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MINIREVIEW

Meningococcal Urethritis: Old and New

Bethany L. Burns,[a] Daniel D. Rhoads[a,b,c]

[a]Department of Laboratory Medicine, Cleveland Clinic, Cleveland, Ohio, USA
[b]Department of Pathology, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio, USA
[c]Infection Biology Program, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

ABSTRACT *Neisseria meningitidis* is a common commensal bacterium found in the respiratory tract, but it can also cause severe, invasive disease. Vaccines have been employed which have been successful in helping to prevent invasive disease caused by encapsulated *N. meningitidis* from the A, C, W, Y, and B serogroups. Currently, nonencapsulated *N. meningitidis* groups are more common commensals in the population than in the prevaccine era. One emerging nonencapsulated group of bacteria is the U.S. *N. meningitidis* urethritis clade (US_NmUC), which can cause meningococcal urethritis in men. US_NmUC has unique genotypic and phenotypic features that may increase its fitness in the male urethra. It is diagnostically challenging to identify and distinguish meningococcal urethritis from *Neisseria gonorrhoeae*, as the clinical presentation and microbiological findings are overlapping. In this review, the history of meningococcal urethritis, emergence of US_NmUC, laboratory diagnosis, and clinical treatment are all explored.

KEYWORDS meningococcal urethritis, *Neisseria meningitidis*, US_NmUC, urethritis

The majority of *Neisseria* species are considered commensal organisms found in the upper respiratory tract (1, 2). Although *Neisseria meningitidis* is typically found as a commensal, it is unique among *Neisseria* in that it can cause outbreaks of community-onset meningitis, which can be fatal (3–6). In contrast to other *Neisseria*, *Neisseria gonorrhoeae* is an obligate pathogen and is never considered part of the healthy microbiome, regardless of symptomatology (7, 8). *N. gonorrhoeae* is a sexually transmitted infection (STI) agent that is capable of infecting the urethra, cervix, rectum, and oropharynx. The majority of *N. gonorrhoeae* infections present clinically as urethritis in men or cervicitis in women (9).

Meningococcus and gonococcus are considered distinct taxa causing distinct diseases, but recent discoveries have revealed that there may be more overlap between the species than was previously recognized. For example, meningococcus is now recognized as a cause of urethritis which is clinically indistinguishable from gonococcal urethritis (10). In one study, 20% of urethritis caused by *Neisseria* spp. was attributable to meningococcus (11). Genetic analyses of these *N. meningitidis* strains have revealed genomic features of *N. gonorrhoeae* (12). These findings challenge our traditional understanding of the role of *N. meningitidis* in causing disease. Dissimilar to other STIs, meningococcal urethritis has been documented in long-term monogamous relationships in which the partner has no disease. *N. meningitidis* is increasingly recognized as a cause of urethritis, and in this review, we will explore this emerging disease.

MENINGOCOCCAL URETHRITIS, PRE-2010: THE EARLY DAYS

Small case series of meningococcal urethritis have been documented in the literature intermittently since the mid-1900s (13). Beginning in the 1970s and continuing into the 1980s, interest in meningococcal urethritis rose in parallel to the HIV/AIDS pandemic (14–17). The majority of meningococcal urethritis research during this time

Editor Romney M. Humphries, Vanderbilt University Medical Center

Address correspondence to Bethany L. Burns, pathologyburns@gmail.com.

