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Influence of immune mechanisms on pathogenesis and treatment of complicated urinary tract infections

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SUMMARY

Introduction. Urinary tract infections (UTIs) include a number of pathological conditions characterized by microbial colonization of urine and microbial invasion with the development of an infectious process in any part of the genitourinary tract from the outer opening of the urethra to the renal cortex. UTIs lead to suppression of immunity, both cellular and humoral, as well as factors of nonspecific protection. Reduction of anti-infective factors, changes in the reactivity of the body during UTIs leads to prolonged persistence of the infectious agent, chronicity and recurrence of inflammatory processes.
The purpose of the study is optimization of complicated urinary tract infections treatment.
Material and methods. A comparative analysis of the treatment results of 120 patients with complicated urinary tract infections (patients with surgeries on the urinary tract organs in medical records and patients who subsequently planned surgical treatment to rehabilitate the organs of the urinary tract). These patients were divided into 2 groups: group 1 (n = 60) had a short course of antibiotic therapy, group 2 (n = 60) patients were prescribed a prolonged course of antibiotic therapy. In turn, each group was divided into subgroup A, where patients received targeted monotherapy, and subgroup B, where patients were prescribed immunocorrector and probiotic in addition to antibiotic therapy. We studied in details the antibiotic therapy results of all 120 patients, considering the results of bacteriological examination of urine to determine complicated forms of urinary tract infections (reinfection, superinjection and recurrence).
Results. At the beginning of treatment, patients had lymphopenia, initially low levels of absolute T-lymphocytes (38.2 ± 1.5% and 42.4 ± 1.4%, respectively, in groups 1B and 2B, $p < 0.01$) and a significant increase in T -suppressors (36.7 ± 1.6% and 35.4 ± 1.1%, respectively, by groups, $p < 0.01$) with a significant reduction in the number of T-helpers (24.5 ± 1.6% and 25.8 ± 1.6%,

respectively, by groups, p <0.01). We also determined a significant increase in the concentration of IgG (by 1.59 times, p <0.01, respectively, in both groups), unreliable IgM (1.51 and 1.54 times, p = 0.02, respectively, by groups), and a significant decrease in IgA levels (by 59.6%, p <0.03 and 61.9%, p <0.01, respectively, in the groups) before treatment compared with the control group. The overall clinical cure in patients of the prolonged antibiotic therapy group in combination with probiotics and immunocorrector reached 93.3% of patients, which was significant (p <0.05) compared with other groups. The level of IgA increased by 33.3%, the level of IgG decreased by 55.8%, IgM decreased by 37.4%, which almost reached the values obtained in almost healthy people. Conclusion. Using recombinant human interferon alfa-2b (1-2 million IU once a day) and a probiotic, the active substance of which is the spores of the multidrug-resistant strain Bacillus clausii (1 vial 5 ml twice a day), in the complex treatment of patients with CUTIs throughout the antibacterial cycle led to normalization of the level of immunocompetent cells and immunoglobulins, increased the functional (phagocytic) activity of segmental neutrophils, and improved cellular and humoral immunity. But the obtained values were significantly close to control values only for the duration of treatment up to 15 days.

INTRODUCTION
Вступ

Urinary tract infections (UTIs) include a number of pathological conditions characterized by microbial colonization of urine and microbial invasion with the development of an infectious process in any part of the genitourinary tract from the outer opening of the urethra to the renal cortex [1]. In the structure of infectious diseases, UTIs take the second place yielding only to respiratory infections. It is the most common group of diseases in urological practice around the world. Uncomplicated UTIs most often occur in healthy women due to the penetration of uropathogenic bacteria into the bladder overcoming innate immunity, while complicated urinary tract infections (CUTIs) occur due to structural and functional lesions of the urinary tract or on the background of comorbidities like diabetes mellitus or immunodeficiency conditions, which affect the protective mechanisms of the macroorganism and increase the risk of infection or ineffective treatment [2-3].

