

ORIGINAL

Haemophilus urethritis in males: A series of 30 cases

Alvaro Vives^a, Gabriel Veber Moisés da Silva^b, Carles Alonso-Tarrés^c,
Jaime Borrás Suarez^d, Franco Palmisano^e, Marco Cosentino^{f,*}



^a Head of the Sexually Transmitted Infection Department, Andrology Service, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

^b Department of Urology and Reconstructive Surgery, Universidade Federal do Rio Grande do Sul – UFRGS – Hospital de Clínicas de Porto Alegre/RS, Brazil

^c Microbiology, Laboratory, Fundació Puigvert, Barcelona, Spain

^d Fundació Puigvert, Barcelona, Spain

^e Department of Urology, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, University of Milan, Italy

^f Head of Andrology and Urology Department, Casa di Cura Villa Maria, Padova, Italy

Received 11 November 2019; accepted 19 January 2020

Available online 17 June 2020

KEYWORDS

Haemophilus;
Sexual infection;
Urethritis;
STD

Abstract

Introduction and objectives: Pathogens such as *Haemophilus* spp. have been associated with non-gonococcal urethritis, but their role is unproven. To describe the clinical characteristics and therapeutic outcomes in male patients diagnosed with *Haemophilus* spp. urethritis.

Methods: We carried out a retrospective study of all patients who presented to our hospital (in either the emergency department or the outpatient clinic) between July 2016 and April 2018 in whom *Haemophilus* spp. was isolated in the urethral samples. We enrolled 30 men with *Haemophilus* spp.-positive urethritis, including coinfections with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Clinical, laboratory, demographic, and behavioral data were obtained by reviewing medical histories.

Results: The mean age of the patients was 36.6 years (range 21–87). Seventeen patients (63%) reported being exclusively heterosexual. Three patients (10%) were HIV infected, all of them with an undetectable viral load. The most common clinical presentation was mucopurulent urethral discharge, in 13 patients (43%). The antibiotic treatment achieved a complete clinical resolution in 73%.

Conclusions: *Haemophilus* urethritis affected men regardless of their sexual orientation or HIV status. Unprotected oral sex may play a role in its transmission. The limitations of the study preclude verification of the pathogenic role of *Haemophilus* spp. in acute urethritis, but clinical response after antibiotic treatment suggests that *Haemophilus* spp. can play such a role.

© 2020 Asociación Española de Andrología, Medicina Sexual y Reproductiva. Published by Elsevier España, S.L.U. All rights reserved.

* Corresponding author.

E-mail address: doccosentino@gmail.com (M. Cosentino).

<https://doi.org/10.1016/j.androl.2020.01.002>

1698-031X/© 2020 Asociación Española de Andrología, Medicina Sexual y Reproductiva. Published by Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE

Haemophilus;
Infección sexual;
Urethritis;
Infección de
transmisión sexual

Urethritis por Haemophilus en varones: serie de 30 casos**Resumen**

Introducción y objetivos: Patógenos como *Haemophilus* spp. se han asociado con urethritis no gonocócica, pero su papel no está probado. El objetivo de nuestro trabajo ha sido describir las características clínicas y los resultados terapéuticos en varones diagnosticados de urethritis de *Haemophilus* spp.

Métodos: Realizamos un estudio retrospectivo de todos los pacientes que se presentaron en nuestro hospital (ya sea en el departamento de emergencias o en la clínica ambulatoria) entre julio del 2016 y abril del 2018 en quienes *Haemophilus* spp. se aisló en las muestras uretrales. Se incluyó a 30 hombres con urethritis positiva para *Haemophilus* spp., incluidas las coinfecciones con *Neisseria gonorrhoeae* y *Chlamydia trachomatis*. Los datos clínicos, de laboratorio, demográficos y de comportamiento se obtuvieron al revisar las historias clínicas.

Resultados: La edad media de los pacientes fue de 36,6 años (rango 21–87). Diecisiete pacientes (63%) informaron ser exclusivamente heterosexuales. Tres pacientes (10%) estaban infectados por el VIH, todos ellos con una carga viral indetectable. La presentación clínica más común fue secreción uretral mucopurulenta, en 13 pacientes (43%). El tratamiento antibiótico logró una resolución clínica completa en el 73%.

