Prognosis of purulent-septic pathologies in veterinary propaedeutics of generalization of bacterioses on a dog model

Sergey Laptev, *Nikolai* Pimenov, *Saida* Marzanova[1], *Kristina* Permyakova

Federal State Budgetary Educational Institution of Higher Education «Moscow State Academy of Veterinary Medicine And Biotechnology – MVA named after KI. Skryabin», Moscow, Russian Federation

Abstract. This article analyzes data from a study of 72 dogs aged from 8 months to 11 years. A method that helps predict the possible development of complications in animals with obstetric-gynecological and cryptogenic sepsis, as well as purulent wounds and abscesses, was tested on a dog model. Evaluation criteria on PIRO and SAPS scale in the propaedeutics of sepsis in dogs have been formed. A clinical version of the model has been developed to divide patients with sepsis into groups based on their condition. The system is based on the assessment of criteria of sepsis development, based on a set of clinical and laboratory signs that determine risk factors and prognosis of the course of the disease. The prognostic role of the determination of cationic neutrophil proteins in the clinical manifestation of purulent inflammation in dogs was also noted.

1 Introduction

Sepsis is uncontrollable due to the imbalance of simultaneously existing forces, some of which support the inflammation (systemic inflammatory response syndrome - SIRS) and others limit it (compensatory anti-inflammatory response syndrome - CARS). Sepsis is a multifactorial disease. The disease development mechanism is still the subject of much debate. In 2003, an international council of experts proposed using the PIRO system in assessing sepsis (Levy M.M. et al., 2003). However, the PIRO scale has some drawbacks since all its criteria were included in the scale arbitrarily. An example of an attempt to improve the diagnostic criteria of sepsis is the development of the previously proposed PIRO concept (Alves F, et al., 2020; Laptev S.V., 2021; Pimenov et al., 2022a). The SAPS (Simplified Acute Physiology Score) scale consists of easily measured clinical and laboratory criteria that are evaluated during the first day after the patient's admission and range from 0 to 4 points [J.-R. Le Gall et al., 1984].

The aim of the study was to clarify the significance of indicators on PIRO and SAPS scales, as well as the mean cytochemical coefficient (MCC) of non-enzymatic cationic proteins (cationic proteins, CP) in neutrophilic granulocytes (neutrophilic granulocytes, NG) for the prediction of septic complications in dogs referred for examination with suspicion on obstetric-gynecological and cryptogenic sepsis, as well as purulent wounds and abscesses.

---

[1]Corresponding author: s.marzanova@mail.ru

2 Materials And Methods

The studies were carried out at veterinary clinics in different administrative districts of Moscow and the Moscow region, where sick pets and dogs from the animal shelter "Avtomobilnye Dorogy" of the Western Administrative District of Moscow (1460 animals) are treated. Immunologycourse students took an active part in the collection of primary data. During the study, we analyzed the examination results from clinic databases(outpatient cards) for 2020-2022. 72 dogs aged from 8 months to 11 years, included: dogs suffering from obstetric-gynecological sepsis (n = 22), cryptogenic sepsis (n = 18), purulent wounds and abscesses (n = 10). The control group included clinically healthy animals (n=22) kept in the shelter. All dogs that participated in this study were examined by a clinic veterinarian. The target of the study were dogs with a record of clinical examinations, hemogram, biochemistry blood tests and recorded outcome resulted in discharge or death. All dogs that did not meet the mentioned criteria were excluded from the study. The sample size was 50 dogs with signs of sepsis. In terms of outcome, 43 (86%) dogs with sepsis were discharged and 7 (14%) dogs died.

