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Classification of non-gonococcal urethritis: a review

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Abstract
Non-gonococcal urethritis (NGU) is the most common disease of the genital tract in men. Recent studies have recommended avoiding the empiric antibiotic administrations that constitute the classical treatment approach in NGU and to aim toward treatment of causative pathogens. However, the classification of NGU agents remains controversial. In addition, the relevance of the commensalism of *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Gardnerella vaginalis*, which are among the opportunistic pathogens found in the urethral flora, has yet to be determined. Furthermore, there are certain pathogens on which sufficient studies have not been conducted, although they are known to be NGU pathogens, and their statuses should be updated. In this review, the classification of NGU pathogens is summarized in the light of the current literature.

Keywords Non-gonococcal urethritis · Classification · Urethritis · PCR

Abbreviations

CDC	Centers for disease control and prevention
CT	*Chlamydia trachomatis*
EBV	Epstein–Barr virus
EAU	European Association of Urology
GSS	Gram-stained urethral smear
GU	Gonococcal urethritis
GV	*Gardnerella vaginalis*
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
MC	*Moraxella catarrhalis*
MG	*Mycoplasma genitalium*
MH	*Mycoplasma hominis*
MSM	Men sex with men
NAAT	Nucleic acid amplification test
NGU	Non-gonococcal urethritis
NM	*Neisseria meningitidis*
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PMNL/HPF	Polymorphonuclear leucocytes/high-power fields
STD	Sexually transmitted disease
TV	*Trichomonas vaginalis*
UP	*Ureaplasma parvum*
UU	*Ureaplasma urealyticum*

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Introduction

Urethritis is the inflammation of urethra. While it often develops due to infectious pathogens, urethritis may rarely develop due to local chemical irritations. Characteristic findings of urethritis include complaints of urethral discharge occurring following sexual intercourse, itching and burning in the anterior urethra. It is classically defined as gonococcal urethritis (GU) if Gram-negative diplococci are seen in the microscopy of a urethral Gram stain smear (GSS) in the presence of polymorphonuclear leukocytes. In the absence of Gram-negative diplococci, it is defined as non-gonococcal urethritis (NGU). Non-gonococcal urethritis (NGU) is the most common genital tract syndrome in men [1].

Today, acute urethritis is a serious socio-economic burden worldwide. The number of new diagnoses of urethritis is increasing worldwide every year, and its incidence is reported to be approximately 150 million cases [2]. Especially, the incidence of NGU is increasing at a higher rate. One of the reasons for increased incidence is the fact that

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more NGU pathogens are being identified as the nucleic acid amplification test (NAAT) has become more common. This advancement in diagnostic methods has also enabled researchers to conduct more studies on NGU pathogens. However, in the literature, there are controversies in the classification of NGU pathogens. The controversy is centered on whether certain NGU pathogens that are present commensally in the urethra flora can be considered as real pathogens. Since the "classical" urethritis pathogens are absolute sexually transmitted pathogens and the urethritis symptoms start after sexual intercourse, urethritis and sexually transmitted disease terms have become intertwined, and this makes the evaluation of opportunistic pathogens difficult.

As it is known, most NGU pathogens are difficult to identify with conventional culture methods. Empirical treatments are frequently used in NGU due to the long time required to obtain culture results. NGU diagnosis is established with the absence of gr(−) diplococci in the presence of polymorphonuclear leukocyte in GSS due to its easy application. However, recent publications showed that urethritis in men can manifest itself without conventional urethral discharge, only with symptoms such as itchiness, tingling or dysuria and even can be asymptomatic [3, 4].

