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Overactive bladder, inflammation and urinary tract infection: pathogenetic parallels

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ABSTRACT

The review is devoted to modern ideas about the role of inflammation and urinary tract infection in the pathogenesis of overactive bladder. The molecular mechanisms of the mechanosensory function of the urothelium and the influence of bacterial colonization of the urothelium on it are described in detail. It has been shown that infectious inflammation, even in the absence of clinical symptoms, enhances the urothelial response to stretching and increases the excitability of afferent nerves. Bladder hypersensitivity and increased detrusor activity are pathogenetic basis for the development of overactive bladder. Data on the relationship between urinary infection and refractory overactive bladder are presented. The feasibility of conducting extended microbiological studies in patients with overactive bladder , especially when standard therapy is ineffective, has been demonstrated. A pathogenetic rationale for prescribing anti-inflammatory and immunoactive drugs to patients with overactive bladder is presented.

Keywords: overactive bladder; hypersensory bladder; bladder outlet obstruction; detrusor overactivity; urinary tract infection; urothelium.

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Гиперактивный мочевой пузырь, воспаление и инфекция мочевыводящих путей: патогенетические параллели

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АННОТАЦИЯ

Обзорная статья посвящена современным представлениям о роли воспаления и мочевой инфекции в патогенезе гиперактивного мочевого пузыря. Подробно описаны молекулярные механизмы механосенсорной функции уротелия и влияние на нее бактериальной колонизации. Показано, что инфекционное воспаление даже в отсутствие клинической симптоматики усиливает реакцию уротелия на растяжение и повышает возбудимость афферентных нервов. Гиперчувствительность мочевого пузыря и повышенная сократительная активность детрузора являются патогенетической основой развития заболевания. Приведены данные о связи мочевой инфекции и рефрактерности гиперактивного мочевого пузыря. Показана целесообразность проведения расширенных микробиологических исследований у пациентов с гиперактивным мочевым пузырем, особенно при неэффективности стандартной терапии. Представлено патогенетическое обоснование назначения таким пациентам противовоспалительных и иммуноактивных препаратов.

Ключевые слова: гиперактивный мочевой пузырь; гиперсенсорный мочевой пузырь; инфравезикальная обструкция; детрузорная гиперактивность; инфекция мочевых путей; уротелий.

Как цитировать

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INTRODUCTION

The term overactive bladder (OAB) is used to describe a complex of symptoms that includes an urgent urge to urinate, with or without urge urinary incontinence. OAB is usually accompanied by an increased frequency of daytime and/or nighttime urination in the absence of infectious or other obvious bladder lesions. The prevalence of OAB in adults ranges from 15% to 25%. The incidence is higher in women and older patients. Men and women have notable differences in the clinical and urodynamic manifestations of OAB. Women tend to experience approximately twice the frequency of urgency urinary incontinence; however, involuntary detrusor activity is significantly less frequently detected by cystometry. This latter phenomenon is registered in approximately 15% of women with non-neurogenic OAB. In contrast, the situation is reversed in men with OAB, and detrusor overactivity is detected in the majority of them [4, 5].

PATHOGENESIS OF OAB

The clinical course and results of urodynamic studies in men and women with OAB are largely associated with the sex-specific features of the disease pathogenesis.

OAB has two main forms: neurogenic and non-neurogenic. In neurogenic OAB, the neurological disease is the basis for the onset of urinary retention symptoms, resulting in the dysregulation of the lower urinary tract function. Infravesical obstruction, bladder wall ischemia, and urothelial dysfunction are recognized as the leading factors of non-neurogenic OAB [6]. The significance of these factors differs depending on sex and age of the patients. Infravesical obstruction is more frequently diagnosed in men. The resulting compensatory hypertrophy with partial denervation of the detrusor was believed to be the main cause of its uncontrolled activity, as evidenced by involuntary detrusor contractions on urodynamic examination [6]. Bladder wall ischemia, which is frequently attributed to concomitant diseases, such as widespread atherosclerosis, plays a considerable role in older patients [7]. The degree of deterioration in bladder blood flow correlates with the severity of OAB symptoms, regardless of the sex of the patient. In older patients, identifying a single cause of OAB is often difficult because infravesical obstruction, neurological deficit, and hemodynamic disorders often co-occur.

