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**The association of *Mycoplasma genitalium* with balanoposthitis
in men who have non-gonococcal urethritis**

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Key words: *Mycoplasma genitalium*; balanoposthitis; balanitis; non-gonococcal urethritis

Author contribution: Patrick Horner contributed equally to the study design, drafting and revising the manuscript. He recruited the majority of the patients and undertook the data analysis. Prof Taylor-Robinson conceived the study and obtained funding and contributed equally to the study design, drafting and revising the manuscript.

ABSTRACT

Objective: To determine whether *Mycoplasma genitalium* is associated with balanitis and/or posthitis in a previous study of the role of *M. genitalium* in men with acute non-gonococcal urethritis (NGU).

Methods: In a previous study of men with acute NGU, the existence of balanitis and/or posthitis was recorded. *Chlamydia trachomatis*, *M. genitalium* and ureaplasmas were sought in urethral swabs and urine by using a direct fluorescent antibody test and in-house polymerase chain reaction, an in-house polymerase chain reaction and a culture method, respectively. Men were treated with doxycycline or erythromycin.

Results: *M. genitalium* was associated significantly ($p=0.01$) with balanitis and/or posthitis in 114 men with acute NGU. This association persisted when there was control for *C. trachomatis* and urethral discharge ($p=0.021$, OR 4.1, CI 1.2 – 13.5). *C. trachomatis* and ureaplasmas were not associated with balanitis and/or posthitis.

Conclusion: Detection of *M. genitalium* in men with acute NGU was associated significantly with balanitis and/or posthitis. The association is biologically plausible and may have a role in HIV-1 transmission and susceptibility.

Inflammation of the glans penis (balanitis) and inflammation of the prepuce (posthitis) frequently occur together (balanoposthitis). Balanitis alone is seen occasionally in circumcised men. However, primary infections of the glans and prepuce with discharge and urethral involvement may occur, due to, for example, herpes simplex virus or *Candida albicans* and sometimes it may be difficult to ascertain whether a primary infection of the urethra (gonococcal or non-gonococcal) has led to balanoposthitis.

Following the detection by culture of *Mycoplasma genitalium* organisms in specimens from men with non-gonococcal urethritis (NGU)¹ and the development a decade later of a polymerase chain reaction (PCR) to detect the organisms sensitively, we undertook a study of the aetiology of NGU^{2,3,4}. In this, *Chlamydia trachomatis* and *M. genitalium* were independently and significantly associated with the disease. We also observed that some of the men had balanitis and/or posthitis. *M. genitalium* can infect vaginal epithelial cells, *in vitro*.⁵ These are stratified non-keratinized squamous epithelial cells⁶ which suggests that *M. genitalium* might, therefore, be capable of infecting skin epithelia, particularly the foreskin which is poorly keratinised.⁷ This prompted us to look at the association of *M. genitalium* with balanoposthitis in men we had studied before with urethritis. We also felt it was worthy of analysis in view of the importance of foreskin as a co-factor in HIV transmission, the ability of sexually transmitted infections to increase the transmission of HIV and the recent association of *M. genitalium* with HIV infection^{8,9,10}.

PATIENTS AND METHODS

As detailed before^{2,3,4}, 114 men with acute clinically symptomatic NGU were studied between 1991 and 1993 as part of a larger study investigating the aetiology of acute and chronic NGU. Ethical approval was obtained from the St Mary's Hospital Research Ethics Committee and signed consent was obtained from all patients. Men attending the Jefferiss Wing at St Mary's Hospital for a sexual health assessment were eligible for inclusion. Clinically symptomatic (i.e. either complaining of a discharge, dysuria, penile irritation, genital discomfort or have an urethral discharge on examination after an urethral massage) and clinically asymptomatic men were recruited as part of the study. For this study NGU was diagnosed at initial presentation if there were ≥ 5 polymorphonuclear leucocytes (PMNLs) per high power field (HPF; x1000) in five or more fields of a Gram-stained urethral smear. As part of the larger study we also included clinically symptomatic men who had a negative urethral smear but evidence of urethritis on Gram-staining a first pass urinary thread which had ≥ 10 PMNLs per HPF, and clinically asymptomatic men if there were ≥ 5 PMNLs per HPF (x 1000) in five or more fields of a Gram-stained urethral smear or, if negative, ≥ 10

