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Histopathological alterations in kidney tissue following experimental endotoxemia in a murine model

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Abstract. *Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid decline in kidney function and represents a serious threat to human health. One of the most common causes of AKI is endotoxemia or sepsis, triggered by the hyperactivation of the immune system in response to gram-negative bacterial infections. The pathogenesis of AKI is highly complex and not yet fully understood. The present study aimed to investigate histostructural changes in kidney tissue using a model of inflammation induced by lipopolysaccharide (LPS), a key component of the outer membrane of gram-negative bacteria.*

Methods. Systemic endotoxemia was induced in mice by intraperitoneal injection of LPS (E. coli O111:B4, Sigma, USA) at a dose of 3 mg/kg body weight. Control animals received saline injections. After 24 hours, the animals were anesthetized with ether, and kidney tissue samples were collected for analysis. For histological evaluation, kidney tissue specimens were fixed in 10% neutral formalin, processed using standard histological techniques, embedded in paraffin, sectioned, stained with hematoxylin-eosin, and examined under a light microscope.

Results. LPS injection resulted in pronounced neutrophilia in the blood leukogram: the percentage of rod-shaped neutrophils increased 3.6-fold while the percentage of segmented neutrophils increased 2.7-fold ($p < 0.05$), which indicates systemic inflammatory response. Significant histostructural damage to kidney tissue was detected under these conditions. Dystrophic and necrotic changes were observed in Bowman's capsules. Circulatory disturbances were evident, with morphological alterations in all layers of the vascular walls and destruction of the epithelium in the proximal and distal convoluted tubules.

Conclusions. The findings indicate that systemic inflammation induced by LPS leads to substantial morphological alterations in kidney tissue. These changes include circulatory disturbances, structural damage to vascular glomeruli, and epithelial injury in the proximal and distal convoluted tubules. The observed damage results in a reduction in the number of functioning nephrons, which may contribute to the progression of kidney failure.

Key words: *lipopolysaccharides, endotoxemia, acute kidney injury, mice, histological techniques.*

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Гістоструктурні зміни тканини нирок за умов експериментальної ендотоксемії

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Резюме. *Вступ. Гостре пошкодження нирок (ГПН) – це клінічний синдром, який характеризується стрімким порушенням ниркової функції і являє собою серйозну загрозу для здоров'я людини. Однією з найбільш поширених причин його виникнення є ендотоксемія або сепсис, індуковані гіперактивацією імунної системи грам негативними бактеріями. Патогенез ГПН надзвичайно складний та недостатньо вивчений. Метою представленої роботи було дослідити гістоструктурні зміни тканини нирок на моделі запалення, індукованого ліпополісахаридом (ЛПС) – компонентом мембрани грам-негативних бактерій.*

Методи. Системну ендотоксемію моделювали за допомогою внутрішньоочеревинного введення ЛПС (E. coli 0111:B4, Sigma, USA) в дозі 3 мг/кг маси миші. Контрольним тваринам вводили фізіологічний розчин. Через 24 год тварин піддавали ефірному наркозу і вилучали матеріал для досліджень. Для гістологічної оцінки шматочки тканини нирок фіксували 10% нейтральним формаліном, потім обробляли за загальноприйнятою гістологічною методикою і заливали у парафін. Зрізи забарвлювали гематоксилін-еозином і аналізували під світловим мікроскопом.

Результати. Введення ЛПС призводило до вираженої нейтрофілії в лейкограмі крові: відсоток паличкоядерних нейтрофілів збільшувався у 3,6 рази, а сегментоядерних – у 2,7 рази ($p < 0,05$), що свідчить про системну запальну відповідь. За цих умов виявлено значні гістоструктурні пошкодження тканини нирок. Спостерігались дистрофічні та некротичні зміни в капсулах Боумена. Виявлялось порушення кровообігу з морфологічними змінами всіх шарів судинних стінок та деструкцією епітелію проксимальних та дистальних звивистих канальців.