The role of GSS has particularly become disputable in cases with low inflammation. Taking the cut-off value for positivity as ≥ 5 PMNL/HPF (polymorphonuclear leukocytes per high-power field) in a GSS will yield false-negative outcomes in the diagnosis of NGU. Therefore, the Centers for Disease Control and Prevention (CDC) dropped the cut-off value to ≥ 2 PMNL/HPF in its *2015 Sexually Transmitted Disease (STD) Treatment Guidelines* [5]. A recent study reported 55.6% sensitivity in NGU diagnosis when the threshold was ≥ 5 PMNL/HPF in GSS, whereas sensitivity increased to 92.6% when the threshold was lowered to ≥ 2 PMNL/HPF [6]. In 2017 European Association of Urology (EAU) guidelines, ≥ 5 PMNL/HPF threshold in GSS is only recommended for the diagnosis of pyogenic urethritis related to *Neisseria gonorrhoeae* [7]. However, there is no recommendation in EAU guidelines about the value of GSSs in NGU cases.

Another disadvantage of the GSS is the presence of polymicrobial urethritis. Two or even three pathogens may be associated in a case of acute urethritis. Establishment of a diagnosis of GU and initiation of the treatment based only on GSS findings may fail to take into account NGU pathogens in the presence of an existing co-infection. Therefore, the possibility of polymicrobial infection should also be taken into consideration in urethritis. This condition, defined as the simultaneous detection of multiple urethritis pathogens, can manifest itself in different ways. And in the literature, it is also termed as concomitant infection, dual infection or multi-infection. In particular, higher incidence of urethritis cases associated with polymicrobial infection can be considered as related to the increasing use of Multiplex polymerase chain reaction (PCR) test. The prevalence of polymicrobial infection among acute urethritis cases reaches up to 16.7% [8]. Therefore, NAAT tests, as with multiplex PCR, are also recommended in the guidelines for the diagnosis of acute urethritis for its ability to detect multiple pathogens in a single sample with high sensitivity [9, 10]. Another reason that NGU is becoming a global burden is the presence of NGU-related inflammation, which may increase the risk of acquisition and transmission of HIV [11]. Therefore, prevention and appropriate management of NGU is also crucial for HIV prevention and protection.

Today, empirical treatment approach for NGU has also become controversial. In a recent study, 20% failure rate was found in empirical treatments administered for NGU diagnosis based on GSS evaluation [12]. And the latest review study stated that empirical treatments should be avoided as the use of PCR has become more common, and that cause-specific treatments are important for preventing both the unnecessary antibiotic use and the development of resistant strains [3]. The classification of NGU pathogens should be renewed with the recognition of cause-specific treatment approaches. Literature review revealed that certain pathogens are widely discussed in recent studies on acute urethritis, while certain pathogens that used to be recognized as NGU causes in the past were not included in the evaluation. The objective of this review is to evaluate and reclassify the pathogens that are accepted as NGU agents, in the light of the literature.

Bacteria

Chlamydia trachomatis

Chlamydia trachomatis (CT) are Gram-negative bacteria growing as intracellular parasites. They are the predominant and most known cause of NGU [13]. CT is the most common acute urethritis cause in sexually active young population. Although its prevalence varies geographically, it accounts for 20–50% of NGU cases [14]. CT is an absolute sexually transmitted pathogen, and it is isolated more in developed countries. It must be noted that CT may be asymptomatic in men and women. CT can also cause cervicitis in women, and epididymitis and male infertility in men. NAATs are the most sensitive tests for detecting CT infection [15]. Azithromycin should be considered as the first option in the treatment.

Mycoplasma genitalium

Mycoplasma genitalium (MG) is an intracellular parasite. In contrast with *Mycoplasma hominis*, MG is included in the

guidelines as an NGU cause, for which the sexual transmission characteristic is recognized. It has 6–16.7% prevalence in acute urethritis [16, 17] and it can cause PID, cervicitis and infertility in women. However, its association with infertility in men is controversial [18]. NAAT is the only clinically useful method to detect MG [16]. Azithromycin and/or moxifloxacin therapy should be considered.