The primary data of the examination of animals was converted into scores on PIRO and SAPS scales, as a generalizing result of clinical signs during the initial examination of animals, the results of ultrasound, complete blood count (CBC) and biochemistry blood tests. The level of cationic proteins in neutrophils was calculated using the average cytochemical coefficient (MCC) according to a modified formula and expressed in arbitrary units [Pimenov, 2022b]. All four indicators are considered during the evaluation of PIRO indicators to predict the development of sepsis in the body. After summing all 4 indicators with the maximum score of each indicator in the scoring system from 0 to 3, the forecast formula is:

0-2 points - the prognosis is favorable;

3-4 points - a favorable prognosis with necessary treatment and preventive measures;

5-9 points - questionable, cautious prognosis, inpatient treatment is necessary;

10-12 points - unfavorable prognosis (septic shock).

The predictive value was assessed using PIRO indices (iPIRO). Estimates by indicators were converted into arbitrary units depending on deviations from the norm from 0 to 3. iPIRO was calculated using the formula: $iPIRO = (P + I + R + O)/4$

According to the dynamics of the development of the disease/recovery, considering the PIRO indicators, a forecast was made, if iPIRO is less than 1, the prognosis is positive. If 1-2 - moderate, 3 - septic shock and possible animal death.

The criteria for the development of sepsis were considered: a decrease or lack of appetite, depression of the general condition, fever, vomiting, presence of an infection focus,development of toxic leukocytosis and hemodynamic disorder.

The criteria "P - predisposition", "I - infection", "R - response" and "O - organ dysfunction" were evaluated according to [Alves, et al. 2020]. Age, breed and vaccination status were taken into account to determine predisposition (P). The response (R) was characterized by temperature, heart rate, respiration rate and leukocyte count. Organ dysfunction (O) according to biochemical and clinical markers of dysfunction of the kidneys, cardiovascular, respiratory, hepatic and coagulation systems.

Table 1. Criteria for evaluating the indicator: predisposition (P)

Criteria	Points
Bullmastiff, Golden Retriever, Dogue de Bordeaux, Bernese Mountain Dog, Great Dane, Leonberger, Irish Wolfhound, German Wolfspitz, Bull Terrier,	1

Pekingese, Caucasian and Central Asian Shepherd Dog, Russian Toy Terrier, French Bulldog, Yorkshire Terrier, Chow Chow	
German Shepherd, Rottweiler, American Staffordshire Terrier, Dachshund, Cocker Spaniel, Poodle, Boxer, other breeds	0
Ages up to 1 year and 7 years and older	1
Not completed the full course of vaccination	1

Note. In the presence of 3 or more criteria, the indicator P = 3 points. Index P (iP) is calculated as the sum of all indicators divided by 3.

Table 2. Criteria for assessing the indicator: infection (I)

Criteria	Points
Blood culture detection	3
Bacterial microflora in smears:	
Gram-positive	1
Gram negative	2
Mixed	2
Absence of purulent accumulations (discharge) and microflora in smears	0

Note.Indicator I corresponds to the criterion with the highest score. Index I (iI) is calculated as the sum of all indicators divided by 3.

Table 3. Scoring scale for R assessment (systemic response of the body to infection)

Criteria	Points			
	0	1	2	3
T (°C) body temperature	37.8–39.4	39.5–40.4	36–37.7 or 40.5–41.4	< 36 or > 41.4
HR (bpm) heart rate	60–140	141–150	151–170	< 60 or > 171
RR (bpm) respiratory rate	10–30	31–40	41–50	> 50 or < 10
White blood cells (cells/µL)	6000–16.000	4.200–5.999 or 16.001–20.800	2.940–4.199 or 20.801–27.040	< 2.939 or > 27.041

Note.If there are 2 or more criteria, the indicator R = 3. The index R (iR) is calculated as the sum of all indicators divided by 3.

