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Original article

Clinical significance of isolation of *Haemophilus* no *ducreyi* in genital samples. Systematic review

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ABSTRACT

Introduction and objectives: Currently, the microbiological diagnosis of genital infections is carried out with molecular methods, which allow the detection of less frequent etiological agents but with potential pathogenic importance, such as *Haemophilus* spp. The objective of this review is to analyse and highlight the clinical importance of the isolation of *Haemophilus* spp. in genital and rectal infections, excluding *Haemophilus ducreyi*.
Material and methods: A systematic review was carried out based on an exhaustive search of the publications included in the MEDLINE database up to August 5, 2021, on the presence of *Haemophilus* spp. in genital and rectal infections, excluding *H. ducreyi*.
Results: After reviewing what was described in the literature, *Haemophilus* spp. (excluding *H. ducreyi*: HSNOD) was detected in 2397 episodes of genital infection, the most frequently isolated species being *H. influenzae* and *H. parainfluenzae*. Most of the episodes (87,6%) are constituted by single isolation. There is a slight predominance in women (48,3%) where it can cause vaginitis, salpingitis, endometritis or complications during pregnancy. In men, the clinical picture usually corresponds to urethritis. Most of the samples correspond to vaginal and urethral exudates, with a minority representation at the rectal level (2.3%).
Conclusion: HSNOD plays a relevant pathogenic role in episodes of genital infection, so microbiological diagnostic protocols must include methods that allow their detection, as well as include them in the etiological spectrum of this type of clinical picture.

Importancia clínica del aislamiento de *Haemophilus* spp. (excluyendo *H. ducreyi*) en muestras genitales. Revisión sistemática

Palabras clave:
Haemophilus
Uretritis
Proctitis
Vulvovaginitis
Infecciones de transmisión sexual

RESUMEN

Introducción y objetivos: Actualmente el diagnóstico microbiológico de las infecciones genitales se realiza con métodos moleculares, los cuales permiten detectar agentes etiológicos menos frecuentes, pero con potencial importancia patogénica, como *Haemophilus* spp. El objetivo de esta revisión es analizar y resaltar la importancia clínica del aislamiento de *Haemophilus* spp. en infecciones genitales y rectales, excluyendo *H. ducreyi*.
Material y métodos: Se ha realizado una revisión sistemática en base a una búsqueda exhaustiva de las publicaciones incluidas en la base de datos MEDLINE hasta el 5 de agosto de 2021, sobre la presencia de *Haemophilus* spp. en infecciones genitales y rectales, excluyendo *H. ducreyi*.

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Resultados: Tras revisar lo descrito en la literatura, las especies de *Haemophilus* (excluyendo *H. ducreyi: HSNOD)* se detectaron en 2397 episodios de infección genital, siendo las especies más frecuentemente aisladas *H. influenzae* y *H. parainfluenzae.* La mayoría de los episodios (87,6%) están constituidos por aislamiento único. Existe un ligero predominio en mujeres (48,3%) donde puede producir cuadros de vaginitis, salpingitis, endometritis o complicaciones durante el embarazo. En hombres, el cuadro clínico suele corresponder a una uretritis. La mayoría de las muestras corresponde a exudados vaginales y uretrales, con una representación minoritaria a nivel rectal (2,3%).
Conclusión: HSNOD desempeña un papel patogénico relevante en episodios de infección genital, por lo que los protocolos de diagnóstico microbiológico deben incluir métodos que permitan su detección, así como incluirlos en el espectro etiológico de este tipo de cuadros clínicos.

Introduction

Genital tract infections are common entities that share a clinical presentation but can be caused by myriad aetiological agents apart from the microorganisms commonly regarded as pathogens[1]. In addition, there is a large diversity of microbiota and significant inter-individual variability that makes it even more difficult to distinguish between a possible pathogenic role or not[2]. These less common agents that play a possibly pathogenic role include the species of the genus *Haemophilus*, excluding *Haemophilus ducreyi* (HSNOTD). The genus *Haemophilus*, belonging to the *Pasteurallaceae* family, is made up of small non-sporulating, pleomorphic, non-motile, facultative anaerobic gram-negative bacilli. It is characterised by having demanding nutritional requirements and requires chocolate agar medium for proper growth and identification. The species of HSNOTD most frequently involved *are Haemophilus influenzae (H. influenzae)*, *Haemophilus parainfluenzae (H. parainfluenzae)* and *Haemophilus haemolyticus (H. haemolyticus)*. The first one is well-known, it is a colonising agent of the upper respiratory and genital tract and can behave as an opportunistic pathogen. In recent years, more and more cases of urethritis associated with *H. influenzae*, and more recently its association with non-gonococcal urethritis, have been described both in men who have sex with men (MSM) and women[3]. In addition, it is the second most common cause of vulvovaginitis in girls not linked to sexual transmission[4]. *H. parainfluenzae* predominantly colonises the oropharynx and can lead to infections through contiguity, bacteraemia, endocarditis and genital infections[5]. *H. haemolyticus* is difficult to distinguish from the non-encapsulated species of *H. influenzae* due to its morphological, biochemical and genetic similarities, and it is sometimes difficult to distinguish between them by conventional microbiological methods, hence some authors advocate the combination of conventional methods and polymerase chain reaction (PCR) analysis; [6] mass spectrometry (MALDI-TOF) has also shown good results in differentiation capacity[7]. It rarely has pathogenic potential.

In addition, there are the biotype IV cryptic genospecies, genetically related to *H. haemolyticus*, but with a different phenotype and location, such as *¨Haemophilus quentini¨*, whose presence has been described in the genitourinary tract and can cause genital infections in pregnant women, chorioamnionitis and preterm delivery, and even pneumonic or septic conditions in newborns[8].

The objective of this study is to analyse the presence of HSNOTD species in the development of genital infections through a systematic literature review.

Materials and methods

A search was made in the MEDLINE database, through PubMed, for studies that describe the presence of *Haemophilus* spp. in genital (vaginal, endocervical and urethral) and rectal exudates (in MSM). The following search terms were used: *¨Haemophilus* and urethritis¨; *¨Haemophilus* and proctitis¨; *¨Haemophilus* and vaginitis¨; *¨Haemophilus* and cervicitis¨; *¨Haemophilus* and salpingitis¨; *¨Haemophilus* and endometritis¨; *¨Haemophilus* and bartholinitis¨; *¨Haemophilus* and tubo-ovarian abscess¨; *¨Haemophilus* and septic abortion¨; *¨Haemophilus* and chorionamnionitis¨. The inclusion criteria were: studies published up until 1 September 2021; and studies published in English or Spanish. The exclusion criteria were: studies referring to the *H. ducreyi* or *Haemophilus vaginalis* species; and studies that analysed samples from sources other than genital or rectal. The references listed in the studies were also reviewed to reduce the number of losses.