Infravesical obstruction and blood flow disorders in the bladder rarely in women, particularly young and middle-aged women; however, OAB is very common. Urothelial dysfunction leading to bladder hypersensitivity is considered the leading factor in the pathogenesis of OAB in this category of patients [6]. In these patients, OAB without detrusor overactivity is referred to as a hypersensitive bladder. The severity of symptoms in these patients is often greater than in patients with detrusor overactivity, particularly because of severe pollakiuria [12].

To comprehend the underlying mechanisms responsible for the observed increase in sensitivity, the role of the urothelium in the sensory function of the bladder must be examined.

UROTHELIUM AND AFFERENT INNERVATION OF THE BLADDER

The urothelium primarily plays sensory and barrier functions, which are closely related. The functional potential of the urothelium is attributed to the peculiarities of its anatomical structure and innervation. The urothelium consists of three layers of cells: large superficial cells (umbrella), smaller urothelial cells (intermediate), and pluripotent urothelial cells (basal). Together with the connective tissue lamina propria (*lamina propria*), it forms the bladder mucosa. The urothelial barrier is established by a complex network of interconnected urothelial cells, hydrophobic uroplakin plaques, and a glycosaminoglycan (GAG) layer comprising glycoproteins and proteoglycans. The suburothelial layer contains myofibroblasts, interstitial cells, and telocytes, also known as interstitial cells of Cajal. The urothelium normally provides an impermeable barrier for bacteria and various substances from the urine, so they cannot penetrate deeper into the bladder wall. Sensory function is provided by a complex system of interaction between the urothelium and afferent nerves of the bladder wall [14]. The latter contains two types of nerve fibers, namely, unmyelinated C-fibers located in the suburothelium and myelinated Aδ-fibers located in the detrusor (Fig. 1). Surface afferent C-fibers do not respond directly to stretching; however, they are sensitive to neurotransmitters released in the urothelium in response to various stimuli, including stretching. Aδ-fibers are responsible for detrusor contraction and serve an important afferent function. Their terminals perceive bladder wall stretching and send signals to the central nervous system (CNS). In the experiment, only 20% of afferent nerve endings are located in the urothelium and suburothelium, and 80% are found in the detrusor [15]. However, the urothelium is considered to play a crucial role in bladder sensitivity.

In the past decade, significant progress has been made in understanding the mechanosensory function of the bladder. In response to mechanical stretching, specific ion channels of proteins, designated as Piezo1 and Piezo2, open in urothelial cells [16]. The opening of the Piezo channels allows Ca^{++} ions to enter the cells, which in turn initiates the release of the neurotransmitter sodium adenosine triphosphate (ATP) from urothelial cells into the intercellular space. The receptors for these neurotransmitters are located at the terminals of afferent C-fibers [17] (Fig. 2).

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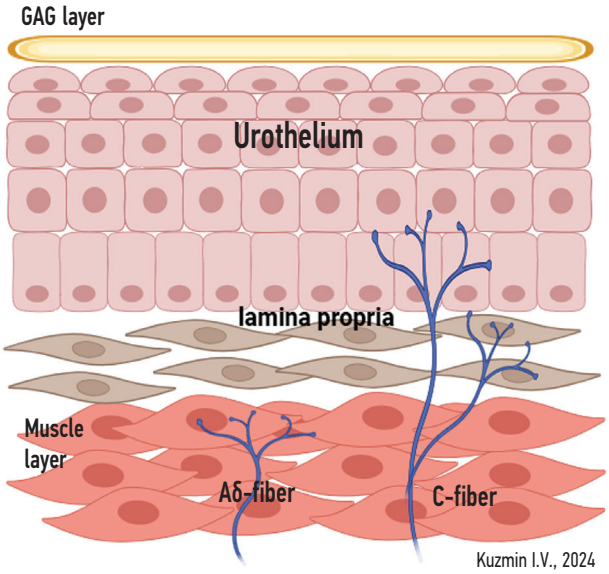