Conclusiones: La urethritis por *Haemophilus* afectó a los hombres independientemente de su orientación sexual o estado de VIH. El sexo oral sin protección puede desempeñar un papel en su transmisión. Las limitaciones del estudio impiden la verificación del papel patológico de *Haemophilus* spp. en urethritis aguda, pero la respuesta clínica después del tratamiento con antibióticos sugiere que *Haemophilus* spp. puede desempeñar ese papel.

© 2020 Asociación Española de Andrología, Medicina Sexual y Reproductiva. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Urethritis, one of the most common sexually transmitted infections (STI) among men, is classified as gonococcal (GU) or non-gonococcal (NGU) depending on the presence or absence of *Neisseria gonorrhoeae*.¹ In 20–50% of cases of NGU the cause is not identified. *Chlamydia trachomatis* accounts for 30–40% of cases and *Mycoplasma genitalium* for around 10–30%.² Other pathogens, such as *Haemophilus* spp., have been associated with NGU, but their role is unproven.^{2,3} Both *Haemophilus influenzae* and *Haemophilus parainfluenzae* are colonizers of the upper respiratory tract and are part of the normal oral microflora.^{4,5} They are not only commensal within the pharynx but also pathogens causing various infections, mainly in relation to the respiratory tract.⁶ Sexual transmission of both has been described. Transmission of oropharyngeal commensal flora to the urethra via insertive oral sex is recognized as a mode of transmission of several pathogens, including *Haemophilus* spp.⁵

Materials and methods**Study population**

This is a retrospective study of all patients who presented to our hospital (in either the emergency department or the outpatient clinic) between July 2016 and April 2018,

reporting symptoms of urethritis in whom a *Haemophilus* sp. was isolated from urethral samples. Symptoms suggestive of urethritis included urethral discomfort, dysuria, and/or mucopurulent or clear discharge. The study was approved by our institutional medical and research ethics committee. Clinical, laboratory, demographic, and behavioral data were obtained by reviewing medical charts.

Laboratory studies

Urethral samples were obtained by convenient swabs for conventional bacteriological and Multiplex PCR studies. Conventional bacteriological study included microscopic examination by Gram stain of the sample and culture. Petri dishes of chocolate agar (BD), Martin-Lewis agar (BD), Gardnerella agar (BD), and Sabouraud agar with gentamicin and chloramphenicol (BC) were used. Chocolate agar, Martin-Lewis agar, and Gardnerella agar were incubated at 35–37°C with enriched 7% CO₂ atmosphere for 3 days (chocolate and Martin-Lewis agar) or 2 days (Gardnerella agar). Sabouraud agar was incubated at 35–37°C for 2 days in room air. *Neisseria* and *Haemophilus* strains were identified by API NH test (bioMérieux). Multiplex PCR was performed by Anyplex™ II STI-7 assay (Seegene), which detects five major pathogens in a single reaction: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Mycoplasma genitalium*, and *Ureaplasma urealyticum*.

Table 1 Causes of urethritis diagnosed between July 2016 and April 2018.

<i>Neisseria gonorrhoeae</i>	73
<i>Chlamydia trachomatis</i>	69
<i>Haemophilus parainfluenzae</i>	19
<i>Haemophilus influenzae</i>	10
<i>Haemophilus</i> sp.	1
<i>Ureaplasma urealyticum</i>	17
<i>Mycoplasma genitalium</i>	13
<i>Trichomonas vaginalis</i>	1
<i>Neisseria meningitidis</i>	1
Total	204

Statistical analysis

Statistical analysis was conducted using Statistical Product and Service Solutions Version 18.0 (SPSS). Descriptive statistics were used to evaluate the study outcomes. Mean values and standard deviations or median values and ranges are presented for continuous measurements. Frequencies and percentages are reported for dichotomous and ordinal variables.

