Etiology of urethral discharge in West Africa: the role of *Mycoplasma genitalium* and *Trichomonas vaginalis*

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Objective To determine the etiological role of pathogens other than *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in urethral discharge in West African men.
Methods Urethral swabs were obtained from 659 male patients presenting with urethral discharge in 72 primary health care facilities in seven West African countries, and in 339 controls presenting for complaints unrelated to the genitourinary tract. Polymerase chain reaction analysis was used to detect the presence of *N. gonorrhoeae, C. trachomatis, Trichomonas vaginalis, Mycoplasma genitalium*, and *Ureaplasma urealyticum*.
Findings *N. gonorrhoeae, T. vaginalis, C. trachomatis*, and *M. genitalium* — but not *U. urealyticum* — were found more frequently in men with urethral discharge than in asymptomatic controls, being present in 61.9%, 13.8%, 13.4% and 10.0%, respectively, of cases of urethral discharge. Multiple infections were common. Among patients with gonococcal infection, *T. vaginalis* was as frequent a coinfection as *C. trachomatis*. *M. genitalium, T. vaginalis,* and *C. trachomatis* caused a similar clinical syndrome to that associated with gonococcal infection, but with a less severe urethral discharge.
Conclusions *M. genitalium* and *T. vaginalis* are important etiological agents of urethral discharge in West Africa. The frequent occurrence of multiple infections with any combination of four pathogens strongly supports the syndromic approach. The optimal use of metronidazole in flowcharts for the syndromic management of urethral discharge needs to be explored in therapeutic trials.

Keywords: urethral diseases, etiology; Gram-negative bacterial infections; Mycoplasma; Trichomonas vaginalis; Neisseria gonorrhoae; Chlamydia trachomatis; genital diseases, male; Africa, Western.

Mots clés: urètre, maladies, étiologie; infection bactérienne, Gram-négatif; Mycoplasma; Trichomonas vaginalis; Neisseria gonorrhoeae; Chlamydia trachomatis; appareil génital masculin, maladies; Afrique de l'Ouest.

Palabras clave: enfermedades uretrales, etiología; infecciones bacterianas gramnegativas; Mycoplasma;Trichomonas vaginalis; Neisseria gonorrhoae; Chlamydia trachomatis; enfermedades de los genitales masculinos; Africa occidental.

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Introduction

The control of sexually transmitted diseases (STDs) can lead to a substantial reduction in the transmission of human immunodeficiency virus (HIV) in sub-Saharan Africa (*1*). In most African countries, STD

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control is based on the syndromic approach: patients presenting with a genitourinary complaint are treated with a combination of drugs that target the most frequent etiological agents of the corresponding syndrome, and there is no attempt to make a precise microbiological diagnosis (*2–4*). This approach is attractive, given the high cost and poor availability of laboratory assays for sexually transmitted pathogens. It does, however, require a proper understanding of the most common etiological agents of a syndrome, and appropriate selection of drugs that are both cheap and effective against these pathogens.

Urethral discharge is by far the most common syndrome seen in men with STD in sub-Saharan Africa (*5, 6*). Non-ulcerative diseases play an important role in facilitating the spread of HIV, and gonococcal urethritis increases the seminal shedding of HIV several fold (*7, 8*). Studies of the etiology of urethral discharge syndrome in Africa have shown that *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are involved in 53–80% and 3–16%, respectively, of such cases (*9, 10*). Up to 40% of cases are of unknown etiology, so management of a significant fraction of patients with urethral discharge remains empirical. Current WHO guidelines recommend the simultaneous administration of drugs that are effective against *N. gonorrhoeae* and *C. trachomatis*, but not against other potential pathogens (*2*). Development of protocols for the management of patients in whom this therapy fails and in whom reinfection is unlikely, is left to the discretion of each country. Proper laboratory investigation is advocated but seldom available. To delineate better the etiology of urethral discharge syndrome in West Africa, we organized a regional study in which molecular diagnostic methods were used on specimens obtained in a large number of primary health care facilities.

