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ORIGINAL ARTICLE

Coexistence of urethritis with genital ulcer disease in South Africa: influence on provision of syndromic management

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Objective: To assess whether syndromic management of genital ulcer disease was sound, if based on the premise that men with genital ulcers rarely have a concomitant urethral infection.
Methods: Specimens were taken in 1998 from 186 mine workers in Carletonville, South Africa, who were seen consecutively with genital ulcers. The specimens comprised a swab from the ulcer, a urethral swab for a Gram stained smear, and 10–15 ml of a first catch urine sample. The latter was tested by ligase chain reaction assays for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* specific DNA sequences and by a polymerase chain reaction (PCR) assay for *Mycoplasma genitalium*. Ulcer inducing micro-organisms were detected either by a multiplex PCR assay, or in the case of lymphogranuloma venereum (LGV) serologically, and human immunodeficiency virus (HIV) infection was detected by an enzyme linked immunosorbent assay (ELISA) test.
Results: Most (54%) of the ulcers were chancroidal, 18% were herpetic (HSV type 2), 6.5% primary syphilitic, and 3.2% due to LGV. More than one micro-organism was detected in 9.1% of the ulcers and less than 10% were undiagnosed. Microscopic examination of the urethral smears showed that 99 (53%) of the men had urethritis, of whom 45 (45%) were infected with *N gonorrhoeae*. Of the 54 men (55%) who had non-gonococcal urethritis (NGU), 11 (19.6%) harboured *C trachomatis* or *M genitalium*. Almost two thirds (64.5%) of the men had HIV infection, but this did not seem to have influenced the aetiology of the ulcers. Nor was a particular ulcer associated with one type of urethritis more than the other. Neither *C trachomatis* nor *M genitalium* was associated significantly with non-gonococcal urethritis (NGU) in either HIV positive or HIV negative men.
Conclusion: The combination of antibiotics used for the management of genital ulcer disease in men in this South African mining population needs to be widened to encompass frequently occurring concomitant gonococcal urethritis and NGU infections. This means treatment with long acting penicillin, combined with ciprofloxacin and azithromycin or erythromycin. A similar situation may exist in other geographical locations with a need to provide appropriate antimicrobial combinations depending on the patterns of infection detected.

Syndromic management is an important component of the strategy advocated by the World Health Organization to control sexually transmitted diseases in developing countries and in settings where sophisticated diagnostic tests often are not available.[1] Application of syndromic management requires the clinical identification of a defined clinical syndrome among symptomatic individuals, knowledge of the patterns of disease which comprise that syndrome, and the local antimicrobial susceptibilities of prevalent sexually transmitted disease bacterial pathogens. Thereafter, combination therapy which covers the major aetiological agents, and which would theoretically be effective in 95% of cases, is provided.

However, in many developing countries infection with more than one sexually transmitted agent is common and this not only results in identification of more than one aetiological agent in a single infected anatomical site, but also infection of more than one site by different sexually transmitted pathogens. In view of this, we assessed the extent to which men presenting with genital ulcer disease in South Africa also had microscopic evidence of urethritis and the extent to which the latter might be associated with gonococcal, chlamydial, or mycoplasmal infection.

PATIENTS AND METHODS

The study comprised 186 consecutive migrant mine workers who presented in 1998 with non-vesicular genital ulcerations at the East Driefontein clinic for sexually transmitted diseases near Carletonville, Gauteng, South Africa. In each case, swab specimens were obtained directly from the ulcers and tested for *Haemophilus ducreyi*, herpes simplex virus (HSV), and *Treponema pallidum* specific DNA sequences by using a multiplex polymerase chain reaction (PCR) technique (Roche Molecular Systems, Alameda, CA, USA).[2] A very small proportion (not recorded) of the men had an overt urethral discharge but none of them complained of symptoms of urethritis. Nevertheless, a swab specimen was taken from the urethral meatus for the assessment of urethritis. This was diagnosed if there were five or more polymorphonuclear leucocytes (PMNLs) per high power microscope field (hpf; ×1000 magnification) in a Gram-stained urethral smear. Also, a first catch urine specimen (10–15 ml) was collected and tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* specific DNA sequences by ligase chain reaction (LCR) assays (Abbott Laboratories, Chicago, IL, USA)[3 4] according to the manufacturer's instructions, and for *Mycoplasma genitalium* by