Results

Over the study period a total of 204 patients were diagnosed with acute urethritis, and *Haemophilus* spp. were isolated in 30 urethral samples received in our laboratory (Table 1). The mean age of the patients was 36.6 years (range 21–87). Seventeen patients (63%) reported being exclusively heterosexual, eight (30%) were men who have sex with men (MSM), and two (7%) reported having sexual intercourse with both men and woman; data on sexual activity were not available for three patients. The mean number of sexual partners in the last 60 days before the hospital visit was 3.5 (range 1–20). Patients were asked about their sexual exposures during the 2 months before consultation. With the exception of three patients, all reported having practiced unprotected insertive sex, most commonly oral sex. Three patients (10%) were HIV infected, all of them with undetectable viral load. Thirteen patients (43%) reported a previous STI.

The most common clinical presentations were mucopurulent urethral discharge (13 patients, 43%), dysuria (seven patients, 23%), and testicular pain (five patients, 17%). Complete demographic data are listed in Table 2. Ten cases (33%) corresponded to *Haemophilus influenzae*, 19 (63%) to *Haemophilus parainfluenzae*, and one (3.3%) could not be identified at the species level. In five of the 30 cases (17%), *Haemophilus* was isolated with another pathogen: in four cases with *C. trachomatis* (80%) and in one with *N. gonorrhoeae*.

Discussion

In the present study, we retrieved clinical data from the medical records of men with *Haemophilus* spp. Culture-positive urethritis who were treated in our institution. In our series, *H. parainfluenzae* was more frequent than *H. influenzae* (63% vs 33%), which is in concordance with

Table 2 Patient demographics.

Characteristic	No. (%)
Total no. of patients	30
Age, years	
Average	36.6
Range	21–87
Sexual orientation ^a	
Heterosexual	17 (63)
Homosexual	8 (30)
Bisexual	2 (7)
Sexual practices ^b	
Oral sex	21 (75)
Vaginal intercourse	15 (54)
Anal intercourse	10 (36)
Comorbidities	
HIV	3 (10)
Previous STI	13 (43)
Symptoms	
Urethral discharge	13 (43)
Dysuria	7 (23)
Testicular pain	5 (17)
Genital ulcer	2 (7)
Hematospermia	1 (4)
Painful ejaculation	1 (4)
Lower abdominal pain	1 (4)

HIV, human immunodeficiency virus.

STI, sexual transmitted infection.

^a Twenty-seven patients with available data.

^b Twenty-eight patients with available data.

the literature.^{5,7,8} Interestingly, *Haemophilus parainfluenzae* was the third most common pathogen in urethral samples in the overall total of 204 patients with symptoms of acute urethritis, being isolated in 19 patients (9.3%) as compared with *Neisseria gonorrhoeae* in 73 cases (35.7%) and *Chlamydia trachomatis* in 69 (33.8%). In other studies, the third most frequent cause of urethritis has been *Mycoplasma genitalium* (Ito 2016, Rane 2014). The most common clinical symptoms were urethral discharge, which was present in 13 patients (43%), followed by dysuria in 7 (23%) and testicular pain in 5 (17%). Urethritis caused by *Haemophilus* spp. has indistinctive clinical symptoms compared with other causes of urethritis, which can cause difficulties in differentiating them.⁵ Patients were asked about their sexual behavior (orientation and practice) during the 2 months before consultation. The mean number of sexual partners was 3.5 (range 1–20). To our knowledge, this is the only study to report these data. The majority were heterosexual (17, 63%) and practiced unprotected oral sex. This finding is discrepant in comparison with previously published studies, which show a higher prevalence of *Haemophilus* urethritis in MSM. Rane et al.⁹ suggested that MSM may be acquiring established and unidentified urethral pathogens more commonly than would be anticipated via low-risk sexual practices, perhaps reflecting the widespread practice of unprotected orogenital sex in MSM.⁹ Ito et al.¹⁰ reported that all men with *Haemophilus influenzae*-NGU