Fig. 1. Sensory innervation of the bladder. GAG-layer — glycosaminoglycan layer
Рис. 1. Сенсорная иннервация мочевого пузыря. ГАГ-слой — гликозаминогликановый слой

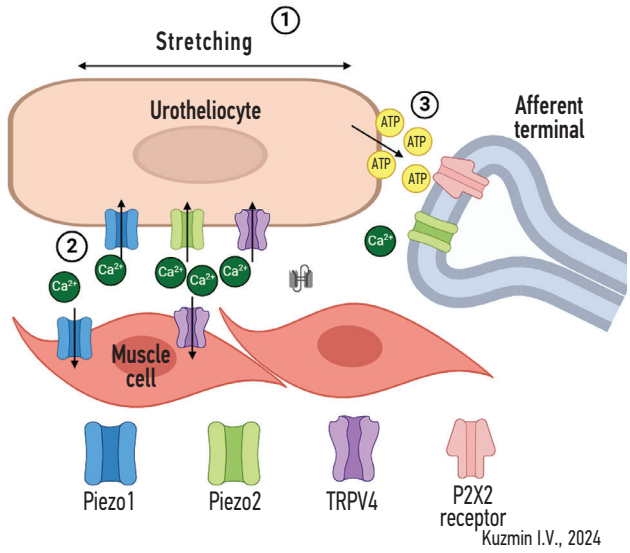

Fig. 2. Mechanosensory function of the urothelium
Рис. 2. Механосенсорная функция уротелия

Consequently, the urothelium may be considered analogous to a sophisticated mechanoreceptor, or touch screen, which can perceive mechanical stimuli generated by bladder filling and subsequently converting them into chemical substances (neurotransmitters) and then into electrical signals that convey information about the state of the urinary tract to the higher parts of the CNS. In 2021, for their discovery of the function of ion channels and the mechanism of converting mechanical signals into neurobiological signals, molecular biologist Ardem Patapoutian and physiologist David Julius were jointly awarded the Nobel Prize in Physiology and Medicine [18]. Ion channels play a pivotal role in the mechanotransduction process in the mammalian urinary tract. The conformational change in ion channel proteins serves as the molecular basis by which urothelial cells perceive stretching. A mechanical stimulus is converted nearly instantaneously into a biochemical signal, occurring within a few milliseconds, and represents one of the fastest conduction processes observed in living organisms [19].

In addition to urotheliocytes, Piezo1 ion channels are localized in interstitial cells of the intrinsic lamina and detrusor smooth muscle cells. Piezo2 are found in the terminals of afferent neurons. Vanilloid receptors, particularly transient receptor potential vanilloid 4 (TRPV4) ion channels, which are expressed on detrusor myocytes in addition to urotheliocytes, are also involved in the perception of stretching. The activation of TRPV4 during bladder muscle stretching leads to the influx of Ca^{2++} ions into smooth muscle cells, which in turn causes their contraction. This process appears to play a pivotal role in the initiation of involuntary detrusor activity [21]. The function of Piezo1 channels in the detrusor is analogous to that of TRPV4 channels [22]. Consequently, all the aforementioned cellular structures can also be designated as mechanosensitive. However, the urothelium plays the primary role in this process.

