Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 5955 - 5965

In-depth exploration of Common Communicable Diseases, Including Influenza, Respiratory Infections, and Sexually Transmitted Infections (STIs) with a Focus on Urethritis

[1]- Ahmed Abdu Ahmed Amri,[2]- Abdullah Mahdi Ali Khawaji,[3]- Mohamed Abdu Ali Al Bakkary,4- Ali Mulhi M Althurwi,[5]- Essa Mohammed Ahmed Sultan,[6]- Naif Hamoud Jebreel Qasiri,[7]- Mosawa Abdu Mohammed Otaify,[8]- Albader Ali Menahsh.,[9]- Ahmed Nami Mustafa Al-Nami,[10]- Abdulkhaliq Mohsen Hussain Alhazimy.,[11]- Mohammed Ahmed A Althurwi,[12] -Naif Bin Mohammed Tahir Khawaji,[13]- Ryadh Ali Bokur Hobani

1. Ksa, Ministry Of Health, Vector Control Center In Haroub
2. Ksa, Ministry Of Health, Vector Control Center In Haroub
3. Ksa, Ministry Of Health, Vector Control Center In Haroub
4. Ksa, Ministry Of Health, Vector Control Center In Haroub
5. Ksa, Ministry Of Health, Vector Control Center In Haroub
6. Ksa, Ministry Of Health, Vector Control Center In Haroub
7. Ksa, Ministry Of Health, Vector Control Center In Haroub
8. Ksa, Ministry Of Health, Vector Control Center In Haroub
9. Ksa, Ministry Of Health, Vector Control Center In Haroub
10. Ksa, Ministry Of Health, Vector Control Center In Haroub
11. Ksa, Ministry Of Health, Health Affairs In Asser
12. Ksa, Ministry Of Health, Maintenance Management In Jazan Health
13. Ksa, Ministry Of Health, Vector Control Center In Haroub

Abstract

Background: Communicable diseases such as sexually transmitted infections (STIs), influenza, and respiratory infections remain significant public health challenges globally. Urethritis, often resulting from STIs like Chlamydia trachomatis and Neisseria gonorrhoeae, can lead to severe complications if untreated.

Methods: This review synthesizes recent literature on the causes, clinical manifestations, diagnostic approaches, and therapeutic interventions for common communicable diseases. We emphasize the role of nucleic acid amplification tests (NAATs) for accurate diagnosis and describe syndromic management strategies for urethritis.

Results: The findings indicate that urethritis is frequently underdiagnosed, with up to 50% of cases classified as idiopathic. NAATs have emerged as the gold standard for diagnosing STIs due to their high sensitivity and specificity. For gonococcal urethritis, clinical symptoms are present in nearly 90% of males, with significant morbidity associated with untreated infections. Treatment regimens have evolved, with concerns over antimicrobial resistance necessitating updated guidelines.

Conclusion: Effective management of communicable diseases requires accurate diagnosis and appropriate therapeutic strategies. Continuous monitoring of antibiotic resistance patterns is essential to adapt treatment protocols. Public health initiatives focused on education and prevention are critical to reducing the incidence of STIs and other communicable diseases.

Keywords: Communicable diseases, sexually transmitted infections, urethritis, nucleic acid amplification tests, antimicrobial resistance.

Received: 16 october 2023 **Revised**: 29 November 2023 **Accepted:** 13 December 2023

1. Introduction

Urethritis is characterized by the inflammation of the urethra. This condition is often induced by sexually transmitted diseases, including Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), Mycoplasma genitalium (MG), and seldom by pathogens such as Herpes simplex viruses 1 and 2, *Trichomonas vaginalis* (TV), or Adenovirus, among others (1–6). Nonetheless, the cause may remain unclear in up to 50% of instances, subsequently classified as idiopathic urethritis (6–8).

Clinical manifestations of urethritis mostly consist of urethral discharge and dysuria, with less frequent occurrences of urethral irritation, pruritus, or mastitis (1, 2, 4, 6, 9). Acute and chronic urethritis may lead to considerable morbidity, including arthritis, epididymal-orchitis, or prostatitis (6, 8). Urethritis is confirmed by an elevated count of polymorphonuclear leukocytes (PMNLs) in urethral exudate, sometimes referred to as symptoms of urethritis. The urethral smear may be stained using either Gram stain or methylene blue (1). Microscopically, urethritis is diagnosed in most contexts if there are ≥5 polymorphonuclear leukocytes (PMNL) per high power (x1,000) microscopic field, based on an average of 5 fields (1, 4, 9). Some investigators, however, opted for elevated thresholds of PMNLs for diagnosis (high cut-off urethritis: ≥10 PMNLs) (10). This differs from the new guidelines of the Centers for Disease Control and Prevention (CDC), which suggest a lower threshold (2 PMNLs/HPF; irrespective of symptomatology) for diagnosing non-gonococcal urethritis (NGU) in males (6). This modification was implemented due to the observation that reducing the cutoff to 2 PMNLs/HPF resulted in a substantial enhancement in the detection of CT by Gram stain smear. Detection of causative agents by nucleic acid amplification assays (NAATs) of first void urine or urethral swab (4, 6).

