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LOWER URINARY TRACT SYMPTOMS & VOIDING DYSFUNCTION (J SANDHU, SECTION EDITOR)

Recurrent Urinary Tract Infections in Females and the Overlap with Overactive Bladder

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Abstract

Purpose of Review There are an estimated 33 million men and women with overactive bladder (OAB) in the USA. Despite the prevalence of OAB, it remains a frequently misdiagnosed condition. OAB has shared symptomatology with other common urologic conditions, namely recurrent urinary tract infections (UTIs). Here, we will review key distinguishing features of OAB that aid in establishing an accurate diagnosis and recent advances in OAB management.

Recent Findings Recent studies have shown that among women presenting with lower urinary tract symptoms, the majority were diagnosed with UTIs and treated without performing a urine culture as routine care. The authors found that when urine cultures were obtained, less than half of women had a positive urine culture, suggesting that empiric treatment of UTIs without cultures commonly led to a misdiagnosis of UTI. The symptoms of OAB have overlap with other common conditions, most notably UTI, BPH, and bladder cancer/carcinoma in situ. Despite the shared symptomatology of OAB and UTI, the timing of symptom onset is usually very different between the two. UTI symptoms are generally acute, whereas those of OAB are generally chronic. OAB and UTI share the common features of urgency, frequency, and nocturia. However, dysuria and hematuria are not features of OAB, while they are frequently seen in UTI. Of note, urgency, frequency, and nocturia are rarely seen in bladder cancer/carcinoma in situ; when these symptoms do occur, it is generally in the setting of microhematuria. One study of patients with carcinoma in situ found that 41% had macroscopic hematuria and 44% had microscopic hematuria at presentation. In patients with lower urinary tract symptoms, it is important to perform a urinalysis (UA) to evaluate for microhematuria to rule out the possibility of malignancy. First-line treatment of OAB (outside the setting of UTI) involves behavioral modification, including bladder training, fluid management, and pelvic floor exercises. Numerous studies have supported behavioral modification strategies as the most efficacious initial step in treatment. Although routinely given for recurrent UTIs and vaginal atrophy in postmenopausal women, several review articles have shown that vaginal estrogen is an effective treatment of lower urinary tract symptoms.

Summary The importance of distinguishing OAB from other conditions presenting with similar symptoms is key in preventing misdiagnosis, treatment delays, and antibiotic overuse. Here, we have reviewed key parameters distinguishing OAB from UTI, the most commonly misdiagnosed condition among those presenting with lower urinary tract symptoms (LUTS). Given that UTI is the most commonly misdiagnosed condition among women with OAB, we recommend relying on urine cultures and the constellation of acute-onset dysuria, frequency, and urgency as more important diagnostic factors in distinguishing these conditions.

Keywords Overactive bladder · LUTS · Recurrent urinary tract infections · Voiding dysfunction

This article is part of the Topical Collection on *Lower Urinary Tract Symptoms & Voiding Dysfunction*

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Introduction

In the USA alone, approximately 33 million men and women are estimated to have overactive bladder (OAB) [1], although the actual number is likely higher as people with OAB symptoms may not seek care or be accurately diagnosed. The National Overactive Bladder Evaluation (NOBLE) program found an overall OAB prevalence of ~16%, with no

significant differences between men and women [1]. Historically, diagnosing OAB was complicated by a lack of universal criteria. In 2002, the International Continence Society defined OAB as a "symptom syndrome suggestive of lower urinary tract dysfunction," specifically, "urgency, with or without urge incontinence, usually with frequency and nocturia" in the absence of underlying pathology [2, 3]. Since the adaptation of this universal definition, the EpiLUTS study surveyed a large, population-representative sample of men and women in the USA, UK, and Sweden for the presence of lower urinary tract symptoms (LUTS). They found that, among the 30,000 individuals surveyed, 22.4% of men and 35.7% of women surveyed endorsed urgency "at least sometimes" [4]. Thus, it is likely that the prevalence of OAB is underrepresented, as OAB-type symptoms occur with very high frequency and patients may not seek a formal diagnosis. Interestingly, the authors also found that the frequency of these symptoms increases with age for both men and women. Although OAB and urinary tract infection (UTI) can have overlapping symptoms, their treatments differ widely, making careful diagnosis and workup essential to proper management. Here, we will review the diagnosis of recurrent UTIs and OAB, key differentiators between OAB and recurrent UTI, and how to better tailor management once OAB has been diagnosed.

