CONSIDERATIONS

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URINARY TRACT INFECTION AND OVERACTIVE BLADDER. IS THERE AN ASSOCIATION?

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A discussion of key research findings dedicated to the relationship between urinary tract infection (UTI) and overactive bladder (OAB) is presented in the article. The results of the publications support the concept that UTI may be an underappreciated contributor to the development of OAB in some patients and vice versa. This information raises a number of questions regarding the treatment and diagnosis of OAB and UTI. The main question is the potential use of antibiotics, anti-inflammatory drugs, and other drugs in the treatment of patients with OAB, as well as the rationale for the use of therapy that normalize lower urinary tract (LUT) function in the presence of chronic recurrent UTI.

K e y w o r d s: *chronic recurrent cystitis, recurrent infection, bacterial infection, lower urinary tract dysfunction, overactive bladder*

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Urinary tract infection (UTI) is among the most common bacterial infections, affecting more than 150 million people worldwide every year [1, 2]. Recurrent UTIs are traditionally defined as 2 or more acute UTIs within 6 months or 3 in a year [3]. It was estimated that 27% of young women who had a first episode of UTI experienced at least one recurrence within the next 6 months, compared to 53% of women over 55 years of age [5]. Recurrent UTIs are usually not life-threatening, but its high incidence can significantly increase healthcare costs and negatively impact patients' quality of life [6, 7]. New evidence suggests a different pathogenesis between primary and recurrent UTI.

Overactive bladder (OAB) is a clinical syndrome characterized by urinary urgency, increased urinary frequency, and/or nocturia, with or without urgency urinary incontinence [8]. Urgency is the main symptom of OAB syndrome [9]. OAB is clinically characterized by the absence of other organic causes, including UTIs.

According to the literature, the prevalence of OAB symptoms in European countries in patients over 40 years of age is 17% [10]. These symptoms negatively impact on the quality of life, contributing to significant psychosocial comorbidities, including increased incidence and severity of depression, anxiety, and social isolation, resulting in poor mental and physical health [11, 12].

Currently, the main drugs used in the treatment of OAB are M-anticholinergic blockers or β3-adrenergic agonists. According to literature, anticholinergics may not always be effective and has limitations on the duration of therapy [13–15]. After 8 years, only 20% of patients receiving antimuscarinics showed sustained improvement. Unfortunately, some studies showed that about 30-40% of patients do not respond to drug treatment.

In this case, "refractory OAB" is suggested. Treatment of OAB with botulinum toxin type A is invasive, may be associated with side effects, and requires repeated injections at approximately 6-month intervals, which may indicate that the treatment masks rather than treats the underlying cause of OAB [16–18].

Recent evidence has shown that chronic bacterial colonization of the bladder may aggravate OAB symptoms and cause recurrent UTIs [21]. Functional impairment further compromises the integrity of the urothelial barrier and makes it vulnerable to invasion by uropathogens. Impaired barrier function, insufficient basal proliferation and cell maturation may be a consequence of chronic suburothelial inflammation, leading to activation of sensory innervation (causing OAB) and the inability to eliminate intracellular bacterial communities (resulting in recurrent UTIs). Accurate diagnosis and a multidisciplinary approach to understanding the pathophysiology of OAB and recurrent UTI are necessary.

Chronic bladder inflammation also inhibits basal cell proliferation, causing defective apical cell maturation and impaired barrier function [22]. Chronic "neural plasticity" due to chronic inflammation and activation of sensory receptors can alter afferent activity, impairing antinociceptive activity, and lead to bladder hypersensitivity or detrusor overactivity (DO).

According to a study of urothelial dysfunction, in women with recurrent UTI an increased cell apoptosis,

defective E-cadherin, and chronic inflammation were found compared with controls, suggesting that defective urothelial barrier function may be a cause [23]. There is also an increase in urinary biomarkers of inflammation, including monocyte chemoattractant protein-1, macrophage inflammatory proteins, and epidermal growth factor, suggesting that inflammation is involved in the pathogenesis of OAB [24]. One study found that serum C-reactive protein levels were significantly higher in those with OAB (p=0.012) or interstitial cystitis (IC) (p=0.049) than in controls. However, there was no significant difference in C-reactive protein levels between patients with OAB and IC (p=0.43). These data support the association between chronic bladder inflammation in patients with OAB and IC [25].

Manifestations of cystitis in women may mimic OAB, which makes exclusion of UTI a key component of the diagnosis of OAB. Clinically, OAB is differentiated from acute UTI by the absence of bacteriuria and/or leukocyturia on urine dipstick. Since symptoms of OAB and chronic recurrent cystitis in women are similar, in most patients OAB is often misdiagnosed as UTI and treated empirically without urine culture as a routine approach. In fact, when urine culture results are obtained, less than half of women are positive, suggesting that empirical treatment without urine culture is usually associated with misdiagnosis of URI [26].

In a prospective, blinded, case–control study, 23% of patients with OAB were found to have positive urine culture compared with 10% of controls [27]. The proportion of patients with OAB and positive urine culture increased from 15% at 105 CFU/ml to 21% at 102 CFU/ml [28].

An increasing number of publications has shown that uropathogenic *Escherichia coli (E. coli)* invades urothelial cells and forms intracellular bacterial colonies. In addition, various studies have identified large numbers of bacteria not detected by conventional tests in specimens obtained from bladder biopsies or isolated urothelial cells from patients with OAB examined by immunohistochemistry or confocal microscopy of centrifuged/cytospin samples [29–36].

According to Cheng et al. (2016), a detailed analysis of urothelial cell samples obtained from urine showed that filamentous bacteria are significantly more common in patients with OAB compared to a control group [32]. Filamentous bacteria are associated with intracellular bacterial growth and the release of bacteria from urothelial cells to recolonize the bladder [34].

In this context, *E. coli* as a major uropathogen was more closely associated with urothelial cells from urine sediment (by confocal microscopy) only in OAB patients [31]. Similarly, further study of urothelial cells showed that high level of intracellular bacteria correlated with the severity of symptoms (urinary frequency and urge incontinence) [35].