Nucleic acid amplification assays represent the gold standard for diagnostics, primarily because they provide non-invasive samples and exhibit exceptional specificity and sensitivity (11, 12). No more than 20 ml of initial void pee must be used for examination. Due to NAATs' ability to identify non-viable organisms, tests of cure (TOCs) should typically be conducted no sooner than three weeks after the conclusion of therapy (11). A positive leukocyte esterase test on the first void urine or microscopy of sediment reveals more than 10 PMLS/HPF (6). Microscopy and NAATs should be conducted in cases with symptomatic urethritis. Clinicians should first screen for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), and *Mycoplasma genitalium* (MG). If none of the aforementioned pathogens is identified, alternative causative agents should be considered, including Herpes simplex virus types 1 and 2 (HSV-1, HSV-2), Adenovirus, *Neisseria meningitidis* (NM), *Trichomonas vaginalis* (TV), *Haemophilus influenzae*, *Mycoplasma penetrans* (MP), *Treponema pallidum* (TP), or enteric bacteria, among other potential infectious causes.

Symptomatic non-gonococcal urethritis is often addressed syndromically, with prompt medication administered. Contact tracing is thereafter initiated based on NAAT findings and/or point-of-care urethral smear for Neisseria gonorrhoeae. Upon identification of a sexually transmitted infection (STI), partner communication is essential to avert re-infection, mitigate possible morbidity, and inhibit further transmission. Furthermore, individuals diagnosed with one sexually transmitted infection (STI) should be evaluated for other pertinent serologically detectable STIs, including Hepatitis B and C, syphilis, and HIV (6).

2. Gonococcal urethritis

Neisseria gonorrhoeae

Gonorrhea is the second most prevalent bacterial sexually transmitted infection in Europe, with an incidence rise of several hundred percent over the last five years (12, 16). Neisseria gonorrhoeae, the causal agent, is a Gram-negative bacterium that may be transferred by unprotected sexual intercourse or direct inoculation of the epithelial mucosa via other pathways. Infections caused by this virus often have a brief incubation period of 1 to 10 days. It is estimated that up to 20% of all urethritis cases are attributable to NG (12). An infection provides no immunity. Antimicrobial resistance (AMR) in gonorrhea constitutes a worldwide public health issue, since *Neisseria gonorrhoeae* exhibits all primary resistance pathways, with

instances of multi-drug-resistant gonorrhea documented. Numerous antimicrobial resistance determinants have been identified for all pertinent antibiotics, including ceftriaxone, cefixime, azithromycin, spectinomycin, ciprofloxacin, and ofloxacin (17). The World Health Organization (WHO) has provided a gonococcal antimicrobial surveillance program (GASP) since 1992. The most recent retrospective investigation found resistance rates of 0 to 22% for cephalosporins, 0 to 60% for azithromycin, and 0 to 100% for ciprofloxacin globally (18). Worldwide, resistance to ciprofloxacin is significantly elevated, ranging from 49% in the European area to 93% in Southeast Asia. Ciprofloxacin should generally be provided just for NG infections that are confirmed to be susceptible.

Clinical manifestations

Nearly 90% of infected males exhibit symptoms, mostly discharge (>80%), followed by dysuria (12, 19). In cases of severe or persistent illness, ascending infections may occur, potentially resulting in prostatitis, epididymitis, or epididymal-orchitis (12, 19, 20). Gonococcal septicemia, or disseminated gonococcal infection (DGI), may manifest with clinical signs such as petechiae or pustules in acral regions, tenosynovitis, polyarthralgia, or septic arthritis (6).

3. Diagnostic techniques

The detection of *Neisseria gonorrhoeae* can be conducted microscopically, achieving a specificity of up to 99% and a sensitivity of up to 95% in symptomatic males, by identifying intracellular Gram-negative diplococci within polymorphonuclear leukocytes using Methylene blue or Gram staining. Additionally, culture methods are crucial for subsequent susceptibility testing, and direct detection can be accomplished through nucleic acid amplification tests (NAATs). Preferred specimens include urethral smears or first-void urine. The first 15–30 ml of void pee should be collected after a minimum abstinence from micturition for 60 minutes (11, 12). The culture of this bacteria is often required for antibiotic susceptibility testing (11–13, 19). Undoubtedly, NAATs are the preferred state-of-the-art diagnostic tests for gonorrhea (12, 13, 19).

In males exhibiting Gram-negative diplococci on Gram stain smear that test negative for *Neisseria gonorrhoeae* by nucleic acid amplification test (NAAT), *N. meningitidis* Strains of clonal complex 11 should be taken into account. Recent investigations, mostly from the United States, indicate that these bacteria may significantly contribute to urethritis in healthy men and may sometimes spread to produce deadly disseminated illness in immunocompromised patients (6, 14).

Therapeutic Intervention

The European division of the International Union Against Sexually Transmitted Infections (IUSTI) advises, in instances of unidentified antimicrobial sensitivity, the administration of ceftriaxone 1 g in conjunction with azithromycin 2 g as separate doses, or ceftriaxone 1 g as monotherapy in a single dosage (12). The CDC advises administering ceftriaxone 500 mg intramuscularly. for those weighing less than 150 kg, and 1 g for those beyond this weight (6). The treatment for Neisseria meningitidis adheres to the same protocol (6).

The European IUSTI recommendations advocate testing for additional STIs and a period of sexual abstinence for seven days post-treatment (12, 17). A test of cure (TOC) is obligatory for ceftriaxone monotherapy or alternate treatment regimens, as per the European IUSTI recommendations (12). There is contention on the need for TOC in Europe owing to the infrequent occurrence of ceftriaxone resistance. The CDC states that a test of cure for those treated with an approved regimen for oro-ano-genital gonorrhea is unnecessary (6). All sexual partners from the last 60 days to 3 months must be notified (6, 12).

