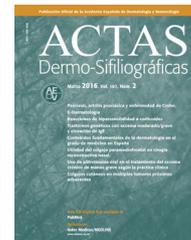




ACTAS Derma-Sifiliográficas

Full English text available at
www.actasdermo.org



ORIGINAL ARTICLE

Haemophilus Species Isolated in Urethral Exudates as a Possible Causative Agent in Acute Urethritis: A Study of 38 Cases[☆]



J. Magdaleno-Tapial,^{*} C. Valenzuela-Oñate, M.M. Giacaman-von der Weth, B. Ferrer-Guillén, Á. Martínez-Domenech, M. García-Legaz Martínez, J.M. Ortiz-Salvador, D. Subiabre-Ferrer, P. Hernández-Bel

Servicio de Dermatología, Hospital General Universitario de Valencia, Valencia, España

Received 28 July 2018; accepted 3 September 2018

Available online 15 December 2018

KEYWORDS

Urethritis;
Haemophilus;
Antibiotics;
Sexually transmitted
infections

Abstract

Introduction: The incidence of urethritis due to *Haemophilus* species is increasing. The main aim of this study was to describe the clinical and microbiological characteristics of patients with this form of urethritis. A secondary aim was to discuss the adequacy of treatments in patients with different types of antibiotic resistance.

Material and methods: We studied patients with a microbiologically confirmed diagnosis of urethritis seen at the Sexually Transmitted Infections Unit of our hospital between July 2015 and July 2018. We selected all patients in whom *Haemophilus* species were isolated on chocolate agar. Antibiotic resistance was tested using the disk-diffusion method. Cross-sectional data were collected prospectively during outpatient visits.

Results: *Haemophilus* species were isolated in 33.6% of cases. The most common clinical manifestation was urethral discharge (57.6%); 60% of the patients were men who have sex with men and in this subgroup *Haemophilus* species were significantly more common than either *Neisseria* or *Chlamydia* species. *Haemophilus* species were found in isolation in 39.5% of patients and the most common one was *Haemophilus parainfluenzae* (isolated in 84.2% of cases). In total, 34.2% of patients were resistant to azithromycin and 26.3% were resistant to both azithromycin and tetracycline. Empirical treatment achieved clinical and microbiologic cure in 11 of the patients who were not lost to follow-up (n = 17; 44.7%). The remaining 6 patients required treatment with a new antibiotic.

[☆] Please cite this article as: Magdaleno-Tapial J, Valenzuela-Oñate C, Giacaman-von der Weth MM, Ferrer-Guillén B, Martínez-Domenech Á, García-Legaz Martínez M, et al. *Haemophilus* Species Isolated in Urethral Exudates as a Possible Causative Agent in Acute Urethritis: A Study of 38 Cases. Actas Dermosifiliogr. 2019;110:38–42.

^{*} Corresponding author.

E-mail address: jormagta@gmail.com (J. Magdaleno-Tapial).

PALABRAS CLAVE

Urethritis;
Haemophilus;
 Antibióticos;
 Infecciones de
 transmisión sexual

Conclusions: *Haemophilus* species are a new cause of nongonococcal urethritis, whose incidence is rising, particularly in men who have sex with men who engage in unprotected oral sex. The clinical manifestations are similar to those seen in gonococcal urethritis. Eradication of infection must be confirmed due to the high rate of antibiotic resistance associated with *Haemophilus* species.

© 2018 Elsevier España, S.L.U. and AEDV. Published by Elsevier España, S.L.U. All rights reserved.

Aislamiento de *Haemophilus* spp. en exudados uretrales como posible agente etiológico de uretritis aguda: estudio de 38 casos

Resumen

Introducción: La incidencia de uretritis por *Haemophilus* está aumentando. Nuestro objetivo principal es describir las características clínico-microbiológicas de estos pacientes. Como objetivo secundario discutiremos el tratamiento más adecuado en función de las resistencias antibióticas testadas.

Material y métodos: Seleccionamos los pacientes de la Unidad de Infecciones de Transmisión Sexual diagnosticados microbiológicamente de uretritis entre julio de 2015 y julio de 2018. De ellos, seleccionamos aquellos en los que se aisló un *Haemophilus* mediante cultivo agar chocolate. Las resistencias antibióticas se testaron mediante método de difusión disco-placa. De estos pacientes se recogieron los datos de forma transversal y prospectiva durante las visitas en consultas externas.