Висновки. Аналіз отриманих даних свідчить про те, що за умов системного запального процесу, індукованого ЛПС, відбуваються значні морфологічні зміни тканини нирок, які включають порушення кровообігу з вираженим пошкодженням гістоструктури судинних клубочків та епітелія проксимальних і дистальних звивистих канальців, що веде до зменшення рівня маси діючих нефронів та в подальшому може призвести до ниркової недостатності.

Ключові слова: *ліпополісахариди, ендотоксемія, гостре ураження нирок, миші, гістологічні методи.*

Introduction. The kidneys function to remove waste products and toxins from the bloodstream (approximately 20–25% of cardiac output) and maintain fluid and electrolyte homeostasis. Additionally, the kidneys play a crucial role in regulating blood pressure and hormone secretion. Toxic damage and ischemia of the kidneys lead to structural and functional disruptions [1]. In particular, toxic effects on the kidneys can result from urinary tract infections (UTIs), which, in the vast majority of cases, are caused by uropathogenic *Escherichia coli* (E. coli) [2-4]. According to bacteriological studies, *E. coli* is responsible for approximately 70–80% of UTIs [5-9]. The presence of pathogenic microorganisms can trigger systemic inflammation. Under these conditions, macrophage infiltration into kidney tissue occurs, pro-inflammatory mediator expression is activated, and oxidative stress develops, potentially leading to acute kidney injury (AKI) [10-12].

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AKI is a common clinical complication associated with increased morbidity and mortality [13]. In clinical practice, AKI is defined as a rapid decline in kidney function, impairing the ability to maintain water-electrolyte and acid-base balance. It is characterized by a sudden decrease in the glomerular filtration rate, resulting in the retention of creatinine, urea, and other metabolic waste products, along with impaired excretion. Additionally, AKI leads to reduced urine output (oliguria) and increased concentrations of potassium and phosphate in the body, which contribute to serious complications [14].

AKI induced by bacterial endotoxins is a syndrome of systemic inflammation that not only affects the kidneys but can also lead to multiple organ failure [15]. During the early excessive inflammatory response triggered by endotoxins in the bloodstream, T cells, B cells, and dendritic cells become severely depleted, leading to immune suppression. As a result, immunosuppression develops, which is one of the primary causes of high mortality in affected patients [16].

Significant attention has been given to studying the mechanisms underlying renal inflammation. However, investigations into the morphological changes in the kidneys associated with endotoxins from gram-negative bacteria remain limited.

The present study aimed to investigate histostructural changes in kidney tissue using a lipopolysaccharide (LPS)-induced model of experimental acute kidney injury associated with endotoxemia.

Materials and methods. The study protocol was reviewed and approved by the Biomedical Ethics Committee of the Bohomolets Institute of Physiology, NASU, Kyiv (Protocol No. 1/25, dated 08.01.2025).

The study was conducted using Albino mice (weighing 18–22 g), housed under standard conditions in the vivarium of the Bohomolets Institute of Physiology, National Academy of Sciences of Ukraine. All procedures followed the International Principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the EU Council Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes (22.09.2010), and the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV, 21.02.2006).

The use of LPS is a well-established model for studying both systemic and organ-specific immune-induced processes. However, variations in species and strains of laboratory animals, as well as differences in LPS preparations from various Escherichia coli serotypes, can lead to differing responses to endotoxin exposure [17]. In this study, female mice were maintained in a temperature-controlled room (22±2°C) under a 12-hour light/dark cycle and provided with a certified rodent diet, along with ad libitum access to filtered water. The mice were randomly assigned into two groups (9 mice per group):

- Experimental group: received intraperitoneal injections of LPS (3 mg/kg body weight; *E. coli* O111:B4, Sigma, St. Louis, MO, USA).
- Control group: received intraperitoneal injections of an equivalent volume of saline.