Ureaplasma urealyticum

Ureaplasma urealyticum (UU) is also formerly known as Ureaplasma biovar 2. It is an opportunistic pathogen that can commensally exist in the urethra. In a meta-analysis consisting 1507 NGU patients and 1223 control subjects, it was shown that UU should be assessed as an NGU cause [19]. The latest EAU guideline also indicates UU as an acute urethritis cause [7]. UU prevalence in acute urethritis is 5–26% [9]. As UU growth in culture medium is difficult and UU and *Ureaplasma parvum* cannot be differentiated in culture, NAATs are gold standard as with PCR. UU can also exist commensally; therefore, it can be detected in asymptomatic individuals. In studies conducted with volunteers, UU was detected in 26% of male participants [20]. In two studies by Sarier et al., where acute urethritis cases were evaluated, UU prevalence was found to be 27.1% with a non-quantitative PCR [21], and only 9.5% UU prevalence was found in the study conducted with quantitative PCR [6]. Therefore, quantitative PCR is a valuable test for demonstrating microbial load and avoiding false-positive results. UU also accounts for infertility in men. In a recent meta-analysis, a significant relation was found between male infertility and UU, whereas no relation was detected with *U. parvum* [19]. Doxycycline should be the priority in treatment.

Haemophilus species

Among Haemophilus species, *Haemophilus influenzae* and *Haemophilus parainfluenzae* strains are held responsible for acute urethritis. Although it is not a common cause of acute urethritis, its prevalence reaches up to 12.6%, and *Haemophilus influenzae* accounts for 87%, and *Haemophilus parainfluenzae* for 13% of the strains responsible for acute urethritis [22]. The oro-genital transmission is particularly relevant. It is more common in men who have sex with men (MSM) [23]. As in GU, clinical findings are accompanied by pyogenic urethral discharge. Antibiotic resistance is an important problem in Haemophilus species. In a study consisting 38 Haemophilus urethritis series, azithromycin resistance was found in 34.2% of the cases and both azithromycin and tetracycline resistance in 26.3% of the cases [24]. Therefore, antibiotics that are effective against beta-lactamase activity of *Haemophilus* species should be considered for the treatment [25].

Neisseria meningitidis

Neisseria meningitidis (NM) is another pathogen in etiology of acute urethritis. However, as it is a gr(−) diplococci like *Neisseria gonorrhoeae* (NG), misdiagnosis can occur in acute urethritis cases diagnosed with GSS. Therefore, maybe, its incidence is demonstrated only in case presentation, unlike NG. It is more common in heterosexual men and its prevalence in acute urethritis is 0.3–0.7% [26]. As NM can exist commensally in the oropharyngeal flora, orogenital contact is considered to be the most important form of transmission in acute urethritis cases [27]. More studies with large series are required for NM to be considered as part of the routine evaluation of acute urethritis.

Mycoplasma hominis

The status of *Mycoplasma hominis* (MH) as a cause of acute urethritis is controversial. On the contrary to *M. genitalium* in the same genus, it can exist commensally in urethral flora of 9% of healthy men [20]. As its sexual transmission is still being discussed like other opportunistic pathogens, its role in acute urethritis also raises questions. Although there are studies evaluating MH as an NGU cause [28], there are also other publications suggesting that it is not an NGU pathogen [29]. It has 3% prevalence in men with acute urethritis confirmed with GSS assessed by quantitative PCR [30]. It may be often seen as a cause of co-infection. This suggests that it may be a secondary cause of infection due to disrupted flora. In a study about NGU pathogens, all MH cases were found as co-infection form, and interestingly even an individual case was not found [28]. It can be a serious pathogen in immunosuppressed patients. Most of the patients are asymptomatic due to its low inflammatory characteristics. Therefore, it can be considered as a urethritis cause under high microbial load. Thus, quantitative PCR analysis plays an important role in the diagnosis since it also can show microbial load. And there is also evidence suggesting that MH can cause male infertility. In a recent meta-analysis, MH was shown to be associated with male infertility [18]. Although doxycycline can be an effective treatment, eradication of MH through antibiotic therapy may be difficult due to the insufficient cidal activity of antibiotics on MH [25]. Today, it is early to rule out MH as a cause of acute urethritis. Case-controlled and particularly quantitative PCR-supported studies will be instructive.

