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A Method of Personalized Therapy in Patients with Various Clinical and Immunological Phenotypes of Chronic Infections of the Upper Urinary Tract

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Abstract The personalized therapy LDA developed by us enables differentiated treatment strategies for patients with chronic inflammatory bowel disease (CNI HMP), taking into account the clinical and immunological phenotype of the disease and its severity. This ensures the use of a basic or enhanced therapeutic strategy aimed at correcting the leading immunopathogenetic mechanisms of the inflammatory process.

Keywords Upper urinary tract infections, Personalized therapy, Immunological phenotypes

1. Introduction

Research is ongoing to understand the risk factors for the development and clinical features of chronic nonspecific upper urinary tract infections. According to these studies, both the persistence of the infectious agent and immunological factors play a crucial role in the development of chronic inflammation. Understanding the pathogenesis of these changes is essential for the development of new prevention and treatment methods aimed at reducing the risk of recurrence and complications in patients with urinary tract infections [1,3].

A number of scientific studies are being conducted worldwide aimed at early detection of chronic urinary tract infections and preventive measures, as well as improving patients' quality of life and reducing the incidence of complications. However, despite this, there is still insufficient information on the role of immunological factors in the development of various variants of chronic urinary tract infections (CUTIs) [2,4,6].

A number of scientific studies have been conducted in Uzbekistan on the development of infectious and inflammatory diseases of the urinary tract. The clinical features of chronic inflammatory diseases of the urinary tract have been identified [7,9]. A comprehensive approach to the treatment of urinary tract infections and the specifics of surgical and conservative treatments for complicated forms of the disease have been demonstrated. Approaches to treating urinary tract infections, taking into account clinical features, have been studied, and the principles for applying modern treatment technologies have been substantiated. Treatment methods for chronic urinary tract infections have been improved. The immediate and long-term results of comprehensive treatment of this pathology have been studied [5,8,10].

It should be noted that these studies have insufficiently explored the role of immunological mechanisms in the development of chronic urinary tract infections, necessitating further research to identify potential links between immune response characteristics and the likelihood of developing different disease courses. Therefore, comprehensive clinical and immunological studies in this area are particularly important in Uzbekistan, as they enable a more in-depth understanding of the pathogenesis of chronic urinary tract infections, identify and evaluate the role of immunological risk factors for an unfavorable course of the disease, and develop personalized approaches to their treatment.

All of the above has determined the main direction of this work.

The aim of the study: to develop a method of personalized therapy in patients with various clinical and immunological phenotypes of chronic non-specific upper urinary tract infections.

2. Materials and Methods

This study is based on an analysis of clinical data obtained at a multidisciplinary medical center in the Bukhara region and the clinic of the Bukhara State Medical Institute. The study was prospective and retrospective in nature and aimed to systematically examine the clinical and laboratory characteristics of chronic non-communicable diseases of the high-tech medical system, evaluate the immunological mechanisms underlying these characteristics, and develop a

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personalized approach to treating this disease. The study involved the phased formation of clinical groups and a gradual intensification of diagnostic testing, moving from traditional examination methods to immunological analysis and subsequent integration of the data into a clinical and immunological phenotyping system.

The clinical material included 187 examined individuals, of whom 167 were patients with chronic non-infectious diseases of the upper respiratory tract, and 20 people were included in the control group of practically healthy individuals, which was formed by the method of targeted selection taking into account gender and age, which ensured comparability with the main clinical groups and excluded the influence of these factors on the interpretation of immunological indicators.

3. Results and Discussion

Establishing clinical and immunological phenotypes of chronic upper respiratory tract infections (CNIH) creates the possibility of moving from standardized treatment regimens to differentiated therapeutic tactics focused on the leading mechanisms of immune restructuring in this disease. The phenotypic variants we identified reflect different directions of the body's immune response to a persistent infectious process and are accompanied by varying expression of innate antibacterial mechanisms, proinflammatory cytokine activity and regulatory links of the immune system. This distribution of immunopathogenetic mechanisms allows us to consider clinical and immunological phenotyping not only as a diagnostic tool, but also as a basis for choosing the optimal treatment strategy.

At the first stage of the algorithm of treatment and diagnostic measures, a patient with chronic inflammatory diseases of the upper urinary tract is considered, in whom the clinical picture of the disease already suggests the presence of a long-term or recurrent infectious and inflammatory process in the renal pelvis and interstitial tissue of the kidneys.

