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The role of intestinal translocation of E.coli in the development of acute obstructive pyelonephritis in an experiment

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Abstract

Aim: To study the role of *E. coli* intestinal translocation in the development of acute obstructive pyelonephritis in an experiment.

Material and methods: An experimental study was conducted on 60 male rabbits weighing 3000±500 g. The animals were divided into 3 groups of 20 animals each: experimental, control and intermediate control group. The acute obstructive pyelonephritis with the ureter blocking by laparotomy and introduction of the strain into the intestine were simulated in the animals of the experimental group. In the control group, the model was performed anologically as in the experimental group, but without the ureter blocking. In the intermediate control group, laparotomy was performed, the ureter was isolated without blocking and without the introduction of a bacterial strain. 10 animals of each group were removed from the experiment on the 3rd and 5th days, kidney tissue and urine were intake. As a reference marker strain, the laboratory strain *E. coli* No. 49579 was used, which was obtained from a patient with a urological infection and had resistance to cefepime, ciprofloxacin and tetracycline. Biomaterials were studied by microbiological examination and subspecific typing of strains using the MALDI-TOF MS method, antibiotic sensitivity was determined.

Results: *E. coli* strain was isolated in all animals of the experimental group and in 2 animals of the control group on the 5th day. During subspecific typing by the MALDI-TOF MS method, the isolated strains were identical in ribosomal proteins, and also had the same sensitivity to the said antibiotics. When analyzing the amount of lg CFU *E.coli* in urine after the experiment between the experimental and control group, we found that, on day 3, there were statistically significant differences between the groups (p=0.005), and on day 5, the amount of lg CFU *E.coli* was 13 times greater (p=0.004).A comparative analysis of the lg CFU *E.coli* index in kidney tissue on 3 (p=0.004) and 5 (p=0.003) days revealed statistically significant differences between the experimental group and the control group.

Conclusion: The results of identification and subspecific typing of isolated microorganisms confirmed that the strains isolated from the urinary tract were identical to the reference strain introduced into the gastrointestinal tract during the experiment, which confirms the role of translocation of intestinal microorganisms in the development of acute obstructive pyelonephritis.

Key words: urinary tract obstruction, acute pyelonephritis, intestinal translocation, *E. coli*

Introduction

Acute obstructive pyelonephritis is a common pathology among acute infectious and inflammatory diseases in urology and occupies about 14% in the renal diseases structure [1].

Infectious pathology occupies a leading position among kidney diseases and accounts for 11.1% of the total number of diseases of the urinary system. The main etiological factors are: *E. coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae* [2, 3].

Kidney disease occurs with a frequency of 766.8 cases per 100,000 people in the Republic of Kazakhstan. In 2020, 7625.7 cases of diseases of the genitourinary system per 100,000 people were registered in medical and preventive organizations [4].

R. D. Berg (1979) argued that one of the causes of bacteremia development is also bacterial translocation of microorganisms from the intestine. V. N. Titov and S. F. Dugina (2010) confirmed that microorganisms get into the blood after 15-20 minutes after introduction into the gastrointestinal tract (GIT) [5]. There are also experimental studies that confirm the intestinal translocation of bacteria into the blood and lymph nodes [6]. G. G. Gromova et al. (2019) showed that intestinal dysbiosis is the cause of infection of the urinary system. E. coli isolated from the urinary tract and intestines had the same set of biological properties [7].

About a hundred years ago, the phenomenon of bacterial translocation (BT) was first described as the process of microorganisms' penetration through the epithelial barrier of the intestinal mucosa into mesenteric lymph nodes, bloodstream and internal organs [8].

The increasing interest of scientists in the problem of BT is explained by the supposed possibility of penetrating bacteria and toxins to cause an inflammatory process in organs. Accordingly, it is very important to study not only the clinical and pathogenetic mechanisms of BT, but also microbiological and morphological, besides, research is needed in the field of diagnostics of the formation and development of diseases at BT.

Currently, several different models of acute pyelonephritis are known. Models of acute obstructive pyelonephritis are usually created by an obstruction in the ureter or urethra.

