

## Enzyme test – early diagnosis of kidney inflammation

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сечокам'яна хвороба, пієлонефрит, NGAL, IL-1 $\beta$ ,  $\beta$ 2-мікроглобулін, MCP-1

**SUMMARY**

The aim of the work is to improve the results of early diagnosis of acute infectious kidney diseases at the molecular level in urolithiasis (urinary stone disease) through the study of enzymatic test indicators. Enzymatic tests (NGAL, IL-1 $\beta$ ,  $\beta$ 2-microglobulin) were investigated at the molecular level using the IFA method in the urine of patients with urolithiasis. Comparative and prognostic significance of the conducted treatment was established between the groups of patients, and an algorithm was developed based on the results of kidney damage predictors. It was found that the indicators of general laboratory analysis in patients with urolithiasis within the first 24-48 hours do not reliably indicate the absence of an infectious-inflammatory process in the kidneys and the development of renal failure. It was determined that an increase in the inflammation predictor indicators in more than 50% of patients indicates the development of infectious-inflammatory complications within the first 12-24 hours before the occurrence of general laboratory and clinical changes. The assessment of the effectiveness of conservative therapy in groups IA and II revealed that complications of the inflammatory process in the kidneys were observed five times more frequently in group II (comparison) than in group IA. The use of enzymatic tests as markers for early kidney damage allows for the classification of two main groups of patients: those requiring conservative treatment and those requiring urgent surgical intervention. This significantly reduces the frequency of inflammatory, purulent-septic complications and improves the treatment outcomes for patients with upper urinary tract obstruction in urolithiasis.

**РЕФЕРАТ**

**Ферментний тест – рання діагностика запалення нирок. Бачурін Г.В., Бачурін А.В., Коломоєць Ю.С.** Мета роботи – покращення результатів ранньої діагностики гострих інфекційних захворювань нирок, на молекулярному рівні, при СКХ на основі вивчення показників ферментних тестів. Здійснили дослідження ферментних тестів (NGAL, IL-1 $\beta$ ,  $\beta$ 2-мікроглобулін) на молекулярному рівні в сечі хворих на сечокам'яну хворобу методом ІФА, встановили прогностичне та порівняльне значення проведеного лікування між групами та розробили алгоритм на тлі результатів предикторів пошкодження нирок. Визначено, що у хворих на СКХ показники загальнолабораторних аналізів у перші 24–48 годин достовірно не вказують на відсутність інфекційно-запального процесу в нирках та розвиток ниркової недостатності. Підвищення показників предикторів запалення більш ніж у 50% вказує на розвиток інфекційно-запальних ускладнень у перші 12–24 години, до виникнення клінічних та загальнолабораторних змін. При оцінці ефективності консервативної терапії у хворих IA та II групах, у порівняльному аспекті, визначено, що ускладнення перебігу запального процесу в нирках у II групі (порівняння)

спостерігалось у 5 разів частіше, ніж в групі ІА. Використання ферментних тестів маркерів раннього пошкодження нирок дають можливість поділити на два основні потоки хворих – консервативне та невідкладне хірургічне лікування, що значно зменшує частоту виникнення запальних, гнійно-септичних ускладнень та врази покращує результати лікування хворих з обструкцією верхніх сечових шляхів при СКХ.

## INTRODUCTION

Despite the progress in the study of urolithiasis (urinary stone disease), the problem of its occurrence remains one of the most challenging and unresolved (Vozianov et al., 1984; Mishra et al., 2003; Jindal & Ramchandani, 2007). Among all urological problems, urolithiasis holds the second place in Ukraine in terms of the growth rate of incidence (0.16-0.22) and occurrence frequency (30-40%), indicating an unfavorable prognosis in terms of its spread (Vozianov et al., 2010; Yermolenko & Zhulay, 2011; Pasichnikov et al., 2013; Grutzniz, 1982; Knoll et al., 2003). The course of the disease is accompanied by infectious-inflammatory processes and frequent recurrences in more than 50% of cases, which can lead to complications such as renal failure, disability, and even death (Pasichnikov et al., 2013; Kuwabara et al., 2009; Moe, 2006; Miller, et al. 2006). In 60-70% of urolithiasis patients, the presence of infection not only exacerbates the disease but also significantly worsens its further prognosis (Pasichnikov et al., 2010; Grottsch & Mattenheimer, 2003; Ray et al., 2010; Knoll et al., 2003; Moe, 2006). Urinary tract infection is one of the most widespread infectious diseases (Pasichnikov et al., 2013; Mishra et al., 2006; Knoll et al., 2003). The combination of upper urinary tract dysfunctions with infectious-inflammatory processes leads to a vicious cycle. Infections and inflammatory processes, along with sclerotic changes in the kidneys, result in urinary flow disturbances. According to scientific studies found in the literature, chronic pyelonephritis contributes to recurrences and complicates urolithiasis in 85% of patients (Vozianov et al., 1984; Grottsch & Mattenheimer, 2003; Miller et al., 2007; Miller et al., 2006).