4. Non-gonococcal urethritis

Non-gonococcal urethritis is mostly attributed to *Chlamydia trachomatis* (up to 50%), followed by *Mycoplasma genitalium*, which accounts for 15–50%, and *Trichomonas vaginalis* (1–20%), varying by country prevalence (1–6, 8). Uncommon pathogens include Herpes simplex virus 1, Herpes simplex virus 2, Adenovirus, and *Trichomonas vaginalis* (7, 8). Recent studies have identified many novel pathogens associated with non-gonococcal urethritis (NGU), including *Haemophilus influenzae* (HI) and *Mycoplasma penetrans* (MP) (8). Recent investigations indicate that no pathogen was found in up to 50% of males with

non-gonococcal urethritis (NGU) (1, 2, 7, 8). In instances with characteristic symptoms and microscopically confirmed urethritis, therapy based on the syndrome should be initiated (Figure 1) (1, 6). The primary suggested treatment regimen is doxycycline 100 mg twice a day for 7 days, with azithromycin 1 g orally as an option. Administered as a single dosage (20).

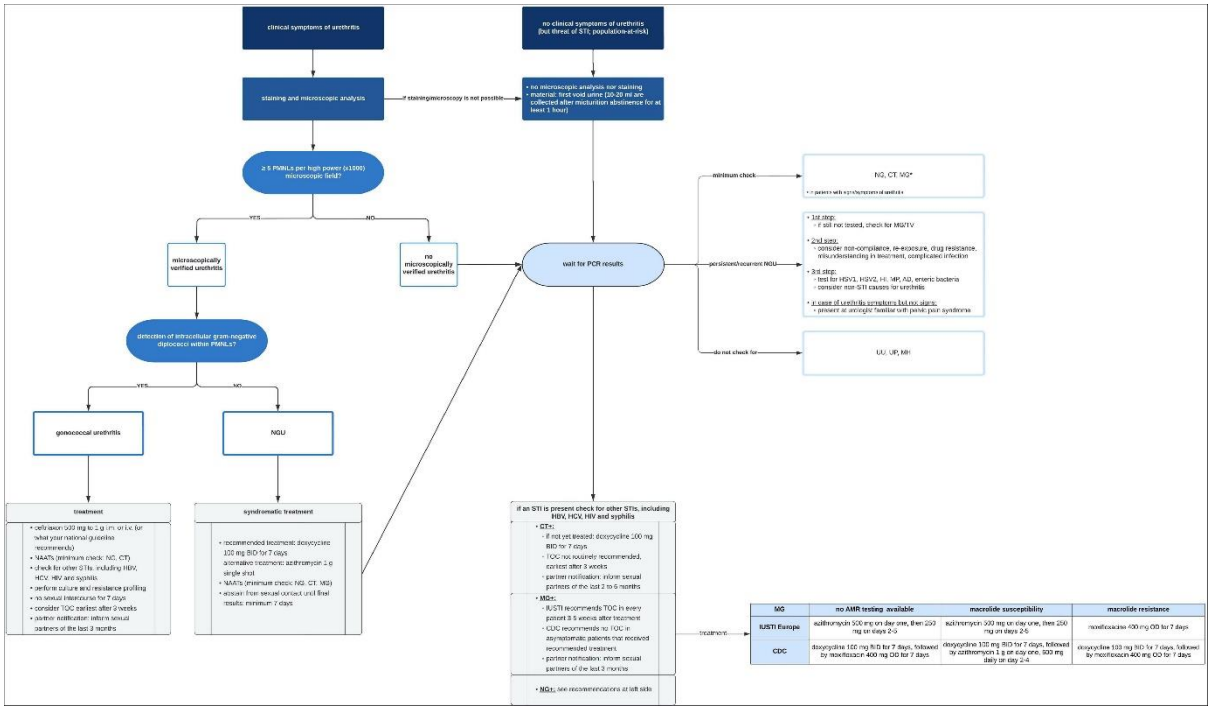

Figure 1. Proposed diagnosis and treatment methodology for urethritis or potential urethral sexually transmitted infection.

Recently, Toh et al. (21) assessed many cure outcomes (clinical, Gram stain, microbiological) in males treated with azithromycin for non-gonococcal urethritis (NGU). Clinical cure (resolution of symptoms) was shown to predict microbiological cure (as determined by NAATs) in individuals infected with CT, UU, and TV. Nonetheless, this did not apply to MG, since microbiological failure was seen in males who had clinical cures (21). Macrolide-resistant Mycoplasma genitalium infections were strongly associated with microbiological failure (21). The authors concluded that in males infected with MG-NGU who are treated with azithromycin, microbiological cure is essential, particularly in contexts where macrolide resistance cannot be assessed (21). Remarkably, as of today, there has been no examination of NGU outcomes by the new CDC guidelines in the United States.

5. Recurrent or persistent non-gonococcal urethritis

In instances of recurrent (symptoms reappearing within 30–90 days post-treatment, prevalence up to 20%) or persistent (ongoing symptoms despite treatment, prevalence up to 25%) non-gonococcal urethritis (NGU), factors such as non-compliance, re-exposure, drug resistance, treatment misunderstandings, or complicated infections should be considered. If not conducted earlier, MG testing is essential in this circumstance (6).