The methodology of «ascending» acute obstructive pyelonephritis modeling is described in detail in foreign literature. An infectious agent in the volume of 0.4 ml was injected into the bladder using an angiocatheter. In most cases, *E. coli* in the amount of 10^9 CFU/ml was used as a bacterial suspension. Then a clamp was placed on the urethra or the external opening of the urethra was closed for 4 hours, which ensured the reflux of infected urine into the kidney pelvis and the development of kidney inflammation. The authors described this technique as a model of bilateral reflux obstructive pyelonephritis [9,10].

P. V. Kosareva et al. (2008) proposed another model of acute pyelonephritis. After the kidney was isolated by laparotomy, a direct injection of an infectious agent (0.1 ml of *E. coli* culture in the amount of $5x10^9$ CFU/ml) was performed. According to the authors, this model corresponds to the clinic of acute non-obstructive pyelonephritis [11].

In recent years, the method of experimental modeling of acute pyelonephritis by open ligation of the ureter and subsequent injection of an infectious agent into the renal pelvis has been increasingly used. This technique was proposed by E. J. Giamarellos-Bourboulis et al. (2004). After premedication and anesthesia of the animal, the abdominal cavity was opened through an upper-median abdominal incision. After visualization, the ureter was surrounded by a thread distal to the pelvis and pulled up to the anterior abdominal wall. Both ends of the thread were passed through the anterior abdominal wall outward and tied on the skin, thereby causing partial obstruction. To create a complete obstruction of the ureter, a thread is wound under it and bandaged, followed by the injection of bacterial suspension into the renal pelvis at a concentration of 10^5 CFU/ml in 1 ml of saline solution through a needle [12].

Also, this technique was used in the work of M. I. Kogan et al. (2012). In the experimental work, the involvement of non-clostridial anaerobic bacteria in the etiology of acute obstructive pyelonephritis was studied. Animals (rabbits) were removed from the experiment on the 1st, 3rd, 7th, 14th and 21st days. The authors recorded foci of purulent inflammation and septic phlebitis in the wall of the pelvis and, to an even greater extent, in the cellular tissue of the renal sinus. It was also revealed that later purulent inflammation progressed, capturing the paranephrium and the system of collecting ducts, interstitial medulla [13].

Our study was devoted to the study of the role of *E. coli* intestinal translocation in the development of acute obstructive pyelonephritis. The pathogenesis of obstructive pyelonephritis is a topical issue in both clinical urology and urological research.

Material and methods

Before the experiment, each animal underwent general anesthesia by injecting ketamine into the femoral muscle area at a dose of 50 mg/ml in an amount of 1 ml once, calculated on a body weight of 15 mg/kg.

Animals of each group were removed from the experiment on 3rd and 5th day by exsanguination under general anesthesia, then material was taken for morphological and microbiological studies. The experiment involved 60 animals, which were divided into 3 groups of 20 individuals.

In the experimental group (n=20), acute obstructive pyelonephritis with blockage of the ureter was simulated to study translocation of *E. coli* from the intestine. In this group, an upper-median laparotomy 4 cm long was performed, a suspension of bacteria in the amount of 10^8 CFU/ml was injected into the small intestine 3 cm from Tracer ligament through a 26G needle. After visualization of the left ureter at the level of the upper third, the left ureter was tied with a 3/0 thread (Figure 1, 2).

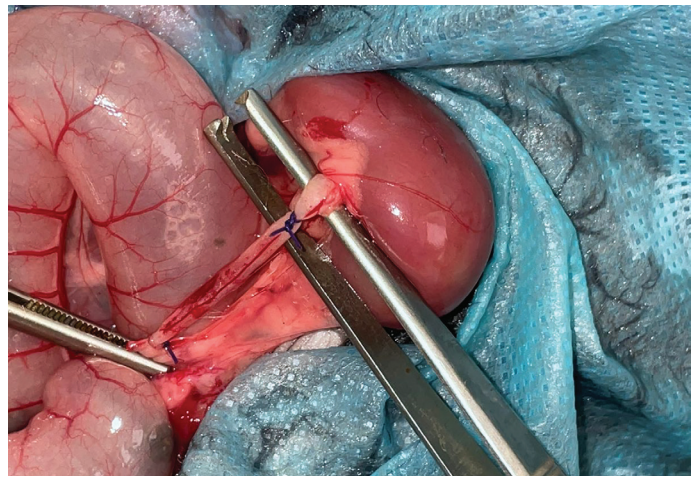

Figure 1 - Blocking of the upper third of the left ureter.

