidence de *Treponema pallidum* (TPHA) pour la syphilis.

En utilisant les données cliniques et les résultats du test RPR, on a opéré une simulation du diagnostic découlant de l'emploi des diagrammes OMS. On a ensuite comparé ce diagnostic et un diagnostic clinique avec le diagnostic de laboratoire afin de déterminer la sensibilité des diagrammes et la proportion de cas de chancre mou et/ou de syphilis correctement pris en charge suivant chacune des approches.

La prévalence de l'infection à VIH chez les patients consultant pour des ulcères génitaux était élevée (83% chez les femmes et 67% chez les hommes). Il n'y avait pas de différence entre les malades positifs pour le VIH (VIH+) et ceux qui étaient négatifs (VIH-) quant à l'aspect clinique des ulcères, à l'exception des abcès inguinaux, moins fréquents chez les hommes VIH-. L'étiologie la plus couramment trouvée était le chancre mou; on a diagnostiqué une infection à *H. ducreyi* chez 27,7% des sujets VIH+ et 33% des sujets VIH-. Un test sérologique positif pour la syphilis était de façon significative plus fréquemment observé chez les sujets VIH+ (89 sur 289 (30,8%) contre 21 sur 106 (19,8%); $p = 0,03$), mais cette différence disparaissait après stratification selon le sexe, le test étant plus souvent positif chez les femmes.

Le diagnostic d'herpès basé sur la présence de vésicules avait une sensibilité de 4,5%. La sensibilité du plus simple des deux algorithmes OMS était de 98,2% pour la syphilis et 100% pour le chancre mou. En ajoutant un test RPR comme étape hiérarchique dans le diagramme, on abaissait la sensibilité pour le chancre mou (72,2%). La sensibilité du diagnostic clinique pour la syphilis était de 18,2% et pour le chancre mou de 64,3%. En utilisant une approche syndromique, on obtenait une proportion de 99% de cas de chancre mou et/ou de syphilis correctement pris en charge, cette proportion étant de 82,1% en appliquant un algorithme hiérarchique avec test RPR, et de 38,3% en utilisant un diagnostic clinique.

Cette étude montre qu'en l'absence de moyens de laboratoire, une approche syndromique simple est préférable à l'approche clinique pour la prise en charge des ulcères génitaux, car elle permet de traiter convenablement davantage de cas de chancre mou et de syphilis. Si un test RPR peut être inclus dans la stratégie de diagnostic, les malades ayant un test positif devront

être traités à la fois pour la syphilis et pour le chancre mou.

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