Chlamydia trachomatis

Chlamydia trachomatis is the predominant bacterial sexually transmitted infection and the leading cause of urethritis in both Europe and the United States. CT is an obligatory intracellular bacterial pathogen that only replicates inside live human epithelial mucosa (13, 22–24). Currently, twelve pertinent uro-ano-genital serovars have been identified. Serovars D to K are responsible for typical urogenital sexually transmitted infections (STIs), whereas three variations may lead to the less often identified STI known as lymphogranuloma venereum (LGV) (22, 23). Chlamydia trachomatis is spread by unprotected sexual

intercourse and has an incubation period of 1 to 4 weeks. The extent to which a previous infection provides protective immunity is uncertain; nonetheless, some protection is probable.

Clinical manifestations

Certain investigations have noted asymptomatic presentations in around 50% of males (22). Nevertheless, further research has shown that urethral inflammation is prevalent among most males with chlamydia trachomatis (CT), and in a case-control study conducted by Jordan et al., which examined symptoms and inflammation in both cases and controls, very low percentages of asymptomatic CT infections were noted. Dysuria and clear or white discharge are prevalent in symptomatic males (24). Gathering a comprehensive medical history is crucial, since some men may neglect to disclose minor symptoms otherwise. Ascending infections may lead to infrequent but severe consequences, such as epididymitis and orchitis (22–24).

Diagnostic techniques

Urethritis may be identified using a Gram stain. Due to the difficulty in reliably seeing CT in urethral specimens, NAATs are the preferred method for confirmation and are thought to provide positive results between 3–14 days post-coitus (6, 22, 24). Culture is feasible, although not often advised, due to its technical complexity, time demands, and reduced sensitivity compared to NAATs (22, 24). In contrast, NAATs are more prone to producing false positives due to residual DNA, and testing of cure using NAAT should not occur sooner than three weeks after the conclusion of therapy. Appropriate specimens include urethral smears or first void pee (6).

6. Therapeutic Intervention

The European IUSTI guideline advises first-line therapy with doxycycline 100 mg administered bi-daily for one week, or second-line treatment with azithromycin 1 g orally. Administered as a single dosage (22). The CDC currently recommends doxycycline as the primary treatment, since azithromycin is less effective in eradicating simultaneous rectal CT infections (6, 25).

All partners from the last 2 to 6 months will be notified (6, 22). For complex CT infections, the treatment time should be prolonged to two weeks. Individuals infected should refrain from sexual intercourse for one week after the completion of therapy and the resolution of symptoms for both them and their partners. If the indicated medication was administered, a TOC is not often advised but may be conducted either 3–4 weeks or 3 months post-treatment (6, 22). The CDC recommendations advocate for a follow-up appointment for re-testing after three months (6).

Mycoplasma genitalium

Mycoplasma genitalium is an unconventional, diminutive parasitic bacteria. This pathogen has an incubation period of between 4 to 8 weeks. Transmission occurs via unprotected sexual intercourse (27). Following years of disregard, it has recently been shown that *Mycoplasma genitalium* (MG) is a significant etiological factor in urethritis, particularly in cases resistant to therapy, and may also be implicated in other conditions such as epididymal-orchitis and proctitis, with MG incidence reaching up to 4% in the general population. The incidence of MG in NGU, however, varies from 10% to 35% (27). The significance of silent MG infections is still unclear (6).

Owing to the absence of a cell wall, only a limited number of antibiotics exhibit efficacy against mycoplasmas, including tetracyclines, macrolides, streptogramins (which inhibit protein synthesis), and fluoroquinolones (which impede DNA synthesis) (27–28). The antimicrobial resistance of these bacteria is increasing, and successive treatment failures with both macrolides and fluoroquinolones have been noted (28, 29). Macrolide resistance is escalating swiftly, with estimates varying from less than 4% in Russia to 69% in Japan, and *Mycoplasma genitalium* has been identified as a growing public health concern. Resistance rates for fluoroquinolones are lower (8–20%) and seem to be more uniform worldwide (28, 29). In 2017, research by Murray et al. noted a rising prevalence of macrolide- and fluoroquinolone-resistant *Mycoplasma genitalium* in Australia. A significant prevalence of ParC S83 alterations associated with moxifloxacin resistance was identified, with 10% of the MG isolates anticipated to exhibit resistance to

macrolides and fluoroquinolones (31). Certain individuals with these isolates have a favorable response to pristinamycin (31).

In light of the heightened resistance, other therapeutic alternatives must be investigated. One such compound is sitafloxacin, a fluoroquinolone (30). Murray et al. researched to discover mutations responsible for fluoroquinolone resistance. The findings demonstrated that mutations in parC G248T/S83I correlate with the ineffectiveness of both moxifloxacin and sitafloxacin, suggesting the need to consider their implications for the advancement of next-generation resistance tests (30). Untreatable MG is now a reality; hence, resistance-guided treatment regimens must be implemented, preferably including monitoring of MG AMR (27, 28, 30).

7. Clinical manifestations

Numerous MG infections have an asymptomatic progression. In symptomatic males, urethral discharge or dysuria are the predominant symptoms (27).

8. Diagnostic techniques

The recommended diagnostic procedures are NAATs, with a suggested temporal interval of at least two weeks post-exposure. Testing is strongly advised for symptomatic patients exhibiting signs of urethritis, recurrent or persistent non-gonococcal urethritis (NGU), dysuria with no identifiable cause, proctitis (after excluding Neisseria gonorrhoeae and Chlamydia trachomatis), or for male patients under 50 years presenting with acute epididymal-orchitis. Initial void urine and urethral swabs (less advisable owing to invasiveness) are appropriate (27).