The initial stage of the disease, known as serous pyelonephritis, lasts approximately from 6 to 36 hours. Subsequent stages are characterized by purulent-destructive changes that lead to irreversible processes in the kidneys (Honcharenko, 2003; Vozianov et al., 2010; Grottsch & Mattenheimer, 2003; Mishra et al., 2003; Ray et al., 2010). The mortality rates for acute purulent pyelonephritis can reach 30% among elderly individuals, making it one of the leading causes of mortality in urological hospitals (Vozianov et al., 1984; Pasichnikov et al., 2010; Pasichnikov et al., 2013; Jindal & Ramchandani, 2007; Ray et al., 2010). If the infectious-inflammatory process is not detected and properly treated in

individuals with weakened immune systems, the complications can progress to a purulent-septic form (Vozianov et al., 1984; Pasichnikov et al., 2013; Fink et al., 2013; Miller et al., 2006). During the development of the purulent process, the prognosis becomes extremely dangerous, with potential functional organ loss and the development of bacteriotoxic shock, resulting in a mortality rate ranging from 45% to 55% (Honcharenko, 2003; Pasichnikov et al., 2010; Ray et al., 2010; Miller et al., 2007).

Early diagnosis, timely establishment of the diagnosis, and determination of treatment tactics play a crucial role in the final outcomes of the disease and significantly reduce complications related to the kidneys (Vozianov et al., 1984; Grottsch & Mattenheimer, 2003; Lowe & Knudsen, 2018; Fink et al., 2013; Moe, 2006). It is essential to conduct general clinical blood and urine tests to assess the overall kidney function (Vozianov & Liulko, 2002; Grottsch & Mattenheimer, 2003; Mishra et al., 2003; Jindal & Ramchandani, 2007). Despite significant progress in diagnosing and treating acute pyelonephritis, there remains a high frequency of complications, such as urosepsis, bacteriotoxic shock, acute and chronic renal failure, leading to high mortality rates among these patients (Vozianov & Liulko, 2002; Pasichnikov et al., 2013; Ray et al., 2010). According to some literature, there is not always a direct correlation between the severity of the disease and the changes observed in the complete blood count (CBC) and complete urine analysis (CUA). In cases of severe infection and patient debilitation, leukocytosis may be absent, and sometimes leukopenia is observed. This phenomenon is associated with the suppression of the immune system in the body (Yermolenko & Zhulay, 2011; Mishra et al., 2003; Lowe & Knudsen, 2018; Fink et al., 2013). In cases of urinary tract obstruction from the kidneys, purulent forms of acute obstructive pyelonephritis may develop at the end of the first day of the disease.

By the end of the second day, the inflammatory process begins to spread and affect the parenchyma of the affected kidney, leading to significant disturbances in enzymatic processes, indicating the development of renal failure. An important characteristic of its course in the case of nephrolithiasis is the difficulty in determining the moment of sepsis and multiple organ failure (Vozianov et al., 1984; Vozianov & Liulko, 2002; Pasichnikov et al., 2013; Mishra et al., 2003; Miller et al., 2006). According to

Kuzmenko et al., 2007, the restoration of renal function occurs only when the upper urinary tract remains unobstructed within the first 24 hours after the onset of acute pyelonephritis (Honcharenko, 2003; Mishra et al., 2003; Ray et al., 2010).

