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INFLAMMATORY/INFECTIOUS BLADDER DISORDERS (M. SHERIF MOURAD, SECTION EDITOR)

Updates on Sexually Transmitted Urethro-cystitis

Mostafa M. Mostafa[1,2] · **Ayman Mahdy**[1,3] · **Gamal Ghoniem**[4]

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Abstract

Purpose of Review We performed recent literature review with the aim to address the updates in diagnosis and management of sexually transmitted urethro-cystitis.

Recent Findings There are multiple, recently published studies that collectively lead to an organized stepwise plan for diagnosis and management of sexually transmitted urethro-cystitis.

Summary Sexually transmitted urethro-cystitis is a common health condition that can be managed efficiently if the appropriate steps are taken in diagnosis and management.

Keywords Sexually transmitted urethro-cystitis · Gonococcal urethro-cystitis (GU) · Non-gonococcal urethro-cystitis (NGU)

Abbreviations

STI	Sexually transmitted infection
GU	Gonococcal urethro-cystitis
GSS	Gram-stained smear
NAAT	Nucleic acid amplification test
FVU	First-void urine
NGU	Non-gonococcal urethro-cystitis
HSV	Herpes simplex virus
PMNL	Polymorphonuclear leucocytes
HPF	High-power field

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✉ Gamal Ghoniem
gghoniem@hs.uci.edu

Mostafa M. Mostafa
mostafmm@ucmail.uc.edu

Ayman Mahdy
mahdyan@uc.edu

[1] Division of Urology, Department of Surgery, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML 0589, Cincinnati, OH 45267, USA

[2] Asiut University Hospitals, Asiut, Egypt

[3] West Chester Hospital, West Chester Township, OH 45069, USA

[4] Department of Urology, University of California, Irvine, 333 City Blvd West, Suite 2100, Orange, CA 92868, USA

Introduction

Urethro-cystitis, traditionally encompassing all conditions involving urethral discharge, has recently been proven to occur in asymptomatic patients as well as those with dysuria, itching, and/or tingling without discharge [1]. Based on the underlying etiology, urethro-cystitis is classified into infectious and non-infectious. Sexual contact is the mode of transmission of the infectious urethro-cystitis. Sexually transmitted urethro-cystitis can be further classified into gonococcal and non-gonococcal [2]. Sexually transmitted infections (STIs), in general, have recently become globally concerning owing to both their increasing prevalence and wide range of negative consequences [3]. Increasingly alarming, approximately 50% of the 20 million newly diagnosed STIs in the USA every year occur in young people, possibly explained by the increased prevalence of risk-taking behavior associated with the developmental period of adolescence [4, 5]. Having multiple and simultaneous sex partners, inconsistent condom use, unprotected sex, limited immunocompetence, adolescent female cervical ectopy with subsequent increased infection susceptibility, lower access to STI prevention health services, and drug use also potentially contribute to the increased STI prevalence in this age group [5–8].

Gonococcal Urethro-cystitis (GU)

Gonorrhea is the second most common STI after chlamydia with up to 700,000 new cases diagnosed annually in the USA [3, 9].

Clinical Manifestations

Classically infecting mucous membranes, *Neisseria gonorrhoeae* has been implicated in the pathogenesis of a wide range of infections including urethro-cystitis, pharyngitis, conjunctivitis, proctitis, epididymitis, cervicitis, pelvic inflammatory disease, and disseminated infections besides increasing the rates of human immunodeficiency virus transmission [10] (Table 1).

Table 1 Symptomatology of gonococcal versus non-gonococcal urethro-cystitis

Points of comparison	GU	NGU
Asymptomatic patients	< 3%	> 10%
Incubation period	2–5 days	2–3 weeks
Onset	Abrupt onset	Insidious onset
Symptom severity	Severe	Less severe
Discharge	• Almost always present • Purulent • Profuse	• May be absent with just peri-meatal crusting • Mucoid or mucopurulent • Scanty
Dysuria	Severe	Mild
Systemic symptoms (e.g., fever, malaise)	More common	Less common
Reactive arthritis	Less common	More common

GU, gonococcal urethro-cystitis; *NGU*, non-gonococcal urethro-cystitis

Diagnosis

Although microscopic examination of a gram-stained urethral smear (GSS) is useful, diagnosis of GU is best accomplished by nucleic acid amplification tests (NAAT) performed on either cervical or vaginal swabs in case of females or first-void urine (FVU) in both males and females [1, 5]. Vaginal swabs are preferred in females, while FVU is preferred in males [5] (Table 2).