Methods

Sample collection

Primary health care facilities (governmental health centres, private non-profit or for-profit nursing posts in urban areas of seven West African countries covered by a regional HIV/STD control programme were invited to participate. Between July 1996 and December 1997, a total of 72 health care facilities provided specimens from the following countries: Benin (6 facilities in Cotonou), Burkina Faso (11 in Ouagadougou), Côte d'Ivoire (5 in Abidjan and four in Bouaké), Ghana (5 in Accra), Guinea (18 in Conakry and 1 in Kamsar), Mali (6 in Bamako and 3 in Koutiala) and Senegal (13 in the Rufisque, Kolda and Tambacounda areas). Eligible patients comprised men who presented with a complaint of urethral discharge, regardless of whether a discharge was actually seen during the examination or whether prior treatment had been administered. All consecutive cases with urethral discharge were enrolled until the target for a given country had been reached. In each country, we attempted to enrol 100 cases of urethral discharge and, as controls, 50 sexually active male patients who presented to some of these institutions with complaints unrelated to the genitourinary tract. After obtaining verbal consent from the patients, a questionnaire was administered by the health care provider (medical doctors, medical assistants or nurses), and two urethral swabs were obtained. These were put into the Amplicor Swab Specimen Collection and Transport Kit (Roche Diagnostic Systems, Branchburg, New Jersey), kept in a refrigerator, and later sent by air mail to a central laboratory for polymerase chain reaction (PCR) analysis. Patients were treated according to the national STD flowcharts.

PCR analysis

PCR analysis was carried out for the following potential pathogens: *N. gonorrhoeae* (NG), *C. trachomatis* (CT), *Trichomonas vaginalis* (TV), *Mycoplasma genitalium* (MG) and *Ureaplasma urealyticum* (UU). Specimens were prepared for PCR by adding an equal volume of Amplicor Specimen Diluent, followed by storage at 4 °C for at least three days prior to analysis, to reduce the frequency of inhibition (*11*). Inhibition was monitored using Amplicor Internal Control or home-made internal controls, obtained by cloning the amplicon and removing or inserting a DNA fragment (*12*). For NG and CT, the Roche Amplicor *C. trachomatis/N. gonorrhoeae* Test Kit was used according to the manufacturer's instructions. Modifications of published procedures (*13–16*) for the detection of MG, UU, and TV were used (a full description of the primers is available from the authors). Each organism was detected separately using PCR or semi-nested PCR (for MG and TV). Presence of the amplicon was determined by agarose gel electrophoresis.

Prepared samples (25 µl) were added to a master mix (25 µl) composed of 2X buffer (20 mmol TrisHCl pH 8.3, 100 mmol KCl), 400 µmol of dNTPs, 1.25 units of Taq polymerase (Roche Diagnostic Systems), and 0.5 µmol primers. The amplification procedure comprised 5 min at 95 °C and 40 cycles of denaturation (95 °C), annealing (62 °C), and extension (72 °C) for 20 s at each step followed by a hold cycle at 72 °C for 15 min prior to cooling the reactions to 4 °C.

After the first series of amplification, a semi-nested series of PCR was undertaken for MG and TV using 1 µl of the first series and 49 µl of a master mix to give the final concentration of reagents as in the initial series. Positive and negative controls were included in each series. Samples negative for all five microorganisms were monitored for inhibition and those showing inhibition were re-tested after 10-fold dilution of the initial specimen.

Data analysis

Data were entered into the computer using the EpiInfo 6.0 package, and analysed with Stata 5.0

and SAS 6.12. Proportions were compared using chi-squared tests or Fisher's tests if the sample numbers were small. Continuous data were compared using the Wilcoxon test. Logistic regression was used for multivariate analysis.

Results

A total of 659 specimens were obtained from patients with urethral discharge: 86 from Benin, 100 from Burkina Faso, 81 from Côte d'Ivoire, 105 from Ghana, 97 from Guinea, 96 from Mali, and 94 from Senegal. Samples from 50 controls without urethral discharge were obtained from each country except from Benin (55 samples), Côte d'Ivoire (49 samples), Mali (45 samples), and Senegal (40 samples).