After 24 hours, the animals were anesthetized with ether, and kidney tissue samples were collected for histological analysis. Blood leukogram changes were also recorded at this time.

For histological examination, kidney tissue sections were fixed in 10% neutral formalin, processed using standard histological techniques, and embedded in paraffin [18]. Sections were stained with hematoxylin-eosin [19] and examined under a light microscope.

Statistical Analysis. Statistical analysis was performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA). The Kolmogorov-Smirnov test confirmed that all data followed a normal distribution. Results were expressed as mean ± SEM. Group comparisons were conducted using Student's t-test, with $P < 0.05$ considered statistically significant.

Results. The blood leukogram revealed that the percentage of rod-shaped neutrophils increased 3.6-fold (from 5.3±1.5% in the control group to 19.1±1.9% in the LPS group, $p < 0.05$), while the percentage of segmented neutrophils increased 2.7-fold (from 14.0±2.2% in the control group to 37.6±3.7% in the LPS group, $p < 0.05$). This indicated significant neutrophilia with a left shift in the leukogram, a hallmark of a systemic inflammatory response.

Histological examination of kidney tissue from control mice revealed no morphological abnormalities. Bowman's capsules retained a regular shape and contained vascular glomeruli, with capillary loops arranged in freely positioned spherical structures. The blood supply was consistent and moderate. The tubular basement membranes were well-defined. The epithelial cells of the proximal convoluted tubules were cuboidal or columnar, with spherical nuclei and eosinophilic cytoplasm. The lumens of the proximal tubules were minimal. In contrast, the distal tubules exhibited significantly enlarged lumens, which appeared empty (Fig. 1).

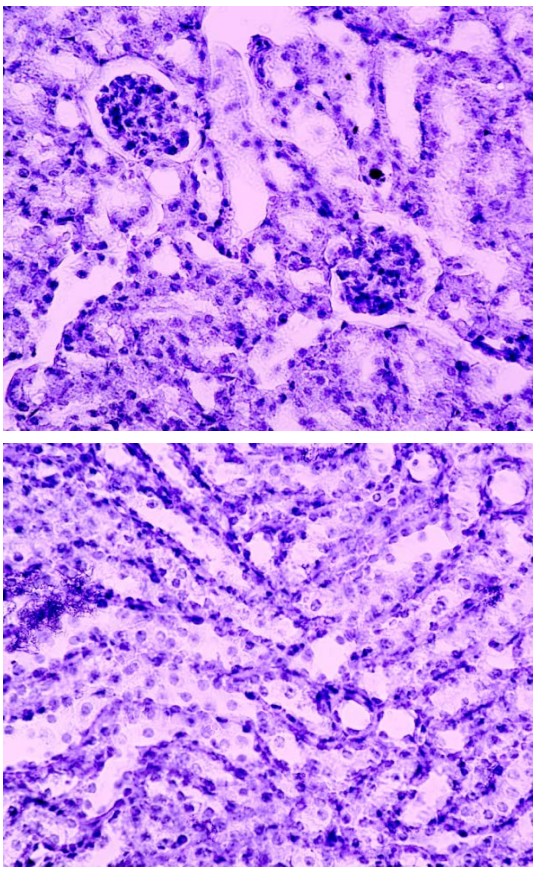

Fig. 1. Micrograph of a section of kidney tissue in the control. Staining with hematoxylin and eosin. Objective lens 40, Ocular lens 10. (A): The histological structure of the kidney is preserved. Bowman's capsules, renal glomeruli, and tubules are not changed. (B): The distal tubules have a significant lumen, which is free of content.

Histological examination of kidney tissue under conditions of LPS-induced inflammation revealed morphological changes in both the Bowman's capsules and the proximal and distal tubules. The Bowman's capsules were reduced in size, with vascular glomeruli occupying nearly the entire volume of the capsule. Some glomeruli were compressed against one edge of the capsule. In the central zone of the glomerular lobule, the number of nuclei was reduced. Additionally, some Bow-

man's capsules contained glomeruli that had become a homogeneous mass with separate nuclei, showing signs of dystrophic and necrotic changes. Erythrocytes were detected in the cavity of some Bowman's capsules (Fig. 2A).