Currently, proteinuria, elevated serum creatinine levels, and reduced glomerular filtration rate are considered markers of kidney damage. However, these markers are detected only in the late stage of chronic kidney disease when conservative therapy may not be effective, and the damage process becomes irreversible. Therefore, there is significant attention being given to the search for biomarkers of acute and chronic kidney injury that can be detected in urine, as well as studying the role of cytokines in the inflammatory response. This allows for the detection of pathological changes in the kidneys at early stages, assessment of the degree of damage, and evaluation of the intensity of inflammation and fibrogenesis (Vozianov et al., 1984; Honcharenko, 2003; Pasichnikov et al., 2010; Myhal et al., 2005; Mishra et al., 2006). To assess the functional status of renal parenchyma, investigations of the activity of tissue enzymes in urine and blood are conducted. However, the activity of enzymes in blood remains almost unchanged in kidney diseases and does not reflect the severity of kidney damage (Vozianov et al., 1984; Myhal et al., 2005; Grotsch & Mattheimer, 2003; Lowe & Knudsen, 2018; Fink et al., 2013). Enzymatic tests provide a better reflection of metabolic processes at the molecular level, even when clinical and laboratory indicators have minimal expression (Honcharenko, 2003; Yermolenko & Zhulay, 2011; Myhal et al., 2005; Lowe & Knudsen, 2018; Miller et al., 2006).

The purpose of this study was to improve the results of early diagnosis of acute infectious kidney diseases at the molecular level in urolithiasis (urinary stone disease) through the study of enzymatic test indicators.

The research was conducted at the urology department of the Emergency and Ambulance Hospital in Zaporizhzhia, which serves as the clinical base for the Department of Urology at Zaporizhzhia State Medical University.

## MATERIALS AND METHODS

The inclusion criteria for the study were individuals of both genders aged 18 years and older with ureteral or urinary stone(s) of various localizations. The exclusion criteria were active concomitant pathologies and the presence of oncological diseases requiring specific therapy.

To achieve the set goal, the results of examination and treatment of 142 patients during the period

from 2018 to 2019 were analyzed. Among them, 70 patients were analyzed using the enzyme-linked immunosorbent assay (ELISA) of urine. For the determination of reference values, 30 individuals who were considered clinically healthy were examined. To evaluate the course of pyelonephritis and long-term complications after conservative treatment, a retrospective analysis of the medical histories of 42 patients with urolithiasis was conducted, excluding the results of enzymatic tests.

In this study, patients and healthy individuals were divided into three clinical groups, as described below:

Group I: This group consisted of patients with urolithiasis (urinary stone disease) who underwent enzymatic urine tests. A total of 70 patients were included in this group.

Subgroup IA: This subgroup included patients from Group I whose inflammatory markers were within normal range or showed elevated levels of only one of the three early kidney damage markers. These patients received conservative therapy. The number of patients in this subgroup was 48.

Subgroup IB: In this subgroup, patients from Group I were identified with elevated levels of two or more inflammation markers. These patients received surgical treatment. The number of patients in this subgroup was 22.

Group II: This group consisted of patients for whom a retrospective analysis of their medical histories was conducted, specifically comparing the treatment outcomes of pyelonephritis and long-term complications. There were 42 patients in this group.

Group III: This group comprised 30 individuals who were considered conditionally clinically healthy and served as the control group.

All groups were homogeneous in terms of gender and age ( $p \geq 0.05$ ).

All patients included in the study underwent a collection of anamnestic data and comprehensive clinical and laboratory examinations. The main criterion for the clinical – diagnostic effectiveness of using inflammation predictors was the deflection of early signs of infectious – inflammatory complications in patients with urinary tract dysfunction in groups IA and IB

The obtained results were entered into a Microsoft Excel 2010 database and underwent statistical processing using a licensed Statistical 13.0 software package (license number JPZ804I382130ARCN10-J).

Conservative therapy ( $n=48$ ) was based on providing immediate urgent care for renal colic according to the current protocols of medical care.

For patients who showed signs of infectious – inflammatory processes along with urinary tract

obstruction and persistent pain syndrome, urgent surgical intervention was performed (n=22). The choice of the surgical method depended on the results of the IFAs of early kidney damage markers, the overall condition of the patient, as well as the results of general

laboratory and instrumental examinations. All patients in Group IB, diagnosed with infectious – inflammatory processes, underwent lithotripsy or stone extraction, kidney drainage, and received antibacterial, anti-inflammatory, and infusion therapy (Table. 1).