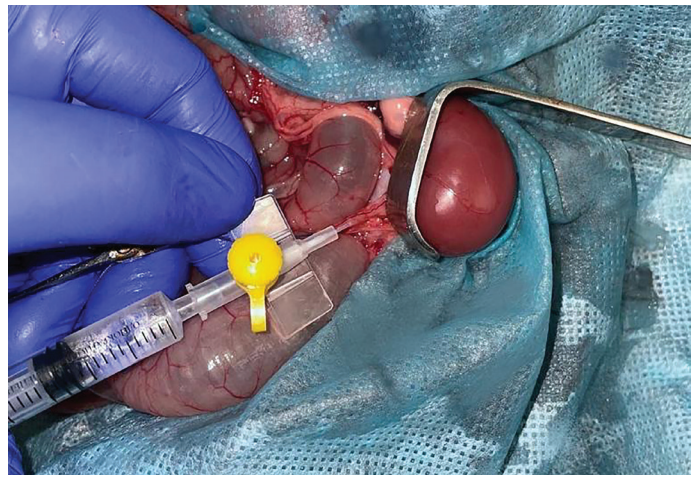

Figure 2 - Introduction of bacterial suspension into the ureter.

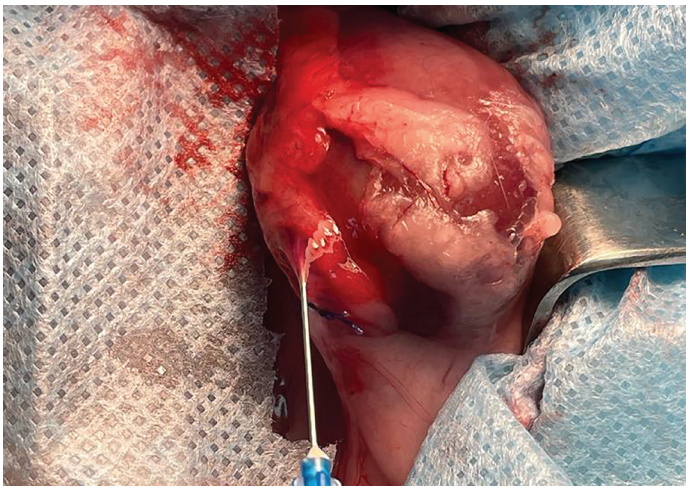

Figure 3 - Urine sampling from the renal pelvis.

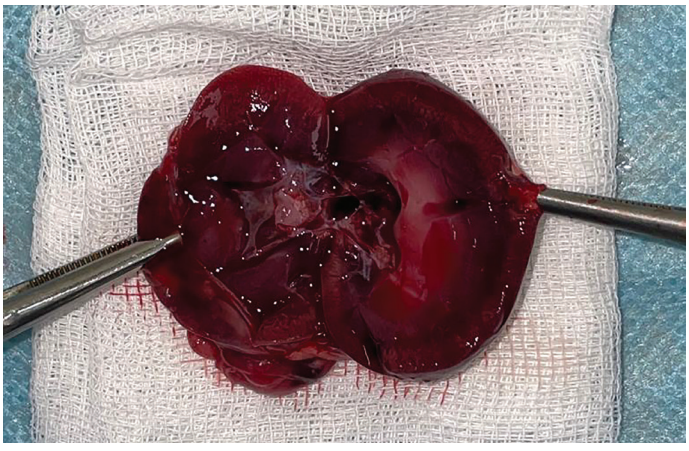

Figure 4 - Renal tissue sampling.