Resultados: Se aisló un *Haemophilus* spp. en 33,6% de los pacientes diagnosticados de uretritis. De estos pacientes, la manifestación clínica más frecuente fue la supuración uretral (57,9%) y el 60% eran hombres que tienen sexo con hombres, siendo el aislamiento de este microorganismo más frecuente de forma estadísticamente significativa entre los hombres que tienen sexo con hombres que el aislamiento de *Neisseria* o *Chlamydia*. *Haemophilus* spp. se encontró de forma aislada en el 39,5% de los pacientes, siendo el más frecuente *H. parainfluenzae* en el 84,2%. El 34,2% de los casos de *Haemophilus* aislados fueron resistentes a azitromicina y el 26,3% eran resistentes tanto a azitromicina como a tetraciclinas. En los casos en los que no se perdió el seguimiento del paciente (n=17; 44,7%), el tratamiento administrado de forma empírica consiguió una remisión clínica y microbiológica en 11 pacientes, mientras que en 6 fue necesario administrar una pauta de un nuevo antibiótico.

Conclusiones: *Haemophilus* es un nuevo agente etiológico de uretritis no gonocócicas cuya incidencia está en aumento, especialmente entre hombres que tienen sexo con hombres que practican sexo oral sin protección. Estos pacientes pueden presentar una clínica similar a una uretritis gonocócica. Es necesario confirmar la erradicación debido al elevado número de resistencias antibióticas testadas en *Haemophilus* spp.

© 2018 Elsevier España, S.L.U. y AEDV. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Urethritis is the syndrome most frequently associated with sexually transmitted infections (STIs),¹ and is etiologically classified as either gonococcal urethritis (GU), caused by *Neisseria gonorrhoeae*, or nongonococcal urethritis (NGU), caused by other etiological agents, such as *Chlamydia trachomatis*, *Mycoplasma* species, or *Ureaplasma* species.² However, the etiology of 30% to 40% of NGU cases is unknown.³ Bacteria of the genus *Haemophilus* are among several newly proposed etiological agents of NGU, especially among men who have sex with men (MSM).³

Here, we describe the clinical and microbiological characteristics of patients with urethritis caused by *Haemophilus* species, and discuss the most appropriate treatment strategies in patients with antibiotic resistance.

Material and Methods

This was a descriptive, observational study, in which data were collected in a structured, prospective interview. The study included all patients with a microbiologically confirmed diagnosis of urethritis who were seen between July 2015 and July 2018 at the Sexually Transmitted Infections Unit of the Hospital General Universitario de Valencia, Valencia, Spain. From this group of patients we selected those in whom *Haemophilus* species were isolated on chocolate agar. Antibiotic susceptibility of the *Haemophilus* isolates was evaluated using the disc-plate diffusion method.

Cross-sectional clinical and epidemiological data were collected during the patients' first visit. All patients were managed in accordance with the clinical guidelines of the