According to some publications, patients with OAB are significantly more likely to have leukocyturia (39 versus 9%) than the control group [36], and 30–40% of them have pyuria on urinalysis [31, 37]. In a study by K. Gill et al. (2018) patients with OAB were also more likely to have leukocyturia compared to the control group [33]. Interestingly, the authors showed that pyuria detected by urinalysis is the most important correlate of symptom severity, with urgency being highly correlated with both pyuria and epithelial cell yield [33].

The normal urothelium is essentially quiescent with a low turnover rate and regenerates after bladder damage due to bacterial infection, toxins, or trauma [38–41].

Changes in urothelial differentiation may lead to increased permeability and decreased protective function of the urothelium [42]. Acute bacterial inflammation (cystitis) damages the urothelium, causing tissue swelling and accumulation of large numbers of inflammatory cells in the urothelium and suburothelium. These inflammatory cells can trigger a cascade of inflammatory changes in tissues involving several sensor proteins and cytokines, accompanied by pain and symptoms of OAB [23].

Proliferation and differentiation of basal layer stem and progenitor cells regulate the integrity of the bladder epithelium. Chronic inflammation in the bladder can affect the proliferative capacity of these basal cells and alter the rate of proliferation, leading to defects in apical urothelial cells and barrier function [43].

According to N.T. Liu et al. (2015), urothelial dysfunction is common in patients with recurrent UTI and other bladder disorders, such as OAB and bladder outlet obstruction (BOO). In addition, severe urothelial inflammation and urothelial cell apoptosis appear to share a common pathophysiology of various lower urinary tract symptoms (LUTS) [44]. As a result, urothelial dysfunction and underlying chronic inflammation may be part of the pathogenesis of bladder hypersensitivity, bladder pain, and recurrent UTIs in the presence of certain LUTS.

Cytokines are important regulators of both the innate immune response to infection and the inflammatory response to injury. Urinary cytokine level correlates with UTI symptoms [45]. Bacterial inflammation of the bladder stimulates the release of large amounts of pro- and anti-inflammatory cytokines and chemokines. Various studies have reported increases in the levels IL-1β [47, 48], IL-6 [47–49], TNFα [47–49], IL-8 [48–51], and c-10 [48, 51].

Several trials have examined urinary cytokines as biomarkers of UTI in patients with OAB. In support of the concept that in some patients with OAB, symptoms are due to inflammation, a number of publications showed altered cytokine and chemokine profiles in urine [49, 52–56]. This may manifest as changes in either pro- or anti-inflammatory cytokines, or both. In addition, some studies have demonstrated that changes in urinary cytokine level correlate with the severity of OAB symptoms [1, 36, 56], as well as bacterial growth and the severity of leukocyturia [36]. There is no doubt that large-scale studies are needed to expand our understanding of the problem of changes in cytokines in urine of patients with OAB and their role in the development of this syndrome.

It is also possible that bacteria are able to directly or indirectly sensitize sensory neurons that modulate the pain sensation [57]. In addition, studies have shown that toxins and metabolites released during bacterial growth and invasion can sensitize neurons and indirectly activate neurons and cause pain [57–60]. A number of experimental studies in mice proved that various inflammatory mediators increase the excitability of sensory neurons innervating the bladder [61, 62].

According to experiments, in addition to direct activation of the bladder afferent nerves, the infectious and inflammatory process also contributes to the

urothelium exfoliation, i.e. a protective mechanism that quickly removes infected urothelial cells from the bladder wall [29, 63–65]. Although this mechanism is effective in preventing bacterial adhesion, it temporarily increases bladder permeability until the infection is cured and injury-induced proliferation of urothelial cells restores the integrity of the urothelial barrier [40, 41]. Increased urothelial permeability allows toxic urine contents to impact underlying sensory nerves. By developing a model of experimentally induced bladder permeability in mice, the authors of a study showed that increased urothelial permeability causes excitability of mechanosensitive bladder afferent neurons [66], suggesting that it may cause dysfunction manifested by sensory impairments.

To test the hypothesis of a relationship between UTI and increased bladder sensory activity, the authors examined how inflammatory mediators released during acute UTI in mice altered sensory nerve activity ex-vivo [66–69]. Inflammatory supernatants containing a set of cytokines were isolated from mice 8 hours after infection with uropathogenic *E. coli*. Then, this combination was injected into the bladder lumen of healthy mice. After that, both intravesical pressure and sensory nerve activity during gradual distension of the bladder were recorded. Through these experiments, the authors showed that in UTI, inflammation can sensitize bladder sensory neurons to distension, enhancing the response to bladder filling [68]. Thus, neurons that normally respond only to bladder overdistension produce robust reaction to physiological distension in the presence of UTI supernatant. There is considerable experimental evidence that increased excitability of sensory neurons innervating the bladder is triggered by inflammation and may play a critical role in the pathogenesis of OAB [69, 70].

Another study showed that microorganisms in urine may have an important place in the etiology of refractory OAB or aggravate symptoms [71]. Additionally, the urinary microbiome in the human is thought to have a potential association with LUTS [72]. A decrease in urinary microbiome diversity has been found to correlate with the severity of urge urinary incontinence [71]. Certain Lactobacillus species may contribute to maintenance of a bladder environment, and higher bacterial diversity in the absence of Lactobacillus dominance has been associated with urge urinary incontinence and resistance to antimuscarinic therapy [73].

K.J. Thomas-White et al. (2016) found that women with urge urinary incontinence had more bacteria and a more diverse urine microbiome. Patients who did not respond to the M-anticholinergic drug solifenacin had a more diverse bacterial community, including bacteria not typically found in responders [74]. *E. coli* and *G. vaginalis* induce calcium influx and detrusor contraction, whereas *Lactobacillus crispatus* and *Lactobacillus gasseri* do not [75]. From 39 women who had refractory urge urinary incontinence and concomitant recurrent UTIs, 9 (23.1%) patients with significant clinical manifestations had a diverse urinary microbiota, determined by bacterial 16S RNA profiling, suggesting that persistent urinary colonization may exist and aggravate the manifestations of OAB [76]. Based on these data, patients with OAB refractory to anticholinergic therapy may have a subclinical form of UTI in which the pathogen cannot be cultured by conventional methods. Imbalance of urinary microbiota may play an important role in refractory OAB.