In the control group (n=20), animals underwent *Sham* surgery: an upper-median laparotomy 4 cm long, a suspension of bacteria in the amount of 10^8 CFU/ml was injected into the small intestine 3 cm from Tracer ligament through a 26G needle, the left ureter was isolated at the level of the upper third, but it was not bandaged.

In the intermediate control group (n=20), upper-median laparotomy was performed without ligation of the ureter and without injection of bacteria.

For microbiological examination, urine and kidney tissue above the level of obstruction were selected as the material (Figure 3, 4).

Biological material was taken from animals on the 3rd and 5th day. After taking the studied samples, the material in accordance with biosafety standards in a container was immediately delivered to the Shared laboratory of the Scientific-Research Center of NC JSC «Karaganda Medical University» [14], where primary plating on blood agar was carried out using a calibrated loop (10 µl) . Petri dishes with bacterial inoculation were incubated at a temperature of 37 °C for 24 hours. Plating for microflora was carried out on blood agar with 5% mutton blood with the release of pure cultures by conventional methods. Quantitative accounting of microorganisms in the studied material was carried out by counting the number of grown colonies on a Petri dish. The strains of microorganisms isolated during the study were considered clinically significant in the amount of >105 CFU/ml.

The strains that were in deep freeze were restored on nutrient agar (37 °C, 18 hours). Next, the samples were applied to the MBT Biotarget 96, dried in air with the application of 1 ml of saturated cyano-4-hydroxycinnamic acid (HCCA) matrix solution in 50% acetonitrile and 2.5% trifluoroacetic acid. The mass spectra were obtained using a Microflex LT Mass spectrometer (Bruker Daltonics) using default parameters (detection in linear positive mode, laser frequency – 60 Hz, ion source voltage – 2.0 and 1.8 kV, lens voltage – 6 kV) within m/z 2000-20000. 6 spectra were obtained for the strain in accordance with the Mass Spectrum Profile (MSP). External calibration of the mass spectra was performed using the Bruker Bacterial Test with ethanol/formic acid extraction in accordance with the manufacturer's recommendations (Bruker Colorblind, Bremen, Germany) [15].

The data files (obtained bacterial spectra) were transferred to flexAnalysis software (version 2.4; Bruker) for automatic peak extraction, as shown in Figure 5. Lists of peaks containing masses and intensities were exported as Excel files [16]. Sensitivity determination, as well as interpretation of the load to antimicrobial drugs – cefepime, ciprofloxacin and tetracycline were carried out by the disco-diffusion method on Muller-Hinton agar in accordance with EUCAST recommendations [17].

Statistical analysis

Statistical analysis was carried out using «Statistica 8.1 (Statsoft)» and StatTech v. 2.8.8. programs.

Quantitative indicators were evaluated for compliance with the normal distribution using the Kolmogorov – Smirnov criterion.

Quantitative data were described using median (Me) and lower and upper quartiles (Q1-Q3). The comparison of the two groups by a quantitative indicator, the distribution of which differed from the normal one, was performed using the Mann – Whitney U-test.

Ethics

The study design was approved by the decision of the Bioethics Committee of the NC JSC «Karaganda Medical University» (Protocol No. 7, dated 22.02.2022, assigned number No. 28).

Results

According to the results of the study, the following indicators of positive detection of *E. coli* in urine and kidney tissue were obtained, the occurrence frequency of which is indicated in Table 1.

In the experimental group, positive bacterial inoculation of *E. coli* was recorded – 100% positive results in urine and kidney tissue on the 3rd and 5th day. In the control group, where *Sham* surgery was performed without blocking the ureter with the injection of the strain into the intestine, on the 5th day, 2 animals were found to have positive E. coli culture, the number of CFU was 10^3, and it was not clinically significant. No bacteria were found in the intermediate control group (Table 1).