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TABLE 1 Diagnostic challenges in distinguishing *N. gonorrhoeae* and *N. meningitidis* as causes of urethritis

Diagnostic approach	Testing option	Challenges in distinguishing *N. gonorrhoeae* from *N. meningitidis*	Practical challenge(s)
Direct exam	Clinical presentation	Cannot distinguish. Both have similar clinical presentations.	Testing is required for definitive diagnosis.
	Gram stain	Cannot distinguish. Both are Gram-negative diplococci.	*N. meningitidis* could be misinterpreted as *N. gonorrhoeae*.
Culture	Selective medium	Cannot distinguish. Both grow on agar media selective for gonococcus.	Multiple specimens would need to be collected to be able to culture for *Neisseria* spp. and also investigate the presence of other potential causes of urethritis (e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Mycoplasma genitalium*).
	Oxidase reaction	Cannot distinguish. Both are oxidase positive.	
	Carbohydrate fermentation	Cannot reliably distinguish. Overlapping carbohydrate fermentation profiles have been described (28).	
	MALDI-TOF MS	Able to distinguish. *N. meningitidis* and *N. gonorrhoeae* can be distinguished, but misidentifications within the genus have been reported.	
Molecular characterization	NAAT	Cannot reliably distinguish or detect. *N. meningitidis* cross-reactivity with *N. gonorrhoeae* NAAT has been described (65).	*N. meningitidis* testing of urethral specimens is not commercially available.
	WGS	Able to distinguish. *N. meningitidis* and *N. gonorrhoeae* can be distinguished using WGS.	Not routinely performed in contemporary clinical practice.

focused on men who have sex with men (MSM). A large population study of MSM (n = 815) who presented to a community clinic had infrequent carriage of *N. meningitidis* in the urethra (0.7%, 6/815) (14). In the study, participants agreed to cultures of the urethra, oropharynx, and rectal canal, and subjects were included in the study whether or not symptoms of urethritis were reported. Of the men from which *N. meningitidis* was recovered from urethral cultures (n = 6), most (83%, 5/6) had symptomatic meningococcal urethritis (14). In total, 2.2% (5/227) of those with urethral discharge had meningococcal urethritis (14). Those with positive rectal cultures (2.0%, 16/815) less frequently reported symptoms (25%, 4/16), suggesting *N. meningitidis* could potentially be a commensal organism or an asymptomatic infection in the rectum (14). Although rates of *N. meningitidis* recovery from the urogenital tract were low, the rate of *N. meningitidis* carriage in the oropharynx of this MSM cohort was much higher (42.5%, 347/815) (14, 16).

A study published in 1980 described men with presumed gonococcal urethritis (n = 482). This study concluded that *N. meningitidis* was more likely to cause urethritis in homosexual men (13%, 15/114) than heterosexual men (1%, 4/368) (15). Using these findings, the authors argued against the standard laboratory practice of presumptive identification of *N. gonorrhoeae* when oxidase-positive, Gram-negative diplococci were recovered by culture using Thayer-Martin medium. This study highlighted that although *N. meningitidis* is an uncommon cause of urethritis in the general population, it could be underrecognized and misdiagnosed as an *N. gonorrhoeae* infection due to the laboratory practices of the time (Table 1).

Studies performed through the 1990s reached similar conclusions; meningococcal urethritis was an uncommon entity. One retrospective study from London, England, by Maini et al. identified low incidence of genital *N. meningitidis* carriage when using urethral and cervical cultures among patients being screened for STIs. Meningococcal urethritis was identified rarely in the MSM cohort (0.2%, 11/5571) (18), and meningococcus was not isolated from a man identifying as heterosexual (0%, 0/8,992) (18). *N. meningitidis* was not isolated in a cervical culture (0%, 0/15,976) (18), although rare case reports of

encapsulated *N. meningitidis* associated with cervicitis have been published (19). Later, studies identified asymptomatic *N. meningitidis* carriage in the upper respiratory tract of sexual partners of monogamous men who developed meningococcal urethritis, which fostered the hypothesis that oral sexual contact may be the means of transmission for individuals with meningococcal urethritis (20, 21). At the end of the 20th century and beginning of the 21st century, meningococcal urethritis seemed to be a rare STI, nearly exclusively impacting MSM and thought to be transmitted by fellatio (20, 22–25).