Gardnerella vaginalis

Gardnerella vaginalis (GV) is the most known bacteria causing bacterial vaginosis. Although it is an important factor of acute vaginitis in women, its role as a cause of urethritis in men is questionable [31]. In a case-controlled

study, GV was found to be, statistically significantly, a cause of acute urethritis [32]. However, GV is a pathogen that is also detected in the male urethritis developing in men after sexual intercourse with women who have GV-related vaginitis [33]. In a study with a large series of patients with acute urethritis, its prevalence was found as 14% [34]. It can be present in women and men commensally. In a study, GV was found in 37% of asymptomatic men [35], and it becomes symptomatic under high microbial load. GV is particularly common in the urethral flora of homosexual men [36]. It is still not included as a cause of acute urethritis in the latest EAU guideline [7]. Metronidazole or tinidazole should be considered for the treatment. In line with the information above, it should be highlighted that GV can be considered as a cause of acute urethritis in high microbial load.

Ureaplasma parvum

On the contrary to UU, there is very few evidence for *U. parvum* (UP) to be considered as an acute urethritis cause. It is also recognized as Ureaplasma biovar 1. It is a pathogen than can commensally exist in the urethra like UU. Despite the publications considering it as a cause of acute urethritis under high microbial load, today it is not recognized as an acute urethritis pathogen due to low level of evidence. In a case-controlled study, bacterial load of UP was found to be similar both in the NGU group and the control group [37]. In a recent meta-analysis evaluating the case-controlled studies, UP was shown to be not associated with NGU [19]. Similarly in another meta-analysis, in contrast to UU and MH, no relation was found between male fertility and UP [18].

Streptococcus species

The role of Streptococcus species in acute urethritis is also questionable. In three different acute urethritis prevalence study, prevalence of *Streptococcus pneumoniae* was found to be 0.48% [37], *Streptococcus agalactiae* was 1.5% [38] and *Streptococcus pyogenes* was 0.16% [39]. In general, its prevalence in acute urethritis patients is less than 1%. The insufficient number of case-controlled studies is making it difficult to establish a clear understanding on the subject. In a case-controlled study, *Streptococcus pneumoniae* was found to be more common in control subjects than the acute NGU patients [37]. Today, there is no sufficient evidence to consider them as acute urethritis causes. Case-controlled studies with large series will provide guidance.

Moraxella catarrhalis

Moraxella catarrhalis (MC) is a gr(−) diplococci that exist commensally in 1–5% of healthy individuals and can frequently cause respiratory tract infection [40]. Oro-genital transmission-related acute urethritis cases are published as case presentation in the literature [41]. Its symptoms are typically similar to GU. There is no sufficient evidence to label MC as an absolute NGU cause due to the lack of case-controlled studies with large series.

Virus

Adenovirus

There are limited number of studies on the prevalence and role of adenovirus as a cause of urethritis. The literature review revealed mostly case reports on the subject. Oro-genital transmission is typical and its prevalence within acute urethritis can reach up to 4% [42]. However, the most characteristic symptom of infection is the frequently accompanying conjunctivitis. Therefore, the presence of meatitis and/or conjunctivitis draws attention as a typical finding along with urethritis symptoms. In an adenovirus urethritis series consisting 102 cases, meatitis or conjunctivitis was found to be accompanying in 89% of the cases [43]. Another important aspect of this study was the fact that 5 ≥ PMNL/HPF in GSS was present in only 37% of the patients. Most of the adenovirus infections are spontaneously limited in immune-competent individuals and recovery is achieved without requiring treatment. It should be noted that this pathogen can be isolated more in acute urethritis cases with the increasing use of rapid tests like NAAT.

Herpes simplex virus

Herpes simplex virus (HSV) Type I and Type II is another virus responsible for acute urethritis. Although its prevalence varies, a recent study found total of 3.8% prevalence within acute urethritis (2.9% for HSV Type I and 0.9% for HSV Type II) [44]. Unprotected oral sex history is common in patients. Clinically, it is accompanied by meatitis as with adenovirus. In male patients with HSV-positive acute urethritis, unlike genital HSV infections, herpetic lesions were found only in 26.3% of the patients [14]. Therefore, the absence of classical vesicular herpetic lesions cannot eliminate HSV urethritis. HSV urethritis should be taken into consideration due to the fact that mononuclear leukocytes are more common in GSS instead of polymorphonuclear leukocytes [14]. Valacyclovir or famciclovir should be considered for the treatment.