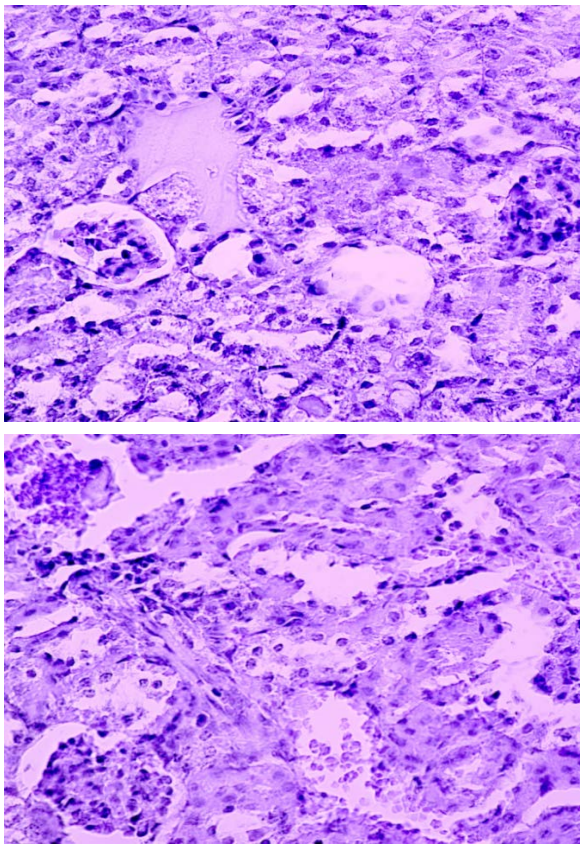

Fig. 2. Micrograph of a kidney tissue section under LPS-induced inflammation conditions. Staining with hematoxylin and eosin. Objective lens 40x, ocular lens 10x. (A): Bowman's capsules are reduced, glomeruli are deformed and compressed to one edge; some glomeruli have transformed into a homogeneous mass with dystrophic and necrotic nuclei. Some proximal tubules have no lumen. (B): Distal tubules are severely dilated, with signs of epithelial destruction and desquamation, along with hyperchromatic nuclei.

Significant changes also occurred in the capillary network of the kidneys. In some areas of the kidneys, there were areas where the proximal tubules had no lumen at all or were filled with eosinophilic content. Near the Bowman's capsules, as a result of blood stasis in the afferent vessels, areas with an accumulation of a small number of erythrocytes were observed. A significant number of epithelial cells were marked by intensely stained cytoplasm with signs of granular dystrophy. Expansion of the distal tubules was observed, while the cells of the epithelial layer were flattened with signs of destruction. Areas with desquamation of epithelium were noted. In addition, the nuclei of both proximal and distal tubules often acquired an irregular shape and became hyperchromic (see Fig. 2B).

Discussion. Although AKI induced by endotoxemia is a well-studied phenomenon, this study provides detailed histological insights into kidney tissue damage caused by LPS, specifically highlighting structural alterations in Bowman's capsules, vascular walls, and renal tubules. Using LPS as a model for AKI gives important insights into how inflammation affects kidney structure, which can help guide future studies on the cellular and molecular mechanisms behind endotoxemia-induced AKI.