These patients include those with recurrent exacerbations, persistent or intermittent leukocyturia, bacteriuria, lumbar pain, dysuria, and signs of renal instability. At this stage, it is important not only to establish the presence of a chronic inflammatory process but also to recognize that this is a category of patients characterized by clinical heterogeneity and potentially requiring a differentiated, rather than standardized, approach to further diagnosis and treatment.

The next step is a clinical and laboratory examination to confirm the diagnosis of chronic upper urinary tract infections. This involves collecting complaints and anamnestic information, clarifying the duration of the disease, the frequency of relapses, the duration of remissions, the characteristics of previous antibacterial therapy, and its effectiveness. The clinical examination is supplemented by general laboratory tests, including a complete blood count, a urinalysis, a quantitative assessment of leukocyturia using the Nechiporenko method, and a urine culture to determine the degree of bacteriuria and the sensitivity of the isolated microflora to antibacterial agents. A biochemical assessment of the functional state of the kidneys is simultaneously performed, including determination of the blood creatinine level and calculation of the SCF. To clarify the nature of morphofunctional changes in the urinary system, instrumental examination methods are used, primarily ultrasound of the kidneys and upper urinary tract, and, if necessary, radiographic and other imaging techniques. The totality of the obtained data allows us to confirm the presence of a chronic infectious and inflammatory process, assess its activity, the degree of bacterial persistence and the severity of structural and functional disorders of the kidneys.

After confirming the diagnosis, the clinical and immunological phenotype of the disease is determined. This is a key component of the LDA, as it is at this stage that the dominant immunopathogenetic mechanism maintaining the chronic inflammatory process is identified. This approach shifts the diagnostic process from a general assessment of inflammation to a refinement of the underlying mechanism of immune dysregulation, which subsequently determines the choice of a personalized therapeutic strategy.

In patients with ***the antibacterial defense deficiency phenotype,*** complete elimination of microorganisms is impaired, leading to persistent bacterial persistence in the urinary tract. This leads to recurrent episodes of inflammation, persistent bacteriuria, and unstable clinical remission. In this disease course, therapeutic strategies should focus not only on eradicating the microbial agent but also on correcting the deficiency of the antibacterial immune defense. Without addressing this pathogenetic mechanism, even adequate antibiotic therapy does not always ensure sustained suppression of the infectious process. Therefore, the choice of treatment strategy for this phenotype is based on the severity of the patient's phenotypic classification, as determined by the KIOF classification scale. Patients with a low probability of developing the antibacterial defense deficiency phenotype were treated with basic therapy, based on rational etiotropic antibiotic therapy, taking into account the results of urine culture and the susceptibility of the isolated pathogen to antibacterial agents. In cases of preserved renal function and microbial susceptibility, fluoroquinolones, which are capable of achieving therapeutic concentrations in renal tissue, were used as first-line agents. Specifically, ciprofloxacin was prescribed at 500 mg twice daily for 7-10 days or levofloxacin at 750 mg once daily for 5 days. If the SCF decreased, the dosage was adjusted based on renal function. This regimen was aimed at relieving clinical and laboratory activity of the inflammatory process and sanitizing the urinary tract.

In patients with a "high" probability of the antibacterial defense deficiency phenotype, the treatment strategy was intensified, since in this group the risk of bacterial persistence and recurrent inflammation remained highest. In addition to basic antibiotic therapy, immunocorrective treatment was administered, aimed at enhancing the innate mechanisms of antibacterial defense. For this purpose, after completion of the main course of antibiotic therapy, OM-89

bacterial lysate was prescribed at a dose of 6 mg once daily in the morning on an empty stomach for 3 months. This drug promotes the activation of neutrophil phagocytic activity, increases the effectiveness of innate antibacterial defense, and enhances local resistance of the urinary tract mucosa to repeated bacterial colonization. With frequent In the case of disease recurrence after achieving clinical and laboratory remission, anti-relapse antibacterial prophylaxis may be administered. Fosfomycin was used in these cases. Tromethamine 3 g once every 10 days or trimethoprim 100 mg once daily for 3-6 months. This strategy was aimed at preventing recurrent bacterial colonization of the urinary tract and maintaining more stable clinical remission.