Table 4. Criteria for assessing organ dysfunction (O)

Dysfunction	Criteria (all identified changes are taken into account, in all organs, each one is evidence of organ dysfunction)
Uterine	Ultrasound: signs of an acute inflammatory process
Renal	Ultrasound: pronounced changes Creatinine and urea
Hepatic	Ultrasound: pronounced changes. Bile acid and/or total bilirubin Alkaline phosphatase (ALP) ALT (alanine aminotransferase) Albumen
Cardiovascular	Hypotension requiring vasopressor drugs
Respiratory	Need of oxygen or ventilation, ARI

Note. Each criterion is worth 1 point. If there are 2 or more criteria, the indicator O = 3. Index O (iO) is calculated as the sum of all indicators divided by 3.

Sepsis in animals was distinguished by the severity of the response and the development of complications, metabolic changes, multiple organ failure, and was divided into three stages:

Stage I - focus of infection + systemic inflammatory response syndrome (SIRS);

Stage II - focus of infection + systemic inflammatory response syndrome (SIRS) + multiple organ failure syndrome (MODS);

Stage III - focus of infection + systemic inflammatory response syndrome (SIRS) + multiple organ failure syndrome (MODS) + septic shock.

SIRS is diagnosed when three of the following criteria are met, one of which must be a leukocyte reaction: temperature response > 39.7°C or <37.5°C; leukocyte reaction> 20.0*109/l or <4.0*109/l; tachycardia>160 in 1 min; tachypnea > 24 in 1 min.

Table 5. SAPS (Simplified Acute Physiology Score) assessment criteria

Indicators of morphological and biochemical parameters of blood	Points								
	4	3	2	1	0	1	2	3	4
	Below normal				Norm	Above normal			
Deviation of the norm, %	Over 50	25-50	11-24	1-10	0	1-24	25-50	51-100	Over 100

3 Results

Dogs with sepsis had a decreased appetite, increased body temperature, respiratory and heart rate. All dogs had elevated ESR levels, most of them significantly (2-3 points). In 60% of dogs, on average, the mean value of erythrocyte volume and potassium content decreased by 1 point. In 50% of dogs with sepsis, the level of red blood cells was slightly elevated (1 point).

Table 6 presents the scores on SAPS scale of cellular and biochemical blood parameters of dogs with obstetric-gynecological and cryptogenic sepsis, as well as chronic septic complications manifested by purulent wounds and abscesses.Neutrophilia was observed in most sick dogs, which varied from just left neutrophil shift in animals with abscesses (1 point), to a hyper regenerative shift in animals with cryptogenic sepsis (3-4 points).

Dogs with accidental purulent wounds had increased leukocyte count by an average of 2 points and reached their maximum in the group of animals with sepsis (4 points).

Relative lymphopenia and an increased alkaline phosphatase were observed in half of the sick dogs. 80% of dogs showed a significant increase in rod-shaped neutrophils (2-3 points). In general, the development of septic complications was reflected, as a rule, in an increase in the number of leukocytes, platelets, neutrophils (young, rod-shaped and segmented) and monocytes. At the same time, erythrocytes and lymphocytes in 50% of sick animals were determined below the physiological norm. Among the biochemical indicators, a decrease in potassium and phosphorus was noted in 60 and 30% of animals, respectively.

Table 6. Changes in cellular and biochemical blood parameters of dogs with developed septic complications of various severity.

Name of indicator	Reference range of indicators of the physiological norm (lim). Control (n=22)	SAPS scores (lim - limits, Mo - fashion, x - arithmetic mean)			Changes in indicators in sepsis:	
		Obstetric-gynecological sepsis (n=22)	Cryptogenic sepsis(n =18)	Purulent wounds, abscesses (n =10)	Hypoallergenic type	Hyperergic type
1	2	3	4	5	6	7
WBC Leukocytes	< 6 | 17 > 10^9/l	lim2-4, **Mo 3,** x3,27	lim2-4, **Mo 3,** x2,5	lim1-4, **Mo 2,** x2,25	10%	90%
RBC red blood cells	< 5,5 | 8,5 > 10^12/l	lim0-2, **Mo 1,** x1,3	lim0-1, **Mo 1,** x0,5	0	50%	0%
HGB Hemoglobin	< 110 | 190 > g/l	lim0-2, **Mo 1,** x1,1	lim0-1, **Mo 1,** x0,4	0	44%	10%
HCT Hematocrit	< 39 | 56 > %	lim 0-3, **Mo 1,** x1,33	lim0-1, **Mo 1,** x0,6	0	50%	0%
MCV erythrocyte	< 66 | 77 > fL	lim0-2, **Mo 1,** x0,75	lim0-1, **Mo 1,** x0,5	0	60%	0%
MCHC hemoglobin	< 320 | 360 > g/l	lim0-2, **Mo 1,** x0,72	lim0-1, **Mo 0,** x0,3	0	20%	20%