Results

145, 3, 583, 595, 21, 73, 14, 6, 16 and 30 publications were obtained for the criteria *¨Haemophilus*and urethritis¨; *¨Haemophilus*and proctitis¨; *¨Haemophilus*and vaginitis¨; *¨Haemophilus*and cervicitis¨; *¨Haemophilus*and salpingitis¨; *¨Haemophilus*and endometritis¨; *¨Haemophilus*and bartholinitis¨; *¨Haemophilus*and tubo-ovarian abscess¨; *¨Haemophilus*and septic abortion¨; *¨Haemophilus* and chorionamnionitis¨, respectively, which were subsequently submitted to the inclusion and exclusion criteria, yielding 117 studies. Of these, 13 could not be located (Northwest Med. 1955;54(9):992–3, J Pathol Bacteriol. 1967;93(1):109–18, Am J Vet Res. 1971;32(12):2067–9, Am J Clin Pathol. 1980;73(2):285–7, Med J Aust. 1985;143(5):223, Med J Aust. 1985;142(9):531, J Infect Dis. 1986;153(1):165–7, Acta Paediatr Scand. 1987;76(2):363–4, Med Clin (Barc). 1989;92(9):335–7, Med Clin (Barc). 1989;93(19):758–9, Pediatr Infect Dis J. 1994;13(3):243, Am J Obstet Gynecol. 1994;170(4):1008–17, J Am Board Fam Pract. 1994;7(4):335–41). Table 1 shows 104 works, which group together a total of 2397 episodes of genital infection caused by *Haemophilus* spp. The most frequently isolated species were *H. influenzae* (57.7%; 1383/2397) and *H. parainfluenzae* (35.7%; 855/2397). No species was identified in 6.7% (159/2397) of the episodes. In most episodes (87.6%; 2099/2397), *Haemophilus* was isolated in monomicrobial culture. Otherwise, it was often detected along with *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma* spp. *or Mycoplasma* spp.

Most of the studies adequately described the method used in the laboratory for the isolation of *Haemophilus*. Until 2011, mainly culture techniques and biochemical tests were used. From 2011 onwards, molecular biology techniques, such as PCR or the sequencing of the 16S subunit of rRNA, became more prominent. More recently, mass spectrophotometry has been used (MALDI - TOF).

Regarding patient gender, 34.8% (835/2397) were men; 48.3% were women (1158/2397) and 16.9% (404/2397) were not reported. Only half of the studies provided data on patient age. The men were all adults with a mean age of 30 years[20–55]. The women were

Table 1
Studies reporting the isolation of *Haemophilus* spp. in genital samples.

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Skirrow MB (1970)[9]	1	*H. influenzae*	48/F	NP	Tubo-ovarian abscess	Abscess exudate	Culture	Surgery and ampicillin
Hurley R (1970)[10]	1	*H. influenzae*	29/F	Intrauterine device	Endometritis	Vaginal exudate	Culture	Removal of device
Farrand RJ (1971)[11]	1	*H. influenzae*	4/ F	NP	Vaginal dischargeand irritation Inflamed vagina with purulent exudate	Vaginal exudate	Culture	Ampicillin
	1	*H. influenzae*	35/ F	Tubal ligation surgery 7 years previously.	Right tubal abscess	Puncture-aspiration of the abscess	Culture	Ampicillin + cloxacillin
Berczy J (1973)[12]	1	*H. influenzae*	27/F	NP	Septic abortion	Vaginal exudate	Culture	NP
Khuri-Bulos N (1975)[13]	8	*H. influenzae*	NP/F	NP	Neonatal sepsis	Vaginal and/or cervical exudate	NP	NP
Herva E (1975)[14]	1	*H. influenzae*	NP/F	NP	Salpingitis	Tubal exudate	Culture	NP
Nicholls S (1975)[15]	1	*H. influenzae*	31/ F	NP	Neonatal sepsis	Vaginal exudate Placental biopsy	Culture	Penicillin + kanamycin (NR) Ampicillin
	1	*H. influenzae*	18/ F	NP	Antepartum haemorrhage and vaginal discharge. Neonatal sepsis and death	Vaginal exudate and respiratory samples from the newborn	Culture	Penicillin + kanamycin
Bowie WR (1977)[16]	10	7 *H. parainfluenzae* 4 + *C. trachomatis* 3 *H. influenzae*	NP/M	NP	4 urethritis and 3 asymptomatic 3 asymptomatic	Urethral exudate	Culture (Virginia Polytechnic Institute)	NP
Albritton WL (1978)[17]	5	*H. influenzae*	18 F, 20 F, 22 F 30 F,33/F	2 Pregnancy	1 vulvovaginitis, 2 septic abortion, 1 acute salpingitis	Vaginal exudate, blood cultures	Culture	Ampicillin, kanamycin
Gibson M (1978)[18]	1	*H. influenzae*	NP/F	28 weeks pregnant. Premature rupture of membranes	Amnionitis	Amniotic fluid	Culture	NP
Ogden E (1979)[19]	1	*H. influenzae*	NP/F	16 weeks pregnant	Amnionitis	Amniotic fluid	Culture	NP
Simon HB (1980)[20]	1	*H. influenzae*	36/F	NP	Salpingitis/endometritis	Vaginal exudate	Culture	NP
Arias JW (1981)[21]	1	*H. parainfluenzae*	18/F	29 weeks pregnant	Chorioamnionitis	Placenta	Culture	NP
De Pass EE (1982)[22]	1	*H. influenzae*	22/F	NP	Bilateral salpingitis and abscess	Tubal exudate	Culture	Bilateral salpingo-oophorectomy, hysterectomy and ampicillin
Pastorek J (1982)[23]	2	*H. influenzae*	26 F and 17F	Pregnant (37 and 40 weeks)	Chorioamnionitis Endometritis	Placenta and cervical exudate	Culture	Ampicillin, gentamicin
Chowdhury MN (1983)[24]	1	*H. parainfluenzae*	NP/M	NP	Urethritis, urethral discharge	Urethral exudate	NP	Amoxicillin
Hall GD (1983)[25]	11	11 *H. influenzae*	NP/F 2 M	NP	4 vaginitis, 2 IUD-associated endometritis, 1 incomplete septic abortion, 1 urethral syndrome and 1NP 2 urethritis	Vaginal, cervical or urethral exudate	Biochemical tests	NP
Messing M (1983)[26]	1	*H. parainfluenzae*	NP/M	NP	Nongonococcal urethritis: genital erythema and urethral discharge	Urethral exudate	Culture and biochemi-cal tests	NP