The prevalence of each potential pathogen among cases with urethral discharge and asymptomatic controls is shown in Table 1. NG, CT, and TV were all found significantly more often in cases with urethral discharge than in controls, whereas UU was not associated with urethral discharge. For MG, the association with urethral discharge became apparent only when cases were divided into two subgroups, according to whether or not NG and/or CT had also been found. MG was found more frequently in cases of non-gonoccocal, non-chlamydial urethral discharge than in patients whose samples contained either NG or CT, or in controls.

Cases and controls differed in a number of characteristics that were not related to the presence of potential pathogens (e.g. prior contact with sex workers or past history of urethritis). There were also differences between cases and controls for factors related to the presence of potential pathogens — namely, age, and number of sexual partners. The median ages of cases and controls were 27 and 29 years, respectively ($P = 0.02$); and the median number of sexual partners in the preceding 12 months were two and one, respectively ($P < 0.001$). The associations between the potential pathogens and urethral discharge were confirmed in multivariate logistic regression models, where all relevant pathogens as well as the age of cases and controls, and number of sexual partners in the preceding 12 months, were entered as independent variables.

In addition, we examined all potential second-degree interactions between the different pathogens.

Table 1. **Prevalence of potential pathogens in cases with urethral discharge and in asymptomatic controls**

Pathogen	Prevalence % (No.)			
	All cases with urethral discharge ($n = 659$)	Cases with urethral discharge, negative for NG and CT ($n = 209$)	Cases with urethral discharge, positive for NG and/or CT ($n = 450$)	Controls ($n = 339$)
Neisseria gonorrhoeae (NG)	61.9 (408) **32.81**[a]; *18.84–57.99*** 41.06[b]; *21.60–78.05***	NA[e]	NA	4.7 (16)
Chlamydia trachomatis (CT)	13.4 (88) **3.58**; *1.94-6.72*** 5.57[b]; *2.62–11.87***	NA	NA	4.1 (14)
Trichomonas vaginalis	13.8 (91) **2.70**; *1.57–4.69*** 2.74[b]; *1.41–5.33**	15.3 (32) **3.04**; *1.61–5.80*** 2.62[c]; *1.33–5.17**	13.1 (59) **2.54**; *1.44–4.54*** 2.62[d]; *1.43–4.82***	5.6 (19)
Mycoplasma genitalium	10.0 (66) **1.15**; *0.71–1.86* 1.96[b]; *1.13–3.43**	17.7 (37) **2.22**; *1.28–3.85** 2.06[c]; *1.17–3.62**	6.4 (29) **0.71**; *0.40–1.25* 0.62[d]; *0.35–1.11*	8.8 (30)
Ureaplasma urealyticum	26.3 (173) **0.91**; *0.67–1.24* 1.03[b]; *0.68–1.55*	29.7 (62) **1.08**; *0.72–1.62* 1.05[c]; *0.68–1.62*	24.7 (111) **0.84**; *0.60–1.18* 0.85[d]; *0.59–1.23*	28.0 (95)

Figures in italics are 95% confidence intervals.

* $P < 0.05$; ** $P < 0.001$. *P*-values correspond to comparisons between the appropriate category of cases and all controls.

[a] Odds ratios (in bold) correspond to comparisons between the appropriate category of cases and all controls.

[b] Adjusted odds ratios (underlined), adjusted in a logistic regression model with all five potential pathogens, age, and number of sexual partners. All cases with urethral discharge and all controls were included.

[c] Adjusted odds ratios (underlined), adjusted in a logistic regression model with the same variables as in[b], except that NG and CT were not included. All controls, but only cases without NG/CT were included.

[d] Adjusted odds ratios (underlined), adjusted in a logistic regression model with the same variables as in[b], except that NG and CT were not included. All controls, but only cases with NG and/or CT were included.

[e] NA = not applicable.