9. Therapeutic Intervention

The European IUSTI recommendation advises, in the absence of resistance testing or macrolide susceptibility, the administration of either azithromycin 500 mg on day 1, followed by 250 mg on days 2–5, or josamycin 500 mg thrice daily for 10 days (9, 27). For macrolide resistance, a regimen of moxifloxacin 400 mg for 7 days is advised (27). For complex MG infections, such as epididymitis, a regimen of moxifloxacin 400 mg for 14 days is advised.

The Centers for Disease Control's guidelines are predicated on the elevated rates of macrolide resistance in the United States and adhere to a two-stage methodology (6). If AMR testing is unavailable or if MG exhibits macrolide resistance, therapy will consist of doxycycline 100 mg administered twice daily for 7 days, followed by moxifloxacin 400 mg taken once daily for an additional week (6). This regimen aims to use doxycycline to reduce bacterial load, hence enhancing the efficacy of moxifloxacin (6). If the MG isolate exhibits sensitivity to macrolides, it is advised to provide doxycycline 100 mg twice daily for 7 days, followed by azithromycin 1 g orally on day 1, and 500 mg daily from days 2 to 4.

Resistance-guided sequential treatment has shown high cure rates, as evidenced by research conducted by Durukan et al. (29). They assessed the effectiveness and tolerability of doxycycline–moxifloxacin and doxycycline–2.5 g azithromycin (29). In the instance of NGU, patients were administered doxycycline 100 mg twice daily for 7 days. For MG infection, macrolide-susceptible individuals were administered 1 g of azithromycin, followed by 500 mg daily for three days. Cases resistant to macrolides were administered 400 mg of moxifloxacin for 7 days. A TOC was advised 2–3 weeks post-treatment (29). Both cure rates exceeded 92%, demonstrating great tolerability (29). Resistance-guided sequential treatment has been adopted by Australia and adapted to the recommendations of the United Kingdom. Doxycycline (100 mg BID for 7 days) is used as the first treatment for NGU. If this is unsuccessful, it is advised to provide azithromycin 1 g orally on day 1, followed by 500 mg daily on days 2–4, or moxifloxacin for 7–10 days.

Males infected with MG should refrain from sexual intercourse until they and their sexual partners have completed therapy, are asymptomatic, and have had a negative test for cure (3–5 weeks post-treatment) (27). Toh et al. noted that 1-week abstinence is inadequate for azithromycin-treated MG–-NGU cases and advocated doing a test of cure in all MG-infected individuals. They further advise refraining from unprotected sexual intercourse until a test of cure is conducted, to prevent the spread of MG (21). The CDC

does not endorse TOC for asymptomatic individuals who have completed the approved CDC treatment regimen (6). Nonetheless, due to the recency of these suggestions, it may be essential to reassess them when further follow-up data becomes available.

10. Pathogens responsible for non-gonococcal urethritis

Besides the aforementioned infections, several additional bacteria may induce urethritis. Included are Herpes simplex viruses 1 and 2, *Trichomonas vaginalis*, Adenovirus, *Treponema pallidum*, *Haemophilus* species, and *M. penetrans* (6).

Herpes simplex virus type 1 and herpes simplex virus type 2

The predominant DNA viruses are HSV-1 and HSV-2, which may induce NGU and account for 2–10% of NGU cases (32, 33). Only one-third of patients have herpetiform lesions on the skin; the remainder experience mastitis and dysuria without discharge (32). Constitutional symptoms are prevalent (32). Transmission is mostly by insertive oral intercourse (33). The diagnosis of HSV–NGU may only be achieved using NAATs utilizing urethral swabs or first void urine, demonstrating great sensitivity (6). The majority of patients do not need targeted antiviral therapy.

Adenovirus

Adenovirus is a transmissible DNA virus including seven serotypes (A-G), mostly responsible for respiratory tract infections, conjunctivitis, and less often urethritis (2–4% of non-gonococcal urethritis cases; serotype D seems to be the most prevalent variant) among other conditions. Transmission is more probable during unprotected oral sexual intercourse within the preceding month (33, 34). A standard clinical presentation mostly includes mastitis, dysuria, clear or mucoid discharge, and predominantly bilateral conjunctivitis (33, 34). Diagnosis may be established clinically upon the observation of the triad of mastitis, urethritis, and conjunctivitis, particularly between September and March. NAATs may be conducted on urethral and conjunctival swabs for academic purposes (33, 34). Targeted intervention is superfluous in this self-resolving condition. Patients must refrain from sexual intercourse until the symptoms have subsided.

Trichomonas vaginalis

Trichomonas vaginalis is the most prevalent parasitic sexually transmitted infection globally, known as trichomoniasis, with an annual incidence of several hundred million cases. However, it is infrequent in the European population and rare in the United States, affecting merely 0.5% of men, with higher rates observed among incarcerated individuals (prevalence: up to 8%). TV is a flagellated, extracellular protozoan capable of infecting urogenital squamous epithelia (35–37). The incubation time varies from a few days to one month (35). Transmission occurs with unprotected sexual intercourse or direct mucosal contact (35). Men seldom exhibit symptoms; nonetheless, manifestations of urethritis, epididymitis, or prostatitis may occur (6, 35, 36). NAATs are the preferred diagnostic test. Urine is the recommended specimen for symptomatic people (35, 36). The protozoan may be identified microscopically if the procedure is conducted promptly; nonetheless, it exhibits limited sensitivity (about 50%). Kissinger et al. and Van Gerwen et al. do not advocate for culturing in men; nevertheless, the CDC states that numerous specimens may be used for the inoculation of a single culture (6).