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
	1	*H. parainfluenzae*		NP	Ulcerative lesions on the genitals			
	1	*H. parainfluenzae*		Secondary syphilis	Genital erythema and inguinal adenopathy			
	1	*H. parainfluenzae*		Pubic folliculitis	Erythematous genital lesions			
	1	*H. parainfluenzae*		Gonorrhoea and condyloma acuminata	Urethral discharge and genital lesion			
	1	*H. influenzae*		NP	Dysuria and urethral discharge			
	1	*H. influenzae*		Primary syphilis	Ulcerative lesions on the genitals			
	1	*H. influenzae*		NP	Nongonococcal urethritis: dysuria and urethral discharge			
Tebbutt GM (1984)[27]	6	*H. influenzae* 1 + *N. gonorrhoeae*	NP/F	NP	3 girls with vaginal discharge 2 postnatal infection 1 pelvic inflammatory disease	Vaginal exudate	Culture and biochemical tests	NP
Nakamura KT (1984)[28]	1	*H. parainfluenzae*	24/F	28 weeks pregnant.	Premature rupture of membranes	Placenta and cervical exudate	Culture	Ampicillin and gentamicin
Paavonen J (1985)[29]	2	*H. influenzae*	22/F, 29/F	1 Previous risky sexual relationship	1 pyosalpinx 1 tubo-ovarian abscess	Tubal and abscess exudate	Culture	Doxycycline and metronidazole Penicillin G and metronidazole
Campognone P (1986)[30]	17	*H. influenzae*	17 F	17 pregnant. 1 diabetic	Chorioamnionitis	Placenta and maternal blood	Culture	NP
Crowe HM (1987)[31]	2	*H. influenzae*	NP/F	1 Crohn's disease	2 tubo-ovarian abscesses	Abscess exudate	Culture	Chloramphenicol and tobramycin
LW Davis (1987) [32]	1	*H. influenzae*	NP/F	NP	Tubo-ovarian abscess	NP	NP	NP
Winn HN (1987)[33]	1	*H. influenzae*	25/F	22 weeks pregnant.	Chorioamnionitis	Maternal blood and amniotic fluid	Culture	Ampicillin
Casin I (1988)[34]	60	60 *H. influenzae* 52 solitarily 3 + *C. albicans* 3 + *T. vaginalis* 1 + *N. gonorrhoeae* 1 + *C. trachomatis*	NP/37 M, 20 F and 3 NP	NP	NP	37 Urethral exudate 19 Vaginal and/or cervical exudate 3 urine 1 Bartholin's gland	Culture and biochemical tests	NP
Andreu A (1989)[35]	10	7 *H. parainfluenzae* 3 *H. influenzae* 7 solitarily 3 + other*	NP/M	NP	7 urethritis	Urethral exudate	NP	NP
	20	15 *H. influenzae* 5 *H. parainfluenzae* + others*	NP/F	5 IUD carriers	8 vaginitis, 3 salpingitis and 9 NP	Vaginal or endocervical exudate	NP	NP

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Drouet EB (1989)[36]	244	216 *H. parainfluenzae* 28 *H. influenzae*	NP	NP	NP	NP	NP	NP
Houang E (1989)[37]	73	*H. parainfluenzae*	NP/71 M and 2 F	NP	NP	71 urethral exudate 2 vaginal exudate	MicroScan	NP
Martel AY (1989)[38]	103	*Haemophilus* spp.	NP/56 M, 33 F and 14 NP	NP	NP	55 genital exudate 48 rectal exudate	Biochemical tests	NP
Leiberman JR (1989)[39]	1	*H. influenzae*	35/F	16 weeks pregnant.	Amnionitis	Amniotic fluid	Culture	NP
van Bosterhaut B (1990)[40]	3	*H. influenzae*	NP/F	NP	3 bartholinitis	Gland exudate	Culture	NP
Christensen JJ (1990)[41]	17	*Haemophilus spp.*	NP/F	NP	Bartholinitis, salpingitis and/or vaginal discharge	NP	NP	NP
Quentin R (1990)[42]	8	*H. influenzae*	NP/F	Bartholin's gland cyst or abscess surgery	Bartholinitis	Aspirated cyst or abscess	NP	NP
Silverberg K (1990)[43]	1	*H. influenzae*	17/F	29 weeks pregnant.	Chorioamnionitis	Amniotic fluid and placenta	Culture	Ampicillin, gentamicin, clindamycin
Pinhas-Hamiel O (1991)[44]	1	*H. influenzae*	28/F	13 weeks pregnant Previous risky sexual relationship	Septic abortion	Blood cultures	Culture	NP
Facinelli B (1991)[45]	1	*H. parainfluenzae*	NP	Risky sexual relationship	Urethritis	NP	NP	NP
Bendig JW (1991)[46]	2	*H. influenzae*	35/F, 29/F	1 IUD	2 purulent salpingitis	Peritoneal and tubal exudate	Culture	Drainage, ceftriaxone, metronidazole
Lefevre JC (1991)[47]	21	*H. parainfluenzae*	NP/M	NP	Urethritis	Urethral exudate	NP	NP
Bosch J (1991)[48]	9	*H. influenzae*	NP/F	NP	7 Bartholin's gland abscesses 1 post-caesarean section endometritis 1 chorioamnionitis	Vaginal and gland exudate	NP	Ampicillin
Rusin P (1991)[49]	13	*H. influenzae*	NP/F	NP	13 endometritis/chorioamnionitis	NP	NP	NP
Mazor M (1991)[50]	1	*H. influenzae*	28/F	29 weeks pregnant. Premature rupture of membranes	Amnionitis	Amniotic fluid and neonatal blood	Culture	Ampicillin and gentamicin
Kragsberg P (1993)[51]	6	*H. influenzae*	NP/F	6 pregnancies 1 Recurrent endometritis	3 tubo-ovarian abscesses 2 septic abortions 1 postpartum sepsis	Abscess exudate Vaginal exudate	Culture	Cephalosporin, ampicillin, metronidazole, doxycycline
Ault KA (1993)[52]	3	*H. influenzae*	18 F, 22 F, 29F	3 Pregnancies (29, 31 and 31 weeks)	Amnionitis	Placenta and maternal blood	Culture	Vancomycin and gentamicin Ampicillin and gentamicin Ceftizoxime
Kinney JS (1993)[53]	6	*H. influenzae*	NP/F	Pregnant 24–40 weeks	Chorioamnionitis	Placenta and neonatal blood	Culture	1 Ampicillin, 1 cephalosporin
Gill MV (1995)[54]	1	*H. influenzae*	36/F	35 weeks pregnant, placenta percreta	Chorioamnionitis	Blood cultures and cervical exudate	Culture	Ceftazidime and aztreonam