EMERGENCE OF A CONTEMPORARY MENINGOCOCCUS CLADE: THE RECENT DECADE

In the 2010s, the U.S. Center for Disease Control and Prevention (CDC)'s Gonococcal Isolates Surveillance Program (GISP) detected several unusual clusters of meningococcal urethritis (26). Novel findings were published detailing the unexpected demographics and microbial genetics associated with the clusters (11, 25, 27). These novel findings have challenged previous conclusions about the pathophysiology of meningococcal urethritis.

Patient demographics. The clusters of meningococcal urethritis predominately affected heterosexual men (92 to 99%) (11, 25, 27). Interestingly, Bazan et al. identified that significantly more men with meningococcal urethritis identified as heterosexual (99%) than men with gonococcal urethritis (78%) (11). Like other STIs, meningococcal urethritis was frequently observed in younger men, often 20 to 30 years old (median, 31 or 32 years of age) but some men as old as 60 years (25, 27). The population of men with *N. meningitidis* had similar age, race, and ethnicity to those with *N. gonorrhoeae* infection (11).

The clusters of cases were mostly identified in STI clinics in the midwestern United States. Specifically, large clusters in cities in Ohio, Indiana, and Michigan have been reported (11, 25, 27). However, reports of similar cases outside the United States are also published (28).

Clinical presentation, sexual history, and coinfections. Men with meningococcal urethritis were symptomatic (97 to 100%) (25, 27). Most had urethral discharge (>90%), and many had dysuria (11, 25, 27). These findings align with historic studies that identified *N. meningitidis* from male genital specimens where most men were symptomatic at presentation (14). Men reported symptoms ranging from 2 to 7 days with a median of 4 days duration.

The number of days since last sexual encounter ranged from 3 to 10 days with a median of 7 days (11). Days of symptoms and number of days since last sexual encounter were similar to that of patients with gonococcal urethritis (25). Data collected from both self-reporting forms and physician interviews established that almost all men with meningococcal urethritis reported oral sex encounters (93 to 100%) (25). In one cohort, all men reported receiving fellatio (100%) (25). Men with meningococcal urethritis reported a similar number of partners over 90 days (median, 2) and 12 months (median, 3) as men with gonococcal urethritis (median, 2 per month, 3 per year) (11).

It is imperative to consider coinfections when an STI is identified in order to adequately manage all infections that may be present. The urethral specimens collected from the Midwest clusters were tested for *N. gonorrhoeae* (nucleic acid amplification test [NAAT]), *Chlamydia trachomatis* (NAAT), syphilis (serology), and trichomoniasis (culture) (11). Curiously, coinfections with meningococcus and gonococcus have not been described; however, history of prior gonococcal urethritis was common. In one cohort of men with meningococcal urethritis, over half of the men (52%) reported previous *N. gonorrhoeae* infection, with one-third (33%) reporting infection within the last 12 months (25). Whereas coinfection with *N. gonorrhoeae* was not identified, a marked proportion of men with meningococcal urethritis had a concurrent infection with *C. trachomatis* (15 to 19%), which is similar to coinfection rates of gonococcal urethritis and *C. trachomatis* (24.2%) (11, 25, 27, 29, 30). HIV infection was uncommon in those with meningococcal urethritis (0 to 2%) (11, 25, 27). Interestingly, in an MSM cohort, different types of *N. meningitidis* have been isolated from upper respiratory and urethral cultures from the same person (16).