More than 150 million cases of this pathology are registered in the world every year, which accounts for almost 40% of all cases of nosocomial infection [4]. Bacteriuria in young women is 30 times more common than in men, but with age this ratio changes due to comorbid conditions and reduced protective properties of the body. Almost 20% of women and 10% of men over 65 have pyuria [5-6]. The US Centers for Disease Control and Prevention informs that each year at least 2.8 million people are infected with antibiotic-resistant bacteria, and about 35,000 of them die from infectious diseases [7-8]. Annually 700,000 people die of antibiotic-resistant infections worldwide. In particular, methicillin-resistant Staphylococcus aureus (MRSA) alone kills about 50,000 people each year in the United States and as many people in Europe [9-11].

The structure of the microflora depends on the nosology of the disease, the course of the disease, and the factors that cause the inflammatory process. The spectrum of uropathogens is represented mainly by members of the Enterobacteriaceae family, Escherichia coli is among them. According to various authors the share of Escherichia coli is from 40 to 90%. The high proportion of Staphylococcus saprophyticus pathogens (5-10%) is also distinguished by other Enterobacteriaceae, such as Proteus mirabilis, Klebsiella pneumoniae, enterococci, and gram-positive organisms such as group B and D streptococci, which account for about 1-2% [12-13].

UTIs lead to suppression of immunity, both cellular and humoral, as well as factors of nonspecific protection. Reduction of anti-infective factors, changes in the reactivity of the body during UTIs leads to prolonged persistence of the infectious agent, chronicity and recurrence of inflammatory processes [14-15].

The purpose of the study is optimization of complicated urinary tract infections treatment.

MATERIALS AND METHODS
Матеріали і методи дослідження

A comparative analysis of the treatment results of 120 patients with complicated urinary tract infections (patients with surgeries on the urinary tract organs in medical records and patients who subsequently planned surgical treatment to rehabilitate the organs of the urinary tract). These patients were divided into 2 groups: group 1 (n=60) had a short course of antibiotic therapy, group 2 (n=60) patients were prescribed a prolonged course of antibiotic therapy. In turn, each group was divided into subgroup A, where patients received targeted monotherapy, and subgroup B, where patients were prescribed immunocorrector and probiotic in addition to antibiotic therapy. We studied in details the antibiotic therapy results of all 120 patients, considering the results of bacteriological examination of urine to determine complicated forms of urinary tract infections (reinfection, superinjection and recurrence).

RESULTS AND DISCUSSION
Результати та їх обговорення

The factors complicating the course of UTIs in 40.8% of patients were urinary tract obstruction, previous surgery (> 6 months) in 33.3% and diabetes mellitus in 27.5% of patients. The following uropathogens that caused UTIs were observed in our patients: E. coli (diagnosed in 36.7% of patients), Klebsiella (found in 26.7%), Enterococcus faecalis and Pseudomonas aeruginosa (in 10% of patients). We conducted the study of the immune status of 60 patients who received complex therapy (antibiotic therapy + immunocorrector + probiotic). 30 patients of group 1B received a short course of antibiotic therapy (5-7 days) and 30 patients of group 2B received a prolonged course of antibiotic therapy (10-14 days). Indicators of 10 patients who were hospitalized in a planned manner for surgical treatment without any urogenital infection were taken as control values.

We compared the indicators at hospitalization and at the end of hospital treatment. That is, on the first day in both groups, on the 8th day in group 1B and on the 15th day in group 2B (Table 1).

At the beginning of treatment, patients had lymphopenia, initially low levels of absolute T-lymphocytes (38.2 ± 1.5% and 42.4 ± 1.4%, respectively, in groups 1B and 2B, p <0.01) and a significant increase in T -suppressors (36.7 ± 1.6% and 35.4 ± 1.1%, respectively, by groups, p <0.01) with a significant reduction in the number of T-helpers (24.5 ± 1.6% and 25.8 ± 1.6%, respectively, by groups, p <0.01). Patients of both groups had an increased immunoregulatory index (IRI) - 2.8 ± 0.5 and 2.9 ± 0.4 (p <0.01). The increase in the ratio of Ts / Tx due to the increase in the level of Ts was observed in the midst of the disease with significant activity of the inflammatory process (table 2).

In the course of treatment there was an increase and normalization of the total number of lymphocytes, Tx, Ts; reducing the ratio of Tx / Ts, by increasing Ts. The level of Tx significantly increased only in group 2B (up to 38.5 ± 1.4%) and had no significant difference with the control group (p = 0.02).