Treatment

Dual therapy with a single intramuscular injection of ceftriaxone 250 mg and a single oral dose of azithromycin 1 g is currently the mainstay of treatment of GU [2]. It is currently recommended to use the 250 mg rather than the 125 mg dosage of ceftriaxone as the lower dosage has a lower efficacy in treating concomitant pharyngeal infections and higher treatment failure rates [9]. It is also recommended to use the single oral dose of azithromycin rather than the 1-week course of twice daily doxycycline 200 mg due to better compliance and lower risk of tetracycline resistance [9, 11, 12]. Although up to 10% of patients with penicillin allergies have cross-reactivity to cephalosporins, the only

Table 2 Diagnosis and treatment of gonococcal versus non-gonococcal urethro-cystitis

Points of comparison	GU	NGU
Diagnosis		
1) Discharge	Profuse and purulent	Scanty and mucoid
2) Gram-stained urethral smear	• ≥ 5 PMNL/HPF • Intracellular gram-negative diplococci of *Neisseria gonorrhoeae*	• ≥ 2 PMNL/HPF • Lack of gram-negative diplococci (required to exclude GU)
3) Nucleic acid amplification test	Gold-standard	Gold-standard
4) Culture	• Confirmatory • Identify antibiotic sensitivity	• Confirmatory • Identify antibiotic sensitivity
Treatment		
	• Recommended regimen: dual therapy with a single intramuscular injection of ceftriaxone 250 mg and a single oral dose of azithromycin 1 g • Important recommendation: 1. Retest patients 3 months after starting therapy due to high re-infection rates 2. Evaluate and treat all sexual partners in the past 60 days before diagnosis 3. Advise the patients to avoid sexual intercourse for at least 1 week after initiating treatment	• Patients with severe symptoms: immediate empirical treatment with either doxycycline or azithromycin without waiting for the test results • Patients with mild symptoms: pathogen-directed treatment after NAATs, culture, and microscopy • Important recommendations: 1. Abstain from sexual intercourse for at least 7 days after starting therapy 2. Screen and treat all sexual partners over the past 60 days 3. Screen for other STDs including syphilis and HIV

GU, gonococcal urethro-cystitis; *NGU*, non-gonococcal urethro-cystitis

contraindication to the therapy is a history of severe reaction to penicillin because the cross-reactivity is more likely with the first-generation cephalosporins than the third-generation cephalosporins such as ceftriaxone [13]. On the other hand, patients with severe allergic reactions to cephalosporins should consult an infectious diseases specialist. However, desensitization is usually not needed [9]. Cefixime can be used as an alternative to ceftriaxone if ceftriaxone is not available [14, 15]. Quinolones are no longer recommended in the USA for treatment of gonorrhea to avoid development of quinolone-resistant *Neisseria gonorrhoeae* [9, 16]. It is highly recommended to retest the patients approximately 3 months after starting the therapy due to the substantially high re-infection rates [17, 18]. Furthermore, in order to lower the risk of re-infection, it is also recommended to evaluate and, if required, treat all sexual partners in the past 60 days before diagnosis and to advise the patients to avoid sexual intercourse for at least 1 week after initiating treatment [2] (Table 2).