Genomic and phenotypic features of US_NmUC. The recent meningococcal urethritis clusters have been characterized and determined to be a novel clade. This clade

TABLE 2 Summary of approaches to genetic characterization of *N. meningitidis* strains and genetic characterization of the United States *N. meningitidis* urethritis clade (US_NmUC)[a]

Approaches to genetic characterization	Targets for genetic characterization	US_NmUC genetic characterization
MLST		
ST	Housekeeping genes *abcZ*, *adk*, *aroE*, *FumC*, *gdh*, *pdhc*, and *pgm*	ST-11, cc11, 11.2
cc	Housekeeping genes *abcZ*, *adk*, *aroE*, *FumC*, *gdh*, *pdhc*, and *pgm*	ST-11, cc11, 11.2
Sublineage	Housekeeping genes *abcZ*, *adk*, *aroE*, *FumC*, *gdh*, *pdhc*, and *pgm*	ST-11, cc11, 11.2
Fine typing[b]	Additional genes *PorA*, *PorB*, *FetA*, *fHbp*, *nadA*, and *nhbA*	PorA VR1 5-1, VR2 10-8, VR3 36-2, FETA F3-6, and PorB 2-2
MLEE		
ET	Bacterial enzymes (proteins)	ET-15
WGS		
cgMLST	Loci of the core genome (1,605 genes)	WGS data can be interpreted using MLST and fine-typing criteria

[a]MLST, multilocus sequence typing; ST, sequence type; cc, clonal complex; MLEE, multilocus enzyme electrophoresis; ET, electrophoretic profile; WGS, whole-gene sequencing; cgMLST, core genome MLST.
[b]Used in conjunction with MLST.

is often described in publications as "U.S. *N. meningitidis* urethritis clade" (US_NmUC) or "*N. meningitidis*, nongroupable" (NmNG).

Like many bacteria, the relatedness of *N. meningitidis* isolates is commonly characterized using multilocus sequence typing (MLST) (Table 2). Rather than examining the entire genome, MLST identifies genotypic variation in several specific housekeeping genes, and the isolates are classified based on this sequence type (ST). When multiple STs share a certain amount of similarity, they are grouped into a clonal complex (cc) (31). A cc may further be divided into sublineages based on additional genotypic characterization (32).

The MLST approach for *N. meningitidis* was published in 1998 by Maiden et al., who proposed using seven housekeeping genes (*abcZ*, *adk*, *aroE*, *FumC*, *gdh*, *pdhc*, and *pgm*) (33), and this MLST scheme is still used today. Adjunct classification is achieved by "fine typing" of several supplementary genes and their respective variable regions (*PorA*, *PorB*, *FetA*, *fHbp*, *nadA*, and *nhbA*) (34, 35). Fine typing also provides information on a strain's virulence and can provide vaccine development insights. MLST remains a mainstay of classification, but classification based on whole-genome sequencing may be on the horizon (12, 36). Whole-genome sequencing uses 1,605 loci of the core genome with specific molecular typing loci to characterize *N. meningitidis* strains (34, 37).

US_NmUC is considered a novel clade of the ST-11 within the hyperinvasive lineage of *N. meningitidis* (cc11) (11). Specifically, US_NmUC is an ST-11 cc11 and an ET-15 variant of sublineage 11.2 (fine-type PorA VR1 5-1, VR2 10-8, VR3 36-2, FETA F3-6, and PorB 2-2 [or rarely, PorB 2 to 78 and 2 to 52]) (38, 39). The clade was first described in by Bazan and colleagues from isolates cultured in Columbus, Ohio. It has subsequently been identified in Oakland County, Michigan, and in other U.S. cities (11, 12, 25, 27). As its name suggests, the clade has novel phenotypic characteristics that may enable it to cause urethritis more effectively than previously characterized lineage 11 isolates of *N. meningitidis* (Table 3) (32, 37, 39).