E. coli can replicate in the bladder urothelium, forming loose colonies, and then penetrate into the bladder lumen [77, 78]. *E. coli* typically forms intracellular complexes in the superficial umbrella cells of the bladder in mice [79] with formation permanent intracellular reservoir within 2 weeks [80]. Immunofluorescence data showed that 18% of women with recurrent uncomplicated cystitis had intracellular bacterial colonies in the bladder [29]. In patients with OAB, intracellular bacterial colonies can be identified in urothelial cells when concomitant pyuria has been observed [37].

Chronic inflammation in the bladder wall may contribute to urothelial dysfunction and impairment of barrier function, followed by recurrent UTIs. This urothelial dysfunction can occur in several different lower urinary tract diseases, such as IC/chronic pain syndrome, BOO, spinal cord injury, and recurrent UTI [81]. Elimination of chronic inflammation may improve urothelial regeneration and differentiation and restore protective mechanisms in the bladder.

Studying urine microbiome in case of the absence of bacteriuria during standard bacteriological examination is important in patients with OAB who are resistant to traditional treatment [76]. In an analysis of 100 women with recurrent UTI, P.J. Lee and H.C. Kuo (2020) found that 90% of those with recurrent UTI had lower urinary tract dysfunction (LUTD) detected by videourodynamic testing, despite receiving individualized treatment. LUTD included bladder neck dysfunction (19%), detrusor overactivity with abnormal contractility (6%), DO (5%), detrusor underactivity (10%), dysfunctional voiding (25%), bladder hypersensitivity (6%) and poor relaxation of the pelvic floor muscles (20%). Only 10% of patients had normal urodynamic parameters. Interestingly, although a UTI was identified and treated accordingly, only 11.3% of women with recurrent UTIs remained relapse-free after individual treatment of LUTD [81]. Among patients with recurrent UTIs, DO was observed in a quite large percentage of patients (DO with impaired contractility in 100%, dysfunctional urination in 72%, bladder neck dysfunction in 36.8% and poor relaxation of the pelvic floor muscles in 15.8% of cases) [81]. According to S. Hijazi et al. (2016), a videourodynamic study in women with recurrent UTI revealed detrusor hypoactivity in 22%, detrusor-sphincter dyssynergia in 17%, their combination in 11%, and OAB in 28% of patients [82].

Most of these patients with recurrent UTI experienced frequent urination and urgency. These data imply that OAB (as well as LUTD in general) and recurrent UTI are closely interrelated. When treating recurrent UTIs, these functional impairments should be considered in the early stages.

In 2009 and 2013 we published our results of studying of functional state of the urinary tract in 116 patients with chronic recurrent cystitis (average age of 44.56 ± 16.51 years, average duration of the disease from the first episode of acute cystitis of 4.3 ± 1 ,4 years) and 51 patients with chronic non-obstructive pyelonephritis (average age of 37.1±16.28 years) to determine the pathogenetic therapy [83, 84]. According to urodynamic study, 76.7% of women with recurrent cystitis had functional disorders of the urinary tract. In patients with chronic non-obstructive pyelonephritis, urgency and obstructive symptoms were most commonly documented. In all cases, where there was vesicoureteral reflux (VUR) on

cystography, urinary tract dysfunction was also diagnosed. The results of our study allowed to change our view on urinary disorders in this category of patients. Inflammatory diseases of the urinary tract occurred and could be a consequence of urinary tract dysfunction as urgency caused by DO and/or urethral instability (in a form of severe detrusor hypotension), or due to detrusor-sphincter dyssynergia, causing functional obstruction.

In 53 (45.68%) patients with chronic cystitis, urethral instability was detected. The maximum urethral pressure in this group was 82.46±29.26 cm H2O (range of 34.86±19.6). Intravesical pressure at maximum flow rate was 68.48±26.39 cm H2O, and detrusor pressure was 34.6±12.1 cm H2O. DO was detected in 10 (8.62%) patients with chronic cystitis. Fluctuations in detrusor pressure were 22.16±15.8 cm H2O, intravesical pressure at maximum urine flow rate was 79.57±35.22 cm H2O, detrusor pressure was 50.57±28.98 cm H2O. In 26 (22.4%) patients with chronic cystitis, a combination of urethral instability and DO was diagnosed. The maximum urethral pressure was 75.5±21.44 cm H2O, fluctuations in urethral pressure were 37.45±17.44 cm H2O, fluctuations in detrusor pressure were 23.57±14.48 cm H2O.

Detrusor hypotension was detected in 35 (30.17%) patients. Moreover, it was accompanied with urethral instability in 36 cases. A decrease in detrusor contractility was recorded in 25 (21.55%) patients. Symptoms of detrusor-sphincter dyssynergia were seen in 29 (25%) patients. Postvoid residual of more than 50 ml was found in 12 (12.63%) cases.

In the group of those with chronic non-obstructive pyelonephritis, intravesical pressure at maximum urine flow rate reached 67.8±34.16, maximum urethral pressure 83.05±29.9 cm H2O.

Normally, the vesicoureteric junction is able to resist to intravesical pressure up to 60–80 cm H2O [85], while maximum detrusor pressure 70 cm H2O and higher reliably causes upper urinary tract dysfunction [86]. When examining patients with detrusor areflexia, R. Gerridzen et al. [87] found that the upper urinary tract impairment occurred with an average detrusor pressure of 58 cm H2O, while renal dysfunction in those with an average detrusor pressure of 24 cm H2O was absent. In our study, 16 (31.37%) patients had VUR confirmed by cystography. In all patients with chronic non-obstructive pyelonephritis, in whom cystography revealed VUR, urinary tract dysfunction was registered, including urethral instability in 56.25%, severe detrusor hypotonia in 25% and DO in 31.25% cases.

In the group of patients with OAB, fluctuations in detrusor pressure were 30.61±24.8 cm H2O. In the group of those with urethral instability, the fluctuations in maximum urethral pressure were 38.19±26.40 cm H2O. The bladder volume in patients with detrusor hypotension was 573.83±167.9 ml.

After carrying out these studies, we suggested that in the presence of a chronic recurrent inflammation in the urinary tract, a "vicious circle" of dysfunction-inflammation occurred. This is how we imagined the connection between impairment of urinary tract innervation and chronic UTI in women. Based on our results, we hypothesized that a chronic inflammatory process in the bladder and kidneys may be a consequence of urinary tract functional disorders associated with impairment of nervous regulation.