Our results are consistent with those of other studies [20, 21], which show that renal tubular epithelial cell injury and vascular dysfunction are key factors in the development of AKI [22]. One mechanism of cell damage is mitochondrial dysfunction, which leads to the disruption of energy metabolism and ultimately results in cell death [23]. Damaged mitochondria contribute to the accumulation of reactive oxygen species and the development of oxidative stress [24]. We have previously shown that the injection of LPS into mice results in a pronounced inflammatory response. This includes an increase in the functional and metabolic activity of immune cells, activation of nonspecific resistance cells, and enhanced ROS generation, which causes significant DNA damage in the thymus and lymph node cells. Excessive DNA damage promotes genotoxic stress and immune cell death through a pro-inflammatory and immunogenic necrotic pathway [25]. In the liver of mice under these conditions, a significant increase in the content of TBA-reactive products was detected, with malondialdehyde comprising the overwhelming majority. This compound serves as a marker of oxidative stress and cellular damage. In addition, a disruption of the antioxidant system was observed [26]. These endotoxin-induced changes may be important factors in the development of AKI.

Our previous report have shown that the use of an HMGB1 inhibitor (ammonium glycyrrhizinate) reduced the necrosis of thymus and lymph node cells and contributed to the attenuation of LPS-induced inflammation [28]. HMGB1 inhibition also reduced the metabolic activity of neutrophils, the accumulation of reactive oxygen species, and the development of oxidative stress, while improving the state of antioxidant protection. The data obtained regarding the morphological manifestations of AKI under conditions of endotoxemia, along with the results of previous investigations, are planned to serve as a basis for further experimental studies aimed at clarifying the molecular and cellular mechanisms involved in the development of AKI in the context of endotoxemia.

Our study has several limitations. First, the research was conducted in a murine model, and although mice are a widely used model for studying human diseases, further studies in larger animal models or human-derived tissues would help confirm the relevance of these findings. Second, the study primarily focused on histological analysis and did not explore the underlying molecular mechanisms, which could provide a deeper understanding of the pathophysiology of AKI. Third, the study was conducted over 24

hours, and longer follow-up studies would be necessary to assess the full progression and potential long-term effects of endotoxemia on kidney function. Future studies addressing these limitations will be essential to further elucidate the mechanisms of AKI in the context of endotoxemia.

Conclusions. The results obtained indicate that under conditions of a systemic inflammatory process induced by LPS, significant morphological changes occur in the kidney tissue. These changes include circulatory disorders with pronounced damage to the histostructure of the vascular glomeruli and the epithelium of the proximal and distal convoluted tubules, leading to a decrease in the mass of functioning nephrons. One potential cause of kidney tissue damage may be the development of oxidative stress, due to the excessive formation of secondary products from lipid peroxidation and the overactivation of inflammatory effector cells. The data obtained could be important for further studies aimed at elucidating the molecular and cellular mechanisms involved, which would deepen our understanding of the pathogenesis of AKI.

Conflict of interest statement. The authors have no conflicts of interest to declare.

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Authors' contribution.

Vitaliy Antoniuk and ***Svitlana Pavlovych:*** design of the study, data acquisition, analysis and interpretation of the data, literature search, drafting the manuscript;

Bogdan Dzhuran: conceptualization, design of the study, review and editing;

Olena Kondratska: formal analysis, literature search, drafting the manuscript;

Roman Yanchii: conceptualization, project administration, funding acquisition, critical comments on the manuscript.

All authors read and approved the final manuscript.

Data availability statement. The data that support the findings of this study are available upon reasonable request from the corresponding author.

References:

1. *Palipoch S.* A review of oxidative stress in acute kidney injury: protective role of medicinal plants-derived antioxidants. Afr J Tradit Complement Altern Med. 2013;10(4):88-93. doi: 10.4314/ajtcam.v10i4.15.
2. *Ching C, Schwartz L, Spencer JD, Becknell B.* Innate immunity and urinary tract infection. Pediatr Nephrol. 2020;35(7):1183-1192. doi: 10.1007/s00467-019-04269-9.
3. *Ternes B, Wagenlehner FME.* Leitliniengerechte Therapie von Harnwegsinfektionen [Guideline-based treatment of urinary tract infections]. Urologe A. 2020;59(5):550-558. [In German]. doi: 10.1007/s00120-020-01174-0.
4. *Kolman KB.* Cystitis and pyelonephritis: diagnosis, treatment, and prevention. Prim Care. 2019;46(2):191-202. doi: 10.1016/j.pop.2019.01.001.
5. *Schwartz L, de Dios Ruiz-Rosado J, Stonebrook E, Becknell B, Spencer JD.* Uropathogen and host responses in pyelonephritis. Nat Rev Nephrol. 2023;19(10):658-671. doi: 10.1038/s41581-023-00737-6.
6. *Saxena V, Gao H, Arregui S, Zollman A, Kamocka MM, Xuei X, et al.* Kidney intercalated cells are phagocytic and acidify internalized uropathogenic Escherichia coli. Nat Commun. 2021;12(1):2405. doi: 10.1038/s41467-021-22672-5.
7. *Ruiz-Rosado JD, Robledo-Avila F, Cortado H, Rangel-Moreno J, Justice SS, Yang C, et al.* Neutrophil-macrophage imbalance drives the development of renal scarring during experimental pyelonephritis. J Am Soc Nephrol. 2021;32(1):69-85. doi: 10.1681/ASN.2020030362.
8. *Hreha TN, Collins CA, Cole EB, Jin RJ, Hunstad DA.* Androgen exposure impairs neutrophil maturation and function within the infected kidney. mBio. 2024;15(2):e0317023. doi: 10.1128/mbio.03170-23.
9. *Cortado H, Kercsmar M, Li B, Vasquez-Martinez G, Gupta S, Ching C, et al.* Murine ribonuclease 6 limits bacterial dissemination during experimental urinary tract infection. J Innate Immun. 2024;16(1):283-294. doi: 10.1159/000539177.
10. *Kerr AW, Efron PA, Larson SD, Rincon JC.* T-Cell activation and LPS: a dangerous duo for organ dysfunction. J Leukoc Biol. 2022;112(2):219-220. doi: 10.1002/JLB.3CE0122-019R.
11. *Yoo JY, Cha DR, Kim B, An EJ, Lee SR, Cha JJ, et al.* LPS-Induced Acute Kidney Injury Is Mediated by Nox4-SH3YL1. Cell Rep. 2020;33(3):108245. doi: 10.1016/j.celrep.2020.108245.
12. *Li Y, Yuan Y, Huang ZX, Chen H, Lan R, Wang Z, et al.* GSDME-mediated pyroptosis promotes inflammation and fibrosis in obstructive nephropathy. Cell Death Differ. 2021;28(8):2333-2350. doi: 10.1038/s41418-021-00755-6.
13. *Zang D, Li W, Cheng F, Zhang X, Rao T, Yu W, et al.* Accuracy and sensitivity of high mobility group box 1 (HMGB1) in diagnosis of acute kidney injury caused by sepsis and relevance to prognosis. Clin Chim Acta. 2022;535:61-67. doi: 10.1016/j.cca.2022.07.015.
14. *Jha AK, Gairola S, Kundu S, Doye P, Syed AM, Ram C, et al.* Toll-like receptor 4: An attractive therapeutic target for acute kidney injury. Life Sci. 2021;271:119155. doi: 10.1016/j.lfs.2021.119155.