**TABLE 1.** Surgical Treatment of Patients in Group IB, (n/%)

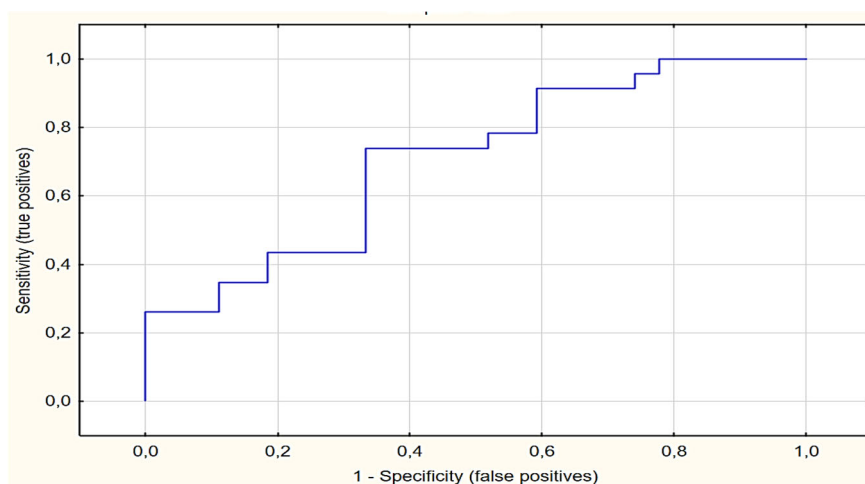
Surgical methods for patients in group IB, (n=22)	Number, (n/%)
Contact Ureterolithotripsy (CUL)	9 (40.9%)
Ureterolithoextraction	8 (36.4%)
Extracorporeal Shock Wave Lithotripsy (ESWL)	4 (18.2%)
Percutaneous Nephrostomy + ESWL	1 (4.5%)

**RESULTS AND DISCUSSION**

According to the findings of the conducted study in patients with urolithiasis who were hospitalized within the first hours, the detection of early preclinical signs of infectious – inflammatory complications was most effective using the Immunoassay (IFA) test for NGAL, IL - 1 $\beta$ , and  $\beta$ 2 – microglobulin in urine. The research revealed that MSR – 1 did not

provide high informative value compared to other predictors, and therefore further analysis of this marker was not carried out.

For  $\beta$ 2 – microglobulin, the following results were obtained: the cut – off point value was 0.13  $\mu$ g/ml sensitivity was 95.5%, specificity was 66.7%, and accuracy was 75.5%. More detailed data can be found in Table 2 and Figure 1 of the study.



**Fig. 1.** ROC-curve for  $\beta$ 2-microglobulin

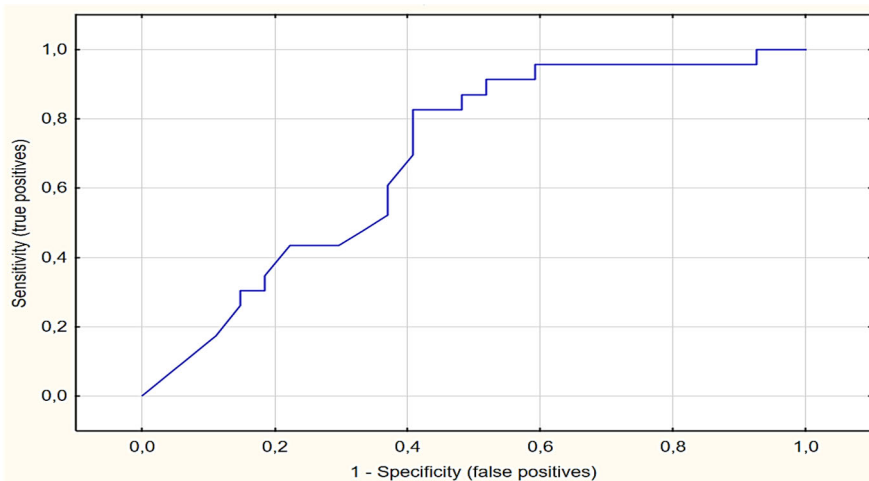
**TABLE 2.** Results of assessment of  $\beta$ 2 – microglobulin in groups IA and IB

Group	Value $\beta$ 2 – microglobulin	
	<0.13 $\mu$ g/ml	$\geq$ 0.13 $\mu$ g/ml
Conservative treatment (IA), (n=48)	32	16
Operative treatment (IB), (n=22)	1	21
In total	33	37

The parameters for IL – 1 $\beta$  were as follows: the cut – off point value was 6 pg/ml, sensitivity was 86,4%, specificity was 85,4%, and accuracy was 85,7% (Fig. 2, Table 3).

The ROC – analysis with the constructed logistic regression model for NGAL yielded the following results: the cut – off point value was 11 ng/ml, sensitivity was 72,7%, specificity was 100%, and accuracy was 91,4% (Fig. 3, Table 4).

