Sepsis: Correlation of laboratory findings and animal survival rate

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ABSTRACT
Sepsis has become one of the biggest challenges in veterinary medicine. Sepsis is defined as an organic dysfunction resulting from an inadequate immune response to an infectious agent, threatening the life of the animal. The aim of this study was to verify the occurrence of the most frequent diseases that led animals to sepsis in the consultations performed at the Veterinary Hospital (HV) of the Universidade Vila Velha (UVV), in Vila Velha/ Espírito Santo, Brazil, observing the laboratorial alterations related to sepsis and correlating them with the life expectancy of those animals. Through a retrospective study, there was a survey of the cases seen in the period from August to December 2019. The data were tabulated and analyzed by software using a 5% significance level. The main diseases that led to sepsis were in order of frequency erliquiosis, pyometra and gastroenteritis; furthermore, it was observed that the factors influencing the survival of these animals were alteration in the values of total leukocytes (p=0.042) and the presence of azotemia (urea p <0.001 and creatinine p=0.003). This demonstrated the importance of laboratory findings in conjunction with clinical changes, allowing agility in the identification of an ongoing systemic inflammatory response syndrome (SIRS).

Keywords: Infectious diseases, Laboratory abnormalities, Mortality, Systemic Inflammatory Response Syndrome (SIRS).

1 INTRODUCTION

Currently, dogs and cats have reached a significant space in family homes, have become members in a multispecies family perspective and, due to the narrowing of this relationship there is a growing demand for care with regard to animal health (Leviski and Duarte, 2019).

In veterinary medicine, sepsis has been the subject of extensive research as well as in human medicine, given its importance for leading to hospitalization and death of patients treated in intensive care units (Sales Junior *et al.*, 2006).

Sepsis is defined as a life-threatening organ dysfunction due to irregular host response to infection (Singer *et al.,* 2016). In some cases, it was related to the systemic inflammatory response syndrome (SIRS), because it resulted from an infectious or non-infectious condition, which courses in excessive inflammation with systemic involvement (Powell, 2003). SIRS can culminate in septic shock due to hypotension (Candido *et al.,* 2012) and when not identified in a timely manner will lead to multiple organ dysfunction (MODS), and possibly the death of the animal.

Laboratory tests have an important role in helping to diagnose diseases, because they show a general parameter of the patient and the variations that occur in his body (Mello and Silva, 2009). The blood count is an examination that provides information at a low cost, through it can exclude differential diagnoses, evaluate the general condition of the animal and the progression of diseases (Aguiar, 2010). Some laboratory signs found in sepsis are neutrophilia leukocytosis with left shift and toxic neutrophils, which may present with marked leukopenia, hyperglycemia with progression to hypoglycemia, increased liver enzymes, azotemia, elevated serum lactate and hypercoagulability (Basso *et al.,* 2012).

To identify the development of sepsis and its evolution, it is proposed to use the concept of sepsis combined with organic dysfunctions recommended by the sepsis-1 and 2 consensus, in addition to the SIRS criteria that serve as a screening tool (Castro and Rabelo, 2017) (Annex I).

Clinical signs, laboratory changes and complementary tests combined with knowledge of regional diseases of greater recurrence can contribute significantly to elucidate the animal's condition and thus reach an early diagnosis and consequently a correct treatment.

Thus, the objective of this study was to carry out a survey of the casuistry of the Veterinary Hospital (HV) of the Vila Velha University (UVV), in Vila Velha, Espírito Santo, focusing on the diseases of greatest occurrence in this hospital in the period from August to December 2019, investigating the laboratory changes related to sepsis and correlating with the life expectancy of these animals.

2 MATERIAL AND METHODS

For the present study, records were collected from animals treated at the Veterinary Hospital "Alexandre Ricardo Hippler" of the Vila Velha University located in Vila Velha, ES (Brazil) from August to December 2019.

Data collection was obtained in two stages: the first consisted of a screening of the tests that were sent to the veterinary clinical laboratory of the hospital and that presented leukocytosis or

leukopenia. If this type of alteration occurred, the patient's data were recorded, such as age, race, sex, clinical suspicion and date of receipt of the sample, in addition to the alterations found in the complete blood count, such as: relative and absolute values of total leukocyte, segmented neutrophil, rod, toxic neutrophil (if present) and platelets; in the biochemical the values of urea, creatinine and alanine amino transferase (ALT).

The second stage consisted of gathering the clinical information of the animal regarding the day of the leukogram. The animal's medical record was requested from the hospital and the parameters rectal temperature (Tº), heart rate (HR) and respiratory rate (RR) were recorded. The evolution of the clinical picture regarding mortality was also monitored, and death was recorded when it occurred within 72 hours, so the animals were divided into two groups, the animals that died and the animals that survived.

After collection, the data were arranged in a table of the Microsoft Excel 2010 program. At that moment, a second screening was performed, including in the study only animals that had a confirmed diagnosis of disease caused by some infectious agent and that manifested initial or progressive signs of SIRS, that is, met two or more SIRS criteria determined by Silverstein and Sanotoro-Beer (2012), as shown in Table 1.

Table 1. Values of rectal temperature, heart rate, respiratory rate, total leukocytes and rods according to the criteria of the Systemic Inflammatory Response Syndrome (SIRS).