Consequently, inflammation in the bladder wall in combination with functional changes in the bladder and/or urethra may impact the normal functioning of the urinary tract. As a result, pathogenetic treatment of recurrent infection and the urinary tract dysfunction should be aimed at breaking this "vicious circle".

This formed the basis for the pathogenetic treatment strategy for this category of patients, which includes drugs that correct functional urinary tract disorders identified during a urodynamic study in addition to antibacterial and anti-inflammatory therapy [83, 84].

Confirming our assumption about the connection between recurrent infection and the urinary tract dysfunction, as well as proposals to revise treatment approaches, some studies showed very similar data. In 76% of patients, along with main diagnosis of "chronic recurrent cystitis", there were severe functional urinary disorders found during a urodynamic study [88].

Thus, numerous studies indicate the involvement of true UTI in the pathogenesis of OAB in a subgroup of patients who are not susceptible to standard therapy. Detection of bacterial invasion of urothelial cells and subsequent inflammation have been shown to be key elements in sensitizing the sensory nerves to bladder distension, which then causes uncreased frequency during the day and at night (nocturia), as well as urgency. Small studies have shown that antibiotics can help treat patients with OAB, but the growing risk of antibiotic resistance makes prescribing them undesirable. Thus, there is a need for alternative treatments for infection and pro-inflammatory conditions in this subgroup, which may include anti-inflammatory agents or target the microbiome and urothelium. Such opportunities can be provided by the use of immunoactive prevention and treatment of UTIs, which has the highest levels of evidence and recommendations, according to European and Russian guidelines.

Uro-Vaxom contains a lyophilized bacterial lysate of 18 strains of *E. coli*, which is the most common causative agent of UTIs. This drug is an oral immunostimulating agent that activates the immune defense mechanism through the lymphoid tissue of the main mucous membrane (MALT, mucosa associated lymphoid tissue, GALT, gut-associated lymphoid tissue and UALT, urinary-mucosa associated lymphoid tissue) and maintains the activity of these mechanisms at a high level [89]. The drug also stimulates humoral and cellular immune responses, which strengthens natural defense against infections caused by various microorganisms. Moreover, Uro-Vaxom may provide protection against a wider range of pathogens that cause UTIs, and not just against *E. coli* [90]. The drug provides immunoactive prevention by enhancing the response of the immune system. Concentrations of immunoglobulins of classes A and G in patients receiving Uro-Vaxom are several times higher than those not taking this drug [91]. A positive feature of the drug is the possibility of using it both for the treatment and for the prevention of UTIs. The frequency of bacteriuria by the end of the 3rd month of taking Uro-Vaxom in combination with an antibiotic is 3 times lower than in patients receiving only an antibiotic [92].

In a study by N.K. Akhmatova et al. (2016) the clinical and bacteriological efficiency of Uro-Vaxom® in women with recurrent cystitis was evaluated. It was shown that a negative urine culture after 3 months of therapy

was preserved after 6 months [93]. Thus, Uro-Vaxom® reduces the frequency of recurrences of UTI, the number and severity of symptoms, the need for antibiotics. The duration of the relapse-free period reaches up to 6 months after stopping taking the drug.

We agree that effective etiologic treatment of cystitis does not always lead to the elimination of urination disorders. Therefore, to clarify the nature of these changes and determine further treatment tactics, it seems appropriate to study the functional state of the urinary tract. Detected disorders may concern all phases of bladder cycle. Functional disorders of the urinary tract can be caused by various processes accompanied by changes in the nervous regulation.

Conclusion. The lack of a systematic approach to the assessment of urinary disorders in patients suffering from chronic recurrent UTI can lead to incorrect interpretation of the clinical manifestations and the development of ineffective treatment tactics. When prescribing treatment for patients with chronic recurrent cystitis, the role of the autonomic nervous system in regulating the bladder contractions is often not considered. It is necessary to emphasize that the treatment of UTIs must be comprehensive with taking account the pathogenetic mechanisms. In addition, we can say that every year there is more and more evidence that clinical manifestations of OAB should be reconsidered, given the their connection with UTI [94]. Thus, it is necessary to continue a more in-depth study of these interrelated chronic conditions and improve methods of examination and treatment of patients with UTI and OAB.