TABLE 3 Summary of genetic alterations identified in United States *N. meningitidis* urethritis clade (US_NmUC) with resulting phenotypic effects and presumed mechanisms for increased urethrotropic fitness

Genetic alteration	Phenotype	Result	Presumed mechanism of increased fitness
Insertion (IS1301) in *cps* locus	Prevents functional production of serogroup C capsule polymerase	US_NmUC is unencapsulated	Facilitates mucosal adherence
fHbp	Elevated protein expression of factor H binding protein	US_NmUC can hinder segments of complement activation	Evasion of host immune response
Acquired *norB-aniA* cassette	Enables denitrification	US_NmUC can thrive in anaerobic conditions	Enhanced ability to grow in the urethra

The US_NmUC clade is nongroupable, which means it lacks a polysaccharide capsule; it is unencapsulated (39). This is one distinguishing feature of US_NmUC, which is in contrast to *N. meningitidis*, which has caused meningitis outbreaks in MSM and has been linked to serotype C (32). US_NmUC capsular biosynthesis gene cluster is disrupted by an insertion sequence (IS1301) that replaces *ccsA*, *cssB*, *cssC*, and part of *csc*. This disruption of the capsular polysaccharide (*cps*) locus prevents production of functional capsule polymerase, so the bacteria are unencapsulated (12, 39). This genetic mutation also yields loss of wild-type lipo-oligosaccharide (LOS) sialylation production, and the loss of function may improve mucosal adherence, which has been demonstrated in studies involving Nm ST-11 (39, 40). Improved mucosal adherence could improve the fitness of *N. meningitidis* living in the urethra (39, 41).

US_NmUC has features that may enable it to better evade innate immunity than other meningococcal strains (Table 3). A unique feature of US_NmUC is its hybrid factor H binding protein gene (*fHbp*). The hybrid *fHbp* in US NmUC is thought to result in high protein expression of factor H binding protein (FHbp) on the surface of US_NmUC isolates. FHbp binds to human factor H, which is a complement regulator that interacts with C3b. When FHbp on the surface of US_NmUC binds to circulating human factor H, the alternative pathway of complement activation is hindered because the human factor H is unavailable for binding to C3b. Tzeng et al. hypothesized that high expression of FHbp may be protective in the urogenital tract where levels of human factor H are inherently low (39). FHbp is an important target protein of *N. meningitidis* vaccines, particularly serogroup B vaccines (42). Although it would seem intuitive that serogroup B vaccines targeting FHbp would be protective against US_NmUC, it is unclear if serogroup B vaccines are cross-protective in preventing meningococcal urethritis by this mechanism or others, as demonstrated in gonococcal urethritis (12, 43). Additionally, point mutations associated with the type IV pillin biogenesis apparatus demonstrated high levels of heteroresistance to antimicrobial peptides (AMPS), which are part of the innate immune system (44). Overexpression of FHbp and mutations in type IV pillin may enable US_NmUC to evade segments of the host immune response (39).

US_NmUC isolates were found to have genetic material normally present in *N. gonorrhoeae* (12, 39). US_NmUC isolates contain a complete *norB-aniA* cassette that enables denitrification. Nitrates are commonly found in urine, and interestingly, reduction of nitrogen compounds is a defining feature of *Enterobacterales*, which cause the majority of genitourinary tract infections. When present in *N. gonorrhoeae*, nitrite reducatase (*AniA*) and nitric oxide reductase (*NorB*) allow for denitrification and, ultimately, anaerobic growth (45), and these pathways may also be important in biofilm formation (46). Compared to *N. gonorrhoeae*, US_NmUC grew robustly on gonococcal agar plates supplemented with sodium nitrite (39). US_NmUC's acquisition of the *norB-aniA* cassette from *N. gonorrhoeae* likely enhances its ability to live in the urogenital tract (39). Although US_NmUC' s novel phenotypic characteristics may enable it to cause urethritis more effectively, other strains of *N. meningitidis* are also capable of causing urethritis in men (47).

US_NmUC has been rarely reported to cause invasive disease. Retchless et al. reported five isolates obtained from 2013 to 2016 that were cultured from cerebrospinal fluid (CSF) ($n = 2$) and blood ($n = 3$) from male and female patients (12). These rare cases of invasive disease caused by unencapsulated US_NmUC occurred in immunocompromised patients (3, 48). Invasive disease caused by unencapsulated meningococcus is often associated with immunodeficiency (49–51).