Non-gonococcal Urethro-cystitis (NGU)

Although *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis* were traditionally considered the main pathogens responsible for the acquisition of NGU, recent advances in NAAT proved the rule of several other pathogens such as Ureaplasmas, Herpes simplex viruses (HSV), and Adenoviruses [1]. While *Chlamydia trachomatis* is the only non-gonococcal bacterium causing urethro-cystitis which is routinely screened for and is detected in approximately 20–50% of patients [19], *Mycoplasma genitalium* has become the second most frequently encountered pathogen in NGU cases [19–21]. A combined infection with *Chlamydia trachomatis* and *Mycoplasma genitalium* has also been reported in up to 5 to 15% of patients [22]. However, neither *Chlamydia trachomatis* nor *Mycoplasma genitalium* has been detected in approximately 30–60% of NGU cases [23, 24]. This finding has classically been demonstrated in older patients and those without symptoms or discharge [23, 25]. Classically implicated in the pathophysiology of NGU besides increasing the risk of human immunodeficiency virus transmission up to threefold, *Trichomonas vaginalis* has a prevalence rate of 2.5–17% in the USA and is more common in females than in males and in African American patients [25–31]. Likewise, Ureaplasmas are ocassionally associated with NGU [32]. Despite initially failing to differentiate between *Ureaplasma urealyticum* (biovar 2) and *Ureaplasma parvum* (biovar 1), there is growing body of literature not only that *Ureaplasma urealyticum* is solely pathogenic but also that *Ureaplasma urealyticum* is not pathogenic in all infected patients [33–35]. Although some studies demonstrated that this pathogenic *Ureaplasma urealyticum* can account for up to 5–10% of NGU cases, these cases often have no evidence of urethro-cystitis making diagnosis and treatment still debatable [36]. Accounting for 2–4% of NGU cases, Adenoviruses often lead to concomitant conjunctivitis [37–39]. HSV types 1 and 2 are another cause of viral urethro-cystitis accounting for 2–3% of cases [39]. HSV-1 is often responsible for the first episode of genital herpes, while HSV-2 is usually encountered in recurrent genital herpes [40, 41]. The presence of monocytes in microscopical smear is a typical feature of viral urethro-cystitis [38]. Other rare etiologies of NGU include *Neisseria meningitidis*, *Haemophilus* species, *Candida* species, bacterial vaginosis-associated bacteria, urethral stricture, foreign bodies, and possibly Epstein Barr Virus [42–44]. Although modern techniques enabled detection of many pathogens, there may still be unidentified pathogens implicated in the pathogenesis of urethro-cystitis. Accordingly, some organism-negative or idiopathic NGU cases that are currently considered non-infective may later prove infective, but we just did not have the sufficient tools to identify all implicated pathogens [45, 46].

Clinical Manifestations

The diagnosis of NGU should be suspected in patients with discharge, dysuria, itching, and/or penile tip irritation especially when the discharge is mucopurulent, sparse, cloudy, and/or clear [47]. Responsible for up to 15–40% of NGU, *Chlamydia trachomatis* is more commonly associated with reactive arthritis than *Neisseria gonorrhoeae* particularly in the presence of human leukocyte antigen-B27 [39, 48] (Table 1).

Diagnosis

Classically, the first step in diagnosis of NGU is the exclusion of gonococcal infections via GSS, NAAT, or culture [47]. However, high-risk symptomatic patients can be diagnosed and empirically treated for both chlamydia and gonorrhea [49]. The validity of the traditional method of diagnosis of NGU via the demonstration of polymorphonuclear leucocytes (PMNL) in the absence of the gram-negative diplococci of *Neisseria gonorrhoeae* in urethral discharge has been recently put into question. This is largely because some NGU patients present with symptoms such as itching, dysuria, and/or tingling in the absence of urethral discharge [1, 50]. Moreover, the conventional definition of urethro-cystitis as the demonstration of ≥ 5 PMNL per high-power field microscopy (HPF) in GSS from the anterior urethra [51] has recently proved non-applicable for NGU. Orellana et al. [52] and Rietmeijer et al. [53] reported high prevalence of *Chlamydia trachomatis* in low-grade urethro-cystitis of 3–5 PMNL/HPF. Additionally, Sarier et al. [54] reported that the sensitivity of GSS for NGU diagnosis was significantly higher