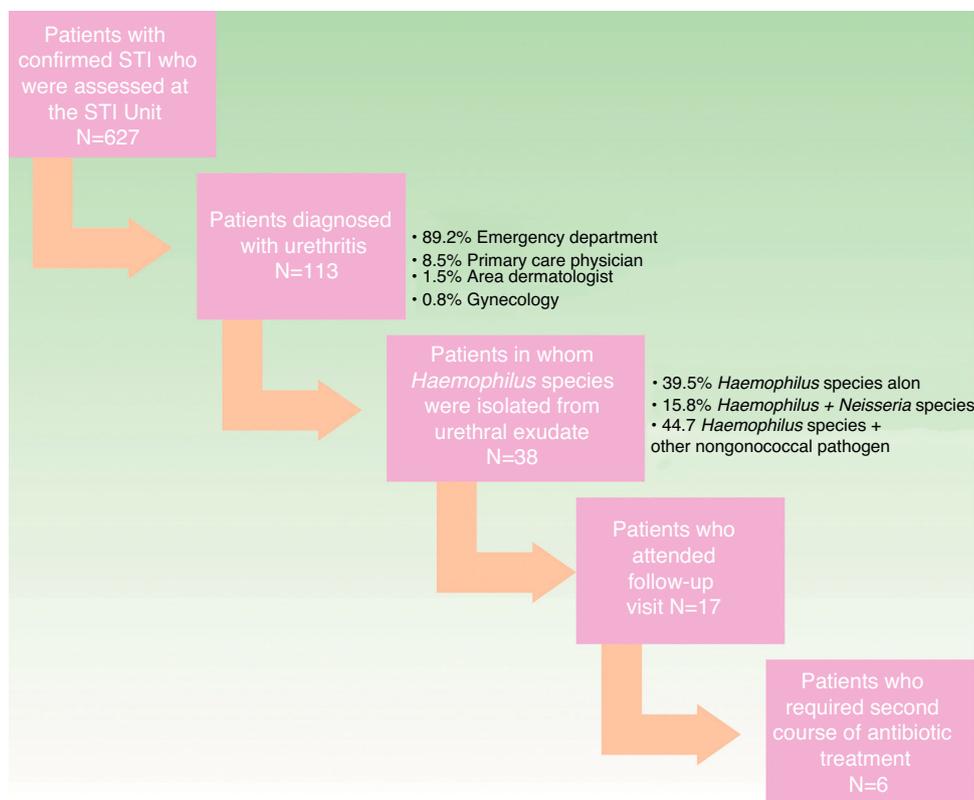


Figure 1 Flow chart illustrating patient inclusion in the study.

Spanish AIDS Study Group (GeSIDA). During the first visit, a urethral exudate sample was taken from all patients with a clinical diagnosis of urethritis for bacterial culture and polymerase chain reaction testing for STIs. This same procedure was performed for all asymptomatic patients who were seen at the STI Unit for unprotected sexual contact with casual partners. Patients with a suspected diagnosis of urethritis were treated empirically with doxycycline (100 mg every 12 h) or a single dose of azithromycin (1 g) at the discretion of their physician. In cases in which GU was suspected owing to the presence of abundant urethral suppuration, a single dose of intramuscular ceftriaxone (250 mg) was also administered.

During a second visit 4 to 6 weeks later, patients were re-evaluated and a second sample collected for microbiological analysis. If the patient's clinical signs and/or the *Haemophilus* isolate proved resistant to the prescribed treatment, a new antibiotic treatment was selected according to the findings of the antibiogram. In such cases, patients were evaluated once again 4 to 6 weeks after the second visit.

A flow chart illustrating the process of patient inclusion in the study is shown in [Figure 1](#).

Results

A total of 113 patients were diagnosed with microbiologically confirmed urethritis, of whom 31 (27.4%) were diagnosed with GU, 66 (58.4%) with NGU, and 16 (14.2%) with mixed urethritis (NG and NGU). *Haemophilus* species were

isolated from 38 patients (33.6%). Clinical and epidemiological data for these patients are summarized in [Table 1](#). Of the 38 patients diagnosed with urethritis due to *Haemophilus* species, 35 were male and 3 were heterosexual women. The mean age was 30.5 years. Of the 35 male patients, 21 (60%) were MSM. Among the MSM patients, *Haemophilus* species were isolated from the urethra significantly more often than either *N gonorrhoeae* ($P=.017$) or *C trachomatis* ($P<.001$).

Thirty-three (86.8%) of the 38 patients had visited the emergency department. The most common presenting complaint was marked urethral suppuration (22 patients [57.9%]). Ten patients (26.3%) were asymptomatic and consulted for unsafe sexual contact; 2 patients reported contact with a person diagnosed with NGU, and the other 8 were seen because they had unsafe sexual contact with a casual partner. The remaining 15.8% were seen for dysuria without evident urethral discharge. In total, 57.1% of patients had a prior STI, the most frequent of which were syphilis, human immunodeficiency virus infection, urethritis, and condylomata acuminata. All patients had received unprotected oral sex within a mean of 22.7 days before the consultation. The most commonly isolated *Haemophilus* species was *H parainfluenzae*, which was isolated in 32 patients (84.2%), followed by *Haemophilus influenzae* (5 patients [13.2%]).

Haemophilus species were found in isolation in 15 (39.5%) of the 38 patients, 9 of whom (60%) presented with marked urethral suppuration. Urethritis caused by *Haemophilus* species was associated with GU in 6 patients (15.8%). One or more classical etiological agents of NGU were detected in 17 patients (44.7%): *C trachomatis* in 7 patients (18.4%); *Mycoplasma genitalium* in 2 patients (5.2%); *Mycoplasma*

Table 1 Clinical and Microbiological Data for Patients Diagnosed With Urethritis Caused by *Haemophilus* Species