OAB Is Commonly Mistaken for UTI

The lifetime risk for a woman to develop a UTI is estimated to be over 50% [4], leading to significant quality of life implications and healthcare expenditures in the USA. Recurrent UTI is defined as ≥ 2 UTIs in 6 months or ≥ 3 infections in 1 year. Once diagnosed with a UTI, women have a 25% chance of having a recurrent UTI in the following 3–6 months [5]. Risk factors for recurrent UTI among women ages 18–30 include 4–8 episodes of sexual intercourse over a 1-month period, spermicide use, new sexual partner during the past year, age at first UTI ≤ 15, and UTI history in the patient's mother [6]. Among postmenopausal women, a case-control study found that urinary incontinence, presence of a cystocele, and postvoid residual volume were strongly associated with recurrent UTI. The authors found that upon further analysis, urinary incontinence, a history of UTI before menopause, and nonsecretor status were the most strongly correlated factors [7, 8]. Estrogen secretion is markedly reduced after menopause, which can lead to vaginal atrophy and predisposes women to LUTS and recurrent UTIs. In fact, the decreased estrogen after menopause predisposes women to developing UTIs, as estrogen normally plays a role in reducing vaginal pH level, proliferating lactobacillus in the vaginal epithelium, and avoiding colonization of Enterobacteriaceae (the main pathogen causing UTIs) [9]. A randomized clinical trial found that treatment with vaginal estrogen prevents recurrent UTIs in postmenopausal women, likely by changing the vaginal flora, increasing commensal lactobacilli, and decreasing vaginal pH level [10].

Vaginal atrophy can present with a primary complaint of vulvar irritation which can sometimes mimic the dysuria of a UTI [11, 12]. An increasing body of evidence suggests that both postmenopausal women not on hormone replacement and premenopausal women on hormonal birth control (particularly drospirenone-containing formulas) experience thinning of the vaginal epithelium and vaginal vestibular pain. For many, this epithelial disruption results in burning of the vaginal opening and distal urethra upon contact with urine, which is easily mistaken as the dysuria of a UTI, especially in a patient with OAB, who will also manifest urinary frequency and urgency.

The Overdiagnosis of UTI

Although UTI often presents with the "classic" symptoms of dysuria, urgency, and frequency, OAB is another common urologic condition that should be considered when patients present with UTI symptoms. The gold standard for confirming a UTI remains a positive urine culture. Given the delay to diagnosis, many providers opt for empiric treatment when women present with LUTS consistent with a symptomatic UTI. However, there is an increasing body of evidence showing that UTI remains overdiagnosed. One observational cohort study of the diagnosis of UTI in the emergency department found that among the 264 women presenting to the ED with lower urinary tract symptoms, 175 (66%) were diagnosed with UTIs, 100 (57%) of whom were treated without performing a urine culture as a routine care. The authors found that when urine cultures were obtained, only 84 (48%) of these women had a positive urine culture, suggesting that in their population, empiric treatment of UTIs without cultures commonly led to a misdiagnosis of UTI [13]. A Swedish study in 2008 found that 43% of patients diagnosed with UTIs were culture negative [14]. A more recent study by Aisen et al. found that among women with vague UTI symptoms, there is utility in obtaining catheterized urine samples in preventing the overdiagnosis of UTIs rather than relying on clean catch samples [15]. Given the growing emergence of drug-resistant organisms secondary to the overuse of antibiotics, we as providers should aim to reduce overtreatment with antibiotics and use documented cultures, particularly when diagnosing recurrent UTI.

Practicing better antibiotic stewardship in an era of increasing microbial resistance is imperative. In patients with unclear diagnoses of OAB vs. uncomplicated UTI, waiting for urine culture results prior to prescribing antibiotics is a

reasonable practice. One significant exception to this is in older patients presenting with symptomatic UTIs. These patients may not only experience dysuria, suprapubic discomfort, frequency, and urgency, but may also have unique symptoms, such as incontinence, lethargy, altered mental status, or anorexia [17]. Given the symptom overlap between recurrent UTI and OAB, it is important to understand key differences between the two common conditions in order to accurately distinguish the two.

Differential Diagnosis of OAB

The symptoms of OAB have overlap with other common conditions, most notably UTI, BPH, and bladder cancer/carcinoma in situ. However, there are some key differences between the four conditions that aid in making an accurate diagnosis. Of note, OAB and UTI share the common features of urgency, frequency, and nocturia. Dysuria and hematuria are not features of OAB, while they are frequently seen in UTI [16]. Urgency, frequency, and nocturia are rarely seen in bladder cancer/carcinoma in situ; when these symptoms do occur, it is generally in the setting of microhematuria. One study of patients with carcinoma in situ found that 41% had macroscopic hematuria and 44% had microscopic hematuria at presentation [17]. Although classically, OAB symptoms in men, or "irritative" symptoms, were attributed to BPH, we now consider OAB and BPH as separate treatable entities in men. Although men with BPH experience frequency and urgency, the features of BPH that are unique from OAB are hesitancy, intermittency, and a sensation of incomplete voiding. Despite the shared symptomatology of OAB and UTI, the timing of symptom onset is usually very different between the two. UTI symptoms are generally acute, whereas those of OAB are generally chronic.

Dysuria Alone Is Not a Reliable Predictor of UTI

In addition to positive urine cultures, pain remains a key differentiator when considering the diagnosis of UTI vs. OAB. Dysuria is one of the hallmark features of UTI, but not routinely seen in OAB. However, dysuria alone cannot be used to diagnose UTI. In patients complaining of pain related to urination, care should be taken to distinguish interstitial cystitis (IC) from UTI, as the two conditions present very similarly, often with coexisting urgency, frequency, and discomfort.