In a logistic regression model comparing cases of non-gonococcal, non-chlamydial urethral discharge to controls, we identified a significant interaction between MG and TV ($P = 0.04$ for the interaction). Indeed, among patients without TV, the odds ratio (OR) relating MG to urethral discharge was 2.44 (95% confidence interval [CI]: 1.35–4.42), whereas among those with TV the corresponding OR was 0.30 (95% CI: 0.04–2.10). Similarly, among patients without MG, the OR relating TV to urethral discharge was 3.39 (95% CI: 1.62–7.10) whereas, among those with MG, the corresponding OR was 0.42 (95% CI: 0.06–2.79). It thus seems that, among cases of non-gonococcal, non-chlamydial urethritis, MG is associated with this syndrome only in the absence of TV, and vice versa. Because UU was not associated with urethral discharge, the following analyses focus on the four other pathogens that we studied.

The high frequency of coinfections between the four pathogens is shown in Table 2. Among the 408 patients with gonococcal infection, TV was a more frequent coinfection than CT. TV was found alone in only one-third of the patients in whose samples it was recovered; in almost two-thirds of cases with TV, a gonococcal infection was also documented. MG was recovered alone in roughly one-half of the patients in whom it was found. Multiple infections were found in 23.6% (122 of 517) of patients with at least one pathogen recovered.

The prevalence of various pathogens among cases with urethral discharge from each country is presented in Table 3. NG was found in 61.9% of cases, CT in 13.4%, TV in 13.8%, and MG in 10.0%. There were significant intercountry variations for NG and TV. For NG, several countries had a prevalence approaching 50%, whereas in two countries the prevalence was close to 80%. The prevalence of TV varied 10-fold between countries: from 2.5% in Côte d'Ivoire to 24.5% in Senegal. The prevalence of MG was similar between countries, with the exception of Senegal. Overall, no pathogen was detected in 21.5% of cases: this varied from 10.6% in Senegal to 30.2% in Mali.

Table 2. **Prevalence of coinfections in cases with urethral discharge which gave positive PCR results for each pathogen**

Pathogen	Prevalence No. (%)				No. of specimens
	NG	CT	TV	MG	
Neisseria gonorrhoeae (NG)	295 (72.3)	46 (11.3)	56 (13.7)	25 (6.1)	408
Chlamydia trachomatis (CT)	46 (52.3)	35 (39.8)	11 (12.5)	7 (8.0)	88
Trichomonas vaginalis (TV)	56 (61.5)	11 (12.1)	30 (33.0)	5 (5.5)	91
Mycoplasma genitalium (MG)	25 (37.9)	7 (10.6)	5 (7.6)	35 (53.0)	66

Shaded cells are the number and percentages of single infections.

Percentages add up to over 100% due to infections with more than two pathogens in some cases.

Table 4 shows the prevalence of TV and MG in each country, firstly in cases who also had NG and/or CT, then in cases in whose samples NG and CT were not found. A substantial intercountry variation in the prevalence of TV was observed whether TV was alone, or present with NG and/or CT. No such variation was seen for MG. Prevalence data for Burkina Faso and Senegal in NG- and CT-negative patients are based on small sample numbers. TV and MG were found in 15.3% and 17.7%, respectively, of patients without NG and/or CT.

The prevalence of the four pathogens according to behavioural and clinical characteristics of the cases and controls is summarized in Table 5. NG and

Table 3. **Prevalence of pathogens in cases with urethral discharge in seven countries**

Country	Prevalence (%)				Negative for all four pathogens (%)	No. of specimens
	Neisseria gonorrhoeae	*Chlamydia trachomatis*	*Trichomonas vaginalis*	*Mycoplasma genitalium*		
Benin	65.1	8.1	8.1	10.5	20.9	86
Burkina Faso	81.0	15.0	12.0	11.0	11.0	100
Côte d'Ivoire	51.9	21.0	2.5	14.8	25.9	81
Ghana	52.4	10.5	19.0	10.5	23.8	105
Guinea	51.5	13.4	4.1	12.4	28.9	97
Mali	53.1	10.4	24.0	8.3	30.2	96
Senegal	77.7	16.0	24.5	3.2	10.6	94
Total	**61.9**	**13.4**	**13.8**	**10.0**	**21.5**	**659**
P-values	< 0.001	0.21	< 0.001	0.24	0.001	

Percentages for countries add up to more than 100% due to multiple infections.

P-values indicate the level of significance of intercountry variation.