Thus, the afferent nerve endings of the mucosa do not respond to stretching but to neurotransmitters released from the urothelium. Sensory signals are transmitted to the CNS through *nn. hypogastrici, nn. pelvici*, and *n. pudendus*, which go to the dorsal horns of the thoracic, lumbar, and sacral spinal cord, respectively. In the spinal cord, neurons transmit signals to the thalamus and midbrain gray matter, subsequently reaching limbic and cortical structures. This process constitutes the afferent component of the urinary reflex. The greater the intensity of the sensory signal in the CNS, the more pronounced the sensation of bladder filling [23].

BLADDER SENSORY FUNCTION AND INFLAMMATION

The sensory function of the bladder is affected by various factors, such as endocrine disorders, metabolic syndrome, emotional and affective disorders, gastrointestinal disorders, autonomic nervous system dysfunction, and numerous others [24–26]. However, mucosal inflammation has been identified as the primary contributor to bladder sensitivity, significantly increasing it and leading to hypersensitivity, in a significant number of patients with OAB.

The pathogenesis of a hypersensitive bladder is based on an increased stimulation of afferent neurons during

the filling phase of the urinary cycle [27]. Depending on the intensity of the hypersensitive response, clinically, this condition may manifest in varying degrees of severity with sensations of bladder filling, urges, and pain. The first two manifestations are attributed to OAB, and the latter to painful bladder syndrome. Many researchers consider the presence of an inflammatory process in the bladder wall, both infectious and noninfectious, as the primary cause of hyperafferentation in both infectious and noninfectious conditions [23, 28, 29]. The relationship between OAB and inflammation is well-established. Bladder wall inflammation is indicated by increased levels of proinflammatory cytokines and chemokines in the urine of patients with OAB compared with controls without clinical signs of cystitis [30–32]. Furthermore, changes in the concentration of inflammatory biomarkers in the urine correlate with the severity of OAB symptoms [30, 32].

Damage to the urothelial barrier is the most common cause of inflammation, allowing various substances and bacteria in the urine to penetrate the deeper layers of the bladder mucosa. In addition, inflammation significantly reduces the effectiveness of regenerative reactions aimed at restoring this damaged barrier [33]. The increased release of neurotransmitters affecting afferent nerve endings during inflammation affects the sensory function of the bladder [28, 34]. Consequently, inflammation stimulates the release of the neurotransmitter ATP from urothelial cells, which has two functions: it activates purinergic receptors P2X2 located on the terminals of afferent nerves and promotes the release of other neurotransmitters involved in the sensory function of the urothelium, particularly acetylcholine, neurokinin A, and prostaglandins [35–37].

OAB AND LOWER URINARY TRACT INFECTION (LUTI)

The effect of LUTI on OAB development has long been the subject of extensive research and debate because these two conditions are the most common causes of urinary disorders in women [38]. Moreover, >10% of women with OAB attribute their symptoms to a history of LUTI [4].

Therefore, whether a causal relationship exists between LUTI and OAB must be explored. Although the current definition of OAB explicitly refers to the absence of urinary infection, sufficient evidence proves this link.

OAB and bacteriuria

The long-held postulate that urine is sterile has now been disproven, with the discovery that bacteria are always present in the urine [39–41]. In this regard, the composition of the urine microbiota and the titer of microorganisms must be considered. Nearly seven decades ago, a bacterial titer of 10^5 CFU/mL was proposed as a threshold level for the diagnosis of LUTI [42]. In contrast to the previous recommendations, modern Russian and international clinical guidelines only consider this threshold for complicated urinary infections in women and the detection of asymptomatic bacteriuria. In uncomplicated LUTI, this value is significantly lower, at 10^3 CFU/mL [43, 44]. Women with OAB are more likely to have significant bacteriuria than healthy women. Consequently, bacteriuria with a titer of $>10_5$ CFU/mL has been identified in 6%–17% of women with OAB, whereas it has been observed in only 0.5%–2% of women without OAB [45–48]. In an extended microbiological study by Z. Khan et al. [49], 23% of patients with OAB exhibited significant bacteriuria, compared with 10% of controls. The authors highlighted the necessity of employing improved methods for detecting bacteriuria in patients with OAB, particularly the identification of bacterial DNA in the urine. Patients with OAB frequently were postulated to exhibit undiagnosed LUTI, which impairs the efficacy of OAB treatment. Other researchers have reached a comparable conclusion, indicating that the degree of bacteriuria influences the outcomes of OAB treatment. Specifically, lower bacterial titers are associated with enhanced anticholinergic therapy efficacy [48].