THE VACCINE ERA AND CHANGES IN MENINGOCOCCUS OROPHARYNGEAL CARRIAGE

Almost all invasive meningococcal disease is caused by groupable (encapsulated) strains of *N. meningitidis*, specifically serogroups A, B, C, W, X, and Y (52). As of early 2022, three quadrivalent meningococcal vaccines (groups A, C, Y, and W) and two recombinant vaccines (group B) are available in the United States (52, 53). Since the late 1990s, the incidence of invasive meningococcal disease has declined (54). The incidence of invasive meningococcal disease declined 2-fold to 3-fold in vaccinated age groups after implementing quadrivalent vaccines (55). In the vaccine era, oropharyngeal carriage of unencapsulated strains is

now more common than in the prevaccine era (56). We raise the possibility that an increase in nongroupable meningococcus carriage may be one variable playing a role in the growing number of meningococcal urethritis cases in the United States today.

Meningococcal serogroup B vaccination has been correlated with a decrease in gonococcal infection (12, 43). Similar cross-protective immunity from the meningococcus B vaccine could provide some protection from US_NmUC urethritis, but no evidence of this cross-protection has been reported.

LABORATORY DETECTION OF MENINGOCOCCAL URETHRITIS

Traditionally, a bedside Gram stain of urethral exudate was used to identify gonococcus, but this approach cannot differentiate *N. gonorrhoeae* and *N. meningitidis*, as they both appear as Gram-negative diplococci (15). In culture, both gonococcus and meningococcus are fastidious organisms that grow to various degrees on nonselective media like chocolate agar and also on selective agars like Thayer-Martin agar and New York City agar (57). Both are oxidase positive. Historical methods of isolate identification include sugar fermentation reaction profiles to differentiate *N. meningitidis* (ferments glucose and maltose, but not lactose and sucrose) from *N. gonorrhoeae* (ferments glucose but not lactose, maltose, or sucrose), although these methods are not routinely used today (58). Some meningococcus isolates that cause urethritis have demonstrated loss in the ability to ferment maltose, so they could be mistaken for gonococcus if using sugar fermentation for identification (28). Biochemical testing, including evaluation of enzyme production, can be used for identification, but these tests also have limitations (59). In contemporary clinical bacteriology practice, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has proven to be a practical and accurate method to identify and discriminate *N. gonorrhoeae* and *N. meningitidis* isolates; however, lack of specificity in distinguishing these species from others within the *Neisseria* genus has been reported (60–63). In our own clinical microbiology practice, we have found the MALDI-TOF MS useful in the identification of *N. meningitidis* recovered in low quantities in routine urine cultures from men who are being evaluated for a potential urinary tract infection and nongonococcal urethritis.

Nucleic acid amplification tests (NAATs) have become the mainstay for clinical detection of the pathogens which cause urethritis. Testing panels for suspected STIs that cause urethritis target the most prevalent pathogens, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Mycoplasma genitalium*, and *N. gonorrhoeae* (64). The Hologic Aptima (San Diego, CA) NAAT that targets *N. gonorrhoeae* has been reported to cross-react with the ST-11 *N. meningitidis* urethritis clade, but this cross-reactivity could not be replicated with the Cepheid GeneXpert (Sunnyvale, CA) NAAT (65). Cross-reactivity with other NAAT diagnostic systems has not been reported, but it is unknown if other NAAT systems have been interrogated for cross-reactivity with US_NmUC. Studies have described genomic mixing in which bacteria can have nucleic acid from both *N. meningitidis* and *N. gonorrhoeae*, and distinguishing between the species using routine nucleic acid diagnostic testing can be challenging in these situations (65, 66). However, it is unclear how frequently these amalgamations are encountered and how frequently cross-reactivity using diagnostic testing might be occurring. Unfortunately, no FDA-authorized NAAT is currently available for the detection of meningococcal urethritis in clinical practice.