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Llanes Caballero R (1996)[55]	1	*H. influenzae*	NP/M	Previous schistosomiasis	Discomfort while urinating and purulent urethral discharge	Urethral exudate	NP	Norfloxacin
Pena MJ (1996)[56]	20	*H. influenzae*	NP/F	Prepubescent girls	Vulvovaginitis	Vaginal exudate	NP	NP
Vázquez F (1996)[57]	155	100 *H. parainfluenzae* 45 *H. influenzae* 10 *Haemophilus* spp. 21 solitarily 134 + others*	2 M, 11 F and 142 NP	Female sex workers and men with urethritis	8 urethritis 2 epididymo-orchitis 9 cervicitis and/or vaginitis 2 Bartholin's gland abscesses 134 NP	NP	Culture	NP
Carmeci C (1997)[58]	1	*H. influenzae*	48/F	NP	Acute salpingitis and septic shock	Peritoneal exudate and blood cultures	Culture	Salpingo-oophorectomy and ceftriaxone
Cox RA (1997)[4]	11	*H. influenzae*	<14/ F	NP	Vulvovaginitis	Vaginal and vulvar exudate	Culture	Amoxicillin
García E (1997)[59]	30	18 *H. influenzae*	NP/F	Pregnant, parturient, puerperal	1 abortion 2 antepartum deaths 1 postpartum death 14 live newborns (5 confirmed infection and 5 suspected infection and 4 healthy)	Vaginal exudate taken intrapartum or in the immediate postpartum	NP	NP
		12 *H. parainfluenzae*			1 antepartum death 12 live newborns (10 suspected infection)			
Aydin MD (1998)[60]	19	11 *H. parainfluenzae* 8 *H. influenzae*	NP/M	NP	Urethritis	Urethral exudate	Biochemical tests	NP
Rodríguez-Guardado (2000)[61]	1	*H. influenzae*	36/F	NP	Bilateral salpingitis	Peritoneal exudate	Culture	Salpingectomy, clindamycin, gentamicin
Cherpes TL (2002)[62]	1	*H. influenzae*	39/F	8 weeks pregnant	Septic abortion. Acute chorioamnionitis Low-grade fever, vaginal bleeding, and headache	Blood culture Placental biopsy	NP	Ampicillin + gentamicin + clindamycin Ceftriaxone Levofloxacin
Cox RA (2002)[63]	39	38 *H. influenzae* 1 *H. parainfluenzae* 8 + mixed anaerobic flora	18 months -11 years/ F	14 recurrent vulvovaginitis 5 two previous episodes of vulvovaginitis due to *H. influenzae*, 1 three previous episodes	Vulvovaginitis: vaginal discharge and irritation	Vaginal and vulvar exudate	Culture	19 amoxicillin 9 amoxicillin/clavulanic acid 6 trimethoprim 6 miconazole 2 metronidazole 2 clarithromycin, erythromycin
Campos J (2003)[64]	2	*H. influenzae* serotype e	NP/F	NP	Vaginitis	NP	NP	NP
Cuadros J (2004)[65]	12	*H. influenzae*	2–12/ F	NP	Vulvovaginitis	Vaginal exudate	NP	NP
Mikamo H (2005)[66]	1	*H. influenzae*	NP/F	NP	Bartholinitis	Gland exudate	Culture	Cefteram pivoxil
Tanaka K (2005)[67]	8	*H. influenzae*	NP/F	NP	Bartholin's gland abscess	Gland exudate	Culture and PCR	NP
Iser P (2005)[68]	2	*H. influenzae*	NP/M	Heterosexual	Nongonococcal urethritis	Urethral exudate	Culture	NP

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Tsai HY (2006)[69]	1	*H. influenzae*	NP/F	Prepubescent girl. No sexual relations, no abuse.	Vulvovaginitis, profuse vaginal discharge	Vaginal exudate	NP	NP
Varela JA (2006)[70]	12	*Haemophilus* spp.	NP/M	Heterosexual Couple with cervical intraepithelial neoplasia (CIN)	Asymptomatic	Urethral exudate	Culture	NP
Kohlberger P (2007)[71]	11	*H. influenzae*	NP/F	Girls with a history of sexual abuse	NP	Vaginal exudate	NP	NP
Santiago JL (2008)[72]	1	*H. parainfluenzae*	41/M	Heterosexual Unprotected oral sex with a sex worker	Dysuria, urethral discharge and inguinal adenopathy. Conjunctival hyperemia with purulent exudate, tarsal follicular reaction, blepharitis and palpebral oedema	Urethral and conjunctival exudate	Culture and biochemical tests	Ceftriaxone + doxycycline
Orellana MA (2009)[73]	36	22 *H. parainfluenzae* 14 *H. influenzae*	NP/M	NP	NP	Urethral exudate	API NH® test	NP
Sikanić-Dugić N (2009)[74]	5	*H. influenzae*	2–8/ F	NP	Vulvovaginitis	Vaginal exudate	Culture	NP
Kakisi (2010)[75]	1	*H. influenzae*	42F	NP	Tubo-ovarian abscess	Abscess exudate	Culture	Surgery and cefoxitin/metronidazole
Glover WA (2011)[8]	1	*H. quentini*	28/M	Previous episodes of urethritis and prostatitis. Unprotected sex	Scarce urethral discharge, painful ejaculation	Urethral exudate	16S rRNA sequencing	Ceftriaxone + azithromycin
	1	*H. quentini*	30/M	NP	NP			NP
	1	*H. quentini* + *N. gonorrhoeae*	32/M	NP	NP			NP
Mc Kechnie ML (2011)[76]	11	*H. influenzae*	2 < 25, 5 25–29, 4 > 35/ F	NP	7 symptomatic 4 asymptomatic	Vaginal exudate Endocervical exudate Urine	PCR	NP
Orellana MA (2011)[77]	77	45 *H. parainfluenzae* 32 *H. influenzae* 4 + *C. trachomatis* 2 + *U. urealyticum*	>15/M	NP	Urethritis	Urethral exudate	API NH® test	NP
Calner PA (2012)[78]	1	*H. influenzae*	36/F	16 weeks pregnant	Septic abortion	Blood cultures	Culture	Curettage, ampicillin, gentamicin, clindamycin
Ranđelović G (2012)[79]	2	*H. influenzae*	2–12/ F	NP	Vulvovaginitis	Vaginal exudate	NP	NP
Martin D (2013)[80]	1	*H. influenzae*	48/ F	Uterine leiomyoma. No IUD	Acute endometritis Lower abdominal pain and fever	Endometrial biopsy	PCR	NP
Tinguely R (2013)[81]	1	*H. parainfluenzae* + *N. gonorrhoeae*	NP/M	Homosexual. Recently treated syphilis	Urethritis	Urethral exudate	16S rRNA sequencing	Ciprofloxacin