Table 4. **Prevalence of *Trichomonas vaginalis* (TV) and *Mycoplasma genitalium* (MG) infections in cases with urethral discharge in seven countries, according to whether *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) were found in the specimen**

Country	Prevalence (%) Cases NG and/or CT positive			Prevalence (%) Cases NG and CT negative		
	TV	MG	No. of specimens NG and/or CT positive	TV	MG	No. of specimens NG and CT negative
Benin	6.7	5.0	60	11.5	23.1	26
Burkina Faso	11.6	11.6	86	14.3	7.1	14
Côte d'Ivoire	1.9	11.3	53	3.6	21.4	28
Ghana	18.8	3.1	64	19.5	22.0	41
Guinea	3.5	3.5	57	5.0	25.0	40
Mali	26.4	5.7	53	20.9	11.6	43
Senegal	20.8	3.9	77	41.2	0.0	17
Total	**13.1**	**6.4**	**450**	**15.3**	**17.7**	**209**
P-values	<0.001	0.17		0.01	0.20	

P-values indicate the level of significance of intercountry variation.

TV were observed less frequently in patients who had received prior treatment elsewhere that had failed, than in those not previously treated. Patients whose prior treatment had failed were more likely to have no pathogen detected. Whether or not the patient admitted having acquired the current disease from a sex worker had only a modest impact on the distribution of etiological agents. A urethral discharge was actually seen in the vast majority of patients; those in whom no discharge was seen had a higher probability that no pathogen would be found or that MG would be recovered, and a lower probability that NG or TV would be found. Having a purulent discharge or having had a discharge for less than two weeks increased the probability that NG would be recovered. Patients without a purulent discharge were more likely to be infected with CT and MG, or to have no pathogen recovered. Patients with discharge for more than two weeks were more likely to have no pathogen recovered.

Some clinical characteristics of patients from whom a single pathogen was recovered are shown in Table 6. Patients with gonococcal urethritis differed from cases infected with the other three pathogens: they had a more severe inflammation, as reflected by the proportions with any discharge seen during the examination, with a purulent discharge seen, reporting dysuria or having had a discharge for less than 2 weeks. Cases of urethral discharge caused by either CT, TV, or MG were quite similar in these respects. No differences were seen between the four groups according to age, or the number of sexual partners in the preceding 12 months (data not shown).

Discussion

This study provides original and comprehensive information about the etiology of urethritis in West Africa. The role of MG and TV in the pathogenesis of urethral discharge syndrome emerges clearly, even though the existence of multiple infections complicates the interpretation. The finding that MG was associated with urethral discharge only in men without gonococcal infection and, among these men with non-gonococcal urethritis, only in those without TV, strongly suggests that this mycoplasma is an etiological agent of urethritis in sub-Saharan Africa rather than an innocent bystander cotransmitted with the true pathogen. Similarly, among patients with non-gonococcal urethritis, TV was associated with urethral discharge only in the absence of MG, suggesting a causal relationship. The contribution of TV to urethral symptoms is less clear, however, in the frequent cases of coinfection with NG.

Prior to the advent of PCR, it was virtually impossible to establish the etiology of urethral discharge in an African primary health care setting — except to distinguish gonococcal from non-gonococcal urethritis — as cultures of CT, TV, or MG were rarely prepared. We chose to use PCR for all potential pathogens, as this would eliminate biases resulting from variable delays during transportation and variable laboratory capabilities among the different countries involved in the study. PCR has already replaced culture methods as the gold standard for diagnosis of CT infections (*17*). The commercial PCR procedure we used for NG detection has been recognized as a satisfactory alternative to culture (*18*). PCR is certainly more practical than the inefficient culture methods that exist for MG (*19*). Only one study has compared non-nested PCR with culture methods for TV detection in men with urethral discharge, which concluded that PCR had a sensitivity of 89% and a specificity of 98% (*20*). Several reports have shown

Table 5. **Prevalence of pathogens in cases with urethral discharge, according to behavioural and clinical characteristics**