Table 1 Indicators of positive detection of E.coli bacteria in urine and kidney tissue

Group	day	N	% detection of bacteria in urine	% detection of bacteria in kidney tissue
Experienced group	3	10	100%	100%
	5	10	100%	100%
Control group	3	10	0%	0%
	5	10	20%	0%
Intermediate Control Group	3	10	0%	0%
	5	10	0%	0%

A comparative analysis of the values of *E. coli* lg CFU in urine after the experiment in all groups on the 3rd and 5th day is described in Table 2. From the presented data, it can be observed that in the experimental group, the level of E. coli lg CFU increased to 8 on the 5th day, which shows a statistically significant change (p=0,005). In the remaining groups, when comparing *E. coli* lg CFU index, no significant changes were detected depending on the modeling period (Table 2).

Table 2 Comparative analysis of lg CFU E.coli in urine on days 3 and 5 between the experimental and control groups

Group	day	lg CFU E.coli in urine after the experiment (CFU/ml)			Z	P
		Me	IQR	n		
Experienced group	3	8,00	7,00 – 8,00	10	2,835	0,005
Control group		0,00	0,00 – 0,00	10		
Experienced group	5	8,00	8,00 – 8,00	10	2,887	0,004
Control group		0,60	0,00 – 0,00	10		
Note: Me is the median, IQR is the interquartile interval, z -the value of the Mann-Whitney criterion, p -the significance level						

According to the presented table, when analyzing E. coli CFU amount in the urine after the experiment between the experimental and control groups, statistically significant differences (p=0,005) were found between the groups on the 3rd day. When conducting a comparative analysis of *E. coli* CFU amount in the urine after the experiment on the 3rd day, the strain was not recorded, there were no statistical differences between the control and intact rabbits. When comparing *E. coli* CFU values in urine after the experiment in all groups, a statistical difference was revealed between the groups on the 5th day. *E. coli* lg CFU in urine after the experiment in the experimental group was 13 times more than in the control group (p=0,004).

A comparative analysis of the *E. coli* lg CFU index in kidney tissue revealed statistically significant differences between the experimental and control groups (p=0,004). A comparative analysis of the values of *E. coli* lg CFU levels in kidney tissue on the 5th day in experimental groups is described in Table 3. It can be observed from the presented data that there was a significant difference between the experimental group and the control group (p=0,003) (Table 3).

Table 3 Comparative analysis of lg CFU E.coli in kidney tissue on days 3 and 5 between the experimental and control groups

Group	day	lg CFU of E.coli in kidney tissue after the experiment (CFU/ml)			Z	P
		Me	IQR	n		
Experienced group	3	8,00	8,00-8,00	10	2,887	0,004
Control group		0,00	0,00 – 0,00	10		
Experienced group	5	8,00	8,00-8,00	10	3,000	0,003
Control group		0,00	0,00 – 0,00	10		
Note: Me is the median, IQR is the interquartile interval, z -the value of the Mann-Whitney criterion, p -the significance level						

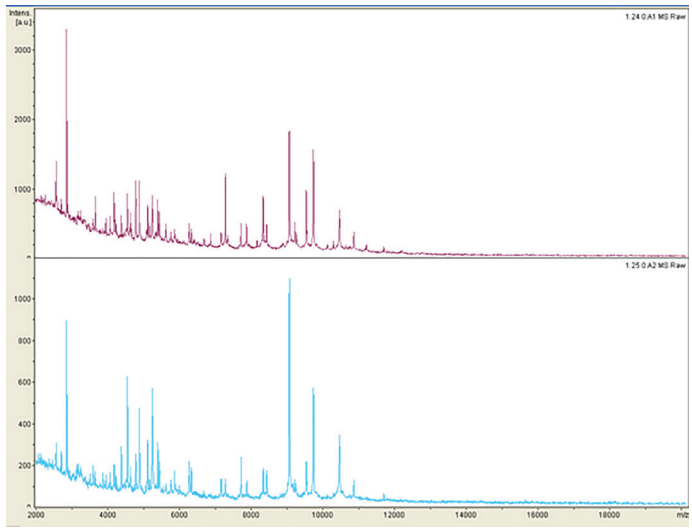

Figure 5 - Mass spectra of E.Coli isolated from urine from the category "isolates before the experiment/ isolates after the experiment".