when the threshold was lowered from ≥ 5 to ≥ 2 PMNL/HPF. Accordingly, the Centers for Disease Control and Prevention (CDC) and the European Association of Urology (EAU) acted in favor of the findings from recent literature with the former lowering the threshold to ≥ 2 PMNL/HPF in its 2015 Sexually Transmitted Disease (STD) treatment guidelines and the latter recommending application of the threshold of ≥ 5 PMNL/HPF only for diagnosis of GU in its 2017 guidelines [55]. Based on the above, NAAT has largely replaced GSS in the diagnosis of both gonococcal and non-gonococcal urethro-cystitis despite having lower efficacy in identification of other infective pathogens [56, 57]. NAAT for chlamydia, gonorrhea, trichomoniasis, and possibly *Mycoplasma genitalium* is generally recommended over culture due to its high sensitivity and specificity [2]. The NAAT should be performed on a maximum of 10 ml of FVU as increasing the volume decreases the sensitivity [47] (Table 2).

Treatment

When approaching a patient with signs and symptoms of urethro-cystitis, the first step is to identify whether it is gonococcal or non-gonococcal urethro-cystitis [58]. After confirming NGU, patient with severe symptoms should receive empirical treatment with either doxycycline or azithromycin immediately without waiting for the test results [57, 59]. On the other hand, patients with mild symptoms should receive pathogen-directed treatment after NAATs, culture, and microscopy as sometimes urethro-cystitis can resolve without treatment, but it is important to consider that NAATs identify pathogen but not susceptibility to antibiotics [57, 60].

In cases of *Chlamydia trachomatis* or *Ureaplasma*, azithromycin or doxycycline is often used for at least 7 days. Fluroquinolones can also be used as a second-line treatment in selected cases [36, 61, 62]. Manhart et al. [63] and Schwebke et al. [64] reported an equal efficacy of both doxycycline and azithromycin in management of NGU. However, doxycycline is still often preferred because of its higher chlamydial cure rates and lower risk of macrolide resistance [47, 63, 64]. Treatment of trichomoniasis often requires a single dose of metronidazole [57, 65, 66]. On the other hand, *Mycobacterium genitalium* can be treated with doxycycline, macrolides, and moxifloxacin [63, 64, 67].

To lower the risk of re-infection, it is important to advise the patient to abstain from sexual intercourse for at least 7 days after starting therapy, to screen and treat all sexual partners over the past 60 days, and to screen for other STDs including syphilis and HIV [6–8, 56, 68, 69] (Table 2).

Discussion

Possibly transmitted by bacteria, viruses, or parasites from one human being to another via vaginal, anal, or oral sexual contact, STIs are often oligo- or asymptomatic highlighting the need for high index of suspicion to efficiently diagnose and treat such infections [70]. The most prevalent mono-infection in sexually transmitted urethro-cystitis is *Chlamydia trachomatis* at a rate of 64.1%, while combined infections occur in a total of 5.6% of patients [71].

Urethral smear microscopy is a very essential diagnostic tool in men presenting with clinical manifestations of urethro-cystitis. It has the advantage of not only confirming the diagnosis by demonstrating excess PMNLs but also ruling out gonorrhea. Additionally, a NAAT is indicated in all patients with clinical manifestations of urethro-cystitis for detection of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, HSV, *Adenovirus*, and *Trichomonas vaginalis* [59].

The first step in management of patients presenting with signs and symptoms of urethro-cystitis is determining whether it is gonococcal or non-gonococcal urethro-cystitis. In the case of GU, dual therapy with ceftriaxone and azithromycin remains the mainstay of treatment. On the other hand, for the NGU, the severity of patients' symptoms often determines the course of treatment: patients with mild symptoms are often re-evaluated after 3–7 days when the results of NAAT become available as they usually recover spontaneously, while those with severe symptoms are often treated once diagnosed with either doxycycline or azithromycin without waiting for laboratory test results.

Conclusions

Sexually transmitted genito-urinary infections are highly prevalent in adolescence due to the major psychosocial changes during this developmental period. High index of suspicion is needed while diagnosing and treating sexually transmitted urethro-cystitis, especially in this age group. Urethral smear microscopy and nucleic acid amplification tests are the main diagnostic tools. The first step in management is almost always identifying whether the urethro-cystitis is gonococcal or non-gonococcal to guide the appropriate treatment plan.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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