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
	1			Homosexual			PCR	Ciprofloxacin + doxycycline (NR) Ceftriaxone + azithromycin
Mendz GL (2014)[82]	1	*H. parainfluenzae* + *C. curvus*	29/ F	Pregnant (25 weeks)	Chorioamnionitis, premature rupture of membranes, neonatal sepsis	Vaginal exudate	16S rRNA sequencing	Penicillin + gentamicin + metronidazole
Cardines R (2015)[83]	46	37 *H. parainfluenzae* 7 *H. pittmaniae* 2 *H. para-haemolyticus*	32.5/ F	Pregnant (25–38 weeks)	Asymptomatic	Vaginal exudate	16S rRNA sequencing	NP
Hsu MS (2015)[84]	1	*H. parainfluenzae* + *Enterococcus* spp.	29/M	Homosexual, unprotected sex	Dysuria, purulent urethral discharge	Urethral exudate	16S rRNA sequencing	Ceftriaxone + doxycycline
	1	*H. parainfluenzae* + *N. gonorrhoeae* + *M. morganii*	32/M		Dysuria, frequency, purulent urethral discharge			Ceftriaxone + doxycycline
	1	*H. parainfluenzae* + *Enterococcus* spp.	27/M		Dysuria, purulent urethral discharge, inguinal adenopathy			Clarithromycin
Deza G (2016)[85]	52	45 *H. parainfluenzae* 7 *H. influenzae* 24 + other microbes 10 + *N. gonorrhoeae* 8 + *C. trachomatis* 3 + *C. albicans* 2 + *G. vaginalis* 1 + *U. urealyticum*	31.8/M	31 (60%) homosexual and 21 (40%) heterosexual 4 (8%) HIV 9 (17%) previous STI 52 (100%) unprotected oral sex 29 (55%) anal sex, 44% unprotected 19 (36%) vaginal sex, 31% unprotected	37 (71%) purulent urethral discharge 13 (25%) non-purulent urethral discharge 2 (4%) dysuria without urethral discharge	Urethral exudate	API20E	48 (92%) ceftriaxone + azithromycin/ doxycycline 2 (4%) doxycycline 1 (2%) azithromycin 1 (2%) ciprofloxacin
	28 solitarily	23 *H. parainfluenzae* 5 *H. influenzae*	33.7/M	15 (54%) homosexual and 13 (46%) heterosexual. 3 (11%) HIV 5 (18%) previous STI 28 (100%) unprotected oral sex (5 (18%) only sexual practice) 13 (46%) anal sex, 39% unprotected 11 (39%) vaginal sex, 32% unprotected	18 (64%) purulent urethral discharge 9 (32%) non-purulent urethral discharge 1 (4%) dysuria without urethral discharge			28 (100%) ceftriaxone + azithromycin/ doxycycline

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Frølund M (2016)[86]	9	6 *H. influenzae* solitarily 2 + adenovirus 1 + *M. genitalium*	NP/M	NP	Acute urethritis Dysuria and urethral discharge	First morning urine	PCR	NP
Ito S (2016)[87]	22	21 *H. influenzae* solitarily 1 + *U. urealyticum*	7 < 31 and 14 > 31/M	11 married and 10 single. 12 prior urethritis. 21 unprotected oral sex (12 exclusively). 9 unprotected oral and vaginal sex. 13 sex worker partner	21 urethral discharge (13 moderate and 8 scant) in 10 serous, 6 mucoid and 5 mucopurulent 15 urethral irritation 12 moderate dysuria 3 meatitis and/or balanitis 3 pharyngeal discomfort Incubation < 7 days	Urethral exudate	NP	NP
Kim H (2016)[88]	1	*H. influenzae*	0–9/ F	Prepubescent girl	Vulvovaginitis	Vaginal or vulvar exudate	Culture	NP
You C (2016)[89]	8	*H. influenzae*	NP/M	NP	Urethritis	First morning urine	16S RNA sequencing	NP
Porter M (2016)[90]	31	*H. influenzae*	21–29/F	31 pregnancies	31 Chorioamnionitis	Placenta	Culture	NP
Baba H (2017)[91]	1	*H. influenzae*	31/ F	17 weeks pregnant. History of upper respiratory infection with cough.	Septic abortion. High fever, vaginal bleeding, and abdominal pain	Vaginal exudate Blood culture	Culture, MALDI-TOF, PCR.	Piperacillin/ tazobactam Cefotaxime + metronidazole
Chen X (2017)[92]	1	*H. influenzae*	6/ F	History of a foreign body in the vagina. Recurrent and chronic rhinitis. In nasal exudate, *H. influenzae* is isolated, derived from the same clone as the one detected in the vagina	Vulvovaginitis associated with rhinitis	Vaginal exudate	NP	NP
Deguchi T (2017)[93]	73	*H. influenzae*	NP/M	NP	67 acute urethritis 4 acute epididymitis 2 urethritis and epididymitis	Urethral exudate	NP	NP
Ito S (2017)[1]	68	54 *H. influenzae* solitarily 5 + *U. urealyticum* 4 + *U. urealyticum* + *M. hominis* 2 + *U. parvum* 1 + *C. trachomatis* 1 + *N. gonorrhoeae*	35/M		Urethritis	Urethral exudate	HN-20 Rapid system identification test	43 azithromycin (5 NR) 20 sitafloxacin 3 levofloxacin 2 ceftriaxone
	6	*H. influenzae*	NP/M	NP	Epididymitis			NP