Abbreviations: ELISA, enzyme linked immunosorbent assay; HIV, human immunodeficiency virus; hpf, high power microscope field; HSV, herpes simplex virus; LCR, ligase chain reaction; LGV, lymphogranuloma venereum; NGU, non-gonococcal urethritis; PCR, polymerase chain reaction; PMNLs, polymorphonuclear leucocytes

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Table 1 Distribution of ulcers in HIV positive and HIV negative men

Type of ulcer	No (%) of men with indicated ulcer who were	
	HIV positive (total=120)	HIV negative (total=66)
Chancroidal	65 (54.2)	35 (53)
Herpetic	24 (20)	10 (15.2)
Syphilitic	5 (4.2)	7 (10.6)
LGV	5 (4.2)	1 (1.5)
Mixed	11 (9.1)	6 (9.1)
Unknown	10 (8.3)	7 (10.6)

a PCR assay as described previously.[5 6] Venous blood was tested for chlamydial antibodies by using a modified microimmunofluorescence test.[7] Broadly cross reacting antibody detected at titres of 1: = or >256 was considered diagnostic for lymphogranuloma venereum (LGV). In addition, serum was tested for HIV antibody (ELISA; Abbott Laboratories, Chicago, IL, USA) and this was confirmed either by western blot (HIV blot 2.2; Diagnostic Biotechnology, Singapore), or by an indirect immunofluorescence test (Serofluor; Virion).

RESULTS

Aetiology of genital ulcers

Of 186 men with genital ulcers, the cause was *H ducreyi* in 100 (53.8%), HSV type 2 in 34 (18.3%), *T pallidum* in 12 (6.5%), and LGV in six (3.2%); 17 (9.1%) of the men had a mixed infection, and 17 (9.1%) had ulcers, the nature of which was not diagnosed.

Occurrence and microbiology of urethritis

Of the 186 men with genital ulcers, 99 (53%) had five or more PMNLs per hpf on microscopic examination of a urethral smear and were considered, therefore, to have concomitant urethritis. Of these, 45 (45.4%) were infected with *N gonorrhoeae*, of whom six (13%) were also infected with *C trachomatis* and another five (11%) with *M genitalium*. Thus, 54 (54.6%) of the men were diagnosed by exclusion as having non-gonococcal urethritis (NGU); five (9%) of these men were infected with *C trachomatis*, another five (9%) with *M genitalium*, and one man with both micro-organisms. Eighty seven (47%) of the men had fewer than five PMNLs per hpf and were deemed not to have urethritis. However, two (2.3%) of these men were infected with *N gonorrhoeae*, another two (2.3%) with *C trachomatis*, and seven (8%) others with *M genitalium*.

Occurrence and effect of HIV infection

One hundred and twenty (64.5%) of the men were infected with HIV. As shown in table 1, the distribution of chancroidal and herpetic ulcers—that is, the majority of ulcers, was not appreciably different in HIV positive and HIV negative men.

The occurrence of urethritis in men with or without HIV infection was compared. Of the 120 HIV positive men, 32 (26.7%) had gonococcal urethritis, 37 (30.8%) had NGU, and 51 (42.5%) did not have urethritis. Of 66 HIV negative men, 13 (19.7%) had gonococcal urethritis, 17 (25.8%) had NGU, and 36 (54.5%) did not have urethritis. The difference between the occurrence of gonococcal urethritis and of NGU in the HIV positive and HIV negative groups is, however, not statistically significant (χ^2 test with Yates's correction: 1.48, 1 df, p= 0.22; and 1.0, 1 df, p=0.32, respectively).