Data	Number of Cases (%)
Sex	
Male	35 (92.1)
Female	3 (7.9)
Mean age, y; SD	30.5; 8.7
Sexual orientation	
Men who have sex with men	21 (55.3)
Heterosexual men	13 (34.2)
Heterosexual women	3 (7.9)
Unknown	1 (2.6)
Previous STI	20 (57.1)
Syphilis	8 (21)
Urethritis	4 (11.4)
HIV infection	5 (13.2)
Pediculosis pubis	1 (2.6)
Condyloma acuminatum	4 (11.4)
<i>Chlamydia trachomatis</i> proctitis	1 (2.6)
Type of consultation	
Emergency department	34 (85.7)
Primary care physician	5 (14.3)
Clinical presentation	
Purulent urethral discharge	22 (57.9)
Dysuria	6 (15.8)
Asymptomatic / unsafe sexual contact	10 (26.3)
<i>Haemophilus</i> species	
<i>H parainfluenzae</i>	32 (84.2)
<i>H influenzae</i>	5 (13.2)
<i>H haemolyticum</i>	1 (2.6)
Coinfections	
<i>Haemophilus</i> species sole agent isolated	15 (39.5)
<i>Haemophilus</i> + <i>Neisseria</i>	6 (15.8)
<i>Haemophilus</i> + <i>Chlamydia</i>	7 (18.4)
<i>Haemophilus</i> + <i>Mycoplasma genitalium</i>	2 (5.2)
<i>Haemophilus</i> + <i>Mycoplasma hominis</i> / <i>Ureaplasma</i> species	9 (23.6)
Treatment outcome	
Clinical signs resolved after antibiotic treatment	11 (28.9)
Clinical signs resolved after treatment with more than one antibiotic	6 (15.8)
Lost to follow-up	21 (55.3)

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation; STI, sexually transmitted infection.

hominis in 4 patients; and *Ureaplasma* species in 5 patients. Triple coinfection with *H parainfluenzae*, *N gonorrhoeae*, and *C trachomatis* was detected in 1 patient.

Information on all antibiotic-resistant strains of *Haemophilus* species isolated from patients is provided in Table 2. Eight patients were sensitive to all drugs

Table 2 Antibiotic Resistance of Isolated *Haemophilus* Species

Antibiotic Tested	Number of Resistant Cases (%)
Cotrimoxazole	20 (53.6)
Azithromycin	13 (34.2)
Tetracyclines	10 (26.3)
Amoxicillin	8 (21)
Cefotaxime	1 (2.6)
Ceftriaxone	3 (7.9)
Cefuroxime	3 (7.9)
Ciprofloxacin	6 (15.8)
Levofloxacin	1 (2.6)

tested, and all cases that were resistant to tetracycline (10 patients) were also resistant to azithromycin. Seventeen patients (44.7%) were treated empirically with a combination of intramuscular ceftriaxone (250 mg) and a single oral dose of azithromycin (1 g), and 12 patients (31.5%) were treated with a combination of intramuscular ceftriaxone (250 mg) and oral doxycycline (100 mg every 12 h) for 7 days. The remaining patients were treated with azithromycin (5 patients) or doxycycline (4 patients) in monotherapy. In total, 21 patients (55.2%) were lost to follow-up. Microbiological eradication of the pathogen was confirmed in the 17 patients (44.8%) who attended follow-up visits, although 6 required treatment with a second, distinct antibiotic, which was selected according to antibiogram results. Of the 21 patients lost to follow-up, 4 (19%) were carriers of *Haemophilus* species that were resistant to the empirical treatment prescribed at the first visit according to antibiogram results.

Discussion

Of the patients diagnosed with microbiologically confirmed urethritis in our STI Unit, we detected *Haemophilus* species in urethral exudate samples from approximately one third, a greater proportion than that previously reported in Spain.⁴

H influenzae and *H parainfluenzae* are microorganisms commonly found in the normal microflora of the human upper respiratory tract.⁵ Urethritis caused by these microorganisms has been described in patients with STIs. The last decade has seen an increase in the incidence of urethritis caused by *Haemophilus* species, especially among MSM, owing to an increase in the practice of unprotected oral sex within this group.⁶ Because this microorganism has been detected in the urethra of 3% to 9.3% of asymptomatic men,⁶ its role as a causative agent of urethritis is controversial. We identified *Haemophilus* species as the sole causative agent of urethritis in 15 of 38 patients (39.5%). A previous study reported detection of *Haemophilus* species in up to 53% of urethritis patients.⁴ In our study, 57.9% of patients presented with purulent urethral syndrome that was characterized by spontaneous abundant whitish-green suppuration and was clinically indistinguishable from GU (Fig. 2). In 36.7% of our patients, a *Haemophilus* species was the only etiological agent isolated, suggesting that this microorganism was the causative agent of acute urethritis in these patients.



Figure 2 Homosexual patient, aged 23 years, with abundant urethral suppuration caused by *Haemophilus parainfluenzae*.