RDW-SD erythrocytes	35 < 12 | 15 > 0	lim0-1, **Mo 0,** x0,31	0	0	0%	24%
PLT platelets	<117 | 460 > 10^9/l	lim0-1, **Mo 0,** x0,33	0	0	0%	24%
ESR	< 2 | 8 > мм\час	lim1-2, **Mo 1,** x 1,6	lim2-4, **Mo 3,** x3,5	0	0%	40%
Young neutrophils	0%	lim1-2, **Mo 1,** x1,3	lim0-1, **Mo 0,** x0,4	0	0%	20%
Stab neutrophils	< 0 | 3 > %	lim1-4, **Mo 3,** x2,74	lim2-3, **Mo 2,** x2,2	0	0%	80%
Segmented neutrophils	< 55 | 70 > %	lim1-2, **Mo 1,** x1,6	lim0-2, **Mo 0,** x1,1	lim2-4, **Mo 3,** x3,5	10%	40%
Eosinophils	< 0 | 5 > %	lim0-1, **Mo 0,** x 0,1	0	0	10%	0%
Lymphocytes	< 13 | 32 > %	lim0-2, **Mo 0,** x0,67	lim0-1, **Mo 0,** x0,5	lim1-2, **Mo 1,** x1,1	50%	10%
Monocytes	< 0 | 3 > %	lim0-2, **Mo 1,** x1,63	0	0	0%	15%
Potassium	< 4,3 | 6,2 >	lim0-2, **Mo 1,** x1,2	lim0-2, **Mo 1,** x1,5	lim0-2, **Mo 1,** x1,2	60%	0%
AST	< 11 | 42 >	lim0-2, **Mo 0,** x1,5	0	0	0%	15%
ALT	< 9 | 52 >	0	lim0-1, **Mo 0,** x0,5	0	0%	10%
Albumen	< 22 | 39 >	lim0-2, **Mo 0,** x0,7	0	0	15%	0%
Urea	< 3,5 | 9,2 >	lim0-2, **Mo 0,** x0,7	0	0	0%	20%
Bilirubin total	< 3 | 13,5 >	lim0-2, **Mo 0,** x0,5	0	lim 0-2, **Mo 0,** x1,25	20%	0%
Total protein	< 40 | 73 >	lim0-2, **Mo 0,** x0,75	0	0	0%	20%

		lim0-2, **Mo 0,** x0,5	lim0-1, **Mo 0,** x0,5	lim 0-2, **Mo 1,** x1,25	30%	0%
Phosphorus	< 1,3 | 3 >					
Alkaline phosphatase	< 18 | 70 >	lim0-2, **Mo 1,** x1,5	lim3-4, **Mo 3,** x3,5	lim 3-4, **Mo 3,** x3,5	10%	50%

Note. The Mo mode is the most frequently occurring value in the sample.X - arithmetic mean.X = 1/n (x1 + x2 + . . . + xn).

Table 7 shows the range of indicators (PIRO, iPIRO, SIRS, CARS and MODS) corresponding to different stages of the septic process in dogs. The most pronounced changes in the indicators of PIRO, SIRS and MODS were noted in dogs with obstetric-gynecological and cryptogenic sepsis. In animals in critical condition, the iPIRO reached 2.25-2.5, and the SIRS and MODS indicators reached the highest score - 3 points. Purulent wounds and abscesses only in rare cases led to sepsis: iPIRO did not exceed 1.75 points, and CARS and MODS – 1 point. At the same time, in half of the dogs with purulent wounds, CARS and MODS were determined within the physiological norm.