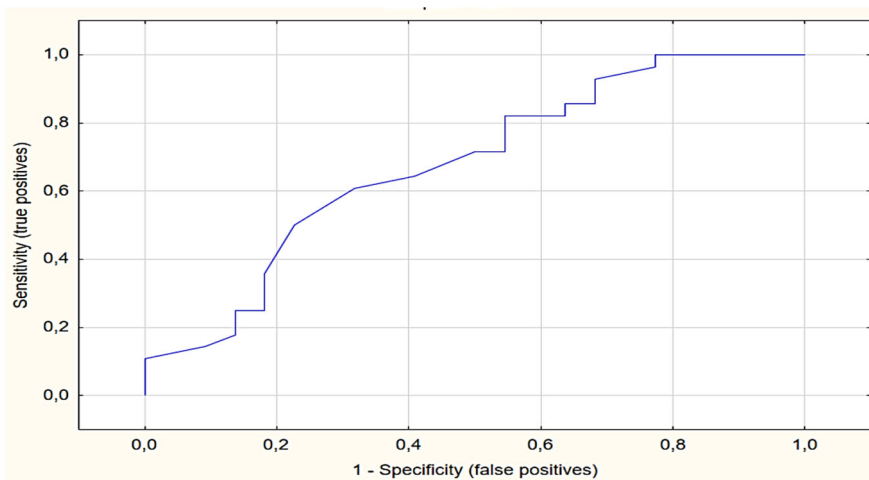
During the examination of results of Group IA, which included 48 patients, it was found that the indicators of leukocytes, neutrophils, erythrocyte sedimentation rate (ESR), and creatinine were within normal limits at the time of hospitalization. This indicated the absence of significant signs of an infectious – inflammatory process and the development of renal insufficiency. Detailed data can be found in Figure 4 of the study.



**Fig. 2. ROC-curve for IL – 1 $\beta$**

**TABLE 3. Results of assessment of IL – 1 $\beta$  in groups IA and IB**

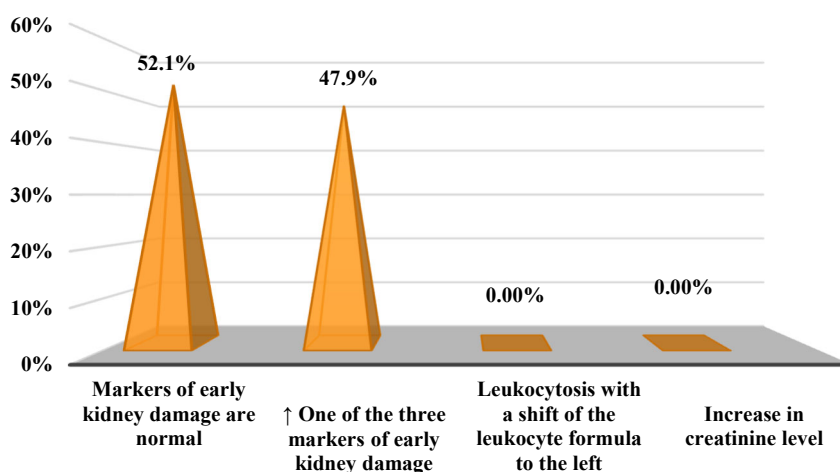
Group	Value IL – 1 $\beta$	
	<6 pg/ml	≥6 pg/ml
Conservative treatment (IA), (n=48)	41	7
Operative treatment (IB), (n=22)	3	19
In total	44	26



**Fig. 3. ROC-curve for NGAL**

**TABLE 4.** Results of assessment of NGAL в групах IA та IB

Group	Value NGAL	
	<11 ng/ml	≥ 11 ng/ml
Conservative treatment (IA), (n=48)	48	–
Operative treatment (IB), (n=22)	6	16
In total	54	16