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
	1				Acute prostatitis			
Li JP (2017)[94]	110	*H. influenzae*	NP/F	Prepubescent girls	Vulvovaginitis	Vaginal exudate	Culture	55 ofloxacin 49 β-lactams 6 NP
Caballero Mateos AM (2018)[95]	1	*H. parainfluenzae* + *C. trachomatis* L2 (lymphogranuloma venereum)	34/M	Homosexual, unprotected sex Hepatitis B previously treated. Secondary syphilis. Drug addict.	Proctalgia, constipation, rectal bleeding, fever. Rectal ulcer	Rectal biopsy	NP	Doxycycline
Horie K (2018)[96]	1	*H. quentini* + *Streptococcus* spp. + *M. hominis* + *U. urealyticum*	34/M	Heterosexual. Single Previous urethritis (no other previous STIs) Casual partners	Moderate mucoid urethral discharge Incubation 12 days	Urethral exudate	16S rRNA sequencing	Azithromycin
	1	*H. quentini*	24/M	Heterosexual Single No previous STIs HIV negative Unprotected oral sex with a sex worker	Scant mucoid urethral discharge, dysuria Incubation 4 days			Sitafloxacin
	1	*H. quentini* + *Streptococcus* spp. +	30/M	Heterosexual Single No previous STIs HIV negative Unprotected oral and vaginal sex with a stable partner and other partners	Condyloma acuminatum on the glans Scant serous urethral discharge, urethral irritation, dysuria			Levofloxacin
Kondo H (2018)[97]	1	*H. influenzae* + *Streptococcus* spp. + *U. urealyticum*	32/M	Heterosexual Married 4 previous episodes of urethritis (no other STIs) Multiple sexual partners	Urethral irritation, mucopurulent urethral discharge	Urethral exudate		Azithromycin ND
	1	*H. influenzae*	27/M	Heterosexual Married No previous STIs Stable sexual partner	Urethral irritation, scant mucoid urethral discharge Incubation 16 days			
	1	*H. influenzae* + *S. agalactiae*	30/M	Heterosexual Single No previous STIs Unprotected oral sex with a sex worker	Urethral irritation, scant mucoid urethral discharge Incubation 5 days			
	1	*H. influenzae*	29/M	Heterosexual Married 1 previous episode of urethritis (no other STIs) Unprotected oral sex with a sex worker	Dysuria, scanty mucoid urethral discharge Incubation 12 days			
	1	*H. influenzae*	21/M	Heterosexual Married 1 previous episode of urethritis (no other STIs) Unprotected oral and vaginal sex with a sex worker	Urethral irritation, mucopurulent urethral discharge Incubation 5 days			
	1	*H. influenzae*	25/M	Heterosexual Married No previous STIs Unprotected oral sex with a sex worker	Dysuria, urethral irritation, mucopurulent urethral discharge Incubation 9 days			

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Saxena A (2018)[98]	1	*H. parainfluenzae*	33/M	No previous STIs HIV negative Unprotected oral sex with a sex worker	Urethral pruritus, urethral discharge	Urethral exudate	MALDI-TOF	Norfloxacin + amoxic-clav + fluconazole (NR) Azithromycin + ciprofloxacin
Cevik M (2019)[99]	1	*H. influenzae*	35/ F	14 weeks pregnant	Septic abortion. Acute chorioamnionitis Abdominal pain, vaginal discharge/bleeding, fever.	Placental biopsy Blood culture Cervical exudate	NP	β-lactams
	1		22/ F	14 weeks pregnant				
	1		33/ F	20 weeks pregnant. Premature rupture of membranes Previous abortion. History of chorioamnionitis				
Magdaleno Tapial J (2019)[100]	38	32 *H. parainfluenzae* 5 *H. influenzae* 1 *H. haemolyticus* 15 *Haemophilus* spp. solitarily 9 + *M. hominis*/ *Ureaplasma* spp 7 + *Chlamydia* 6 + *Neisseria* 2 + *M. genitalium*	30.5/ 35 (92%) M 3 (8%) F	21 (55%) M homosexual 13 (34%) M heterosexual 3 (8%) F heterosexual 1 (3%) NP 5 (13%) HIV 20 (57%) previous STI 38 (100%) unprotected oral sex	22 (58%) purulent urethral discharge 6 (16%) dysuria 10 (26%) asymptomatic, risky sexual contact	Urethral exudate	NP	17 (45%) ceftriax-one + azithromycin 12 (31%) ceftriax-one + doxycycline 5 azithromycin 4 doxycycline 6NR
Wang HJ (2019)[101]	230	*H. influenzae*	NP/F	Prepubescent girls	Vulvovaginitis	Vaginal exudate	Vitek culture system NH	NP
Alsuhaibani MA (2019)[102]	1	*H. parainfluenzae*	26/F	Pregnant	Chorioamnionitis	Placenta and neonatal blood	Culture	Cefotaxime + gentamicin
Ducours M (2020)[103]	1	*H. parainfluenzae* + *S. hominis* + *E. faecalis* + *S. anginosus* + *p. harei*	20/M	Heterosexual Unprotected vaginal sex	Urethral discharge	Urethral exudate	MALDI-TOF	Ceftriaxone + azithromycin
	1	*H. parainfluenzae* + *N. gonorrhoeae* + *S. epidermidis* + *S. anginosus* + *S. mitis*	31/M	Homosexual Unprotected anal sex	Dysuria, urethral discharge			Ceftriaxone + azithromycin

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
	1	*H. parainfluenzae* + *M. genitalium* + *E. faecalis* + *S. mitis*	37/M	Heterosexual	Dysuria, urethral discharge			Minocycline + pristinamycin
	1	*H. parainfluenzae* + *N. gonorrhoeae* + *S. haemolyticus* + *Corynebacterium* sp.	43/M	Homosexual HIV Unprotected oral and anal sex	Dysuria, urethral discharge			Ceftriaxone + doxycycline
	1	*H. parainfluenzae* + *S. haemolyticus* + *E. faecalis*	30/M	Homosexual. PrEP Unprotected oral and anal sex	Dysuria, urethral discharge			Cotrimoxazole (NR) Gentamicin + ciprofloxacin
	1	*H. parainfluenzae* + *S. haemolyticus* + *S. mitis*	28/M	Homosexual Unprotected anal sex	Dysuria, urethral discharge			Ceftriaxone + doxycycline
	1	*H. parainfluenzae* + *S. haemolyticus*	27/M	NP	NP			NP
	1	*H. influenzae*	55/M	Homosexual. PrEP Unprotected oral and anal sex	Urethral discharge			Ceftriaxone + azithromycin
	1	*H. parainfluenzae* + *N. gonorrhoeae* + *E. coli*	33/M	Homosexual. PrEP Unprotected oral and anal sex	Dysuria, urethral discharge			Ceftriaxone
Nishimura Y (2020)[104]	1	*H. influenzae*	51/ F	Polypoid adenomyoma Early stage endometrioid adenocarcinoma	Microabscesses in adenomyoma.	Vaginal exudate Blood culture	MALDI-TOF	Ceftriaxone + hysterectomy

Table 1 (*Continued*)