Epstein–Barr virus

Epstein–Barr virus (EBV) is the third virus in the etiology of acute urethritis, after adenovirus and HSV. However, there are a limited number of studies in the literature investigating

EBV as a cause of acute urethritis. In a case-controlled acute urethritis series confirmed by GSS containing 103 patients, EBV was found to be 21% in the study group and 6% in the control group; in conclusion, researchers reported an independent relation between male urethritis and EBV [45]. However, the 21% prevalence can be considered to be an ambitious figure and should be challenged. The lack of different publications supporting these data is another handicap. Therefore, it is early to considered EBV as a cause of acute urethritis. Epidemiological studies with large series including EBV will be instructive.

Protozoan

Trichomonas vaginalis

Trichomonas vaginalis is a sexually transmitted protozoan NGU cause. It is more common in developing countries; however, it has 2–13% prevalence in developed countries [46]. The NAATs developed in recent years have great diagnostic value, with sensitivity and specificity of 95–100% [47]. Metronidazole should be the first option in treatment.

Fungi

Candida species

Candida species is one of the earliest known pathogens in acute urethritis causes and exists opportunistically in the flora [48]. However, literature review showed that there are very few publications on the association of Candida species with urethritis since the day it was recognized as a cause of acute urethritis. In a study where 1248 acute urethritis patients were evaluated, prevalence of Candida species was found to be 0.48% [14]. Sexual transmission of genitourinary Candida infection is controversial. A study using genotypes showed that vulvovaginal candidiasis can cause balanoposthitis in men after heterosexual intercourse [49]. However, there is no sufficient evidence suggesting that Candida species can cause acute urethritis as a result of sexual transmission. It may be considered as a cause of urethritis with its opportunistic characteristics in relation to the disruption of urethral flora. In conclusion, more studies are required to recognize Candida species as a cause of acute urethritis.

As mentioned above, UU, GV and MH, which can commensally exist in the urethral flora, can cause acute urethritis under high microbial load. Two hypotheses can be considered at this point. Although they are sexually transmitted, they can cause urethritis due to their opportunistic characteristics related to the disruption of urethral flora as a result of sexual intercourse or they can be urethritis causes by way of co-infection due to the changes in the flora invoked by the sexually transmitted urethritis pathogen. Another discussion is the definition of high microbial load for these pathogens. In publications, although high microbial load is defined as > 1000 copy/ml of first-voiding urine [9, 50], there is no consensus on a standard value. Therefore, it is still unclear what amount of microbial load should necessitate treatment for opportunistic pathogens. In conclusion, these pathogens should be treated in "real" high microbial loads regardless of being primary pathogen or concomitant infection.

There is another group, classified as idiopathic or non-specific urethritis, within acute urethritis. This is the clinical condition, where no known pathogens were detected, found to be 20–30% in epidemiological studies [51]. Urethritis developing due to chemical factors and allergic urethritis can also be evaluated within this group. Chemical urethritis can occur as a result of chemical reaction in the urethra caused by the hygiene substances used after sexual intercourse; and allergic urethritis can occur in men after sexual intercourse with female partners using vaginal contraceptive methods and Lubrica used during the intercourse can cause infection by contacting the urethra. Although uncommon, it must be noted that urethritis can occur due to mechanical manipulation.

Conclusion

There is still debate in the literature about the classification of non-gonococcal urethritis pathogens. Among the opportunistic pathogens, only *U. urealyticum* is involved in the guidelines as an agent of urethritis. The other pathogens that may be commensally found in urethral flora including *M. hominis* and *G. vaginalis* can be considered as causes of NGU at a high microbial load. In line with the evidence, there is no need to evaluate *U. parvum* as a causative agent of acute urethritis. Haemophilus species, HSV species, and adenovirus that are accepted as causes of NGU should be pathogens studied in routine evaluation in acute urethritis.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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