Table 7. Indicators of PIRO, iPIRO, SIRS, CARS and MODS in development of septic complications caused by diseases of various etiologies.

Indicators	Clinically healthy (n=22) (control) lim	Purulent wounds, abscesses (n=10) lim	Obstetric-gyne cological sepsis (n=22) lim	Cryptogenic sepsis (n=18)lim
P —predisposition	**0-1**	0-2	0-2	1-3
I — infection	**0**	1	1	1
R — response	**0**	0-2	2-3	0-3
O — organdysfunction	**0**	0-2	2-3	1-3
PIRO	**0-1**	1-7	5-9	3-10
iPIRO	**0-0,25**	**0,25-1,75**	1,25-2,25	**0,75-2,5**
SIRS — systemic inflammatory response syndrome	0	1-2	2-3	1-3
CARS — compensatory antiinflammatory response syndrome	0	0-1	1-2	1-2
MODS — multiple organ dysfunction syndrome	0	0-1	2-3	1-3

Note.When assessing SIRS, the scores obtained with an increase in indicators relative to the physiological norm are summarized.When assessing CARS, the scores obtained with a decrease in indicators relative to the physiological norm are summarized.

Determination of cationic proteins (CP) of neutrophilic granulocytes (NG) was carried out by us only in the group of dogs kept in the animal shelter. Cationic proteins in granulocytes decreased by 21.8% in animals with sepsis.

4 Discussion

Two age peaks of morbidity associated with decreased body resistance were revealed: animals at the age of 7 years and older and aged up to 1 year.

The etiological structure of sepsis in dogs was characterized by the presence of both gram-positive and gram-negative microflora. At the same time, gram-positive sepsis accounted for 18%, gram-negative sepsis - 28%, and associated sepsis accounted for 54% of the animals. Escherichia coli and Staphylococcus aureus were more commonly isolated. Less common were Streptococcus pyogenes, Proteus mirabilis, Clostridium perfringens, Staphylococcus epidermidis. The main etiological agents leading to the development of sepsis were Streptococcus pyogenes, Escherichia coli [Plante L.A., 2019]. The microbial landscape in the focus of inflammation in purulent-inflammatory diseases in modern conditions is characterized by the polymicrobial nature of infectious agents with a predominance of the association of opportunistic microorganisms [Kuznetsova, 2021].

Fulminant sepsis in dogs was noted in 14%, acute sepsis - in 64% of cases. Depending on the primary septic focus, obstetric-gynecological sepsis was observed in 44% and cryptogenic sepsis in 36% of the analyzed cases.

In most dogs, sepsis proceeded with severe leukocytosis. In a smaller part of sick animals, sepsis proceeded with severe leukopenia. The development of inflammation leads to depletion of the leukocyte pool, persistence of infection, and excessive activation of macrophages and neutrophils. The cytokine storm initiates neutrophilia and the release of immature myelocytes, the content of which in the blood is more than 10%, which is a component of the SIRS definition [Mahmudpour, 2020].

The inability of the immune system to cope with a septic pathogen can lead to both excessive inflammation and immunosuppression [Wong, 2019]. NG secrete decondensed chromatin with many enzymes and proteins - NETs (neutrophil extracellular traps). NETs capture and engulf pathogens due to the positive charge of proteins adhered to it, which contributes to the development of MODS [Stiel, 2019]. The balance between the formation and destruction of NETs is important. Thus, a violation of their formation leads to severe purulent-septic processes [Kimberly, 2014].