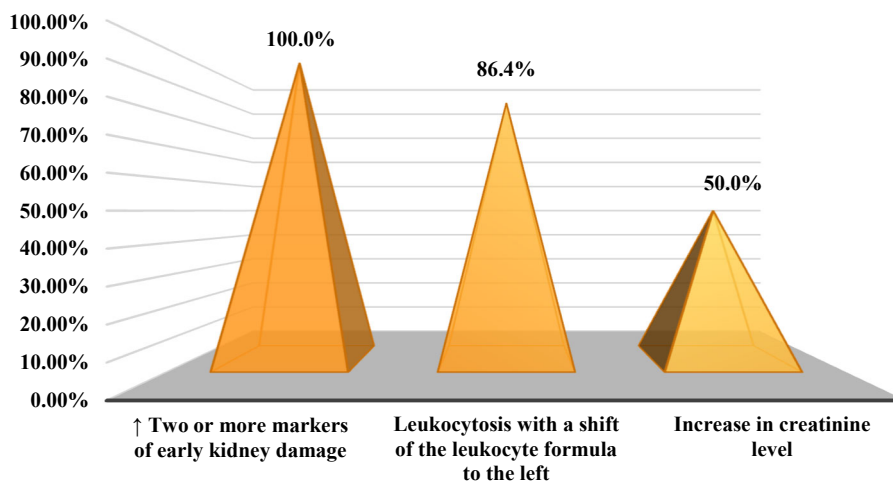


**Fig. 4.** Results of ELISA and general laboratory studies of patients included in the IA group

In Group IB (n=22), leukocytosis with a shift to the left was observed in 19 patients (86,4%) at the time of hospitalization. Elevated creatinine levels were found in 11 individuals (50,0%) (Fig. 5).

The study revealed that the absence of pronounced leukocytosis, left shift in the leukocyte count, elevated ESR (erythrocyte sedimentation rate), and creatinine levels within the first 24-48 hours after

hospitalization cannot fully confirm the absence of an infectious-inflammatory process in the kidneys and the development of renal insufficiency. This means that only CBC (complete blood count) and biochemical analysis of blood are not sufficient for early diagnosis of infectious-inflammatory processes in the kidneys in patients with urinary tract dysfunction.



**Fig. 5.** Results of ELISA and general laboratory studies of patients included in the IB group

In the further analysis of the group of patients with IA, after 7 days of therapy, spontaneous passage of the kidney stone was observed in 34 patients (70.8%). In 11 patients (27.9%), there was no spontaneous passage of the stone, and these patients underwent planned surgical intervention. Additionally, in 3 patients (6.3%), exacerbation of obstructive symptoms occurred on the 5th day of conser-

vative treatment, and they were transferred to group IB for urgent surgical management. After performing the urgent surgical intervention in group IB, normalization of leukocyte and creatinine levels was observed on the 10th day post-surgery. Detailed results of these observations can be found in Tables 5 and Figure 4 of the study.

**TABLE 5.** Methods of removing stones of the upper urinary tract, (n=70)

<b>Conservative treatment, (IA) n=48</b>	<b>n/%</b>	<b>Operative treatment, (IB) n=22+3</b>	<b>n/%</b>
Independent removal of calculi	34 (70.8)	Percutaneous nephrostomy + remote lithotripsy	3 (12.0)
Transferred to group IB	3 (6.3)	Contact ureterolithotripsy	10 (40.0)
Planned surgical treatment:	11 (22.9)	Ureterolithoextraction	8 (32.0)
– remote lithotripsy;	8 (72.7)	Remote lithotripsy	4 (16.0)
– contact ureterolithotripsy	3 (27.3)		

The restoration of kidney microcirculation, as assessed by color Doppler mapping (CDM), was diagnosed in groups IA and IB on the 10th day after the treatment was administered (Table 6).

In the conducted retrospective analysis of 42 medical case histories, a comparative assessment of the effectiveness of conservative treatment was carried out in patients who did not undergo instrumental functional analysis (IFA) of urine with the determination of predictor levels. Based on the obtained data, patients in groups IA and IB, who

underwent IFA of urine, showed a consistently positive trend in laboratory indicators on the 10th day of treatment and on the 30th day after therapy. However, in group II, which was used for comparison, a significant negative trend in the administered treatment was observed, leading to the development of purulent-septic complications and, consequently, necessitating urgent surgical intervention. The proposed information is presented in tabular format in Table 7.

**TABLE 6.** Indicators of kidney dopplerography in patients of group I (n=70) on the 10th day after the treatment, M±m

<b>Indexes</b>	<b>Conservative treatment (IA), (n=48)</b>	<b>Operative treatment (IB), (n=22)</b>
Vmax, m/s	0.68±0.09	0.66±0.09
Vmin, m/s	0.19±0.02	0.17±0.02
RI	0.65±0.04	0.78±0.04
PI	0.96±0.06	1.02±0.02
S/D	0.31±0.03	0.35±0.03

**TABLE 7.** Dynamics of indicators of the nitrogen excreting function of the kidneys (average indicators) in patients of all experimental groups (n=142), M±m