It should be noted that on the 8th day the T-lymphocyte count increased to 48.4 ± 1.1% in patients of group 1B, but in group 2B it increased to 52.1 ± 1.1 on the 15th day, which approached the control values (p = 0.01).

Significant decrease of Ts after treatment was observed in both groups, but in group 2B it was more pronounced and close to control values (21.3 ± 1.5% and 20.1 ± 0.5%) (p = 0.06) on

TABLE 1. Changes in the leukocyte formula under the influence of treatment

Indicator	group 1B (n=30) before treatment, 1st day	group 1B (n=30) after treatment, 8th day	P	group 2B (n=30) before treatment, 1st day	group 2B (n=30) after treatment, 15th day	P
Total number of leukocytes 10^9/l	11.6±1.09	8.8±0.86	0.04	12.3±1.12	6.2±1.17	0.01
Neutrophils (p/i) %	2.0±0.04	2.0±0.03	0.9	3.0±0.07	4.0±0.04	0.04
Neutrophils (s/i) %	52.1±0.1	63.4±0.4	0.01	61.4±0.4	50.4±0.2	<0.01
Eosinophils %	11.1±0.1	3.2±0.2	<0.01	16.6±0.3	3.7±0.1	<0.01
Monocytes %	9.2±0.4	2.1±0.3	<0.01	5.1±0.4	9.2±0.3	<0.01
Lymphocytes %	29.4±0.3	20.2±0.2	<0.01	41.5±0.6	26.1±0.2	<0.01
The absolute number of lymphocytes 10^9/l	2.8±0.2	1.6±0.1	0.02	2.9±0.1	1.4±0.1	<0.01

TABLE 2. Dynamics of cellular immunity in patients with CUTIs

Indicator	control group (n=10)	group 1B (n=30) before treatment, 1st day	group 1B (n=30) after treatment, 8th day	P	group 2B (n=30) before treatment, 1st day	group 2B (n=30) after treatment, 15th day	P
T-lymphocytes (CD_3) %	56.4±1.2	38.2±1.5	48.4±1.1	$p_{1-2}<0.01$ $p_{1-3}=0.01$	42.4±1.4	52.1±1.1	$p_{1-2}<0.01$ $p_{1-3}=0.01$
T-helpers (CD_4) %	42.1±0.9	24.5±1.6	28.5±1.9	$p_{1-2}<0.01$ $p_{1-3}<0.01$	25.8±1.6	38.5±1.4	$p_{1-2}<0.01$ $p_{1-3}=0.02$
T-suppressors (CD_8) %	20.1±0.5	36.7±1.6	25.6±1.4	$p_{1-2}<0.01$ $p_{1-3}=0.02$	35.4±1.1	21.3±1.5	$p_{1-2}<0.01$ $p_{1-3}=0.06$
Immunoregulatory index İ(Ts/Tx)	1.8±0.3	2.8±0.5	2.2±0.4	$p_{1-2}<0.01$ $p_{1-3}=0.05$	2.9±0.4	1.8±0.3	$p_{1-2}<0.01$ $p_{1-3}=1.0$
Active T lymphocytes %	28.3±1.4	36.3±1.6	30.4±1.8	$p_{1-2}=0.01$ $p_{1-3}=0.04$	34.5±1.4	26.5±1.6	$p_{1-2}<0.01$ $p_{1-3}=0.04$
B-lymphocytes (CD_{20}) %	26.4±1.8	18.6±1.8	21.3±1.4	$p_{1-2}<0.01$ $p_{1-3}=0.02$	19.7±1.5	19.7±1.8	$p_{1-2}<0.01$ $p_{1-3}<0.01$
Complement system activity	1.0±0.2	0.7±0.1	0.7±0.1	$p_{1-2}=0.03$ $p_{1-3}=0.03$	0.65±0.1	0.9±0.1	$p_{1-2}<0.01$ $p_{1-3}=0.05$
Autoimmune lymphocytotoxic antibodies	8.9±0.9	18.2±1.3	16.5±1.6	$p_{1-2}<0.01$ $p_{1-3}<0.01$	16.4±1.1	11.2±0.9	$p_{1-2}<0.01$ $p_{1-3}=0.01$
Heterophilic hemolysins, Od. OP	0.4±0.02	0.56±0.01	0.62±0.03	$p_{1-2}<0.01$ $p_{1-3}<0.01$	0.8±0.02	0.7±0.01	$p_{1-2}=0.01$ $p_{1-3}=0.01$

the 15th day of treatment, and in group 1B the decrease in the level of Ts was smaller (25.6 ± 1.4%) and did not reach the control indicators.