One group developed a SimpleProbe real-time PCR assay to detect *N. meningitidis* in urine specimens and evaluated its performance in a proof-of-concept study (67). The probe detects US_NmUC by targeting a region within the *norB* allele. The *norB* gene is found in both *N. gonorrhoeae* and US_NmUC, but a single nucleotide polymorphism (G431A) is specific for US_NmUC. *N. gonorrhoeae* and US_NmUC were able to be distinguished by melt curve analysis of the *norB* amplicon (67).

A few studies have attempted to estimate the prevalence of meningococcal urethritis. At a large sexually transmitted disease (STD) clinic in Columbus, Ohio, Bazan and colleagues conducted an 11-month study in 2015 where all men who presented had a urethral swab and urine specimen collected. In Bazan's cohort, 20% of samples with Gram-negative diplococci had undetectable *N. gonorrhoeae* by NAAT, but *N. meningitidis* was identified in these

samples using multiple testing modalities (strip biochemical testing, real-time PCR, whole-genome sequencing [WGS], etc.), which confirmed all but one of these as cases of meningococcal urethritis (*n* = 74/75) (11, 68). During the same period, 297 culture-positive urethral gonorrhea (GC) cases were identified; all had urethral Gram-negative identification plate (GNID) and positive urine NAAT for *N. gonorrhoeae* (11). Similarly, Toh et al. retrospectively identified an increase in samples with Gram-negative diplococci and negative *N. gonorrhoeae* by NAAT from 2013 to 2016 in Indianapolis, Indiana. These samples with biochemical testing characteristics of *N. meningitidis* increased from 2.8% (*n* = 12/436) to 9.8% (*n* = 50/510) (27). The majority of these samples were not confirmed by MALDI-TOF MS or WGS to rule out other *Neisseria* species, albeit the increase in Toh's presumptive meningococcal urethritis cases correlated with the increase in WGS-proven meningococcal urethritis cases identified in Bazan's cohort. Another study published that 30% of meningococcal urethritis cases had *N. gonorrhoeae* detected by NAAT, and this finding would benefit from additional investigation in other geographic locations (65).

It is difficult to accurately estimate how many cases of meningococcal urethritis are going undetected or may be misidentified as *N. gonorrhoeae*, but overlap in symptomatology and current laboratory detection methods of gonococcus and meningococcus may yield underreporting of the prevalence of meningococcal urethritis.

CLINICAL MANAGEMENT OF MENINGOCOCCAL URETHRITIS

According to 2021 CDC guidelines, meningococcal urethritis should be treated with the same approach as gonococcal urethritis (69). Currently, uncomplicated gonococcal infections in the urethra are treated with a single dose of ceftriaxone intramuscularly (i.m.; 250 mg) when chlamydial infection is excluded. The CDC guidelines also state that sexual partners exposed to meningococcal urethritis may be treated similarly to sexual partners exposed to *N. gonorrhoeae*; however, there are little to no data specific to *N. meningitidis* on the utility of treating sexual partners. In the case of meningococcal urethritis, the sexual partner's oropharyngeal carriage of US_NmUC is likely to be the source of the transmission but is unlikely to be causing disease in the partner.

Bazan and colleagues have described recurrent infections of meningococcal urethritis in men (70). Half of the men (57%, 73/128) in the original US_NmUC cohort returned for follow-up. Of them, five had a recurrent infection with US_NmUC (7%, 5/73). All identified as heterosexual men and reported oral-genital contact (100%, 5/5). The median duration of time between the first and second episode was less than a year (median, 274 days; range, 83 to 576 days). All were previously treated with the CDC-recommended treatment regimen (intramuscular ceftriaxone [250 mg] and oral azithromycin [1 g]). Bazan and colleagues suggest considering treatment with an antibiotic regimen that eradicates meningococcal oropharyngeal carriage in sex partners of men with meningococcal urethritis caused by US_NmUC (70). Currently, the CDC's 2021 treatment guidelines for meningococcal urethritis do not recommend treating people with *N. meningitidis* of the oropharynx (69). Given the potential that meningococcal urethritis may be normal microbiota in the upper respiratory tract of a partner, it is unclear if partner-directed therapy is appropriate or necessary (see "*N. meningitidis* carriage and vaccination" above).