As can be seen in Figure 5, when comparing 22 strains isolated from urine after acute obstructive pyelonephritis modeling, according to the sign «isolates before the experiment/ isolates after the experiment», 2 isolates were characterized by a coincidence of peaks. *E. co*li strains isolated from kidney tissue after the experiment were isolated with the same sensitivity profile to cefepime, ciprofloxacin, tetracycline.

Discussion

In the world literature, most researchers consider bacterial translocation as a pathological process that develops after extreme exposure and organ damage.

V. N. Titov et al. (2010) claim that the main cause of bacterial translocation is infection, stress, hypoxia, bacterial lipopolysaccharides, intestinal dysbiosis [18]. B. Ya. Usvyatsova et al. (2009) established that one of the causes of otitis is the translocation of bacteria to the focus of inflammation from the nasal cavity. The authors also claim that with an unfavorable course of otitis media, the pathogenicity of translocated strains increases [19]. In the work where the role of bacterial translocation in acute pancreatitis was studied, the authors revealed that translocated bacteria in patients with acute pancreatitis mainly consist of opportunistic microorganisms obtained from the intestine, including *E. coli, Shigella flexneri, Enterobacteriaceae, Acinetobacter lwoffii, Bacillus coagulans and Enterococcus faecium [*20]. Also, a number of authors claim that bacteria can pass the intestinal barrier in several clinical conditions, including excessive bacterial growth in the small intestine, impaired intestinal barrier and states of systemic immunosuppression. Bacterial translocation has also been detected in a wide range of other diseases, including depression, Alzheimer's disease, hemorrhagic shock, obstructive jaundice, abdominal surgery, malignant neoplasms, aortic aneurysm repair, heart failure, cardiopulmonary bypass and intestinal transplantation [21, 22].

Our study was devoted to comparing the role of ascending infection and intestinal translocation of *E. coli i*n the development of acute obstructive pyelonephritis. The pathogenesis of obstructive pyelonephritis is an urgent issue in both clinical urology and urological research.

The aim of our research was to study the role of intestinal translocation of *E. coli* in the development of acute obstructive pyelonephritis.

As a result of this study, a model of acute obstructive pyelonephritis in rabbits has been developed, which compares favorably with previously known models of this pathology. The experimental model of acute obstructive pyelonephritis with the urethra blocking proposed by us assumes technical execution of obstruction by ligation of the ureter in rabbits. When modeling acute obstructive pyelonephritis with blocking of the ureter by laparotomy, mortality in rabbits was not registered. In the work of R. Fukushima et al. (1994) it is said that the process of bacterial translocation is intense throughout the intestine. But A. V. Zhigailov (1996) asserts that with intragastric strains injection, the level of translocation through the mucous membrane of the stomach and small intestine is higher than in the large intestine [23].

The results of the microbiological study found that all animals of the experimental groups had positive bacterial culture, unlike the control groups. At the same time, a comparative analysis of the CFU level of the marker strain in the experimental groups showed no statistically significant differences and was higher than 105, which is of clinical significance for the development of pyelonephritis.

During the experiment, positive urine culture was detected in 2 animals of the control group on the 5th day, the CFU amount of bacteria was 10^3. But at the same time, bacteria were not found in the kidney tissue of these animals. There are confirmed hypotheses that translocation of bacteria occurs even in healthy individuals [24].

When comparing the identification and subspecific typing of isolated microorganisms with the reference strain, a 100% match of all isolates was obtained. When identifying isolated *E. coli,* it was revealed that these strains were resistant to cefepime, ciprofloxacin, tetracycline, as well as *E. coli* strain No. 49579, which was used as a reference strain.

Based on the results of our study, we can conclude that obstruction at the ureter level is a trigger for intestinal microorganisms' translocation into the urinary tract. The limitation of the study was that this study is a pilot. But this statement requires further research, both in the experiment and in the clinic.

Conclusion

The experimental results indicate that microbial translocation from the intestine to the urinary tract plays a significant role in the development of obstructive pyelonephritis. Urinary tract obstruction is a trigger for intestinal translocation of microorganisms into the urinary tract.

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