Relation between ulcers and urethritis

The proportion of men with an ulcer of known aetiology who had gonococcal urethritis, NGU, or no urethritis is shown in table 2. For men with chancroidal or herpetic ulcers, the results are shown relative to their HIV status because the numbers involved are sufficiently large. There is a trend, not statistically significant (χ^2 with Yates's correction, p=0.14), for HIV positivity to favour the occurrence of gonococcal urethritis in men whose ulcers were due to *H ducreyi*. However, this apart, HIV positive status seemed to have no influence on the occurrence of urethritis, whether gonococcal or NGU, in men with ulcers of known cause. Overall, the occurrence of gonococcal urethritis (24% of the men), NGU (29%), and no urethritis (47%) was a distribution that was similar irrespective of ulcer aetiology. Gonococcal urethritis dominated in men with LGV, but the numbers involved are too small to determine whether this is meaningful.

Observations on the occurrence of *C trachomatis* and *M genitalium*

As shown in table 3, *C trachomatis* and *M genitalium* occurred almost independently of each other. When HIV status is not considered, *C trachomatis* was found more often in men with any urethritis than in those without (11 (12) of 99 *v* 2 of 87; Fisher's exact test, p=0.02), in men with gonococcal urethritis than in those without (6 of 45 *v* 2 of 87; p=0.02), but the difference did not reach significance in men with NGU (5 of 54 *v* 2 of 87; p=0.11, or 6 of 54 *v* 2 of 87; p=0.054).When HIV status is considered, *C trachomatis* was detected in 11 of 120 HIV positive men compared to two (three if the dual infection with *M genitalium* is included) of 66 HIV negative men (Fisher's exact test; p=0.196). Among HIV positive men, *C trachomatis* was detected more often in men with any urethritis than in those without urethritis (10 of 69 *v* 1 of 51; p=0.02), more often in those with gonococcal urethritis than in those without (5 of 32 *v* 1 of 51; p=0.03) but not significantly more often in men with NGU than in those without urethritis (5 of 37 *v* 1 of 51; p=0.08). Further, among HIV negative men, *C trachomatis* was not found more often in men with gonococcal urethritis, NGU, or any urethritis than in men without urethritis. When HIV status is not considered, *M genitalium* was found no

Table 2 Relation of ulcer to urethritis

Type of ulcer	HIV status	No of men	No (%) of men who had		
			Gonococcal urethritis	NGU	No urethritis
Chancroidal	Positive	65	13 (20)	20 (31)	32 (49)
	Negative	35	3 (8.5)	8 (23)	24 (68.5)
Herpetic	Positive	24	6 (25)	7 (29)	11 (46)
	Negative	10	2 (20)	2 (20)	6 (60)
Syphilitic	*	12	3 (25)	5 (42)	4 (33)
LGV	*	6	4 (67)	1 (16.5)	1 (16.5)
Mixed	*	17	10 (59)	5 (29.5)	2 (11.5)
Unknown	*	17	4 (23.5)	6 (35.5)	7 (41)

*No of cases insufficient to differentiate between HIV positive and HIV negative.

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Table 3 Occurrence of *C trachomatis* and *M genitalium* in urethritis relative to HIV status

Type of urethritis	HIV status (No)	No of men in whom indicated micro-organism detected		
		C trachomatis	*M genitalium*	Both organisms
Gonococcal	Positive (32)	5	4	0
	Negative (13)	1	1	0
NGU	Positive (37)	5	5	0
	Negative (17)	0	0	1
No urethritis	Positive (51)	1	4	0
	Negative (36)	1	3	0

more frequently in men with any urethritis, gonococcal urethritis or NGU, than in men without urethritis. When HIV status is considered, *M genitalium* was detected in 13 of 120 HIV positive men compared to four (five if the dual infection with *C trachomatis* is included) of 66 HIV negative men (Fisher's exact test; p=0.193). Among HIV positive men, *M genitalium* was detected no more frequently in men with any urethritis, gonococcal urethritis, or NGU than in those without urethritis. Among HIV negative men, again *M genitalium* was detected no more frequently in any of the groups than in men without urethritis.

DISCUSSION

An infectious cause for the genital ulcers was defined in more than 90% of the men recruited into this study, the majority having ulcers due to *H ducreyi*. These men were migrant mine workers who were served by a relatively small, but stable, group of sex workers, which accounts for the relatively high prevalence of chancroid recorded here. Since this study, the relative prevalence of chancroid has decreased as a result of the application of periodic preventive treatment with azithromycin for the sex workers.[8] Surprisingly, more than half of all the men also had objective evidence of concomitant urethritis, of which 45% was gonococcal urethritis and 55% was NGU. A few of the men had phimosis so that PMNLs seen in a Gram stained smear may have come from the subpreputial sac rather than the urethra, thus leading to a slight overestimation of the prevalence of NGU but not, of course, of gonococcal urethritis.