NG in the vessels help purify the blood. In response to a large-scale threat, NGs throw out fibers of their DNA and proteins - NETs [Brinkmann, 2004]. Antimicrobial NG peptides are isolated separately, and all components are combined into NETs only outside the cell. The neutrophil left without a nucleus finds pathogens for some time and phagocytizes them [Venizelos, 2018; Selina, 2017]. But when bacteria defend themselves and NG lose control of netosis, inflammation is triggered [Masaki Honda, 2018]. Waste products accumulate in the body, and the tissues receive less oxygen - septic shock develops, the most severe form of sepsis. As a result, NG only aggravates sepsis. Since netosis aggravates sepsis and because of it, patients with sepsis die more often.

The outcome of inflammation depends on the elimination of the etiological factor, the removal of necrotic cells, the accumulation of apoptotic cells, the appearance of immune complexes, annexin-1, the change of Th1 cytokines (IL-1β, TNF, IFN-γ) to Th2 cytokines (IL-4, IL-6), secretion of IL-10, TGFβ, synthesis of resolvins, protectins, maresins. Macrophages complete acute inflammation by activating the processes of proliferation and regeneration and initiate the formation of acquired immunity. When the source of DAMPs is preserved, chronic inflammation is formed [Hu, 2014].

Mortality in sepsis was 14%. At the same time, hyperergic sepsis was prognostically more favorable than hypoergic. Significant death risk factors during sepsis are the site of its onset and underlying pathology [Vincent, 2009].

Non-enzymatic CPs are involved not only in the processes of intracellular digestion, but also in the neutralization and killing of phagocytosed material. CPs have a wide spectrum of activity.

In particular, various studies emphasize their antibacterial effect in the strategy of combating infectious agents, which characterizes the innate ability of the body to resist bacterial infections. Determining the level of CP in NG can be useful as a marker of systemic neutrophil activation in the practice of confirming the pathogenetic role of immune-dependent processes in response to an infectious-inflammatory process. The CP level in dogs with clinical manifestations of purulent inflammation and accumulation of purulent exudate showed significantly lower values than in clinically healthy dogs. During the inflammatory process, CPs are able to be released into the extracellular environment. This leads to an intracellular decrease in the content of CP in NG [Koroleva, 2006].

An increased heart rate in dogs subjected to septic shock was often accompanied by a decrease in ventricular systolic function, an increase in cardiac output, a decrease in mean arterial pressure, and leukocytosis. There is also an increase in IL-6 and TNF-α cytokines during the first hours of SIRS and sepsis development [Belyaeva, 2020].

The apparent decrease in potassium in 60% of dogs has a negative role in the functioning of the nervous system, muscle contraction, maintaining the body's water balance, maintaining normal blood pressure and blood sugar, and other biochemical reactions that ensure vital activity.The greatest danger from a decrease in the level of potassium in the blood plasma may be the development of cardiac arrhythmias, which was noted during the clinical examination of animals.

5 Conclusion

The study focuses on the nature and intensity of changes in the blood picture when examining animals with obstetric-gynecological sepsis, cryptogenic sepsis, purulent wounds, abscesses and highlights the emphasizes on converting the data to PIRO and SAPS scores, which accelerate the prognosis of the development of SIRS and sepsis in sick dogs with primary examination at veterinary clinics.

References

1. Alves, F., Prata, S., Nunes, T. et al. Canine parvovirus: a predicting canine model for sepsis. BMC Vet Res. 2020 Jun 15;**16**(1):199. doi: 10.1186/s12917-020-02417-0
2. Belyaeva E.V., GuschinYa.A. The methods of visualization and research of the git-associated lymphoid tissue of laboratory animals. Laboratory animals for scientific research 2020; **03**: 68–74. https://doi.org/10/29926/2618723X-2020-03-09
3. BrinkmannV. (2004). Neutrophil Extracellular Traps Kill Bacteria. *Science*. **303**, 1532-1535
4. Hu X., Li B., Li X. et al. Transmembrane TNF-alpha promotes suppressive activities of myeloid-derived suppressor cells via TNFR// J. Immunol.Vol. **192**. P. 1320–1331 (2014)
5. Kimberly Martinod K., Wagner D.D. Thrombosis: tangled up in NETs. Blood. Vol. **123**, Is. 18. P. 2768–2776 (2014)
6. Koroleva O. I., Petrova G. K., Shakirova L. Z. Prognostic value of lysosomal cationic proteins of oral neutrophils in acute bronchopulmonary pathology in adolescents. Questions of modern pediatrics. Vol. **5** (1). pp. 282-283. (2006)
7. Kuznetsova D.E., Makarenko T.A., Averchuk E.S. Features of the microbial landscape in the focus of inflammation in postpartum purulent-inflammatory diseases (literature