in their series practiced unprotected oral sex.¹⁰ Another study⁵ reported that all men in their series had practiced unprotected insertive oral sex, and five of them denied having had another sexual contact apart from this exposure.⁵ Other studies have also reported that urethritis caused by *Haemophilus* spp. is characterized by transmission of the pathogens through oral sex.^{5,10} Those data support the contribution of oropharyngeal exposure to this syndrome and require examination in case-control studies using molecular methods. Diagnostic and management approaches to acute NGU do not differentiate between men who have sex with men (MSM) and men who have sex with women (MSW).⁹ Because the patients were treated at different institutional levels, the following treatments were proposed: azithromycin, azithromycin plus ceftriaxone, azithromycin plus ciprofloxacin, ciprofloxacin, doxycycline, or doxycycline plus ceftriaxone. In 22 patients (73%) the empirical treatment achieved a complete clinical resolution. In the eight patients in whom symptoms persisted, the main complaint was urethral discharge. All of them had positive results for culture of a second urethral exudate after the first treatment, in seven (88%) for *H. parainfluenzae* and in one (13%) for *H. paraphrophilus*. The treatment was then guided by the antibiogram. Two patients, both HIV positive, remained symptomatic, presenting persistence of urethral exudate and positive cultures for *H. parainfluenzae*. Oral *Haemophilus* colonization in different amounts is very frequent.¹¹ Patients with treatment failure may benefit from a search strategy for *Haemophilus* colonization in their sexual partner(s) and possible prophylactic measures, such as antimicrobial single dose use after oral insertive sexual practices.

Several limitations of this study have to be pointed out. The lack of a representative control group precludes proof of the pathogenic role of *Haemophilus* spp. in urethritis. As this is a retrospective study involving retrieval of clinical information from clinical records, some items of information were lacking in some patients. Finally, the small sample size does not allow accurate conclusions to be drawn regarding therapeutic outcomes.

The predominance of heterosexual men in our series may be related to the frequency of oral sexual practice in our own population and could also be due to MSM having access to regular screening and treatment in specific community settings. The data presented in our study, as well as in the specific literature, support the contribution of oropharyngeal exposure to this syndrome and warrant further investigations in case-control studies using molecular methods. In men with treatment failure it may be useful to study the partner's oral flora and, hence, to establish a direct relation with oral sex and identify possible antimicrobial prophylaxis measures.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

No funding or conflict of interest for this paper; no need of informed consent.

References

1. Ito S, Hanaoka N, Shimuta K, Seike K, Tsuchiya T, Yasuda M, et al. Male non-gonococcal urethritis: from microbiological etiologies to demographic and clinical features. *Int J Urol*. 2016;23:325–31.
2. Bradshaw CS, Tabrizi SN, Read TRH, Garland SM, Hopkins CA, Moss LM, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. *J Infect Dis*. 2006;193:336–45.
3. Iser P. Symptoms of non-gonococcal urethritis in heterosexual men: a case-control study. *Sex Transm Infect*. 2005;81:163–5.
4. Hsu MS, Wu MY, Lin TH, Liao CH. *Haemophilus parainfluenzae* urethritis among homosexual men. *J Microbiol Immunol Infect*. 2012;48:450–2.
5. Deza G, Martín-Ezquerro G, Gómez J, Villar-García J, Supervia A, Pujol RM. Isolation of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in urethral exudates from men with acute urethritis: a descriptive study of 52 cases. *Sex Transm Infect*. 2015;92:29–31.
6. Deguchi T, Ito S, Hatazaki K, Horie K, Yasuda M, Nakane K, et al. Antimicrobial susceptibility of *Haemophilus influenzae* strains isolated from the urethra of men with acute urethritis and/or epididymitis. *J Infect Chemother*. 2017;23:804–7.
7. Sturm AW. *Haemophilus influenzae* and *Haemophilus parainfluenzae* in nongonococcal urethritis. *J Infect Dis*. 1986;153:165–7.
8. Vázquez F, Andrés MT, Palacio V. Isolation of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in genitourinary infections: a 4-year review. *Enferm Infecc Microbiol Clin*. 1996;14:181–5.
9. Rane VS, Fairley CK, Weerakoon A, Read TH, Fehler G, Chen MY, et al. Characteristics of acute nongonococcal urethritis in men differ by sexual preference. *J Clin Microbiol*. 2014;52:2971–6.
10. Ito S, Hatazaki K, Shimuta K, Kondo H, Mizutani K, Yasuda M, et al. *Haemophilus influenzae* isolated from men with acute urethritis. *Sex Transm Dis*. 2017;44:205–10.
11. Liljemark WF, Bloomquist CG, Uhl LA, Schaffer EM, Wolff LF, Pihlstrom BL, et al. Distribution of oral *Haemophilus* species in dental plaque from a large adult population. *Infect Immunity*. 1984;46:778–86.