

# Study of the pathogenic role of *Haemophilus influenzae* and *H. parainfluenzae* as causative agents of urethritis

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## Introduction

Acute urethritis is one of the most common presentations of sexually transmitted diseases (STD) among men. An increased incidence along with a change in the profile of the involved pathogens has been recently described. Among non-gonococcal urethritis (NGU), *Chlamydia trachomatis* is the most common identified agent, accounting for 30%-50% of the cases. Other pathogens associated with NGU include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, *Streptococcus* spp, *Gardnerella vaginalis* and viruses, such as adenoviruses and herpes virus. *Haemophilus influenzae* and *Haemophilus parainfluenzae* are colonizers of the upper respiratory tract and are part of the normal oral microflora. In the last decades, an increasing number of cases of *Haemophilus* spp other than *Haemophilus ducreyi* causing genital tract infections, such as urethritis, cervicitis and vaginitis have been reported.

## Objectives

To describe the clinical characteristics and therapeutic outcomes from male patients diagnosed of *Haemophilus* spp urethritis.

## Patients & methods

All patients who presented to our Hospital from January 2013 to December 2014 reporting less than one month of symptoms of urethritis in which *Haemophilus* spp was isolated from their urethral samples were included in the study. Clinical, laboratory, demographic and behavioral data were obtained by reviewing medical charts. Specimens were obtained from patients in whom it had been at least 2 hours from last void. If urethral discharge was identified, samples were taken by inserting a sterile Dacron swab into the urethra. If there was no evident discharge, first- stream urine was delivered for processing. Detection of microorganisms in urethral exudates or urine was performed by five methods: Gram-staining of urethral smears, multiplex PCR for detection of *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis*, PCR for detection of herpes simplex virus (if clinical suspicion), detection of *U. urealyticum* and *M. hominis* by the Mycoplasma IST2 system and cultures on 5% sheep blood agar, chocolate agar PolyViteX and PolyViteX VCAT3, Gardnerella selective agar and SGC2 Sabouraud gentamicin-chloramphenicol agar. Identification and characterization of *Haemophilus* spp was performed by the API20E system. The beta-lactamase activities were detected by the chromogenic cephalosporin method. The study was approved by the Comitè Ètic d'Investigació Clínica from l'Institut Mar d'Investigació Mèdica (CEIC-PSMAR)

## Results

*Haemophilus* spp was isolated in 52 out of 413 urethral samples (12.6%) received in our laboratory from patients with symptoms of acute urethritis during the study period. Seven cases (13%) corresponded to *H. influenzae* and 45 cases (87%) to *H. parainfluenzae*. In total, 6.8% (28 of 413) of cases had *Haemophilus* spp identified as a single pathogen. In the other 24 cases, *Haemophilus* spp was isolated with another pathogen, most frequently *N. gonorrhoeae* (10 cases) and *C. trachomatis* (8 cases). Clinical and microbiological data of the 52 patients are summarized in Table 1.

## Discussion

In the present study, *Haemophilus* spp was isolated in 12.6% of the evaluated samples. In concordance with previous studies, *H. parainfluenzae* was much more frequent than *H. influenzae* (87% vs 13%). It is difficult to prove the pathogenic role of microorganisms that can be isolated as colonizers under healthy conditions. In our series, *Haemophilus* spp was detected together with other microorganisms in 24 out of 52 cases (46%). Those cases could correspond to a dual infection, although the pathogenicity of *Haemophilus* spp remains uncertain as it could be merely a colonizer. In the remaining 28 cases, *Haemophilus* spp was isolated as a single pathogen. Taking into account that only symptomatic patients were included and that other agents involved in urethritis were excluded, *Haemophilus* spp could be consider a pathogen in at least 6.8% of the patients. Rates of isolation vary in the literature, from 1.2% to 10%. Urethritis by *Haemophilus* spp seems to affect men regardless of their sexual orientation or HIV status, and indistinctive clinical symptoms make it difficult to differentiate from other causes of urethritis. Symptoms can vary from purulent urethral discharge to mucous clear discharge, with or without meatitis. In our series, the most common clinical presentation was mucopurulent urethral discharge. Patients were asked about their sexual exposures the month before consultation. In our study, all cases reported having practiced unprotected insertive oral sex, and 5 of them denied having had another sexual contact apart from this exposure. These two facts suggest that unprotected oral sex could be the main route of transmission of this pathogen, although vaginal or anal intercourse cannot be completely excluded. Empirical antibiotic therapy is offered in all cases at presentation, and includes ceftriaxone plus azithromycin or doxycycline. In all our cases in which follow-up was available, this empirical treatment achieved a complete clinical resolution. In previous studies that examined antimicrobial susceptibility of *Haemophilus* spp, no cefotaxime-resistant strains were found. This has to be taken into account in cases where ceftriaxone is not indicated as first-line treatment, as in severe penicillin allergy or avoidance of intramuscular route, where resistance can be an issue. We do not perform routinely antibiogram on *Haemophilus* spp strains from the genitourinary area, but it would be advisable to carefully follow cases with persistent symptoms and perform antibiogram on at least such cases.

**Limitations:** The lack of a representative control group does not allow proving the true pathogenic role of *Haemophilus* spp in acute urethritis. As it is a retrospective study, some clinical information retrieved from clinical records could be lacking. Biotypes have not been checked and it could be of interest in order to differentiate commensal from pathogenic strains. The small sample size and the high number of lost cases for follow-up do not allow making accurate conclusions about therapeutic outcomes.

## Conclusions

*Haemophilus* spp was considered a pathogen in at least 6.8% of the patients from the evaluated area. It affected both heterosexual males and men who have sex with men, and mucopurulent urethral discharge was the most common clinical presentation. Unprotected oral sex could play a role in its transmission.

## References

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Table 1: Clinical and microbiological data of the study population

Data	<i>Haemophilus</i> spp. (n=52) Number of cases (%) or mean (range)
Age, years	31.8 (19-62)
Sexual orientation	
Men who have sex with men	31 (59.6)
Heterosexual	21 (40.4)
Known HIV-infection	
Total	4 (8)
<i>H. influenzae</i>	2
<i>H. parainfluenzae</i>	2
Previous STD	
Total	9 (17.3)
Urethritis by <i>N. gonorrhoeae</i>	4
Urethritis by <i>M. genitalium</i>	1
Syphilis	3
Lymphogranuloma venereum	1
Clinical presentation	
Mucopurulent urethral discharge	37 (71.2)
Clear urethral discharge	13 (25)
Dysuria without evident discharge	2 (3.8)
Sexual exposures	
Protected oral sex	0 (0)
Unprotected oral sex	52 (100)
Protected vaginal sex	3 (5.8)
Unprotected vaginal sex	16 (30,8)
Protected anal sex	6 (11,5)
Unprotected anal sex	23 (44,2)
Beta-lactamase-positive strains	
Total	9 (17.3)
<i>H. influenzae</i>	0
<i>H. parainfluenzae</i>	9
Prescribed treatment	
Ceftriaxone + azithromycin/ doxycycline	48 (92.3)
Azithromycin 1g	1 (1.9)
Ciprofloxacin 500mg/12h for 5 days	1 (1.9)
Doxycycline 100mg/12h for 7days	2 (3,8)
Outcomes	
Symptoms resolved	24 (46,2)
Persistent symptoms	0 (0)
Lost follow-up	28 (53,8)