OAB and intracellular bacterial colonization of the urothelium

In recent years, intracellular bacterial colonization of the urothelium has emerged as a crucial mechanism in the development of hypersensitive bladder. Many microorganisms, including uropathogenic *Escherichia coli*, can penetrate the cytoplasm of umbrella urothelial cells, replicate, and form intracellular bacterial communities (IBCs). Uropathogens are more frequently detected as part of the IBCs in urothelial cells sloughed off or biopsied in patients with OAB without significant bacteriuria compared with healthy controls [45, 50]. Bacterial filamentation (elongation) is frequently observed in clinical settings, and it is associated with IBC formation and the possibility of repeated exit of uropathogens into the bladder lumen [51]. IBCs formed by *E. coli* are most frequently detected in patients with OAB, which is not surprising because *E. coli* is the most frequent causative agent of LUTI [45]. The severity of the intracellular invasion of uropathogens correlates with the severity of symptoms of OAB refractory to standard treatment, and clinical improvement was observed after a course of antibiotic therapy [52]. Many authors have proposed that refractory OAB may be associated with underdiagnosed LUTI [53]. Even in the absence of clinical signs of cystitis, leukocyturia is significantly more common in patients with OAB than in controls. Furthermore, the severity of OAB symptoms correlates not only with the severity of leukocyturia but also with the number of sloughed off epithelial cells [54].

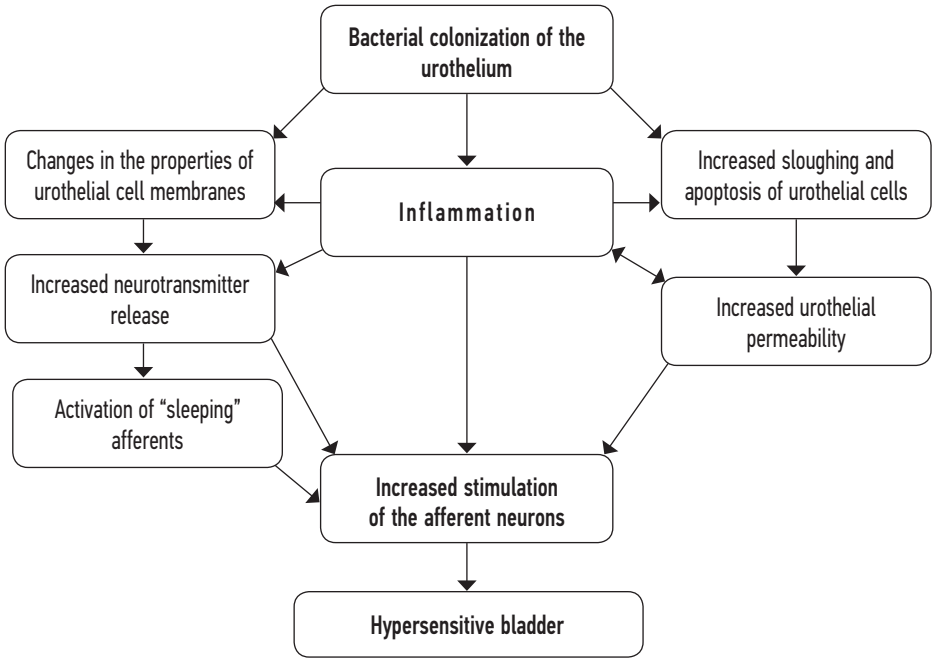

Fig. 3. The role of urinary infection in the pathogenesis of overactive bladder
Рис. 3. Роль мочевой инфекции в патогенезе гиперактивного мочевого пузыря