Characteristics	Prevalence (%)				
	Neisseria gonorrhoeae	*Chlamydia trachomatis*	*Trichomonas vaginalis*	*Mycoplasma genitalium*	None of these four pathogens
Prior treatment					
Yes (332)[a]	55.4	13.0	10.2	11.1	26.8
No (310)	70.0**	14.2	17.4*	8.4	15.2**
Acquired from a sex worker					
Yes (219)	68.5	16.4	10.5	10.5	16.9
No (323)	58.5*	11.5	17.0*	10.2	22.9
Any discharge seen					
Yes (600)	64.5	12.8	14.3	9.3	19.5
No (34)	11.8**	23.5	0.0*	23.5*	55.9**
Purulent discharge seen					
Yes (450)	72.2	10.9	14.4	8.2	16.2
No (167)	34.7**	21.6*	10.8	15.0*	34.7**
Duration of discharge					
0–6 days (248)	73.0	13.3	12.9	10.5	15.3
7–13 days (112)	72.3	10.7	8.0	16.1	15.2
⩾ 14 days (161)	39.8**	13.7	10.6	15.5	32.9**

* $P < 0.05$; ** $P < 0.001$.

[a] Figures in parentheses are the numbers of relevant cases.

Table 6. **Prevalence of pathogens in cases with urethral discharge, infected with a single pathogen, according to clinical characteristics**

Clinical characteristics	Prevalence (%)				*P*-values
	Neisseria gonorrhoeae (*n* = 295)	*Chlamydia trachomatis* (*n* = 35)	*Trichomonas vaginalis* (*n* = 30)	*Mycoplasma genitalium* (*n* = 35)	
Any discharge seen	99.3	88.6	100	88.2	< 0.001
Purulent discharge seen	85.3	40.0	63.0	59.4	< 0.001
Dysuria	96.2	74.3	80.0	79.4	< 0.001
Duration of discharge					
0–6 days	54.0	36.0	33.3	35.7	
7–13 days	24.9	8.0	18.5	17.9	< 0.001
⩾14 days	21.1	56.0	48.1	46.4	
Swollen testis	12.7	0	7.4	3.4	0.07
Inguinal lymphadenopathy	14.0	0	11.5	12.5	0.14

that various nested PCR strategies — similar to that used in this study — are more sensitive than culture methods for detection of TV in women with vaginal discharge (*16, 21*).

Trichomonas vaginalis

TV has long been recognized as an etiological agent of urethritis. In this study, we delineate better its contribution to the burden of urethral discharge syndrome on the African continent using sensitive molecular methods applied to a large number of cases seen in primary health care institutions in several countries. TV had been found in 5–11% of Zimbabwean and Nigerian men with non-gonococcal urethritis, and in 19% of South African men with urethral discharge (*22–24*). It has also been found as a coinfection in 1–15% of men with gonorrhoea (*22, 24*). Our data indicate that TV is found in 15% of cases of non-gonococcal, non-chlamydial urethritis in West Africa. Generally, TV caused a urethral discharge that was less purulent and of longer duration than was seen with gonococcal urethritis, but it was indistinguishable from the discharge caused by other agents of non-

gonoccoccal urethritis, in line with previous reports (*22, 25, 26*).

The wide intercountry variations in the importance of TV are difficult to explain. It seems unlikely that metronidazole is given more systematically as first-line treatment of urethral discharge in countries where few TV infections have been found. A more generous use of metronidazole in women with vaginal discharge, resulting in less transmission to males, also seems unlikely, as most national guidelines recommend giving metronidazole to all women with vaginal discharge. We found TV as a coinfection in 13% of men with gonococcal and/or chlamydial urethritis. Its contribution to urethral inflammation in such patients is unknown; only careful studies looking at the persistence of symptoms in patients given drugs ineffective against this parasite would allow definitive conclusions to be reached. Although TV is clearly associated with urethral discharge in West Africa, our data suggest that current WHO estimates of the burden of trichomoniasis in African men — more than twice the incidence of gonococcal and chlamydial infections (*5, 6*) — are exaggerated. Even among our asymptomatic controls, TV was not significantly more prevalent than NG or CT.