Indexes	IA group, n=48			IB group, n=22			II group (comparison) n=42			III group (contr.) n=30
	I day	10 day	30 day	I day	10 day	30 day	I day	10 day	30 day	
Creatinine, μmol/L	92.3 ±6.8*	89.0 ±6.4*	74.0 ±4.2*	138.0 ±16.1*	108.2 ±12.4*	103.0 ±14.3*	105.0 ±16.3*	123.0 ±14.5*	110.3 ±14.2*	95.0 ±6.8*
leukocytosis, 109/L	8.6 ±0.54*	8.5 ±0.7*	7.9 ±0.44*	11.7 ±0.68*	9.7 ±0.42*	8.0 ±0.52*	9.08 ±0.75*	12.01 ±0.68*	0.6 ±1.2*	6.5 ±0.42*
ESR, mm/hour	9.4 ±1.9*	10.3 ±3.20*	7.3 ±3.4*	19.6 ±3.6*	18.1 ±2.1*	15.3 ±3.2*	16.4 ±3.4*	26.4 ±1.03*	19.1 ±6.9*	8.4 ±2.3*
Rod nuclear, %	6.0 ±1.2*	6.75 ±1.13*	6.01 ±0.84*	9.45 ±1.4*	8.2 ±1.2*	6.05 ±0.72*	9.0 ±1.4*	11.45 ±1.47*	9.01 ±2.3*	5.01 ±0.74*

Note: \* – the difference in indicators regarding treatment is likely, p≤0.05.

During the analysis of the nearest complications that occurred within the first 10-14 days of treatment, it was found that the frequency of complications in group II was 5 times higher compared to group IA. In the comparative assessment of compli-

cations one month after conservative treatment, it was revealed that the frequency of complications in group II was 3 times higher than in group IA. This information is presented in tabular format in Table 8.

**TABLE 8.** Frequency of complications during conservative treatment of patients with ureteral stones, n=90

Complication	IA group (conservative treatment), n=48				II group (comparison), n=42			
	10-14 days		1 month		10-14 days		1 month	
	abs.	%	abs.	%	abs.	%	abs.	%
Exacerbation of hr. pyelonephritis	3	6.25	1	2.1	14	33.3	8	19.0
Acute pyelonephritis	3	6.25	–	–	10	23.8	5	11.9
Kidney carbuncle	–	–	–	–	2	4.8	–	–
Persistent leukocyturia	6	12.5	4	8.3	28	66.7	22	52.4
Increasing the level of azotemia	2	4.2	–	–	31	73.8	19	45.2
In total	14		5		85		54	

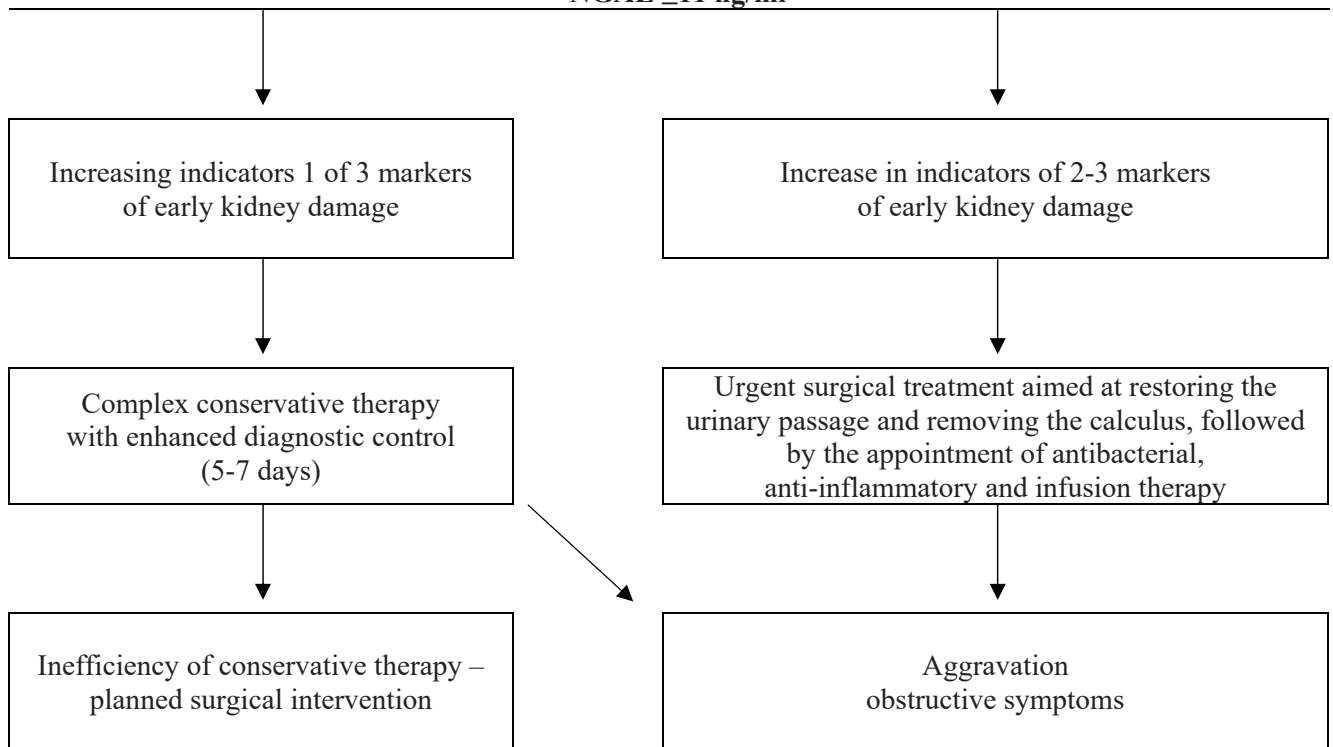
An algorithm has been developed for the examination and selection of treatment methods in patients with urodynamic disorders, which includes the following steps. During hospitalization, data on complaints and a detailed history of past and concomitant somatic diseases are collected. The next step in early diagnosis is the performance of instrumental functional analysis (IFA) of urine with the deter-