When analyzing the immune system of patients with CUTIs we identified multidirectional violation of the level of immunoglobulins, namely: a statistically significant increase in IgG and IgM and a decrease in the concentration of IgA in the blood serum, which indicated a violation of the humoral immune response (table 3).

Before treatment, group 1B patients had a significant increase in the concentration of IgG (by 1.59 times, $p<0.01$) and a decrease in IgA (by 1.67 times, $p<0.03$) and IgM (this decrease was insignificant, $p = 0.02$) in the blood serum compared with control values. These changes reflected violations of anti-infective resistance and humoral immunity, as well as the active development of the inflammatory process in the urinary system.

After a course of treatment, we observed that in patients of group 1B IgG content decreased by 32.7% and approached the control group ($p = 0.02$), as well as the content of IgM (by 19.1%, $p = 0.04$) in blood serum; immunoglobulin A increased slightly (by 5.9%), but not to control values, which indicates incomplete elimination of the inflammatory process.

When analyzing the state of immunoglobulins in group 2B we found out a multidirectional violation of the level of immunoglobulins, namely: statistically

TABLE 3. Dynamics of immunoglobulin concentration

Indicator	control group (n=10)	group 1B (n=30) before treatment, 1st day	group 1B (n=30) after treatment, 8th day	P	group 2B (n=30) before treatment, 1st day	group 2B (n=30) after treatment, 15th day	P
Immunoglobulin A (IgA)	2.81±0.29	1.68±0.31	1.78±0.35	$p_{1-2}<0.03$ $p_{1-3}=0.05$	1.74±0.31	2.32±0.21	$p_{1-2}<0.01$ $p_{1-3}=0.05$
Immunoglobulin G (IgG)	12.34±0.16	19.64±0.81	14.8±0.55	$p_{1-2}<0.01$ $p_{1-3}=0.02$	19.63±0.74	12.6±0.59	$p_{1-2}<0.01$ $p_{1-3}=0.83$
Immunoglobulin M(IgM)	0.95±0.08	1.44±0.13	1.21±0.10	$p_{1-2}=0.02$ $p_{1-3}=0.04$	1.47±0.16	1.07±0.13	$p_{1-2}=0.02$ $p_{1-3}=0.06$

significant increase in IgG (by 1.59 times, p <0.01), inaccurate IgM (by 1.54 times, p = 0.02) and a significant decrease in the level of IgA (by 61.9%, p <0.01) in blood serum compared with control values, which indicates an increase in the immune response of the humoral immune system.

On the 15th day of treatment, the concentration of IgA increased by 33.3% and almost reached control values of 2.32 ± 0.21 (p = 0.05) in patients of group 2B. There was also a tendency to reduce the level of IgG (by 55.8%, p = 0.83) and IgM (by 37.4%, p = 0.06), which almost reached the values obtained in almost healthy people.

Using recombinant human interferon alfa-2b (1-2 million IU once a day) and a probiotic, the active substance of which is the spores of the multidrug-resistant strain Bacillus clausii (1 vial 5 ml twice a day), in the complex treatment of patients with CUTIs throughout the antibacterial cycle led to normalization of the level of immunocompetent cells and immunoglobulins, increased the functional (phagocytic) activity of segmental neutrophils, and improved cellular and humoral immunity. But the obtained values were significantly close to control values only for the duration of treatment up to 15 days.