There would seem to be no biological sense in an ulcer of whatever cause influencing the occurrence of urethritis of a particular aetiology. However, defining the relation between ulcers and urethritis, if any, was complicated by the fact that approximately two thirds of the men were also infected by HIV. It seems that HIV infection did not enhance the occurrence of any type of ulcer, nor did it increase the likelihood of gonococcal urethritis or NGU occurring. Although, for reasons unknown, *C trachomatis* was associated significantly with gonococcal urethritis in HIV positive but not HIV negative men, neither *C trachomatis* nor *M genitalium* was associated significantly with NGU in either HIV positive or HIV negative men. This is of interest because others[9] have reported that they detected *M genitalium* in the urethra of men who had AIDS more often than of men without AIDS. Unfortunately, there are no CD4 data available from the current study to help to determine whether the severity of immunodeficiency might influence microbial detection, but the lack of any association with HIV positivity would seem to make this unlikely. While it is important to define how HIV infection affects the behaviour of *C trachomatis, M genitalium*, and other micro-organisms in the male urethra, it seems that a setting in which HIV infection is so rife is unlikely to be optimal for defining the pathogenicity of *M genitalium* and could give a distorted view in comparison with studies undertaken mainly in developed countries[10] where HIV infection is far less frequent. This apart, the failure to clearly associate *C trachomatis* or *M genitalium* with NGU is, perhaps, at least partially attributable to the fact that the urethritis was probably chronic in most cases and asymptomatic, the patients being seen not because they were complaining of urethral symptoms, but because they had genital ulcers. It is noteworthy that in another study[11] acute symptomatic NGU was associated with these micro-organisms, whereas asymptomatic disease was not. Furthermore, the diagnosis of NGU in a few men may have been spurious because of the inability to distinguish between urethral inflammation and "contaminating" subpreputial inflammatory cells.

Syndromic management is meant to address symptomatic disease only. However, irrespective of the detailed microbial aetiology of urethritis, it is clear that men presenting with genital ulcers in the population that we have studied, and probably in those in other developing countries, have asymptomatic urethritis so frequently as to make syndromic management, based on their ulcers alone, inappropriate. Ideally, it would be useful to have a non-invasive screening test, based on symptoms and/or signs, that was predictive of urethritis, a positive result being confirmed by a Gram stain test. Clearly, this approach is not feasible in this population and probably not in others too. Alternatively, a definitive, but simple screen for urethritis, based on examination of a Gram stained urethral smear, could be made and patients with positive results treated accordingly; or because there is more than a 50% chance of gonococcal urethritis or NGU existing, all patients, irrespective of such definitive diagnoses, could be treated to cover for urethritis, as part of an expanded syndromic treatment programme for genital ulcers. In this population, where chancroid and syphilis were found to be the most frequent causes of curable genital ulceration, an ideal antibiotic combination would be a single intramuscular injection of benzathine penicillin (2.4 U), to cover for syphilis, followed by a single oral dose of 500 mg of ciprofloxacin, to cover for both gonorrhoea and chancroid, and 1 g of azithromycin, to cover for NGU caused by *C trachomatis* or *M genitalium,* and for chancroid. However, in resource-poor settings, azithromycin could be substituted by 500 mg of erythromycin given orally four times daily for 7 days, or possibly by a tetracycline. Furthermore, in geographical locations where the aetiology of genital ulcer disease is different from that described here, other antimicrobial combinations may be more appropriate.

CONTRIBUTORS

RCB was responsible for the overall management of the study and contributed to writing the manuscript; HGF, YH, and FR were responsible for the collection of specimens and for laboratory testing and advised on aspects of the manuscript; JSJ examined specimens for *M genitalium* and advised on aspects of the manuscript; DT-R initiated work on *M genitalium* and was largely responsible for writing the manuscript.

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