PMNLs per HPF on Gram-staining a first pass urinary thread.⁴ Subjects were asked to complete a questionnaire requesting details about discharge, dysuria and penile irritation. Other information, such as age, ethnicity, number of sexual partners and time since last voiding urine, was recorded by the physician. The patient was examined and the occurrence of balanitis and/or posthitis and whether a discharge was present before or after urethral massage was recorded. Balanitis and/or posthitis was/were diagnosed if there was erythema of the glans and/or prepuce; no distinction was made between balanitis and balanoposthitis on the study proforma. Men with *Neisseria gonorrhoeae*, a herpes simplex virus infection or a urinary tract infection were excluded. Men were treated with doxycycline, 200 mg, given initially and then 100 mg per day for 13 days, or enteric-coated erythromycin, 500 mg, given four times per day for 14 days, if they were intolerant of doxycycline. Details of specific treatment for balanitis and/or posthitis were not available. A total of 86 men re-attended at least once 10-92 days after receiving treatment.

As detailed previously^{2,3,4}, *C. trachomatis* was diagnosed using a direct fluorescent antibody test (Syva,UK) in which detection of one or more elementary bodies was regarded as a positive result on a urethral smear and/or the centrifuged deposit from a first-pass urine (FPU) specimen. An in-house *C. trachomatis* PCR was also undertaken at presentation on a FPU deposit from those patients who returned for follow-up. Men were considered *C. trachomatis*-positive if any test was positive and *C. trachomatis*-negative if at least one specimen was available for examination by any test and this was negative. Results were not available for 6 men. Forty-five (42%) of 108 evaluable men were *C. trachomatis*-positive. A PCR was used on the centrifuged deposit from a FPU specimen to detect *M. genitalium*, as described before^{2,3,4}. Results were not available for 4 men. Thirty-one (28%) of 110 evaluable men were *M. genitalium*-positive. At follow-up only men who tested *M. genitalium*-positive at presentation or who had chronic urethritis were tested using the *M. genitalium* PCR.³ Ureaplasmas were sought by culture using a FPU specimen³. Results were not available for 5 men. Thirty-three (30%) of 109 evaluable men were ureaplasma-positive. Speciation of the ureaplasmas was not undertaken as at the time of the study the greater significance of one or other of the two separate ureaplasma species was not appreciated.

Statistical analysis: Univariate associations were explored using Fisher's Exact test with SPSS for windows version 15 and odds ratios with 95% confidence intervals using Epilinfo version 6. Binary logistic regression was used for multivariate analyses, undertaken with

SPSS for windows version 15. As detailed previously the data were not complete for every individual recruited³.

RESULTS

Details of urethral discharge were available for 113 men; of these, 96 (85%) had a discharge, of whom 29 (30%) were unaware since it was present only on examination after urethral massage, 51% (57 of 112) had dysuria, 56% (63 of 113) had penile irritation and/or genital discomfort and 18% (19 of 103) balanitis and/or posthitis. Of the 113 evaluable men with details of urethral discharge available, 17 (15%) did not complain of discharge, dysuria or penile irritation and only had an urethral discharge on examination.

The presence of balanitis and/or posthitis was not associated with discharge, dysuria or penile irritation and/or discomfort (data not shown). The presence of *C. trachomatis* was not associated with balanitis and/or posthitis. In complete contrast, the presence of *M. genitalium* was associated significantly with balanitis and/or posthitis. Ureaplasmas were not associated with balanitis and/or posthitis (Table).

We demonstrated previously^{2,3,4} that *M. genitalium* and *C. trachomatis* were associated with discharge. Because of this we undertook a logistic regression analysis to control for discharge and for the presence of the other micro-organism. The detection of *M. genitalium* continued to be associated with balanitis and/or posthitis ($p=0.021$, OR 4.1, CI 1.2 – 13.5) and discharge ($p=0.07$, OR 7.7, CI 0.86-69.9). At follow-up examination, four men had balanitis and/or posthitis. Of these, two had had *M. genitalium* originally, including one man in whom balanitis and/or posthitis was/were not diagnosed at presentation; both were *M. genitalium*-negative at follow-up.

DISCUSSION

The primary aim of the original study^{2,3,4} had been to determine the relationship between *M. genitalium* and NGU. In this analysis we demonstrate that *M. genitalium* is associated with balanitis and/or posthitis in men with acute NGU and that this is independent of the presence of an urethral discharge.

The strength of the study is that it is a well characterised group, with detailed microbiological investigations undertaken blinded to clinical presentation. Weaknesses are that, despite including 114 men the study is still small and no distinction was made on the study proforma between balanitis and/or posthitis. Also whether any of the men with acute urethritis were

circumcised was not recorded and the result cannot be extrapolated to balanitis and/or posthitis in men who are clinically asymptomatic and in whom urethritis is not present. In future studies it will be important to have balanitis and/or posthitis as the primary focus and to ascertain whether the association is with one or the other or both and consider the relation of micro-organisms to the disease in men who also have urethritis and in those who do not.