H parainfluenzae was isolated in 84.2% of our patients, and *H influenzae* in only 13.2%. These proportions, and the distribution of *Haemophilus* species among MSM described here, are similar to those previously reported,⁴ and demonstrate that *Haemophilus* species are etiologic agents of urethritis mainly among MSM, owing to the low level of condom use during orogenital sexual practices within this group.

Of particular interest was the resistance of the isolated microorganisms to multiple antibiotics. This finding suggests that extra caution is required when selecting empirical adjuvants to intramuscular ceftriaxone when treating urethritis patients. Of the pathogens isolated in our study, 53.6% were resistant to cotrimoxazole and 34.2% were resistant to azithromycin. Furthermore, 26.3% of cases were resistant to both azithromycin and tetracyclines, both of which are recommended first-line drugs for the treatment of NGU.⁷ While greater proportions of antibiotic-resistant strains have been reported elsewhere, particularly for azithromycin resistance in East Asia,⁸ monitoring of these patients is nonetheless necessary owing to the high risk of treatment failure. Another drug combination that may be of interest in clinical practice is amoxicillin and clavulanic acid, against which we detected no resistance. We found only 7 cases of resistance to quinolones, suggesting that drugs of this class may be useful adjuvants for the treatment of urethritis, although higher rates of resistance have been reported among MSM patients with urethritis.⁹ It should be noted that 5 of the *H parainfluenzae* isolates showed resistance to 5 or more of the drugs tested, and were therefore considered multidrug-resistant.¹⁰ It is thus fundamental to confirm microbiological cure and to remind patients of the importance of follow-up visits.

Limitations of this study include its observational nature and the lack of a control group, which would be required to demonstrate a true pathogenic role of *Haemophilus* species in urethritis. Furthermore, it is difficult to draw precise conclusions regarding the therapeutic outcomes owing to the small sample size and the large number of cases lost to follow-up. It is also unknown whether antibiotic treatment was effective in patients in whom antibiotic-resistant

Haemophilus species were isolated but who were subsequently lost to follow-up.

In summary, our findings underscore the importance of *Haemophilus* species as an etiological agent of NGU, especially among MSM patients with a history of unprotected oral sex. Patients may present with urethral discharge similar to that caused by *N gonorrhoeae*, and cure must be confirmed owing to the possibility of *Haemophilus* species antibiotic resistance. Although in theory this ailment is easily treated, dermatologists must take responsibility for the management of urethritis and other STIs.

In this study we describe the presence of *Haemophilus* species in the urethral exudate of approximately one third of patients diagnosed with microbiologically confirmed urethritis in our STI Unit, a greater proportion than that reported to date in Spain.⁴

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- Orellana MA, Gómez ML, Sánchez MT, Fernández-Chacón T. [Diagnosis of urethritis in men. A 3-year review] Spanish. *Rev Esp Quimioter.* 2009;22:83–7.
- Iser P, Read TH, Tabrizi S, Bradshaw C, Lee D, Horvarth L, et al. Symptoms of non-gonococcal urethritis in heterosexual men: A case control study. *Sex Transm Infect.* 2005;81:163–5.
- Frølund M, Lidbrink P, Wikström A, Cowan S, Ahrens P, Jensen JS. Urethritis-associated pathogens in urine from men with non-gonococcal urethritis: A case-control study. *Acta Derm Venereol.* 2016;96:689–94.
- Deza G, Martín-Ezquerria 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.* 2016;92:29–31.
- Ito S, Hatazaki K, Shimuta K, Kondo H, Mizutani K, Yasuda M, et al. *Haemophilus influenzae* isolated from men with acute urethritis: Its pathogenic roles, responses to antimicrobial chemotherapies, and antimicrobial susceptibilities. *Sex Transm Dis.* 2017;44:205–10.
- Hsu MS, Wu MY, Lin TH, Liao CH. *Haemophilus parainfluenzae* urethritis among homosexual men. *J Microbiol Immunol Infect.* 2015;48:450–2.
- Polo R, Palacios R, Barberá MJ, coordinadores. Documento de consenso sobre diagnóstico y tratamiento de las infecciones de transmisión sexual en adultos, niños y adolescentes. GeSIDA; 2017. p. 42–46.
- 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.
- Orellana MA, Gómez-Lus ML. [Which is the best empirical treatment in patients with urethritis?] Spanish. *Rev Esp Quimioter.* 2011;24:136–42.
- Tinguely R, Seiffert SN, Furrer H, Perreten V, Droz S, Endimiani A. Emergence of extensively drug-resistant *Haemophilus parainfluenzae* in Switzerland. *Antimicrob Agents Chemother.* 2013;57:2867–9.