The European IUSTI guideline recommends metronidazole 400–500 mg BID for 5–7 days, accompanied by a minimum 24-hour abstinence from alcohol after therapy completion. The CDC recommends administering a single oral dose of 2 g metronidazole to males; nevertheless, there is a lack of relevant evidence from meta-analyses on the treatment of men. Individuals who are infected must refrain from sexual intercourse when both they and their partners have completed therapy and symptoms have subsided (6, 35, 37). A TOC is unnecessary for asymptomatic individuals (37). Existing partners need to be given presumptive treatment.

Haemophilus influenzae

Haemophilus influenzae (HI) is a meticulous bacterial pathogen that typically inhabits the upper respiratory system, but may also be introduced to the urethra by oral intercourse. The incidence of HI–NGU varies between 7.4% and 14% (8, 38). Diagnosis of HI has been conducted using serotyping, culturing, or nucleic acid amplification tests (NAATs) (8, 38). The 2017 research by Ito demonstrated effective treatment of HI using the suggested Japanese strategy; however, there have been no extensive follow-up studies regarding the response to current European and United States NGU regimens (38). Nonetheless, infections caused by the aforementioned uncommon species are often self-limiting, responsive to current NGU care protocols, or too infrequent to have clinical significance.

Mycoplasma hominis, *Mycoplasma penetrans*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*

In 2018, the European STI Guidelines Editorial Board issued a position statement advising diagnostic laboratories to refrain from testing for *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*, as urethral colonization by these microorganisms is prevalent in the absence of disease. *Ureaplasma urealyticum* (UU) has been identified as a potential causal agent of non-gonococcal urethritis (NGU), albeit its significance is mostly associated with elevated bacterial loads (6, 21, 39). Jordan et al. (7) conducted a case-control study to ascertain the risk of UU in instances with NGU. UU–mono-infection is not correlated with non-gonococcal urethritis. UU seems to inhabit the urethra without inducing inflammation, leading to its increasing classification as a non-NGU pathogen (7, 8, 21). Jordan et al. noted a common co-occurrence with other NGU pathogens (7).

The respiratory or urogenital tract contains the Gram-positive intracellular bacteria *Mycoplasma penetrans*. *Mycoplasma genitalium* constituted 21% of previously idiopathic non-gonococcal urethritis patients in a case-control study conducted by Srinivasan et al. (8). Notably, a greater number of men who have sex with men (MSM) had MP-urethritis compared to men who have sex with women (MSW), with an association of MP-urethritis seen only within the MSM cohort (8). Detection of MP is achievable with the use of NAATs (8). MP was excluded from the latest CDC or IUSTI treatment guidelines, warranting investigation in forthcoming studies (8). However, unpublished clinical findings suggest that the majority of these infections respond well to moxifloxacin, but not to macrolides (DE Nelson, personal communication).

Chronic manifestations of urethritis

If urethritis and/or symptoms continue, persons should undergo re-testing for Mycoplasma genitalium and *Trichomonas vaginalis*. Less common STIs and non-STI-related etiologies of urethral inflammation must also be taken into account. Individuals exhibiting symptoms without evidence of urethritis should be sent to a urologist knowledgeable about pelvic pain syndrome.

11. Conclusions and Future Perspectives

Despite significant advancements in the identification and treatment of STIs over the last several decades, the frequency of many STIs is rising due to various factors. A persistent worry is the fast development of antimicrobial resistance in NG to several antibiotic classes, and a much more pressing issue is the existence of untreatable MG infections, which is currently a reality. Venereologists urgently need adequate vaccinations for the prevention and treatment of gonorrhea, mostly due to the absence of clinical studies to date; nevertheless, preclinical experiments are now in progress addressing this issue (16). Adolescents and young adults (AYA) represent a significant proportion of those infected with STIs, making infections with NG, CT, and MG a critical issue for worldwide sexual and reproductive health. In particular, infections with CT are a significant concern, since many cases are asymptomatic and are presumably acquired during the reproductive period of life (40).

Educational programs for adolescents and young adults exhibiting risky behaviors are crucial. In several nations, folks lack awareness of the specialty of venereology and first see general practitioners or urologists. However, those individuals may not be acquainted with the most recent advancements in sexually transmitted infections. Consequently, identification and appropriate treatment may be postponed, leading to considerable morbidity and a difficult progression of the illness. This paper provides a thorough

summary for all clinicians about the predominant cause of urethritis-like symptoms, and the authors propose a diagnostic and treatment protocol suitable for practical practice.