The effectiveness of therapy in patients with this phenotype was monitored dynamically based on clinical, laboratory, and immunological parameters using the KIOF-AI program. Within the framework of this LDA, the program was considered not only as a tool for initial phenotypic diagnosis but also as a means of assessing the need for escalation or de-escalation of treatment. If signs of bacterial persistence persist, insufficient recovery of innate immunity parameters, or a high phenotype probability based on repeated assessment data, the need for intensified therapy is justified. Upon achieving clinical and laboratory remission, a reduction in the severity of phenotypic signs, and positive dynamics of immunological parameters, a transition to a maintenance or prophylactic treatment option is possible. This approach allowed us not only to individualize the initial choice of therapy but also to adapt its intensity depending on the actual dynamics of the pathological process.

Thus, personalized therapy for the antibacterial defense deficiency phenotype is based on a stratified approach, in which a personalized treatment strategy is determined by the severity of the disease phenotype. The use of basic antibiotic therapy in patients with a low-probability phenotype and an enhanced immunocorrective strategy in patients with a high-probability phenotype allows for targeting the underlying pathogenic mechanisms of the disease, reducing the severity of bacterial persistence, and increasing the stability of clinical remission.

In contrast to the variant under consideration, in which the leading link in the pathological process is the insufficiency of antibacterial immune defense, in patients with ***the phenotype of excessive inflammatory activation,*** the dominant mechanism becomes hyperreactivity of the inflammatory response, requiring a different focus of therapeutic correction. This phenotype was characterized by the predominance of hyperreactive Immune-inflammatory mechanisms, accompanied by increased production of proinflammatory cytokines, activation of humoral immune response factors, and the development of a pronounced inflammatory reaction in the tissues of the kidneys and urinary tract. This variant of the disease course was characterized by increased concentrations of IL-6 and IL-8, elevated levels of Ig classes A and G, and accumulation of circulating immune complexes. Under such conditions, the inflammatory response, initially aimed at limiting the infectious agent, becomes excessively intense and begins to play an independent role in maintaining the pathological process. Increased cellular tissue infiltration, elevated cytokine activity, and prolonged persistence of the inflammatory cascade can contribute to damage to the renal parenchyma and the progression of structural changes in the renal pelvic system. This circumstance determined the need for therapeutic intervention aimed not only at eliminating the infectious agent but also at limiting the excessive inflammatory response.

The choice of treatment strategy for this phenotype is also determined by the severity of the patient's phenotypic status, as determined by the clinical and immunological assessment scale. Patients with a "low" probability of developing the excessive inflammatory activation phenotype are treated with basic therapy, which relies on rational antibiotic therapy based on urine culture results and the susceptibility of the isolated pathogen. If renal function and the susceptibility of the microorganism are preserved, fluoroquinolones, which are capable of achieving therapeutic concentrations in renal tissue, can be used. Specifically, ciprofloxacin was prescribed at 500 mg twice daily for 7-10 days or levofloxacin at 750 mg once daily for 5 days. Antibiotic therapy eliminates the infectious agent and reduces the intensity of antigenic stimulation of the immune system. In patients with a "high" probability of the excessive inflammatory activation phenotype, the treatment strategy should be aimed at more actively correcting the inflammatory mechanisms of the disease. In addition to basic antibiotic therapy, anti-inflammatory treatment is administered to limit the hyperergic inflammatory response and reduce the activity of proinflammatory mediators. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for this purpose. One option is to prescribe nimesulide 100 mg twice daily for 5-7 days or ibuprofen 400 mg three times daily for 5-7 days, taking into account individual tolerance and possible contraindications. The use of anti-inflammatory drugs helps reduce the severity of cytokine activation, decrease the intensity of inflammatory tissue infiltration, and limit immune-mediated inflammatory damage to the renal parenchyma.

Given the increased risk of structural changes in renal tissue in this patient population, the therapeutic strategy is complemented by nephroprotective measures aimed at stabilizing intrarenal hemodynamics, reducing intraglomerular hypertension, and slowing the progression of chronic inflammation in the renal parenchyma. For this purpose, drugs that affect the renin– angiotensin – aldosterone system are used, primarily angiotensin -converting enzyme inhibitors and angiotensin II receptor blockers, which have proven nephroprotective effects.