review). Problems of reproduction. Vol. **27**. No. 2. pp. 101-111 (2021)

8. Laptev, S.V. "Organization of educational and comparative prognosis of purulent-septic complications in feline panleukopenia by the method of score evaluation of PIRO indicators", in Mat. II National Scientific and Practical Conference "Commodity Science, Technology and expertise: innovative solutions and development prospects" (Moscow, Moscow SAVMB, pp. 319-327 (2021)

9. Laptev,S.V., Mezentseva, N.I. Cellular and humoral mechanisms of protection in coronavirus infection. Handbook of the head of CDL. No. 5. pp. 34-43 (2021)

10. Le Gall, J.-R., Loirat, P., Alperovitch, A. et al. A simplified acute physiology score for ICU patients. Critical Care Medicine. 12(11):975–977 (1984)

11. Mahmudpour M, Roozbeh J, Keshavarz M. et al. COVID-19 cytokine storm: e anger of in ammation. Cytokine. (133):155151. (2020) DOI: 10.1016/j.cyto.2020.155151

12. Masaki Honda, Paul Kubes. (2018). Neutrophils and neutrophil extracellular traps in the liver and gastrointestinal system. *Nat Rev Gastroenterol Hepatol*. **15**, 206-221

13. Pimenov,N. "PIRO model as a comprehensive assessment of septic complications in veterinary propaedeutics"/ N.Pimenov,S. Laptev, S. Marzanova, K. Permyakova //Veterinariya, ZootekhniyaiBiotekhnologiya, **4**, 6-15 (2022)

14. N.V.Pimenov, K.Yu. Permyakova, S.N. Marzanova, S.V. Laptev. Scientific Bulletin of Lugansk State Agrarian University. Lugansk: GOU IN LNR LGAU. № **2**(15). pp. 97-100 (2022)

15. Plante L.A., Pacheco L.D., Louis J.M. SMFM Consult Series #47: Sepsis during pregnancy and the puerperium. Am. J. Obstet. Gynecol. 220(4): B2-B10. (2019) https://doi.org/10.1016/j.ajog.2019.01.216

16. Selina K Jorch, Paul Kubes. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat Med*. **23**, 279-287 (2017)

17. Stiel L, Mayeur-Rousse C, Helms J. et al.First visualization of circulating neutrophil extracellular traps using cell uorescence during human septic shock-induced disseminated intravascular coagulation. Thromb Res. (183): 153-158. (2019) DOI: 10.1016/j.thromres.2019.09.036

18. Venizelos Papayannopoulos. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. **18**, 134-147 (2018)

19. Vincent J.L., Rello J., Marshal J. et al. International study of prevalence and outcomes of infection in ICU JAMA. Vol. **302**. P. 2323–2329. (2009)

20. J. L. Vincent, S. M. Opal, J. C. Marshall, K. J. Tracey Lancet. Vol. **381**. P. 774–775 (2013)

21. Wong, J.J.M., Leong, J.Y., Lee, J.H. et al. Insights into the immuno-pathogenesis of acute respiratory distress syndrome. *Annals of Translational Medicine*. 7(19): 504. (2019) DOI: 10.21037/atm.2019.09.28