REFERENCES

1. *Smelov V., Naber K., Bjerklund Johansen T.E.* Improved Classification of Urinary Tract Infection: Future Considerations. Eur. Urol. 2016;Suppl.15(4):71–80. Doi: 10.1016/j.eursup.2016.04.002.
2. *Tandogdu Z., Wagenlehner F.M.E.* Global Epidemiology of Urinary Tract Infections. Curr. Opin. Infect. Dis. 2016;29(1):73–79. Doi: 10.1097/qco.0000000000000228.
3. *Epp A.* Larochelle AUrogynaecology Committee Family Physicians Advisory Committee. . Recurrent urinary tract infection J Obstet Gynaecol Can. 2010;32:1082–1090.
4. *Foxman B.* Recurring urinary tract infection: Incidence and risk factors Am J Public Health. 1990;80:331–333.
5. *Ikäheimo R., Siitonen A., Heiskanen T., Kärkkäinen U., Kuosmanen P., Lipponen P., et al.* Recurrence of urinary tract infection in a primary care setting: Analysis of a 1-year follow-up of 179 women Clin Infect Dis. 1996;22:91–99.
6. *Renard J., Ballarini S., Mascarenhas T., Zahran M., Quimper E., Choucair J. et al.* Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: A prospective, observational study Infect Dis Ther. 2014;4:125–135.
7. *Ciani O., Grassi D., Tarricone R.* An economic perspective on urinary tract infection: The "costs of resignation" Clin Drug Investig. 2013;33:255–261.
8. *Wein A.J., Rovner E.S.* Definition and Epidemiology of Overactive Bladder. Urology. 2002;60(5 Suppl. 1):7–12. discussion 12. Doi: 10.1016/s0090-4295(02)01784-3.
9. *Abrams P., Cardozo L., Fall M., Griffiths D., Rosier P., Ulmsten U., et al.* The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society Neurourol Urodyn. 2002;21:167–178.
10. *Milsom I., Abrams P., Cardozo L., Roberts R.G., Thüroff J., Wein A.J.* How Widespread Are the Symptoms of an Overactive Bladder and How Are They Managed? A Population-Based Prevalence Study. BJU Int. 2021;87(9):760–766. Doi: 10.1046/j.1464-410x.2001.02228.x.
11. *Kinsey D., Pretorius S., Glover L., Alexander T.* The Psychological Impact of Overactive Bladder: A Systematic Review. J. Health Psychol. 2016;21(1):69–81. Doi: 10.1177/1359105314522084.
12. *Coyne K.S., Sexton C.C., Kopp Z.S., Ebel-Bitoun C., Milsom I., Chapple C.* The Impact of Overactive Bladder on Mental Health, Work Productivity and Health-Related Quality of Life in the UK and Sweden: Results from EpiLUTS. BJU Int. 2021;108(9):1459–1471. Doi: 10.1111/j.1464-410x.2010.10013.x.
13. *Wagg A., Compion G., Fahey A., Siddiqui E.* Persistence with Prescribed Antimuscarinic Therapy for Overactive Bladder: a UK Experience. BJU Int. 2012;110(11):1767–1774. Doi: 10.1111/j.1464-410x.2012.11023.x.
14. *Kim T.H., Lee K.-S.* Persistence and Compliance with Medication Management in the Treatment of Overactive Bladder. Investig. Clin. Urol. 2016;57(2):84–93. Doi: 10.4111/icu.2016.57.2.84.
15. *Yeowell G., Smith P., Nazir J., Hakimi Z., Siddiqui E., Fatoye F.* Real-world Persistence and Adherence to Oral Antimuscarinics and Mirabegron in Patients with Overactive Bladder (OAB): a Systematic Literature Review. BMJ Open. 2018;8(11):e021889. Doi: 10.1136/bmjopen-2018-021889.
16. *Schurch B., de Sèze M., Denys P., Chartier-kastler E., Haab F., Everaert K. et al.* Botulinum Toxin Type a Is a Safe and Effective Treatment for Neurogenic Urinary Incontinence: Results of a Single Treatment, Randomized, Placebo Controlled 6-month Study. J Urology. 2005;174(1):196–200. Doi: 10.1097/01.ju.0000162035.73977.1c .
17. *Apostolidis A., Dasgupta P., Denys P., Elneil S., Fowler C.J., Giannantoni A. et al.* Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: a European Consensus Report. Eur. Urol. 2009;55(1):100–120. Doi: 10.1016/j.eururo.2008.09.009.
18. *Chen J.L., Kuo H.C.* Clinical Application of Intravesical Botulinum Toxin Type A for Overactive Bladder and Interstitial Cystitis. Investig. Clin. Urol. 2020;61(Suppl. 1):S33–S42. Doi: 10.4111/icu.2020.61.S1.S33.
19. *Khasriya R.K., Brackenridge A., Horsley L., Sathiananthamoorthy H., Malone-Lee S.J.* The Antibiotic Treatment of OAB Cohort. 36th Annual IUGA Meeting, Lisbon, Portugal, 28 June–2 July 2011. Int. Urogynecology J. 2011;22(1):1–195.
20. *Vijaya G., Puccini F., Dutta S., Singh A., Bray R., Digesu A., et al.* 38th Annual IUGA Meeting, Dublin, Ireland, 28 May–1 June 2013: Oral Presentations. Int. Urogynecology J. 2013;24(1):79.
21. *Ke Qian-Sheng, Lee Cheng-Ling, Kuo Hann-Chorng.* Recurrent urinary tract infection in women and overactive bladder – Is there a relationship? Tzu Chi Medical Journal. 2020;33(1):13–21. Doi: 10.4103/tcmj.tcmj_38_20.
22. *Shie J.H., Kuo H.C.* Pathologic mechanism of the therapeutic effect of botulinum toxin A on interstitial cystitis and painful bladder syndrome. Tzu Chi Med J. 2012;24:170–177.
23. *Chuang F.C., Kuo H.C.* Increased urothelial cell apoptosis and chronic inflammation are associated with recurrent urinary tract infection in women. PLoS One. 2013;8:e63760.
24. *Tyagi P., Barclay D., Zamora R., Yoshimura N., Peters K., Vodovotz Y., et al.* Urine cytokines suggest an inflammatory response in the overactive bladder: A pilot study Int Urol Nephrol. 2010;42:629–635.
25. *Chung S.D., Liu H.T., Lin H., Kuo H.C.* Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder Neurourol Urodyn. 2011;30:417–420.
26. *Tomas M.E., Getman D., Donskey C.J., Hecker M.T.* Overdiagnosis of urinary tract infection and underdiagnosis of sexually transmitted infection in adult women presenting to an emergency department J Clin Microbiol. 2015;53:2686–2692.
27. *Khan Z., Healey G.D., Paravati R., Berry N., Rees E., Margarit L. et al.* Chronic Urinary Infection in Overactive Bladder Syndrome: A Prospective, Blinded Case Control Study. Front. Cell. Infect. Microbiol. 2021;11, 752275. Doi: 10.3389/fcimb.2021.752275.
28. *Khasriya R., Khan S., Lunawat R., Bishara S., Bignal J., Malone-Lee M., et al.* The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms without Acute Frequency and Dysuria. J Urology. 2010;183(5):1843–1847. Doi:

10.1016/j.juro.2010.01.008.
29. *Rosen D.A., Hooton T.M., Stamm W.E., Humphrey P.A., Hultgren S.J.* Detection of Intracellular Bacterial Communities in Human Urinary Tract Infection. PLoS Med. 2007;4(12):e329. Doi: 10.1371/journal.pmed.0040329.
30. *Vijaya G., Cartwright R., Derpapas A., Gallo P., Fernando R., Khullar V.* Changes in Nerve Growth Factor Level and Symptom Severity Following Antibiotic Treatment for Refractory Overactive Bladder. Int. Urogynecol J. 2013;24(9):1523–1528. Doi: 10.1007/s00192-012-2038-y.
31. *Khasriya R., Sathiananthamoorthy S., Ismail S., Kelsey M., Wilson M., Rohn J.L. et al.* Spectrum of Bacterial Colonization Associated with Urothelial Cells from Patients with Chronic Lower Urinary Tract Symptoms. J. Clin. Microbiol. 2013;51(7):2054–2062. Doi: 10.1128/jcm.03314-12.
32. *Cheng Y., Chen Z., Gawthorne J. A., Mukerjee C., Varettas K., Mansfield K. J., et al.* Detection of Intracellular Bacteria in Exfoliated Urothelial Cells from Women with Urge Incontinence. Pathog. Dis. 2016;74(7). ftw067. Doi: 10.1093/femspd/ftw067.
33. *Gill K., Kang R., Sathiananthamoorthy S., Khasriya R., Malone-Lee J.* A Blinded Observational Cohort Study of the Microbiological Ecology Associated with Pyuria and Overactive Bladder Symptoms. Int. Urogynecol J. 2018;29(10):1493–1500. Doi: 10.1007/s00192-018-3558-x.
34. *Justice S.S., Hunstad D.A., Seed P.C., Hultgren S.J.* Filamentation by Escherichia coli Subverts Innate Defenses during Urinary Tract Infection. Proc. Natl. Acad. Sci. U.S.A. 2006;103(52):19884–19889. Doi: 10.1073/pnas.0606329104.
35. *Ognenovska S., Chen Z., Mukerjee C., Moore K.H., Mansfield K.J.* Bacterial Colonization of Bladder Urothelial Cells in Women with Refractory Detrusor Overactivity: the Effects of Antibiotic Therapy. Pathog. Dis. 2021;79(6): ftab031. Doi: 10.1093/femspd/ftab031.
36. *Gill K., Horsley H., Swamy S., Khasriya R., Malone-Lee J.* A Prospective Observational Study of Urinary Cytokines and Inflammatory Response in Patients with Overactive Bladder Syndrome. BMC Urol. 2021;21(1):39. Doi: 10.1186/s12894-021-00809-4.
37. *Contreras-Sanz A., Krska L., Balachandran A.A., Curtiss N.L., Khasriya R., Kelley S., et al.* Altered Urothelial ATP Signaling in a Major Subset of Human Overactive Bladder Patients with Pyuria. Am. J. Physiology-Renal Physiology. 2016;311(4):F805–F816. Doi: 10.1152/ajprenal.00339.2015.
38. *Hainau B., Dombernowsky P.* Histology and cell proliferation in human bladder tumors.An autoradiographic study. Cancer. 1974;33:115–126.
39. *Gandhi D., Molotkov A., Batourina E., Schneider K., Dan H., Reiley M., et al.* Retinoid signaling in progenitors controls specification and regeneration of the urothelium Dev Cell. 2013;26:469–482.
40. *Mysorekar I.U., Isaacson-Schmid M., Walker J.N., Mills J.C., Hultgren S.J.* Bone morphogenetic protein 4 signaling regulates epithelial renewal in the urinary tract in response to uropathogenic infection Cell Host Microbe. 2009;5:463–475.
41. *Shin K., Lee J., Guo N., Kim J., Lim A., Qu L. et al* Hedgehog/Wnt feedback supports regenerative proliferation of epithelial stem cells in bladder. Nature. 2011;472:110–114.
42. *Graham E., Chai T.C.* Dysfunction of bladder urothelium and bladder urothelial cells in interstitial cystitis Curr Urol Rep. 2006;7:440–446.
43. *Tomaszewski J.E., Landis J.R., Russack V., Williams T.M., Wang L.P., Hardy C., et al.* Biopsy features are associated with primary symptoms in interstitial cystitis: Results from the interstitial cystitis database study Urology. 2001;57:67–81.
44. *Liu H.T., Jiang Y.H., Kuo H.C.* Alteration of urothelial inflammation, apoptosis, and junction protein in patients with various bladder conditions and storage bladder symptoms suggest common pathway involved in underlying pathophysiology Low Urin Tract Symptoms. 2015;7:102–107.
45. *Rodhe N., Löfgren S., Strindhall J., Matussek A., Mölstad S.* Cytokines in Urine in Elderly Subjects with Acute Cystitis and Asymptomatic Bacteriuria. Scand. J. Prim. Health Care. 2009;27 (2):74–79. Doi: 10.1080/02813430902757634.
46. *Armbruster C.E., Smith S.N., Mody L., Mobley H.L.T.*. Urine Cytokine and Chemokine Levels Predict Urinary Tract Infection Severity Independent of Uropathogen, Urine Bacterial Burden, Host Genetics, and Host Age. Infect. Immun. 2018;86(9):e00327. Doi: 10.1128/IAI.00327-18.