CONCLUSIONS
Висновки

Among the uropathogens that caused CUTIs, E. coli was diagnosed in 36.7% of patients, Klebsiella in 26.7%, Enterococcus faecalis and Pseudomonas aeruginosa in 10% of patients. At the beginning of treatment, patients had lymphopenia, initially low levels of absolute T-lymphocytes (38.2 ± 1.5% and 42.4 ± 1.4%, respectively, in groups 1B and 2B, p <0.01) and a significant increase in T -suppressors (36.7 ± 1.6% and 35.4 ± 1.1%, respectively, by groups, p <0.01) with a significant reduction in the number of T-helpers (24.5 ± 1.6% and 25.8 ± 1.6%, respectively, by groups, p <0.01). We also determined a significant increase in the concentration of IgG (by 1.59 times, p <0.01, respectively, in both groups), unreliable IgM (1.51 and 1.54 times, p = 0.02, respectively, by groups), and a significant decrease in IgA levels (by 59.6%, p <0.03 and 61.9%, p <0.01, respectively, in the groups) before treatment compared with the control group. The overall clinical cure in patients of the prolonged antibiotic therapy group in combination with probiotics and immunocorrector reached 93.3% of patients, which was significant (p <0.05) compared with other groups. The level of IgA increased by 33.3%, the level of IgG decreased by 55.8%, IgM decreased by 37.4%, which almost reached the values obtained in almost healthy people.

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РЕФЕРАТ

Вплив імунних механізмів на патогенез та лікування ускладнених інфекцій сечовивідних шляхів

І.М. Антонян, О.М. Геглюк

Вступ. Інфекції сечовивідних шляхів (ІСВШ) – термін, що охоплює цілий ряд патологічних станів, які характеризуються мікробною колонізацією сечі і мікробною інвазією з розвитком інфекційного процесу в будь-якій частині сечостатевого тракту – від зовнішнього отвору уретри до кіркової речовини нирок. ІСВШ призводять до пригнічення імунітету, як клітинного, так і гуморального, а також факторів неспецифічно-

РЕФЕРАТ

Влияние иммунных механизмов на патогенез и лечение осложнений инфекций мочевыводящих путей

И.М. Антонян, А.Н. Геглюк

Вступление. Инфекции мочевыводящих путей (ИМВП) – термин, охватывающий целый ряд патологических состояний, которые характеризуются микробной колонизацией мочи и микробной инвазией с развитием инфекционного процесса в любой части мочеполового тракта – от наружного отверстия уретры до коркового вещества почек. ИМВП приводят к угнетению иммунитета, как клеточного, так и гумо-

го захисту. Зниження факторів протиінфекційного захисту, зміни реактивності організму при ІСВШ веде до тривалої персистенції інфекційного агента, хронізації і рецидивування запальних процесів.

Мета дослідження: Оптимізація лікування ускладнених інфекцій сечовивідних шляхів.

Матеріали і методи: Проведено порівняльний аналіз результатів лікування 120 хворих з ускладненою інфекцією сечових шляхів. Хворі були розподілені на 2 групи: у 1-й групі (n=60) проводився короткий курс антибіотикотерапії, у 2-й групі (n=60) був призначений пролонгований курс антибіотикотерапії. В свою чергу, кожна група поділялася на підгрупу А, в якій пацієнти отримували цілеспрямовану монотерапію, та Б – де пацієнтам додатково до АБ-терапії призначали імунокоректор та пробіотик. В усіх 120 пацієнтів вивчався детальний анамнез АБТ за результатами бактеріологічного дослідження сечі з метою визначення ускладнених форм інфекцій СВШ (реінфекції, суперінфекції та рецидиву).

Результати. На початку лікування спостерігалася лімфопенія, початково низькі рівні абсолютної кількості Т-лімфоцитів (38,2±1,5% та 42,4±1,4% відповідно у 1Б та 2Б групах, p<0,01) і достовірне підвищення показника Т-супресорів (36,7±1,6% та 35,4±1,1%, відповідно по групах, p<0,01) при суттєвому зниженні кількості Т-хелперів (24,5±1,6% та 25,8±1,6%, відповідно по групах, p<0,01). Також до лікування визначалося достовірне збільшення концентрації IgG (в 1,59 разу, p<0,01, відповідно в обох групах), недостовірне IgM (в 1,51 та 1,54 разу, p=0,02, відповідно по групах), та достовірне зниження рівня IgA (на 59,6%, p<0,03 та 61,9%, p<0,01, відповідно у групах) порівняно з показниками контрольної групи. Загальне клінічне виліковування у пацієнтів групи пролонгованого курсу АБТ у комбінації з пробіотиком та імунокоректором досягло 93,3% пацієнтів, що було достовірно (p<0,05) порівняно з іншими групами. Рівень IgA підвищився на 33,3%, IgG – знизився на 55,8%, IgM – знизився на 37,4%, що майже досягло показників, отриманих у практично здорових людей.