References

1. Moi H, Blee K, Horner PJ. Management of non-gonococcal urethritis. BMC Infect Dis. (2015) 15:294.
2. Horner PJ, Blee K, Falk L, van der Meijden W, Moi H. 2016 European guideline on the management of non-gonococcal urethritis. Int J STD AIDS. (2016) 27:928–37.
3. Rossignol L, Feuillepain L, Ngangro NN, Souty C, Fournet N, Le Strat Y, et al. Estimate of male urethritis incidences in France between 2007 and 2017 with a specific focus on Neisseria gonorrhoeae, Chlamydia trachomatis, and *Trichomonas vaginalis* infections. BMC Infect Dis. (2019) 19:561.
4. Bachmann LH, Manhart LE, Martin DH, Senþa AC, Dimitrakoff J, Jensen JS, et al. Advances in the understanding and treatment of male urethritis. Clin Infect Dis. (2015) 61:763–9.
5. Gottesmann T, Yossepowitch O, Samra Z, Rosenberg S, Dan M. Prevalence of Mycoplasma genitalium in men with urethritis and high risk asymptomatic males in Tel Aviv: a prospective study. Int J STD Aids. (2017) 28:127–32.
6. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021 CDC. MMWR Recomm Rep. (2021) 70:1–187.
7. Jordan SJ, Toh E, Williams JA, Fortenberry L, LaPradd ML, Katz BP, et al. Etiology and prevalence of mixed-infections and mono- infections in non-gonococcal urethritis in men: a case-control study. Sex Transm Infect. (2020) 96:306–11.
8. Srinivasan S, Chambers LC, Tapia KA, Hoffman NG, Munch MM, Morgan JL, et al. Urethral microbiota in men: association of Haemophilus influenzae and Mycoplasma penetrans with nongonococcal urethritis. Clin Infect Dis. (2021) 73:e1684–93.
9. Horner PJ, Martin DH. Mycoplasma genitalium infection in men. J Infect Dis. (2017) 216:396–405.
10. Randjelovic I, Moghaddam A, Freiesleben de Blasio B, Moi H. The role of polymorphonuclear leukocyte counts from urethra, cervix, and vaginal wet mount in diagnosis of nongonococcal lower genital tract infection. Infect Dis Obst Gyn. (2018) 2018:8236575
11. Bignell C, Ison CA. Gonorrhoea. Sex Transm Inf. (2006) 82:6–9.
12. Unemo M, Ross JDC, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhea in adults. Int J STD AIDS. (2020) 32.
13. Nenoff P, Manos A, Ehrhard I, Krüger C, Paasch U, Helmbold P, et al. Nichtvirale sexuell übertragene infektionen- epidemiologie, klinik, labordiagnostik und therapie. Hautarzt. (2017) 68:43–58.
14. Tzeng YL, Bazan JA, Turner AN, Wang X, Retchless AC, Read TD, et al. Emergence of a new Neisseria meningitidis clonal complex 11 lineage 11.2 clade as an effective urogenital pathogen. Proc Natl Acad Sci U.S.A. (2017) 114:4237–42.
15. Tiplica GS, Radcliffe K, Evans C, Gomberg M, Nandwani R, Rafila A, et al. 2015 European guidelines for the management of partners of persons with sexually transmitted infections. J Eur Acad Dermatol Venereol. (2015) 29:1251–7.
16. Gottlieb SL, Jerse AE, Delany-Moretlwe S, Deal C, Giersing BK. Advancing vaccine development for gonorrhoea and the global STI vaccine roadmap. Sex Health. (2019) 16:426–32.
17. Unemo M, Golparian D, Eyre DW. Antimicrobial resistance in Neisseria gonorrhoeae and treatment of gonorrhea. Methods Mol Biol. (2019) 1997:37–58.
18. Unemo M, Lahra MM, Escher M, Eremin S, Cole MJ, Galarza P, et al. WHO global antimicrobial resistance surveillance for Neisseria gonorrhoeae 2017-18: a retrospective observational study. Lancet Microbe. (2021) 2:e627–36.
19. Unemo M, Seifert HS, Hook EW, Hawkes S, Ndowa F, Dillon JAR. Gonorrhoea. Nat Rev Dis Primers. (2019) 5:79.
20. Wiesenfeld HC, Manhart L. Mycoplasma genitalium in women: current knowledge and research priorities for this recently emerged pathogen. J Infect Dis. (2017) 216:389–95.
21. Toh E, Gao X, Williams JA, Batteiger TA, Coss LA, LaPradd M, et al. Evaluation of clinical, gram stain, and microbiological cure outcomes in men receiving azithromycin for acute nongonococcal urethritis:

discordant cures are associated with Mycoplasma genitalium infection. Sex Transm Dis. (2022) 49:67–75.
22. Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD Aids. (2015) 27:333–48.
23. Witkin SS, Minis E, Athanasiou A, Leizer J, Linhares IM. Chlamydia trachomatis: the persistent pathogen. Clin Vaccine Immunol. (2017) 24:e203–17.
24. Bebear C, de Barbeyrac B. Genital Chlamydia trachomatis infections. Clin Microbiol Infect. (2009) 15:4–10.
25. Lau A, Kong FYS, Fairley CK, Templeton DJ, Amin J, Phillips S, et al. Azithromycin or doxycycline for asymptomatic rectal Chlamydia trachomatis. N Engl J Med. (2021) 384:2418–27.
26. Gnanadurai R, Fifer H. Mycoplasma geniatlium: a review. Microbiology. (2020) 166:21–9.
27. Jensen JS, Cusini M, Gomberg M, Moi H, Wilson J, Unemo M. 2021 European guideline on the management of Mycoplasma genitalium infections. J Eur Acad Dermatol Venereol. (2022) 36:641–50.
28. Machalek DA, Tao Y, Shilling H, Jensen JS, Unemo M, Murray G, et al. Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in Mycoplasma genitalium: a systematic review and meta-analysis. Lancet Infect Dis. (2020) 20:1302–14.
29. Durukan D, Read TRH, Murray G, Doyle M, Chow EPF, Vodstrcil LA, et al. Resistance-guided antimicrobial therapy using doxycycline-moxifloxacin and doxycycline-2.5 g azithromycin for the treatment of Mycoplasma genitalium infection: efficacy and tolerability. Clin Infect Dis. (2020) 71:1461–8.
30. Murray GL, Bodiyabadu K, Danielewski J, Garland SM, Machalek DA, Fairley CK, et al. Moxifloxacin and sitafloxacin treatment failure in Mycoplasma genitalium infection: association with parC mutation G248T (S83I) and concurrent gyrA mutations. J Infect Dis. (2020) 221:1017–24.
31. Murray GL, Bradshaw CS, Bissessor M, Danielewski J, Garland SM, Jensen JS, et al. Increasing macrolide and fluoroquinolone resistance in Mycoplasma genitalium. Emerg Infect Dis. (2017) 23:809–12.
32. Ong JJ, Morton AN, Henzell HR, Berzins K, Druce J, Fairley CK, et al. Clinical characteristics of herpes simplex virus urethritis compared with Chlamydial urethritis among men. Sex Transm Dis. (2017) 44:121–5.
33. Bradshaw CS, Tabrizi SN, Read TR, Garland SM, Hopkins CA, Moss LM, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. J Infect Dis. (2006) 193:336–45.
34. Liddle OL, Samuel MI, Sudhanca M, Ellis J, Taylor C. Adenovirus urethritis and concurrent conjunctivitis: a case series and review of the literature. Sex Transm Infect. (2015) 91:87–90.
35. Kissinger P. *Trichomonas vaginalis*: a review of epidemiologic, clinical and treatment issues. BMC Infect Dis. (2015) 15:307.
36. Van Gerwen OT, Muzny CA. Recent advances in the epidemiology, diagnosis, and management of Trichomonas vaginalis infection. F1000Research. (2019) 20.
37. Sherrad J, Wilson J, Donders G, Mendling W, Jensen JS. 2018 European (IUSTI/WHO) International Union against sexually transmitted infections (IUSTI) World Health Organisation (WHO) guideline on the management of vaginal discharge. Int J STD AIDS. (2018) 29:1258–72.
38. Ito S, Hatazaki K, Shimuta K, Kondo H, Mizutani K, Yasuda M, et al. Haemophilus influenzae isolated from men with acute urethritis: its pathogenic roles, responses to antimicrobial chemotherapies, and antimicrobial susceptibilities. Sex Transm Dis. (2017) 44:205–10.
39. Horner P, Doners G, Cusini M, Jensen JS, Unemo M. Should we be testing for urogenital Mycoplasma hominis, Ureaplasma parvum and Ureaplasma urealyticum in men and women? – a position statement from the European STI Gudielines Editorial Board. J Eur Acad Dermatol Venereol. (2018) 32:1845–51.
40. Shannon CL, Klausner JD. The growing epidemic of sexually transmitted infections in adolescents: a neglected population. Curr Opin Pediatr. (2018) 30:137–43.

الملخص

الخلفية :لا تزال الأمراض المعدية مثل الأمراض المنقولة جنسيًا(STIs) ، والإنفلونزا، والالتهابات التنفسية تشكل تحديات صحية عامة كبيرة على مستوى العالم. يمكن أن يؤدي التهاب الإحليل، الناتج غالبًا عن الأمراض المنقولة جنسيًا مثل *Chlamydia trachomatis* و*Neisseria gonorrhoeae*، إلى مضاعفات خطيرة إذا لم يُعالج.

المنهجيات :تُلخص هذه المراجعة الأدبيات الحديثة حول أسباب، المظاهر السريرية، أساليب التشخيص، والتدخلات العلاجية للأمراض المعدية الشائعة. نركز على دور اختبارات تضخيم الحمض النووي (NAATs) في التشخيص الدقيق، ونصف استراتيجيات الإدارة المتلازمية لالتهاب الإحليل

النتائج :تشير النتائج إلى أن التهاب الإحليل غالبًا ما يكون مُشخصًا بشكل ناقص، حيث يتم تصنيف ما يصل إلى 50% من الحالات كغير معروفة السبب. برزت اختبارات NAATs كمعيار ذهبي لتشخيص الأمراض المنقولة جنسيًا بفضل حساسيتها وخصوصيتها العالية. بالنسبة لالتهاب الإحليل السيلاني، تظهر الأعراض السريرية في حوالي 90% من الذكور، مع وجود معدلات مراضة عالية مرتبطة بالعدوى غير المعالجة. شهدت أنظمة العلاج تطورًا مستمرًا، حيث أثارت مقاومة المضادات الحيوية مخاوف تستلزم تحديث الإرشادات.

الخلاصة :يتطلب التعامل الفعّال مع الأمراض المعدية تشخيصًا دقيقًا واستراتيجيات علاجية مناسبة. يُعد الرصد المستمر لأنماط مقاومة المضادات الحيوية أمرًا ضروريًا لتعديل بروتوكولات العلاج. تعتبر المبادرات الصحية العامة التي تركز على التثقيف والوقاية أمرًا حيويًا لتقليل معدل انتشار الأمراض المنقولة جنسيًا وغيرها من الأمراض المعدية.

الكلمات المفتاحية :الأمراض المعدية، الأمراض المنقولة جنسيًا، التهاب الإحليل، اختبارات تضخيم الحمض النووي، مقاومة المضادات الحيوية.