47. *Davidoff R., Yamaguchi R., Leach G.E., Park E., Lad P.M.* Multiple Urinary Cytokine Levels of Bacterial Cystitis. J. Urology. 1997;157(5):1980–1985. Doi: 10.1097/00005392-199705000-00125.
48. *Sundac L., Dando S.J., Sullivan M.J., Derrington P., Gerrard J., Ulett G.C.* Protein-based Profiling of the Immune Response to Uropathogenic Escherichia coli in Adult Patients Immediately Following Hospital Admission for Acute Cystitis. Pathog. Dis. 2016;74(6):ftw062. Doi: 10.1093/femspd/ftw062.
49. *Tyagi P., Barclay D., Zamora R., Yoshimura N., Peters K., Vodovotz Y., et al.* Urine Cytokines Suggest an Inflammatory Response in the Overactive Bladder: a Pilot Study. Int. Urol. Nephrol. 2010;42(3):629–635. Doi: 10.1007/s11255-009-9647-5.
50. *Hannan T.J., Roberts P.L., Riehl T.E., van der Post S., Binkley J.M., Schwartz D.J. et al.* Inhibition of Cyclooxygenase-2 Prevents Chronic and Recurrent Cystitis. EBioMedicine. 2014;1(1):46–57. Doi: 10.1016/j.ebiom.2014.10.011.
51. *Tyagi P., Tyagi V., Qu X., Chuang Y. C., Kuo H.-C., Chancellor M.* Elevated CXC Chemokines in Urine Noninvasively Discriminate OAB from UTI. Am. J. Physiology-Renal Physiology. 2016;311(3):F548–F554. Doi: 10.1152/ajprenal.00213.2016.
52. *Ghoniem G., Faruqui N., Elmissiry M., Mahdy A., Abdelwahab H., Oommen M., et al.* Differential Profile Analysis of Urinary Cytokines in Patients with Overactive Bladder. Int. Urogynecol J. 2011;22(8):953–961. Doi: 10.1007/s00192-011-1401-8.
53. *Tyagi P., Tyagi V., Qu X., Lin H.-T., Kuo H.-C., Chuang Y.-C., et al.*. Association of Inflammaging (Inflammation + Aging) with Higher Prevalence of OAB in Elderly Population. Int. Urol. Nephrol. 2014;46(5):871–877. Doi: 10.1007/s11255-013-0621-x.
54. *Ma E., Vetter J., Bliss L., Lai H.H., Mysorekar I.U., Jain S.A.* Multiplexed Analysis Approach Identifies New Association of Inflammatory Proteins in Patients with Overactive Bladder. Am. J. Physiology-Renal Physiology. 2016;311(1):F28–F34. Doi: 10.1152/ajprenal.00580.2015.
55. *Alkis O., Zumrutbas A. E., Toktas C., Aybek H., Aybek Z.* The Use of Biomarkers in the Diagnosis and Treatment of Overactive Bladder: Can We Predict the Patients Who Will Be Resistant to Treatment? Neurourol. Urodynam. 2017;36(2):390–393. Doi: 10.1002/nau.22939.
56. *Pillalamarri N., Shalom D.F., Pilkinton M.L., Winkler H.A., Chatterjee P.K., Solanki M., et al.* Inflammatory Urinary Cytokine Expression and Quality of Life in Patients with Overactive Bladder. Female Pelvic Med. Reconstr. Surg. 2018;24(6):449–453. Doi: 10.1097/spv.0000000000000492.
57. *Chiu I.M., Heesters B.A., Ghasemlou N., Von Hehn C.A., Zhao F., Tran J., et al.* Bacteria Activate Sensory Neurons that Modulate Pain and Inflammation. Nature. 2013;501(7465):52–57. Doi: 10.1038/nature12479.
58. *Yang N.J., Chiu I.M.* Bacterial Signaling to the Nervous System through Toxins and Metabolites. J. Mol. Biol. 2017;429(5):587–605. Doi: 10.1016/j.jmb.2016.12.023.
59. *Blake K.J., Baral P., Voisin T., Lubkin A., Pinho-Ribeiro F.A., Adams K.L., et al.* Staphylococcus aureus Produces Pain through Pore-Forming Toxins and Neuronal TRPV1 that Is Silenced by QX-314. Nat. Commun. 2018;9(1):37. Doi: 10.1038/s41467-017-02448-6.
60. *Uhlig F., Grundy L., Garcia-Caraballo S., Brierley S.M., Foster S.J., Grundy D.* Identification of a Quorum Sensing-dependent Communication Pathway Mediating Bacteria-Gut-Brain Cross Talk. Science. 2020;23(11):101695. Doi: 10.1016/j.isci.2020.101695.
61. *de Groat W.C., Yoshimura N.* Afferent Nerve Regulation of Bladder Function in Health and Disease. Handb. Exp. Pharmacol. 2009;194:91–138. Doi: 10.1007/978-3-540-79090-7_4.
62. *Grundy L., Caldwell A., Garcia Caraballo S., Erickson A., Schober G., Castro J., et al.* Histamine Induces Peripheral and Central Hypersensitivity to Bladder Distension via the Histamine H1 Receptor and TRPV1. Am. J. Physiology-Renal Physiology. 2020;318(2):F298–f314. Doi: 10.1152/ajprenal.00435.2019.
63. *Smith Y.C., Rasmussen S.B., Grande K.K., Conran R.M., O'Brien A.D.* Hemolysin of Uropathogenic Escherichia coli Evokes Extensive Shedding of the Uroepithelium and Hemorrhage in Bladder Tissue