Enalapril at a dose of 5-10 mg twice daily or ramipril at a dose of 5-10 mg once daily can be used as angiotensin -converting enzyme inhibitors. An alternative is perindopril at a dose of 4-8 mg once daily. The initial dose is individualized and subsequently titrated based on blood pressure and tolerability. The course of treatment is at least 3-6 months; however, if signs of chronic kidney disease are present, therapy may be continued longer, with monitoring

of creatinine levels and SCF.

Angiotensin II receptor blockers can be used as an alternative to angiotensin -converting enzyme inhibitors. The most commonly used are losartan at a dose of 50-100 mg once daily, valsartan at 80-160 mg once daily, or telmisartan at 40-80 mg once daily. These drugs reduce intraglomerular pressure, improve renal perfusion, and reduce the severity of inflammatory and fibrotic processes in renal tissue. The duration of therapy is also at least 3-6 months, with subsequent dynamic monitoring of renal function.

The use of nephroprotective therapy as part of the complex treatment of chronic inflammatory bowel disease (CNI) of the upper urinary tract helps improve intrarenal hemodynamics, stabilize the functional state of the kidneys, and reduce the risk of progression of structural changes in the renal parenchyma, which is especially important in patients with a long-term and recurrent inflammatory process.

The effectiveness of treatment in patients with this phenotype is assessed dynamically based on clinical, laboratory, and immunological parameters using the KIOF- AI program. If inflammatory activity persists at a high level, cytokine markers are elevated, or bacteriuria persists, the need for escalation of therapeutic measures is considered. If the severity of phenotypic signs decreases and immunological parameters improve, a transition to less intensive maintenance therapy is possible. This approach allows for flexible adjustment of treatment intensity and adaptation of the therapeutic strategy according to the dynamics of the inflammatory process.

Thus, personalized therapy for the excessive inflammatory activation phenotype is based on a combination of antibiotic therapy aimed at eliminating the infectious agent and anti-inflammatory correction, which limits the hyperreactivity of the immune response. A differentiated treatment strategy based on the severity of the phenotype helps reduce the intensity of the inflammatory process, decrease the risk of immune-mediated renal tissue damage, and promotes stabilization of the clinical course of chronic inflammatory diseases of the upper respiratory tract.

Unlike the variants discussed above, in which either insufficient antibacterial defense or hyperactivation of inflammatory mechanisms play a leading role, in patients with ***the immune regulation deficiency phenotype,*** the key pathogenetic link is a disruption of the immunoregulatory balance, which determines the protracted nature of the inflammatory process and the instability of clinical remission. This variant of the disease course is typically characterized by a change in the immunoregulatory ratio of lymphocyte subpopulations, accompanied by a decrease in the CD4/CD8 index and a relative deficiency of anti-inflammatory mediators, primarily IL -10. Under these conditions, the inflammatory response does not reach sufficient intensity to rapidly suppress the infectious agent but persists for a long time, maintaining a chronic infectious and inflammatory process. Clinically, this is manifested by a protracted course of the disease, prolonged laboratory signs of inflammatory activity, unstable remissions, and a tendency toward reactivation of the infectious process.

The treatment strategy for this phenotype is determined by the severity of the patient's phenotypic classification, determined using a clinical and immunological assessment scale. Patients with a "low" probability of developing the immune regulation deficiency phenotype are treated with basic therapy aimed primarily at eliminating the infectious agent. The mainstay of treatment is antibiotic therapy, prescribed based on the results of urine culture and the susceptibility of the isolated pathogen. Fluoroquinolones, which ensure sufficient concentrations in renal tissue, can be used as first-line agents. Specifically, ciprofloxacin is prescribed at 500 mg twice daily for 7-10 days or levofloxacin at 750 mg once daily for 5 days. This therapy eliminates the bacterial infection and reduces antigenic stimulation of the immune system.

In patients with a "high" probability of the immune regulation deficiency phenotype, the treatment strategy should be aimed at restoring the immunoregulatory balance and stabilizing the immune response. In addition to antibiotic therapy, immunomodulatory therapy is used to normalize immune regulatory mechanisms and increase the body's resistance to persistent infection. One option is interferon-inducing therapy, such as tilorone (amixin) at 125 mg once weekly for 6 weeks, or other immunomodulatory drugs at standard therapeutic doses.