The mechanism by which IBCs influence the pathogenesis of OAB remains unclear; however, such an influence exists. The reasons for the increased sensitivity of the bladder when the urothelium is colonized are presented in Fig. 3. Uropathogenic microorganisms penetrate urothelial cells, subsequently forming IBCs, which result in at least two effects. First, bacterial invasion induces a protective immune response, increasing the concentration of proinflammatory substances in the bladder mucosa and the development of inflammation. Second, the infectious process leads to the stimulation of the sloughing off of urothelial cells and increased apoptosis. This process can be considered a kind of defense mechanism aimed at removing the affected urothelial cells. However, it increases the permeability of the urothelial barrier, making it easier for urinary toxicants and bacteria to penetrate deeper into the mucosa, which further worsens inflammation. Furthermore, increased urothelial permeability, even in the absence of inflammation, can lead to the sensitization of the afferent endings because of direct exposure to urinary substances [55]. Inflammation increases the release of cytokines, chemokines, and neurotransmitters from the urothelium and immune cells. These substances bind to receptors and ion channels at the ends of sensory neurons, sensitizing afferents. The sensitized afferents then respond more strongly to bladder distension and send more intense signals to the CNS. The presence of IBCs possibly contributes to the changes in the properties of cell membranes of urotheliocytes and enhances the response of ion channels to stretching. Consequently, even in the absence of clinically significant cystitis, infectious agents play a significant role in the pathogenesis of hypersensitive bladder. In summary, the basis of this pathogenetic relationship is the increased excitability of sensory neurons caused by infectious inflammation of the bladder wall. In this case, the sensitivity of the bladder to stretching increases, whereas the "activation threshold" of mechanoreceptors decreases [56]. Consequently, the "high-threshold" afferent receptors that respond only to marked bladder distension are also activated at lower bladder filling volumes. In addition, the sensitivity of the bladder wall increases because the afferents that were previously insensitive to stretching "silent" or "sleeping" in the presence of inflammatory mediators become mechanosensitive. A reduction in the threshold of perception of bladder filling from the normal range of 120–150 mL to significantly lower values will be clinically evident in the form of frequent urges to urinate, shortened intervals between urinations, nocturia, and urges, which are typical OAB symptoms [55, 56].

The accumulated knowledge indicates that urinary tract infection plays a significant role in OAB development, at least in a significant proportion of patients.

OAB TREATMENT

The use of anticholinergic drugs is the initial pharmacotherapy approach for OAB [57]. They have been employed successfully in these patients for >50 years; however, they are associated with two significant issues. First, they are not always sufficiently efficacious,

which is manifested by the incidence of refractory OAB. The precise incidence of refractory OAB remains a matter of contention, with most researchers estimating it at 20% [58–60]. Refractory OAB is an indication for switching to the next line of treatment, particularly intravesical injections of botulinum toxin [61]. The long-term efficacy of M-choline blockers is also low, with most patients experiencing symptom recurrence immediately after the end of treatment, even if the treatment was successful. A. Kim et al. [62] demonstrated that after a 12-week M-choline blocker therapy, relapses were observed in 25.6%, 42.3%, and 52.2% of the treated patients, with women exhibiting a higher incidence of relapse. A.R. Morris et al. [63] observed patients with OAB for an extended period after successful antimuscarinic therapy and noted long-term improvement in only 20% of women. Anticholinergic therapy was considered inefficacious and OAB recurred early because this approach does not affect the pathogenetic basis of OAB development, being essentially a symptomatic therapy. Bladder wall inflammation and subsequent hypersensitivity appear to be one of the leading causes of refractory OAB. Second, anticholinergic drugs do not have a satisfactory safety profile, particularly with regard to the effect on the CNS, which is crucial in vulnerable groups such as older patients with neurological diseases and cognitive impairment [64]. Thus, such patients must be prescribed drugs that do not increase the anticholinergic load, particularly β3-adrenomimetics [65]. In the Russian pharmaceutical market, only one drug of this group is available, mirabegron (Betmiga, Astellas Pharma), which, when administered at a dose of 50 mg once daily, effectively reduces the severity of OAB symptoms. The pharmacological properties of β3-adrenomimetics provide a favorable safety profile. The results of a meta-analysis of 33 clinical trials conducted by K. Tsubouchi et al. [66] demonstrated that β3-adrenoreceptor agonists, in contrast to antimuscarinic drugs, do not impair bladder evacuation and do not increase the risk of urinary retention. A higher incidence of LUTI was observed in the M-cholinoblocker group compared with the placebo group. In contrast, no such trend was observed in the β3-adrenomimetic group.