within the First 24 hours after Intraurethral Inoculation of Mice. Infect. Immun. 2008;76(7):2978–2990. Doi: 10.1128/iai.00075-08.
64. *Thumbikat P., Berry R.E., Zhou G., Billips B.K., Yaggie R.E., Zaichuk T., et al.* Bacteria-induced Uroplakin Signaling Mediates Bladder Response to Infection. PLoS Pathog. 2009;5(5):e1000415. Doi: 10.1371/journal.ppat.1000415.
65. *Wood M.W., Breitschwerdt E.B., Nordone S.K., Linder K.E., Gookin J.L.* Uropathogenic *E. coli* Promote a Paracellular Urothelial Barrier Defect Characterized by Altered Tight Junction Integrity, Epithelial Cell Sloughing and Cytokine Release. J. Comp. pathology. 2012;147(1):11–19. Doi: 10.1016/j.jcpa.2011.09.005.
66. *Grundy L., Caldwell A., Lumsden A., Mohammadi E., Hannig G., Greenwood Van-Meervald B., et al.* Experimentally Induced Bladder Permeability Evokes Bladder Afferent Hypersensitivity in the Absence of Inflammation. Front. Neurosci. 2020;14:590871. Doi: 10.3389/fnins.2020.590871.
67. *Grundy L., Caldwell A., Brierley S.M.* Mechanisms Underlying Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. Front. Neurosci. 2018;12:931. Doi: 10.3389/fnins.2018.00931.
68. *Brierley S.M., Goh K.G.K., Sullivan M.J., Moore K.H., Ulett G.C., Grundy L.* Innate Immune Response to Bacterial Urinary Tract Infection Sensitises High-Threshold Bladder Afferents and Recruits Silent Nociceptors. Pain. 2020;161(1):202–210. Doi: 10.1097/j.pain.0000000000001692.
69. *Grundy L., Andrea M.H., Ashlee C., Joel C., Vasiliki S., Vladimir P.Z., et al.* Translating Peripheral Bladder Afferent Mechanosensitivity to Neuronal Activation within the Lumbosacral Spinal Cord of Mice. Pain. 2018;160(4):793–804. Doi: 10.1097/j.pain.0000000000001453.
70. *Geppetti P., Nassini R., Materazzi S., Benemei S.* The Concept of Neurogenic Inflammation. BJU Int. 2008;101(Suppl. 3):2–6. Doi: 10.1111/j.1464-410X.2008.07493.x.
71. *Balachandran A.A., Wildman S.S., Strutt M., Duckett J.* Is chronic urinary infection a cause of overactive bladder? Eur J Obstet Gynecol Reprod Biol. 2016;201:108–112.
72. *Drake M.J., Morris N., Apostolidis A., Rahnama'i M.S., Marchesi J.R.* The urinary microbiome and its contribution to lower urinary tract symptoms; ICI-RS 2015 Neurourol Urodyn. 2017;36:850–853.
73. *Govender Y., Gabriel I., Minassian V., Fichorova R.* The Current Evidence on the Association Between the Urinary Microbiome and Urinary Incontinence in Women Front Cell Infect Microbiol. 2019;9:133.
74. *Thomas-White K.J., Hilt E.E., Fok C., Pearce M.M., Mueller E.R., Kliethermes S., et al.* Incontinence medication response relates to the female urinary microbiota Int Urogynecol J. 2016;27:723–733.
75. *Abbasian B., Shair A., O'Gorman D.B., Pena-Diaz A.M., Brennan L., Engelbrecht K., et al.* Potential role of extracellular ATP released by bacteria in bladder infection and contractility mSphere. 2019;4:e00439–419.
76. *Chen Z., Phan M.D., Bates L.J., Peters K.M., Mukerjee C., Moore K.H., et al.* The urinary microbiome in patients with refractory urge incontinence and recurrent urinary tract infection Int Urogynecol J. 2018;29:1775–1782.
77. *Martinez J.J., Mulvey M.A., Schilling J.D., Pinkner J.S., Hultgren S.J.* Type 1 pilus-mediated bacterial invasion of bladder epithelial cells EMBO J. 2000;19:2803–2812.
78. *Mulvey M.A., Schilling J.D., Hultgren S.J.* Establishment of a persistent Escherichia coli reservoir during the acute phase of a bladder infection Infect Immun. 2001;69:4572–4579.
79. *Justice S.S., Hung C., Theriot J.A., Fletcher D.A., Anderson G.G., Footer M.J., et al.* Differentiation and developmental pathways of uropathogenic Escherichia coli in urinary tract pathogenesis Proc Natl Acad Sci USA. 2004;101:1333–1338.
80. *Mysorekar I.U., Hultgren S.J.* Mechanisms of uropathogenic Escherichia coli persistence and eradication from the urinary tract Proc Natl Acad Sci USA. 2006;103:14170–14175.
81. *Lee P.J., Kuo H.C.* High incidence of lower urinary tract dysfunction in women with recurrent urinary tract infections. Low Urin Tract Symptoms. 2020;12:33–40.
82. *Hijazi S., Leitsmann C.* Clinical significance of video-urodynamic in female recurrent urinary tract infections. Int J Womens Health. 2016;8:31–34.
83. *Gadzhieva Z.K.* Urodynamic studies in the diagnosis and treatment of urinary disorders. The author's abstract. diss. Doctor of Medical Sciences, M., 2009. Russian (Гаджиева З.К. Уродинамические исследования в диагностике и лечении нарушений мочеиспускания. Автореф. дисс. докт. мед. наук. М., 2009).
84. *Alyaev Yu.G., Gadzhieva Z.K., Rapoport L.M., Tsarichenko D.G., Kazilov Yu.B.* Imperative and obstructive urinary disorders in patients with chronic inflammatory diseases of the urinary tract. Urologiia. 2013;1:7–12. Russian (Аляев Ю.Г., Гаджиева З.К., Рапопорт Л.М., Цариченко Д.Г., Казилов Ю.Б. Императивные и обструктивные нарушения мочеиспускания у пациентов с хроническими воспалительными заболеваниями мочевыводящих путей. Урология. 2013;1:7–12).
85. *Isakov Yu.F.* Surgical diseases in children. M., 1998. 327. Russian (Исаков Ю.Ф. Хирургические болезни у детей. М., 1998. 327).
86. *Wyndaele J.J.* Development and evaluation of the management of the neuropathic bladder. Paraplegia 1995;33:305.
87. *Gerridzen R.G., Thijssen A.M., Dehoux E.* Risk factors for upper tract deterioration in chronic spinal cord injury patients. J. Urol. 1992;147:416.
88. *Romikh V.V., Zakharchenko A.V., Borisenko L.Yu., Panteleev V.V., Romikh F.D.* Urodynamic disorders of the lower urinary tract and their nature in a group of women suffering from chronic recurrent cystitis. Urological reports. 2017;7(1S):90–91. Russian (Ромих В.В., Захарченко А.В., Борисенко Л.Ю., Пантелеев В.В., Ромих Ф.Д. Нарушения уродинамики нижних мочевых путей и их характер в группе женщин, страдающих хроническим рецидивирующим циститом. Урологические ведомости. 2017;7(1S):90–91).
89. *Pushkar D.Yu., Zaitsev A.V.* Modern possibilities of immunoprophylaxis of uncomplicated urinary tract infection. Consilium Medicum. 2011;13(7):3–7. Russian (Пушкарь Д.Ю., Зайцев А.В. Современные возможности иммунопрофилактики неосложненной инфекции мочевых путей. Consilium Medicum. 2011;13(7):3–7).
90. *Halperin-Walega E.* Drug Metab. Dispos. 1988;16(1):130–104.
91. *Huber et al.* Int J Immunopharmacol. 200;22:1103–1111.
92. *Czerwionska-Szaflarska M., Pawlowska M.* Influence of Uro-Vaxom on sIgA level in urine in children with recurrent urinary tract infection. Arch. Immunol. Ther. Exp. 1996;44:195–197.
93. *Akhmatova N.K., Khomenkov V.G., Volkova E.V., Akhmatova E.A., Semochkin I.A., Perepanova T.S., Zverev V.V.* Bacterial lysates of escherichia coli stimulate production of defensins by peripheral blood neutrophils. Journal of microbiology epidemiology immunobiology. 2016;4:50–55. Russian (Ахматова Н.К., Хоменков В.Г., Волкова Е.В., Ахматова Э.А., Семочкин И.А., Перепанова Т.С., Зверев В.В. Бактериальные лизаты Escherichia coli стимулируют продукцию дефенсинов нейтрофилами периферической крови. Журнал микробиологии, эпидемиологии и иммунобиологии. 2016;4:50–55).
94. *Mansfield K.J., Chen Z., Moore K.H., Grundy L.* Urinary Tract Infection in Overactive Bladder: An Update on Pathophysiological Mechanisms. Front. Physiol. 2022;13:886782. Doi: 10.3389/fphys.2022.886782

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