Mycoplasma genitalium

The contribution of genital mycoplasmas to non-gonococcal urethritis has been debated for some time. While *Mycoplasma hominis* and *M. fermentans* are regarded as commensals of the male lower genital tract, and the association between UU and non-gonococcal urethritis is doubtful, MG has repeatedly been recovered more frequently in patients with non-gonococcal urethritis than in asymptomatic controls (*19*, *27–30*). Studies of the role of MG in causing urethritis have been carried out mostly in Europe, where 13–25% of patients with non-gonococcal urethritis were found to be infected with this organism, and ours is the first study investigating this pathogen in Africa. Our data show that in West Africa, while UU is probably an innocent bystander, MG is involved in some cases of non-gonococcal urethritis. The optimal treatment of MG-urethritis has not been thoroughly investigated. Until randomized trials with large numbers of patients are conducted, it seems reasonable to assume that a 7-day course of doxycycline is appropriate (*27*).

Neisseria gonorrhoeae

More than half of the patients in this study had received prior treatment. NG was found more frequently in patients who had not received prior therapy, presumably because first-line treatments were more likely to be active against NG than against other pathogens. Thus, the total burden of gonococcal infection among all patients with urethritis might be slightly underestimated. However, our figures reflect the reality of STD care in sub-Saharan Africa, where many patients first seek care in the informal sector or in pharmacies, and attend a health centre only if the treatment fails. It is unlikely that a substantial number of these first-line treatments included metronidazole, as this drug is not generally used in the treatment of urethritis in Africa, and the higher frequency of TV in patients without prior treatment probably only reflects its association with the gonococcus.

No pathogens recovered

There are several potential reasons why no pathogens were recovered in some patients. Firstly, the PCR assays, although very sensitive, may have failed to identify pathogens in a small number of patients, especially in those who had received prior treatment or had a long-standing discharge. Secondly, the quality of urethral samples from some patients may have been suboptimal, given the large number of health care facilities that provided specimens. Thirdly, as it was not possible to obtain Gram staining of smears from our patients, it may be that some of the patients did not have urethral inflammation or discharge at all. Finally, it is possible that additional pathogens causing urethral discharge in Africa remain to be identified.

Management flowcharts

What are the implications of our findings for recommended flowcharts for the management of patients with urethral discharge in Africa? The frequency of coinfections with at least two of the four pathogens is certainly a powerful argument in favour of the syndromic management approach, as precise microbiological diagnosis would be even more problematic than previously thought. The overlap between manifestations of disease caused by the four pathogens suggests that no attempt should be made to individualize treatment according to risk factors or clinical characteristics. The current WHO recommendation (*2*), to give systematically a drug effective against NG as well as a second drug (tetracycline or doxycycline) effective against CT to all patients with urethral discharge, will provide adequate coverage not only for these two pathogens but probably for MG as well. To administer such treatment, as currently recommended, only to patients in whom the health care provider actually sees a discharge is debatable, as we found at least one urethral pathogen in almost half of the admittedly small number of patients complaining of a discharge that could not be visualized by the health care provider.

It remains debatable whether metronidazole should be given to all patients with urethral discharge managed through the syndromic approach. Firstly, the contribution of TV to the pathogenesis of the discharge in patients in whom NG and/or CT are also present is unknown. Secondly, limited data suggest that single-dose metronidazole is much less effective in men than the standard 5–7-day course (*22*). Adding a course of metronidazole to a regimen

already containing single-dose treatment of gonorrhoea and a 7-day course of doxycycline might reduce compliance with the overall treatment, because of either cost or adverse effects. However, such an approach should now be tested in countries with a high prevalence of TV among patients with urethral discharge, especially considering that TV might increase the seminal shedding of HIV (*20*). More data are also needed on the efficacy of single-dose metronidazole in such a setting. Metronidazole should certainly be administered to all patients with urethral discharge whose symptoms are unresponsive to first-line dual therapy, although the significance of TV among treatment failures will need to be further evaluated.