IC is defined by SUFU/AUA as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with LUTS of more than six weeks duration, in the absence of infection or other identifiable causes." It is often not recognized and can be misdiagnosed as recurrent UTI for years before diagnosis, with an average delay between symptom onset and condition recognition of 5 years [18–20]. In one retrospective study of 45 patients who had a delayed diagnosis of IC, UTI was the most common diagnosis given upon initial presentation, despite not having a positive urine culture or pyuria on UA [21]. Therefore, a high index of suspicion must be present when women present with UTI symptoms and negative cultures.

Cultures Remain the Gold Standard for Accurate Diagnosis of UTI

The gold standard for diagnosis of a symptomatic UTI is a positive culture. A systematic review found that the diagnosis of UTI by symptomatology alone had a failure rate of approximately 33% [22]. One study of 2252 patients with OAB symptoms found that the dipstick had a sensitivity of 44% and specificity of 86% for the correct identification of UTI, suggesting that dipstick screening is not sufficient to distinguish between UTI and OAB [23]. For those with symptoms consistent with a urine infection and a dipstick positive for leukocyte esterase, nitrates, or blood, a culture is warranted. The importance of a urine culture cannot be understated when trying to distinguish between OAB and UTI, particularly given that OAB is a diagnosis of exclusion.

UTIs may also occur in patients with OAB. OAB patients may present with an exacerbation of their OAB symptoms and dysuria. A study of comorbid conditions among 148 women with OAB found that 11.5% had recurrent UTI [24].

The Role of UA in Suspected OAB

The SUFU/AUA guidelines for diagnosis of OAB suggest an evaluation that includes a history, physical exam, and urinalysis. Hematuria in the presence of LUTS is a key distinguishing feature of bladder carcinoma or carcinoma in situ, although there are numerous conditions that can cause hematuria, including UTIs, nephrolithiasis, and STIs. Although only a small (< 1%) proportion of patients with asymptomatic microscopic hematuria have bladder carcinoma [25, 26], we recommend that patients with OAB symptoms have a urinalysis performed to prompt further investigation when indicated.

Management of OAB in the Setting of UTI

First-line treatment of OAB (outside the setting of UTI) involves behavioral modification, including bladder training, fluid management, and pelvic floor exercises. Numerous

studies have supported behavioral modification strategies as the most efficacious initial step in treatment. Behavioral therapy aims to reduce OAB symptoms by increasing bladder capacity. Strategies include bladder training, behavioral medication including fluid restriction, pelvic floor physical therapy, and scheduled and/or prompted voiding [27, 28]. Pelvic floor or "Kegel" exercises (voluntarily contracting the pelvic floor muscles) not only help to gradually increase bladder capacity, but also to inhibit the micturition reflex and increase bladder outlet resistance. When patients develop OAB symptoms in the setting of an active UTI, first-line therapy is less likely to be effective. Instead, various pharmacologic agents can be used both for chronic OAB and OAB due to UTI. These agents can be used temporarily until symptoms resolve with antibiotics. The most common second-line therapies include antimuscarinic agents and beta antagonists. Third-line treatment options are reserved for chronic OAB (again, unrelated to UTIs) in which the patient does not tolerate or does not respond to medication. These include posterior tibial nerve stimulation, intravesical botulinum toxin injections, and sacral neuromodulation.

Although routinely given for recurrent UTIs and vaginal atrophy in postmenopausal women, several review articles have shown that vaginal estrogen is an effective treatment of LUTS [29–31]. Although vaginal estrogen has been shown in numerous studies to be effective in treating OAB symptoms, few studies exist comparing these anticholinergic agents to vaginal estrogen. A single-site randomized trial among women with OAB symptoms compared short-term outcomes after 12 weeks of single therapy with tolterodine extended-release in comparison to intravaginal estrogen. At 12 weeks, significant improvements in OAB symptoms were achieved in both single-therapy treatment groups, with no difference between tolterodine and intravaginal estrogen. Combination therapy outcomes at 24 and 52 weeks showed a greater improvement in symptoms than single-therapy outcomes at 12 weeks, suggesting that combination therapy should play a more significant role in symptom management [32], although larger studies are needed to validate these findings.

Conclusion

The importance of distinguishing OAB from other conditions presenting with similar symptoms is key in preventing misdiagnosis, treatment delays, and antibiotic overuse. Here, we have reviewed key parameters distinguishing OAB from UTI, the most commonly misdiagnosed condition among those presenting with LUTS. A thorough history, with particular attention to the presence of dysuria and timing of symptom onset, physical exam, UA, and culture help distinguish OAB from UTI. In patients with LUTS, it is important to perform a UA to evaluate for microhematuria to rule out the possibility of malignancy. Given that UTI is the most commonly misdiagnosed condition among women with OAB, we recommend relying on urine cultures and the constellation of acute-onset dysuria, frequency, and urgency as more important diagnostic factors in distinguishing these conditions.

Compliance with Ethical Standards

Conflict of Interest Farnoosh Nik-Ahd declares no potential conflicts of interest. A. Lenore Ackerman reports a 1-year research support grant from Pfizer. Jennifer Anger is an expert witness for Boston Scientific, Inc.

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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