mination of various markers such as NGAL, IL-1β, β2-microglobulin. This helps to detect signs of infectious-inflammatory processes and the development of renal insufficiency. Subsequently, a study of general laboratory indicators is conducted as an additional guide to determine the presence of an inflammatory process and the functional status of the kidneys. This process is illustrated in Figure 6.



**Determination of indicators of predictors of inflammation in patients with urodynamic disorders:**

- IL-1 $\beta$   $\leq$ 6 pg/ml;
- B2-microglobulin  $\leq$ 0.13  $\mu$ g/ml;
- NGAL  $\leq$ 11 ng/ml



**Fig. 6. Algorithm for examination and selection of treatment tactics for patients with urodynamic disorders according to indicators of predictors of inflammation**

Based on the conducted research and obtained results, risk factors have been identified, and criteria for selecting further treatment tactics have been developed. The main recommendations are as follows:

- Upon hospitalization of the patient and detection of an elevation in the level of one of the three early kidney injury markers, it is recommended to initiate comprehensive conservative therapy with intensified diagnostic monitoring over a period of 5-7 days. If the kidney stone does not pass on its own, scheduled surgical intervention is recommended. In cases of exacerbation of obstructive symptoms, urgent surgical treatment is necessary. These guidelines aim to address the risk factors and tailor the treatment approach to each patient's specific condition for better outcomes.

- In cases where the levels of two or more inflammatory markers are elevated upon hospitalization, regardless of the results of general laboratory indicators indicating the presence or absence of an infectious – inflammatory process and renal insufficiency, immediate surgical intervention is recommended. This intervention should involve draining the affected kidney and removing the kidney stone, as

well as administering antibiotic, anti – inflammatory, and infusion therapy.

These recommendations help establish criteria for selecting the optimal treatment approach based on the results of diagnostic studies and the risks of kidney damage and complication development. By promptly addressing multiple elevated inflammatory markers, healthcare providers can effectively manage and treat the condition to minimize potential adverse outcomes.

## CONCLUSIONS

General laboratory analysis indicators in patients with upper urinary tract calculi (Urinary stone disease) within the first 24-48 hours cannot definitively indicate the absence of an infectious-inflammatory process in the kidneys or the development of renal insufficiency.

The elevation of inflammatory predictor markers in more than 50% of cases indicates the development of infectious-inflammatory complications 12-24 hours before clinical and general laboratory changes occur.

The comparative analysis of the effectiveness of conservative treatment in groups IA and II showed that complications of the inflammatory process in the

kidneys occurred 5 times more frequently in group II (comparison group) compared to group IA.

The use of enzymatic tests for early kidney injury markers allows distinguishing two main treatment directions – conservative and urgent surgical, significantly reducing the frequency of inflammatory, purulent-septic complications, and improving the treatment outcomes of patients with upper urinary tract obstruction in urinary stone disease.

**Conflict of interests.** The authors declare no conflict of interest.

These conclusions highlight the importance of using early diagnostic markers for kidney injury and implementing appropriate treatment strategies to manage complications effectively in patients with upper urinary tract calculi. The absence of conflicts of interest ensures the impartiality of the research and recommendations provided.

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