Improving the management of symptomatic STD remains the only intervention that has been proven to slow down the spread of HIV in sub-Saharan Africa (*1*); future flowcharts for syndromic management should also pay attention to patients who fail first-line therapy, to help health workers deal with difficult problems and to enhance the credibility of primary health care institutions. ■

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Résumé

Etiologie en Afrique de l'Ouest de l'écoulement urétral : rôle de *Mycoplasma genitalium* et de *Trichomonas vaginalis*

Objectif Définir le rôle étiologique de germes pathogènes autres que *Neisseria gonorrhoeae* et *Chlamydia trachomatis* dans l'écoulement urétral chez l'homme en Afrique de l'Ouest.

Méthodes Des écouvillonnages de l'urètre ont été obtenus dans 72 centres de soins de santé primaires situés dans sept pays d'Afrique de l'Ouest chez 659 patients ayant un écoulement urétral et chez 339 témoins ayant des symptômes sans relation avec les voies urogénitales. La recherche de *N. gonorrhoeae*, *C. trachomatis, Trichomonas vaginalis, Mycoplasma genitalium* et *Ureaplasma urealyticum* a été faite par PCR (amplification génique).

Résultats *N. gonorrhoeae, T. vaginalis, C. trachomatis* et *M. genitalium*, contrairement à *U. urealyticum,* ont été observés plus fréquemment chez les hommes ayant un écoulement urétral que chez les témoins asymptomatiques, et représentent respectivement 61,9 %, 13,8 %, 13,4 % et 10,0 % des cas d'écoulement. Les polyinfections étaient fréquentes. Parmi les patients atteints de gonococcie, la coinfection par *T. vaginalis* était aussi fréquente que par *C. trachomatis. M. genitalium, T. vaginalis* et *C. trachomatis* sont les agents étiologiques d'un syndrome clinique comparable à celui de l'infection gonococcique, avec toutefois un écoulement urétral moins important.

Conclusion *M. genitalium* et *T. vaginalis* sont des agents étiologiques majeurs de l'écoulement urétral en Afrique de l'Ouest. La survenue fréquente de polyinfections associant les quatre pathogènes de manière diverse est un argument fort en faveur de l'approche syndromique. On recherchera par des essais thérapeutiques comment utiliser au mieux le métronidazole dans des algorithmes de décision adaptés à la prise en charge syndromique de l'écoulement urétral.

Resumen

Importancia etiológica de *Mycoplasma genitalium* y *Trichomonas vaginalis* en los casos de exudación uretral en África occidental

Objetivo Determinar el papel etiológico de patógenos distintos de *Neisseria gonorrhoeae* y *Chlamydia trachomatis* como causa de exudación uretral entre la población masculina de África occidental.

Métodos Se practicaron frotis uretrales en 659 pacientes varones con exudación uretral que acudieron a 72 centros de atención primaria de siete países de África occidental, así como en 339 testigos que acudieron con

síntomas no relacionados con las vías genitourinarias. Se empleó la reacción en cadena de la polimerasa para detectar la presencia de *N. gonorrhoeae*, *C. trachomatis*, *Trichomonas vaginalis, Mycoplasma genitalium* y *Ureaplasma urealyticum.*

Resultados *N. gonorrhoeae*, *T. vaginalis*, *C. trachomatis* y *M. genitalium*, pero no así *U. urealyticum,* fueron detectados con más frecuencia entre los hombres con exudación uretral que en los testigos asintomáticos y representaban, respectivamente, el 61,9%, 13,8%, 13,4% y 10,0% de los casos de exudación uretral. Con frecuencia los pacientes estaban infectados por varios de esos agentes. Entre los pacientes con infección gonocócica, la coinfección por *T. vaginalis* fue tan frecuente como la coinfección por *C. trachomatis. M. genitalium*, *T. vaginalis* y *C. trachomatis* causaban un síndrome clínico similar al asociado a la infección gonocócica, pero con exudación uretral menos grave.

Conclusión *M. genitalium* y *T. vaginalis* son dos importantes causas de exudación uretral en África occidental. La frecuente presencia de varias infecciones por una combinación u otra de cuatro patógenos hace muy recomendable la adopción del enfoque sindrómico. Es necesario realizar ensayos terapéuticos para determinar el uso óptimo del metronidazol en organigramas del manejo sindrómico de la exudación uretral.

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