Висновок. Застосування у комплексному лікуванні хворих на УІСВШ інтерферона альфа-2b рекомбінантний людини (1-2 млн МО 1 раз на добу) та пробіотика, діючою речовиною якого є спори полірезистентного штаму Bacillus clausii (1 флакон 5 мл двічі на добу) протягом всього циклу антибактеріальної терапії призводить до нормалізації рівня імунокомпетентних клітин і імуноглобулінів, підвищує функціональну (фагоцитарного, а также факторов неспецифической защиты. Снижение факторов противоинфекционной защиты, изменения реактивности организма при ИМВП ведет к длительной персистенции инфекционного агента, хронизации и рецидивированию воспалительных процессов.

Цель исследования: Оптимизация лечения осложненных инфекций мочевыводящих путей.

Материалы и методы: Проведен сравнительный анализ результатов лечения 120 больных с осложненной инфекцией мочевых путей. Больные были разделены на 2 группы: в 1-й группе (n=60) проводился короткий курс антибиотикотерапии, во 2-й группе (n=60) был назначен пролонгированный курс антибиотикотерапии. В свою очередь, каждая группа делилась на подгруппу А, в которой пациенты получали целенаправленно монотерапию и Б – где пациентам дополнительно к АБ-терапии назначали иммунокорректор и пробиотик. У всех 120 пациентов изучался подробный анамнез антибиотикотерапии по результатам бактериологического исследования мочи с целью определения осложненных форм ИМВП (реинфекции, суперинфекции и рецидива).

Результаты. В начале лечения наблюдалась лимфопения, изначально низкие уровни абсолютного количества Т-лимфоцитов (38,2±1,5% и 42,4±1,4% соответственно в 1Б и 2Б группах, p <0,01) и достоверное повышение показателя Т супрессоров (36,7±1,6% и 35,4±1,1% соответственно по группам, p<0,01) при существенном снижении количества Т-хелперов (24,5±1,6% и 25,8±1,6% соответственно по группам, p<0,01). Также до лечения определялось достоверное увеличение концентрации IgG (в 1,59 раза, p<0,01, соответственно в обеих группах), недостоверное IgM (в 1,51 и 1,54 раза, p=0,02, соответственно по группам) и достоверное снижение уровня IgA (на 59,6%, p<0,03 и 61,9%, p<0,01, соответственно в группах) по сравнению с показателями контрольной группы. Общее клиническое излечение у пациентов группы пролонгированного курса АБТ в сочетании с пробиотиком и иммунокорректором достигло 93,3% пациентов, было достоверно (p<0,05) по сравнению с другими группами. Уровень IgA повысился на 33,3%, IgG – снизился на 55,8%, IgM – снизился на 37,4%, что почти достигло показателей, полученных у практически здоровых людей.

Вывод. Применение в комплексном лечении больных осложненных ИМВП интерферона альфа-2b рекомбинантный человека (1–2 млн. МЕ 1 раз в сутки) и пробиотика, действующим веществом которого являются споры полирезистентного штамма Bacillus clausii (1 флакон 5 мл

гоцитарну) активність сегментоядерних нейтрофілів, покращує показники клітинного та гуморального імунітету, але показники достовірно наближуються до контрольних значень лише при тривалості курсу лікування до 15 діб.

Ключові слова: ускладнені інфекції сечових шляхів, антибіотикотерапія, пробіотики, імунокоректор.

дважды в сутки) в течение всего цикла антибактериальной терапии приводит к нормализации уровня иммунокомпетентных клеток и иммуноглобулинов, повышает функциональную (фагоцитарную) активность сегментоядерных нейтрофилов, улучшает показатели клеточного и гуморального иммунитета, однако показатели достоверно приближаются к контрольным значениям лишь при продолжительности курса лечения до 15 суток.

Ключевые слова: осложненные инфекции мочевых путей, антибиотикотерапия, пробиотики, иммунокорректор.