We are not aware of other studies which have investigated the association of *M. genitalium* with balanoposthitis. We suspect that this is because nobody has looked for it as information on the presence of balanoposthitis is not routinely collected in studies of men with acute NGU. Because patients with balanitis and/or posthitis also had urethritis, the association of *M. genitalium* might be with NGU and only spuriously with balanitis and/or posthitis. It was, therefore, interesting to find that an apparent real association exists between *M. genitalium* and balanitis and/or posthitis which is independent of the presence of urethral discharge. This is emphasised by the apparent lack of association found for *C. trachomatis*. Furthermore, biologically, this makes sense since *C. trachomatis* organisms infect mucosal columnar epithelial cells and not squamous epithelial cells, and there is evidence that *M. genitalium* can infect non-keratinous squamous epithelial cells.^{5,6} We originally failed to confirm a univariate association of *M. genitalium* with balanitis and/or posthitis following logistic regression analysis in the extended study of all men with urethritis while controlling for co-infection, sexual lifestyle and clinical disease.⁴ The additional men with urethritis consisted of clinically asymptomatic men, whose recruitment as potential controls began later in the study, but were found to have urethritis on Gram-staining. We also included both clinically symptomatic and asymptomatic men who had a negative urethral smear but evidence of urethritis on Gram-staining a first pass urinary thread which had ≥ 10 PMNLs per HPF.⁴ Seven of these additional 55 men had balanitis and/or posthitis, of whom none was infected with *M. genitalium*. For the multi-variate analysis, 70 (41%) of the 169 men could not be included because of missing data, including 11 (42%) of 26 men with balanitis and/or posthitis. We believe that the exclusion of such a large number of individuals from the multi-variate analysis probably introduced unknown bias(es) related to data collection and provided an unreliable result. In addition, 4 clinically asymptomatic men without urethritis (controls) from the original study were *M. genitalium*-positive and none had balanitis and/or posthitis. Although this may have been due to a lower load, it could also be because of the small number of *M. genitalium*-positive men studied in the control group leading to a type 2 statistical error.^{3,4,11}

These results imply that i) men with balano-posthitis should be asked about symptoms of discharge, dysuria and penile irritation and examined for the presence of a discharge by undertaking urethral massage ^{2,3,4,12}. In this study, 15% of men with acute NGU did not have symptoms of urethritis but did have a discharge present on examination before or after urethral massage. If these symptoms and/or sign are present, an urethral smear examination should be undertaken to exclude urethritis. If urethritis is present our results suggest that *M. genitalium* may be the cause and patients should be offered treatment accordingly. Currently testing for urethritis is only recommended in men with a circinate balanitis.¹² It is possible that men in this study did indeed only have circinate balanitis but, from clinical experience, this condition is uncommon and is usually associated with reactive arthritis¹² and we believe this is unlikely. This requires further study. ii) the presence of balano-posthitis could be an important co-factor in increasing both the risk of HIV transmission and acquisition following exposure in men with *M. genitalium* infection.

We believe that the association of *M. genitalium* with balanitis and/or posthitis merits further investigation, particularly the potential to facilitate HIV transmission and acquisition. *M. genitalium* is common (6.6%) in MSM who remain at high risk of acquiring HIV ^{10,13} and is also a common cause of urethritis in men from sub-Saharan Africa.⁹

Word Count: 1931

Key Messages

- Balano-posthitis is associated with *M. genitalium* in men with acute NGU.
- In men with balano-posthitis symptoms of urethritis and the presence of an urethral discharge should be sought and an urethral smear undertaken if present.
- The association of *M. genitalium* with balano-posthitis merits further investigation particularly the potential to facilitate HIV transmission and acquisition.

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Table. Relation of balanitis and/or posthitis with *C. trachomatis*, *M. genitalium* and ureaplasmas

	Balanitis and/or posthitis		Odds ratio (95% confidence intervals)	P value
	present	absent		
<i>C.trachomatis</i> -pos	5 (12%)	36	OR 0.51 CI 0.13-1.75	0.29
<i>C.trachomatis</i> -neg	12 (21%)	44		
<i>M.genitalium</i> -pos	10 (37%)	17	OR 4.12 CI 1.29-13.38	0.01
<i>M.genitalium</i> -neg	9(12.5%)	63		
Ureaplasma-pos	6(19%)	25	OR 1.0 CI 0.28-3.23	1.00
Ureaplasma-neg	13(19%)	54		