Author (year of publication)	No. of episodes	Microorganisms	Age/sex	Possible predisposing factors	Clinical manifestations	Clinical sample	Microbiological diagnosis reflected	Treatment
Sierra Y (2020)[105]	175	*H. parainfluenzae* ± NP 125 NOT multiresistant 50 multiresistant 30 H. parainfluenzae + *C. trachomatis*/ *N. gonorrhoeae*/ *T. pallidum* 10 NP 10 *H. parainfluenzae* solitarily	37.8/ 97 (55%) M 78 (45%) F NP NP NP NP 42/M	NP NP NP NP NP 4 homosexuals, 4 heterosexuals and 2 NP. 4 HIV 6 previous STI 8 unprotected sex with a stranger, 1 unprotected sex with a stable partner and 1 NP	NP NP 26 urethritis and 24 NP 16 urethritis and 14 NP 5 asymptomatic and 5 NP 10 (100%) urethritis	79 (45%) urethral exudate 62 (35%) vaginal 13 (7%) preputial 9 (5%) cervical 6 (3%) rectal 3 (2%) genital ulcer 1 (1%) pharyngeal 1(1%) semen 1 (1%) urine NP NP NP NP 10 urethral exudate	MALDI-TOF	NP NP NP NP NP 5 ceftriaxone + azithromycin 2 ceftriaxone + doxycycline 1 ceftriaxone + azithromycin + doxycycline 1 amox-clav
Snirivasan S (2020)[3]	40	*H. influenzae*	NP/M	23 heterosexual 17 homosexual	16 urethritis and 7 asymptomatic 16 urethritis and 1 asymptomatic	First morning urine	16S rRNA sequencing	NP
Vives A (2020)[106]	30	19 *H. parainfluenzae* 10 *H. influenzae* 1 *Haemophilus* sp. 25 solitarily 5 + other microbes 4 + *C. trachomatis* 1 + *N. gonorrhoeae*	36.6/M	17 (57%) heterosexual, 8 (27%) homosexual, 2 (7%) bisexual and 3 (10%) NP 3 (10%) HIV with no detectable viral load 13 (43%) previous STI 21 (75%) oral sex, 15 (54%) vaginal sex, and 10 (36%) anal sex. N.o sexual partners 3.5 [1–20]	13 (43%) urethral discharge 7 (23%) dysuria 5 (17%) testicular pain 2 (7%) genital ulcer 1 (4%) hematospermia 1 (4%) painful ejaculation 1 (4%) lower abdominal pain	Urethral exudate	API NH® test	Ceftriaxone + azithromycin/ doxycycline Azithromycin ± ciprofloxacin Ciprofloxacin Doxycycline 8 NR
Hu BF (2021)[107]	140	*H. influenzae*	5.8/F	NP	Symptomatic vulvovaginitis	Vaginal exudate	Vitek	Ampicillin
Bruins MJ (2021)[108]	127	*H. influenzae*	37 (<12 y)/F 2(12–17 y)/F 45(18–51 y)/F 43(>51)/F	NP	Symptomatic vulvovaginitis	Vaginal exudate	Culture	NP

F: woman; M: male; NP: not provided; NR: no response to treatment.

[*] + others: these studies do not describe which other microorganisms are isolated concomitantly.

divided into two groups, one of children under 14 years of age (53.9%; 624/1158) and another of adults (14 years of age or older, 28.4%; 329/1158). The age was not recorded in 17.7% of women (205/1158).

In the group of men, *H. parainfluenzae* (44.1%; 367/835) and *H. influenzae* (42.6%; 356/835) were detected with almost equal frequency. The vast majority were diagnosed with urethritis. The most frequent clinical manifestations were urethral discharge, purulent or not, dysuria and urethral pruritus or irritation. Regarding sample type, in the vast majority of cases it was urethral exudates. The most frequently administered treatment was ceftriaxone with azithromycin and/or doxycycline, although the treatment was only specified in 40% (15/37) of the publications referring to men.

We subdivided the group of adult women according to whether the infection occurred during pregnancy (52.9%; 174/329) or not (47.1%; 155/329). In the latter, there were episodes of vaginitis, bartholinitis, salpingitis, endometritis or tubal abscesses. The absence of a significant portion of data prevents us from drawing conclusions about the prevalence of a specific species of *Haemophilus*. In pregnant women, almost all the studies refer to septic abortion, acute chorioamnionitis, premature rupture of membranes and neonatal sepsis. *H. influenzae* was detected more frequently (64.9%; 113/174) than *H. parainfluenzae* (30.5%; 53/174). *H. influenzae* was isolated in all the samples from girls (vaginal or vulvar exudates). Most of them presented vaginal discharge, vulvar irritation or pruritus and did not have predisposing factors. Antibiotic treatment included β-lactams or quinolones.

Samples of rectal origin only represented 2.3% (55/2397). The clinical and epidemiological information available on these patients was very scant, with the exception of one reported case[7].

Table 2 summarises the information on the susceptibility of*Haemophilus* to different groups of antibiotics (penicillin, carbapenems, tetracycline, quinolones, first-, second- and third-generation cephalosporins) contributed by 21 of the 67 studies. Four of these were excluded because they did not disaggregate the results by sample origin, as were those with fewer than five reported cases to avoid bias. Overall susceptibility of *Haemophilus* spp. to penicillins was 78.9%, and the overall rate of β-lactamase production was 26.4%. It should be remembered that although the production of β-lactamases is the main mechanism of resistance in this genus, there are also strains that do not produce β-lactamases but have alterations in the penicillin-binding proteins with a low affinity for β-lactams and even a combination of both mechanisms[109].

In addition, susceptibility to these antibiotics was determined separately for each species. These data are shown in Table 3.

Discussion

It is difficult to demonstrate the pathogenic role of microorganisms that can be colonisers and present together with other species, as in the case of HSNOTD and in particular *Haemophilus influenzae*. There are few studies with a control group on the prevalence of the latter in men with urethritis, although in one of them[3], an association is demonstrated with non-gonococcal urethritis in both MSM and heterosexuals, which would support its aetiological and pathogenic role in urethritis. Doubts remain as to the pathogenic role of the rest of the HSNOTD species since there are no rigorous studies with valid methodology, and most of them are case series.

The acquisition mechanism varies depending on the characteristics of the patient. For example, in girls with no history of sexual intercourse or abuse, there could be an auto-inoculation mechanism from the nasal location to the vaginal area. In contrast, in adults, the transmission route is predominantly sexual. One of the most relevant data items we can extract from this bibliographical review is the high frequency with which urethritis caused by HSNOTD is associated with the practice of unprotected oral sex, which in many cases is the only form of exposure reported. Genital infection by HSNOTD seems to be associated with sexual contact with multiple sexual partners and with the domain of prostitution. However, it is important to be cautious when drawing conclusions about possible predisposing factors to genital infection by HSNOTD, since the information provided by the different publications is scant. Regarding the sexual orientation of male patients, 53.3% were heterosexual and 46.7% homosexual, but the information available is very limited and does not allow us to conclude that the risk of infection is related to sexual orientation. The same occurs with previous having had sexually transmitted infections (urethritis, HIV, syphilis, etc.) as a risk factor. We found the same number of patients with a history of STIs as without them, although once again we cannot draw definitive conclusions due to the general lack of information. The low number of publications in which HSNOTD is considered a pathogenic agent causing proctitis is striking.