15. *Wang S, Zeng M, Li B, Kan Y, Zhang B, Zheng X, et al.* Raw and salt-processed Achyranthes bidentata attenuate LPS-induced acute kidney injury by inhibiting ROS and apoptosis via an estrogen-like pathway. Biomed Pharmacother. 2020;129:110403. doi: 10.1016/j.biopha.2020.110403.
16. *Zhang B, Zeng M, Li M, Kan Y, Li B, Xu R, et al.* Protopine Protects Mice against LPS-Induced Acute Kidney Injury by Inhibiting Apoptosis and Inflammation via the TLR4 Signaling Pathway. Molecules. 2019;25(1):15. doi: 10.3390/molecules25010015.
17. *Kondratska OA, Grushka NG, Kaplunenko VG, Pavlovych SI, Sribna VO, Yanchii RI.* Protective effect of germanium citrate in endotoxin-induced ovarian dysfunction in mice. Med. perspekt. 2018;23(1(part1):71-77. [In Ukrainian]. doi:10.26641/2307-0404.2018.1(part1).127240.
18. *Vareniuk I.M., Dzerzhynskyi M.E.* Methods of cyto-histological diagnosis: a study guide. Kyiv. Interservice. 2019.
19. *Luna LG. (Ed).* Manual of histologic staining methodsof the Armed Forces Institute of Pathology. 3 ed. NewYork: Mac Graw Hill, 1968.
20. *Hu Z, Chen D, Yan P, Zheng F, Zhu H, Yuan Z, et al.* Puerarin suppresses macrophage M1 polarization to alleviate renal inflammatory injury through antagonizing TLR4/MyD88-mediated NF-κB p65 and JNK/FoxO1 activation. Phytomedicine. 2024;132:155813. doi: 10.1016/j.phymed.2024.155813.
21. *Li J, Wang L, Wang B, Zhang Z, Jiang L, Qin Z, et al.* NOX4 is a potential therapeutic target in septic acute kidney injury by inhibiting mitochondrial dysfunction and inflammation. Theranostics. 2023;13(9):2863-2878. doi: 10.7150/thno.81240.
22. *Ludes PO, de Roquetaillade C, Chousterman BG, Pottecher J, Mebazaa A.* Role of damage-associated molecular patterns in septic acute kidney injury, from injury to recovery. Front Immunol. 2021;12:606622. doi: 10.3389/fimmu.2021.606622.
23. *Jian Y, Yang Y, Cheng L, Yang X, Liu H, Li W, et al.* Sirt3 mitigates LPS-induced mitochondrial damage in renal tubular epithelial cells by deacetylating YME1L1. Cell Prolif. 2023;56(2):e13362. doi: 10.1111/cpr.13362.
24. *Zhang M, Dong W, Li Z, Xiao Z, Xie Z, Ye Z, et al.* Effect of forkhead box O1 in renal tubular epithelial cells on endotoxin-induced acute kidney injury. Am J Physiol Renal Physiol. 2021;320(3):F262-F272. doi: 10.1152/ajprenal.00289.2020.
25. *Pavlovych S.I., Grushka N.G., Kondratska O.A., Krasutska N.O., Yanchii R.I.* The state of the cells of the immune system in experimental immune-mediated inflammation of various genesis. Medical Science of Ukraine. 2021;17 (2): 20-26. [In Ukrainian]. doi:10.32345/2664-4738.2.2021.03.
26. *Grushka N.G., Pavlovych S.I., Kondratska O.A., Pilkevich N.O., Yanchii R.I.* Inhibition of poly (ADP-ribose) polymerase contributes to the reduction of oxidative stress in murine liver under the conditions of experimental endotoxemia. Pathologia. 2019;16(3):323-327. [In Ukrainian]. doi:10.14739/2310–1237.2019.3.188796.
27. *Tonnus W, Gembardt F, Latk M, Parmentier S, Hugo C, Bornstein SR, et al.* The clinical relevance of necroinflammation-highlighting the importance of acute kidney injury and the adrenal glands. Cell Death Differ. 2019;26(1):68-82. doi: 10.1038/s41418-018-0193-5.
28. *Kondratska OA, Grushka NG, Pavlovych SI, Stovbun YuR, Plyska OI, Yanchii RI.* Ammonium glycyrrhizinate has a protective effect on oogenesis and reduces genotoxic stress and death of immune cell in lipopolysaccharide-induced endotoxemia. Experimental and clinical physiology and biochemistry, ECPB. 2020;3/4(91):5–11. [In Ukrainian]. doi:10.25040/ecpb2020.03-04.005.