Studies specific to the clinical management of meningococcal urethritis are extremely limited. In order to adequately study clinical management of meningococcal urethritis, NAAT diagnostic testing likely needs to be made available so cases of meningococcal urethritis can be easily diagnosed in routine medical practice (see "Laboratory detection of meningococcal urethritis").

ANTIBIOTIC RESISTANCE

To date, *N. meningitidis* isolates that cause urethritis are generally thought to be susceptible to antibiotics without resistance that can cause treatment failure. One study has documented the majority of isolates to be penicillin resistant (10/13) (65), but these isolates were susceptible to ceftriaxone and ciprofloxacin (13/13) (65). *N. gonorrhoeae* has rarely achieved resistance to third-generation cephalosporins, and

this resistance has not yet been identified in *N. meningitidis* (71, 72). The CDC has declared *N. gonorrhoeae* antimicrobial resistance as a significant threat to public health (73). Rare ciprofloxacin-resistant US_NmUC isolates have been reported, and the resistance mechanism is genetically the same as *N. gonorrhoeae* (mutated DNA gyrase gene [*gyrA*]) and was likely acquired by transmission of the genetic material from *N. gonorrhoeae* to *N. meningitidis* (28). Subpopulations of US_NmUC that are resistant to polymyxins due to MTR efflux and LptA-mediated lipid A modification have been described (44). Azithromycin resistance has also been reported (12, 65).

SUMMARY OF THE CURRENT STATE OF MENINGOCOCCAL URETHRITIS

N. meningitidis is an upper respiratory tract commensal organism that also possesses the ability to cause disease. Asymptomatic oropharyngeal carriage and invasive disease caused by encapsulated strains of meningococcus are more uncommon now than in the prevaccine era, but upper respiratory carriage of unencapsulated *N. meningitidis* is now more common than in previous times. Over the past decade, an increase in the recognition of meningococcal urethritis cases in heterosexual males in the United States and elsewhere has occurred. A novel, unencapsulated strain of *N. meningitidis*, US_NmUC, has been implicated as the predominant cause of these cases of meningococcal urethritis. This urethrotropic clade has unique genetic adaptations that make it more adept at causing infection of the urethra (Table 3). Symptomatology of meningococcal urethritis is indistinguishable from gonococcal urethritis, but the mechanism of transmission of *N. meningitidis* is unique in that it is likely nearly exclusively transmitted during oral sex from the normal upper respiratory tract microbiota of the sexual partner to the individual who eventually develops urethritis.

A number of challenges and opportunities for future study of meningococcal urethritis exist. Currently, no routine diagnostic approach is used for the clinical detection of meningococcal urethritis, and no NAAT is FDA authorized for the detection of *N. meningitidis* from urethral or urine specimens (Table 1). Also, no published studies specifically describe the contemporary prevalence of US_NmUC carriage in the upper respiratory tract, and this clade may be nonspecifically characterized in *N. meningitidis* carriage studies as simply "unencapsulated." Meningococcal urethritis can occur in monogamous relationships, but this scenario is reportedly uncommon and not well studied. CDC's treatment guidelines for meningococcal urethritis are the same as for gonococcal urethritis, although the importance and evidence of treating sexual partners of those with meningococcal urethritis are unclear. Antimicrobial resistance genetic determinants from *N. gonorrhoeae* have been identified in *N. meningitidis* isolates that cause urethritis, which suggests the antimicrobial resistance threat identified in *N. gonorrhoeae* may overlap *N. meningitidis* (28, 74).

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