The susceptibility rates of *Haemophilus* against cephalosporins, especially third-generation, are very high, which together with amoxicillin/clavulanic acid are the treatments of choice. Taking into account the antibiotic susceptibility profile of all the species described above, we can deduce that the empiric treatment administered for STIs could be more effective against *H. influenzae* than against *H. parainfluenzae*, since the latter presents lower rates of susceptibility to macrolides, tetracyclines and quinolones.

Traditionally, vulvovaginitis in girls has been treated with penicillins, and a great tendency to a recurrence of these episodes has been described[3], which could be due to the ineffectiveness of empiric treatment, since the susceptibility rate *of H. influenzae* to these antibiotics is only 72.3%. This hypothesis is reinforced by the fact that the recurrence rate is higher in girls who had received penicillins in the preceding months to treat infections in other locations. One alternative to penicillins are cephalosporins, which show good susceptibility rates and do not have the possible side effects of other antibiotics, such as quinolones, in children. Finally, one of the works reviewed[46] demonstrates the frequency with which *Haemophilus* spp. is detected in the vaginal exudate of asymptomatic pregnant women, with percentages close to 10%. This could entail a greater risk of vertical transmission and infectious complications both at maternal level and regarding neonatal sepsis, and prophylactic eradication may be considered as a strategy. However, a deeper analysis of the risk-benefit ratio of this intervention, which could increase antibiotic pressure, is necessary.

This review has several limitations. An extensive search was carried out. However, articles in Spanish and English were included and we did not have access to a series of published studies, listed at the beginning of the article, meaning that not all published studies may not have been included. In addition, the wide variability of data published between articles regarding epidemiological, microbiological and antibiotic susceptibility data makes it difficult to analyse the data homogeneously and therefore draw conclusions. Furthermore, the methodology of most of the included studies is outmoded and the aetiological role of these microorganisms cannot therefore be firmly established.

Following the review, we can highlight, in HSNOTD, the role of*Haemophilus influenzae* as an aetiological agent in cases of non-gonococcal urethritis in men, both MSM and heterosexuals, and therefore the usefulness of systematically searching for this microorganism in this entity, as it can explain a significant percentage of urethritis without microbiological isolation. It proved impossible to find consistently described epidemiological risk factors and/or an acquisition mechanism, hence more studies are needed. On the other hand, taking the antibiotic resistance profile into account, third-generation cephalosporins, amoxicillin-clavulanic acid and quinolones are postulated as the most successful eradication options. With regard to azithromycin

Table 2
Antibiotic susceptibility (%) of *Haemophilus* spp. isolates.

Author (year of publication)	Species	No. cases	Prod. βL	Pen	CFZ	Ceph 2nd	Ceph 3rd	Ceph 4th	Carba	Macr	Quin	TC	RIF	FOS
Campognone P (1986)[30]	Hi	17	–	100	100					100		100		
Casin I (1988)[34]	Hi	60	16.7	83.3	–	–	–	–	–	100	100	85.8	–	–
Houang E (1989)[37] *	Hp + Hi	73												
Bosch J (1991)	Hi	9		100										
Vázquez F (1996)[57]	Hp	100	29	71	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –
	Hi	45	26.7	73.3										
	H	10	–	–										
Kragsberg P (1993)[51]	Hi	6	0	100	100							100		
Cox RA (1997)[4]	Hi	11	–	100	–	–	–	–	–	–	–	–	–	–
García E (1997)[59]	Hi	18	27	–	–	–	–	–	–	–	–	–	–	–
Cox RA (2002)[63]	Hi + Hp	39	10	95	–	100	–	–	–	95	–	–	–	–
Tanaka K (2005)[67]	Hi	8	37.5	37.5										
Orellana MA (2009)[73]	Hp + Hi	36	–	76.5	–	94.1	100	–	–	64.7	91.1	–	–	–
Orellana MA (2011)[77]	Hp + Hi	77	34.2	75.9	–	92.4	100	–	–	73	87.8	76.8	–	–
Cardines R (2015)[83]	Hp	37	13.5	85.1	– – –	– – –	97.3100100	– – –	100100100	– – –	91.9100100	– – –	– – –	– – –
	H. pittmaniae	7	–	100										
	H. haemolyticus	2	–	100										
Deguchi T (2017)[93]	Hi	73	27.4	67.1	–	58.9	82.6	–	99.5	95.2	100	98.6	–	–
Li JP (2017)[94] *	Hi	110												
Kondo H (2018)[97]	Hi	6	16.7	16.7	–	–	–	–	–	–	33.3	–	–	–
Magdaleno Tapial J (2019)[100]	Hp + Hi + *H. haemolyticus*	38	–	79	–	92.1	94.8	–	–	65.8	90.8	73.7	–	–
Wang HJ (2019)[101] *	Hi	230												
Ducours M (2020)[103]	Hp + Hi	5	–	10	–	–	25	–	100	–	22.2	0	–	–
Sierra Y (2020)[105]	Hp	175	–	87.1	–	92.3	99.4	–	–	88.2	78.6	53.7	–	–
Hu BF (2021)[107]	Hi	136	35	–	–	81.6	98.5	–	100	91.9	100			

Amin: aminoglycosides; ATM: aztreonam (monobactam); Carba: carbapenems; Ceph 2nd: 2nd-generation cephalosporins; Ceph 3rd: 3rd-generation cephalosporins; Ceph 4th: 4th-generation cephalosporins; CFZ: cefazolin (1st-generation cefalosporin); CHL: chloramphenicol; FOS: fosfomycin; Hi: *Haemophilus influenzae*; Hp: *Haemophilus parainfluenzae*; Macr: macrolides; Pen: penicillins; Prod. βL: β-lactamase production; Quin: quinolones; RIF: rifampicin; SXT: trimethoprim-sulfamethoxazole; TC: tetracyclines.

* The data provided by these studies are not included because they include samples of a different origin to the genital apparatus.

Table 3
Rates of antibiotic susceptibility and presence of β-lactamases separated by species (%).

Species	Prod. βL	Pen	CFZ	Ceph 2nd	Ceph 3rd	Carba	Macr	Quin	TC
H. influenzae	27.97	76.14	100	73.7	92.9	99.7	94.9	98.5	93.9
H. parainfluenzae	24.81	81.66		92.3	99	100	88.2	80.9	53.7

Carba: carbapenems; Ceph 2nd: 2nd-generation cephalosporins; Ceph 3rd: 3rd-generation cephalosporins; CFZ: cefazolin (1st-generation cephalosporin); Macr: macrolides; Pen: penicillins; Prod. βL: β-lactamase production; Quin: quinolones; TC: tetracyclines.

and doxycycline, which are widely used in the empiric treatment of STIs, we did not find significant resistance rates in the review, although we are seeing a growing trend of strains with a higher resistance profile and higher minimum inhibitory concentrations for doxycycline[110].

Conflicts of interest

The authors declare that they have no conflicts of interest.

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