Additionally, the combination therapy included medications with antioxidant and metabolic properties aimed at stabilizing immune responses, reducing the severity of inflammation, and improving cellular energy metabolism. This group of medications is necessary because chronic infectious and inflammatory processes in renal tissue are accompanied by activation of free radical oxidation and accumulation of lipid peroxidation products, which leads to damage to cell membranes, impaired function of immune cells, and the maintenance of chronic inflammation. Increased oxidative stress contributes to the destabilization of immune responses and the progression of structural changes in the renal parenchyma. In these conditions, the use of antioxidant therapy helps reduce the intensity of free radical reactions, stabilize cell membranes, and increase tissue resistance to inflammatory damage. For this purpose, antioxidant medications were used, in particular α- tocopherol acetate at 200-400 mg orally per day for 3-4 weeks, which helps reduce the intensity of lipid peroxidation and stabilize cell membranes. Concurrently, ascorbic acid was prescribed at 500 mg twice daily for 3-4 weeks, which has a pronounced antioxidant effect and helps increase the resistance of immune cells to inflammatory damage.

To correct metabolic disorders and improve tissue energy metabolism, metabolic medications are used. One such medication is meldonium (mildronate), which is prescribed at 500 mg orally twice daily for 3-4 weeks and helps improve cellular energy metabolism and microcirculation in kidney tissue. Alternatively, thiotriazoline, 100 mg orally three times daily for 2-3 weeks, has antioxidant and membrane-stabilizing properties.

Thioctic (α- lipoic) acid, which has pronounced antioxidant and cytoprotective effects, was also used for metabolic

therapy. The drug was prescribed at a dose of 600 mg once daily for 3-4 weeks, which helped reduce the severity of oxidative stress, improve cellular metabolism, and stabilize immune responses in chronic inflammation.

Thus, the inclusion of antioxidant and metabolic drugs in the structure of complex therapy of chronic inflammatory bowel disease is aimed at reducing the severity of oxidative stress, stabilizing cell membranes and optimizing the immune response, which helps to reduce the activity of the inflammatory process and increase the duration of clinical remission of the disease.

Given the propensity of this phenotype to a protracted inflammatory process, an important element of LDA is maintenance therapy aimed at prolonging clinical remission and preventing relapse. For this purpose, relapse prevention monitoring is performed after completion of the primary course of treatment, possibly with the use of prophylactic antibiotics or immunomodulatory agents for several months.

The effectiveness of the treatment is monitored dynamically using clinical, laboratory, and immunological parameters. Within the framework of the developed algorithm, the KIOF-AI program is used as a tool for monitoring the dynamics of the disease's phenotypic characteristics and determining the need for treatment adjustments. If signs of immune dysregulation persist or immunological parameters are insufficiently stabilized, the need for enhanced immunocorrective therapy may be considered. Once immunoregulatory parameters normalize and clinical and laboratory remission is achieved, maintenance monitoring may be initiated.

Thus, personalized therapy for the immune regulation deficiency phenotype is based on a combination of rational antibiotic therapy and immunomodulatory interventions aimed at restoring the immune system's regulatory balance. A differentiated assessment of treatment intensity based on the severity of the phenotype helps stabilize the immune response, reduce the duration of inflammatory activity, and promote more sustained clinical remission in this patient population.

The personalized therapy LDA developed by us allows for a differentiated choice of treatment tactics in patients with chronic inflammatory bowel disease (CNI VMP), taking into account the clinical and immunological phenotype of the disease and its severity, which ensures the use of a basic or enhanced therapeutic strategy aimed at correcting the leading immunopathogenetic mechanisms of the inflammatory process.

4. Conclusions

1. Differentiated assessment of the choice of treatment intensity depending on the severity of the phenotype allows for stabilization of the immune response, reduction of the duration of inflammatory activity, and the formation of more stable clinical remission in this category of patients.
2. LDA of personalized therapy allows for a differentiated choice of treatment tactics in patients with chronic inflammatory diseases of the upper respiratory tract, taking into account the clinical and immunological phenotype of the disease and the degree of its severity, which ensures the use of a basic or enhanced therapeutic strategy aimed at correcting the leading immunopathogenetic mechanisms of the inflammatory process.

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