Antibiotics and OAB

Given the pivotal role of LUTI in the pathogenesis of OAB symptoms, the effect of antibacterial agents on the clinical course of OAB symptoms must be ascertained. However, the number of such studies is limited. A study demonstrated that the addition of an antibiotic to standard anticholinergic therapy for OAB improved the treatment outcomes [67]. Another study highlighted the efficacy of antibiotic treatment in patients with refractory OAB [68]. In 2021, Z. Chen et al. published the results of the only placebo-controlled randomized trial to date. This trial compared the efficacy of a combination of antibiotic and standard anticholinergic therapy with M-choline blocker monotherapy in women with refractory detrusor overactivity. The combined treatment group exhibited a more pronounced clinical effect than the control group, with a more significant reduction in the number of episodes and severity of urinary incontinence. Notably, the differences were observed not only during the 6-week treatment but also during the subsequent 6 months of followup. In patients who had received a course of antibiotics, the efficacy of standard anticholinergic therapy subsequently increased. The data obtained allowed the authors to suggest that patients treated with antimicrobials have less severe infectious inflammation underlying the onset of OAB symptoms. Thus, a thorough microbiological examination of patients with refractory OAB, in whom infection may be the cause of the ineffectiveness of standard therapy, should be performed [69]. A separate study conducted by the same research team demonstrated that during antibiotic therapy in women with OAB, clinical improvement was associated with a reduction in urinary inflammation biomarkers, including interleukin (IL)-1α, IL-1Ra, IL-6, IL-8, and C-X-C motif chemokine ligand 10 [70]. Another study demonstrated that antibiotic therapy in patients with OAB significantly decreased the expression of IBCs in sloughed off urothelial cells [52]. Furthermore, the decrease in the number of IBCs correlated with the degree of improvement in OAB symptoms. Concurrently, the authors observed an increase in the number of urotheliocytes lacking IBCs in women exhibiting diminished dysuria severity. This finding indirectly suggests a correlation between OAB and urinary infection.

Alternative treatment options for OAB

Despite the encouraging outcomes of antibiotic therapy in patients with OAB, antimicrobial therapy is constrained by several factors, primarily the challenge of rising antibiotic resistance. In this context, alternative nonantibiotic therapies may be considered, which have been demonstrated to be clinically effective for the treatment and prevention of acute and recurrent LUTI [43]. These therapy types have been particularly intensively developed in recent years. Many local and foreign studies have demonstrated the efficacy and safety of prescribing behavioral, anti-inflammatory, and phytotherapy, antiadhesins, and pre and probiotics to patients with urinary infections [71–76]. Nevertheless, a substantial proportion of these drugs, particularly the majority of herbal remedies, possess a diuretic effect, so they are inadvisable in patients with OAB.

Pathologically, prescribing drugs that reduce the severity of bladder wall inflammation in patients with OAB appears most reasonable. In the late 1980s, two studies indicated that the administration of the nonsteroidal anti-inflammatory drug indomethacin reduced the severity of urinary incontinence in women with OAB [77, 78].

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Nevertheless, further related studies were not pursued, presumably because of the lack of comprehension at the time regarding the role of inflammation and urinary infection in the pathogenesis of OAB.

The persistence of uropathogens in the urothelium and development of an inflammatory reaction are primarily caused by the defects in the immune defense of the macroorganisms [79]. Immunocompetent cells and sensory nerves interact in response to potentially dangerous stimuli. Thus, neuropeptides released from nerve endings can have a direct regulatory effect on immune cells, thus affecting the severity of inflammation and anti-infective defense [80]. Z. Gao et al. [28] demonstrated that uropathogenic *E. coli*-secreted substances can directly affect the nociceptors in the bladder mucosa, resulting in the release of mediators calcitonin-gene-related peptide and substance P. These mediators inhibit the function of neutrophils and macrophages, thereby suppressing local immunity and promoting the persistence of uropathogens.

In this context, immunomodulatory therapy in patients with OAB, in whom infectious inflammation is a factor in the pathogenesis of sensory disorders, appears to be a promising avenue of research. Uro-Vaxom® (Astellas Pharma), a bacterial extract consisting of lyophilized lysates of 18 *E. coli* strains, has the strongest evidence base for efficacy and safety in patients with LUTI among immunoactive drugs on the Russian market. OM-89, which subsequently acquired its contemporary designation as Uro-Vaxom®, was initially published in 1986 [81], and it was initially approved for clinical use in Switzerland in 1988 [81]. In the Russian Federation, the drug was registered in 1999. Over time, extensive experience on its use has been accumulated, confirming its efficacy and tolerability in the treatment and prevention of LUTI [82–86].

The therapeutic effect of Uro-Vaxom® is attributed to its immunotropic action. This action increases the local immune response to uropathogens, including the synthesis of secretory immunoglobulin A, endogenous interferons, stimulation of the functions of T and B lymphocytes, natural killer cells, macrophages, and dendritic cells. These findings are supported by previous studies [83, 86]. Upon administration, serum IgA and IgG levels increased in response to all 18 *E. coli* strains [87]. Furthermore, evidence indicates that Uro-Vaxom® stimulates the production of defensins HNP1-3 and lactoferrin, which are effectors of the innate immune response and have microbicidal, chemotactic, and immunomodulatory activities [88].

In light of the mechanism of action of Uro-Vaxom®, studies are needed to investigate the potential of using it for the complex treatment of patients with OAB, particularly those exhibiting refractory forms, which may be attributed to infectious inflammation.

CONCLUSION

Recently, significant advancements have been achieved in basic biology and physiology, with promising implications for clinical medicine. One such example is the discovery of the mechanism of mechanosensory transduction in the bladder and the role of urothelium and inflammation in this mechanism. This knowledge has enabled a novel perspective on the pathogenesis of OAB, a concept that has required an update. The role of the bacterial colonization of the urothelium and the associated inflammatory response in the development of non-neurogenic OAB, particularly its hypersensitive form, appears to be much greater than previously thought. Although the relationship between OAB and urinary infection is not yet fully understood, evidence suggests that LUTI plays an important role in the pathogenesis of the hypersensitive phenotypes of OAB. Chronic inflammation appears to be a key element in sensory nerve sensitization. In this regard, extended investigations in patients with OAB, particularly those refractory to standard therapy are needed to improve the microbiological diagnosis of urinary infection. Investigating the clinical efficacy of incorporating drugs with anti-inflammatory and immunomodulatory effects into the comprehensive treatment of OAB are warranted. The pathogenesis of OAB is complex, and urinary infection and induced inflammation are among the leading causes. This finding further supports the rationale for a personalized and multimodal approach to the treatment of patients with OAB.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: I.V. Kuzmin — search and analysis of literary data, writing the text of the manuscript; M.N. Slesarevskaya, V.V. Romikh — search and analysis of literary data, editing the text of the manuscript

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