RECTAL TEMPERATURE (ºC)		**HEART RATE (BPM)**		**RESPIRATORY RATE (RPM)**		**TOTAL LEUKOCYTES (THOUSAND//ML)**		**RODS (THOUSAND/ML)**
DOG	**Feline**	**Dog**	**Feline**	**Dog**	**Feline**	**Dog**	**Feline**	**Dog**
<38.1	<37,8	>120	<140	>20	>40	<6	<5	>3%
>39,2	>40		>225			>16	>19	

Source: Silverstein and Sanotoro-Beer, 2012.

Subsequently, in order to facilitate the analysis of the data obtained, two scoring scales were created based on the SOFA (Sequential Organ Failure Assessment) scale proposed by Singer *et al.* (2016), where adaptations were made to assess the severity of sepsis in the patients of this study.

The first scale was structured with quantitative data ordered in increasing severity scale from 0 to 3 (Table 2) using as reference the values proposed by Silverstein and Sanotoro-Beer (2012) and Meyer and Harvey (2004) for leukogram and platelet respectively, and by Kaneko et al. (2008) for serum biochemistry. The second scale was qualitatively classified according to the presence of the clinical alteration, following the SIRS criteria established by Silverstein and Sanotoro-Beer (2012) (Table 3).

As standardization for this project, the values of leukopenia <6 to 4 thousand/µL and leukocytosis >16 to 30 thousand/µL were considered as mild alterations in dogs; thrombocytopenia < 175 to 100 thousand/µL and thrombocytosis 500 to 600 thousand/µL; urea values <21 mg/dL and 60

to 100 mg/dL; creatinine <0.5 mg/dL and >1.5 to 2.5 mg/dL and for ALT <21 IU/L and >102 IU/L to 200 IU/L. For felines, leukopenia <5 to 3 thousand/µL and leukocytosis >19 to 30 thousand/µL were considered; thrombocytopenia <200 to 100 thousand/µL and thrombocytosis >600 to 700 thousand/µL; urea values < 42.8 to 30 mg/dL and >64.2 to 100 mg/dL; creatinine <0.8 to 0.5 mg/dL and >1.8 to 2.5 mg/dL and ALT values >83 IU/L to 200 IU/L.

For moderate degree (grade 2) changes in dogs leukopenia | leukocytosis ranging from <4 to 1 thousand/µL and 31 to 49 thousand/µL respectively; thrombocytopenia <100 to 50 thousand/µL and thrombocytosis >600 to 700 thousand/µL, urea values 100 to 300 mg/dL, creatinine <2.5 to 4mg/dL and ALT values > 200 to 300 IU/L. In felines leukopenia | leukocytosis <3 to 2mil/µL and >30 to 49 mil/µL respectively; thrombocytopenia ranging from <100 to 50 thousand/µL and thrombocytosis >700 to 800 thousand/µL; urea values <30 to 20 mg/dL and >100 to 300 mg/dL; creatinine <0.5 to 0.3 mg/dL and >2.5 to 4 mg/dL and ALT values >200 to 300 IU/L. And for severe changes (grade 3) the values of leukopenia | leukocytosis in dogs and cats >50 mil/µL and <1 mil/µL respectively; thrombocytopenia of <50 mil/µL in both species and thrombocytosis in dogs >700 thousand/µL and in felines >800 thousand/µL; urea values in dogs >300 mg/dL and in felines <20 mg/dL and >300 mg/dL; creatinine in dogs <2.5 to 4 mg/dL and >4 mg/dL and for felines <0.3 mg/dL and > 4mg/dL and ALT values being >300 IU/L for both species.

Table 2. Increasing scoring scale with quantitative data on leukocytes, platelets, urea, creatinine and alanine amino transferase values (reference values following Silverstein and Sanotoro-Beer, 2012; Meyer & Harvey, 2004 and Kaneko *et al.*, 2008).

SCALE	**LEUKOCYTES (THOUSAND/ ML)**		**PLATELET (THOUSAND/ ML)**		**UREA (MG/DL)**		**CREATININE (MG/DL)**		**ALT (UI/L)**	
	Dog	**Feline**	**Dog**	**Feline**	**Dog**	**Feline**	**Dog**	**Feline**	**Dog**	**Feline**
0 = NORMAL (REFERENCE VALUES)	6-16	5-19	175-500	200-600	21-59	42,8-64,2	0,5-1,5	0,8-1,8	21-102	6-83
1 = LIGHT*	<6-4	<5-3	<175-100	<200-100	<21	<42.8-30	<0,5	<0.8-0.5	<21	>83-200
	>16-30	>19-30	500-600	>600-700	60-100	>64,2-100	>1,5-2,5	>1,8-2,5	>102-200	
2= MODERATE *	<4-1	<3-2	<100-50		100-300	<30-20	<2.5-4	<0.5-0.3	>200-300	
	31-49	>30-49	>600-700	>700-800		>100-300		>2,5-4		
3= SEVERE*	>50 e <1		<50		>300	<20	>4	<0,3	>300	
			>700	>800		>300		>4		

Table 3. Scoring scale with qualitative data of rectal temperature, heart rate, respiratory rate, rod neutrophil, toxic neutrophil and survival (Reference values according to Silverstein and Sanotoro-Beer, 2012).

SCALE	RECTAL TEMPERATURE (T°C)		FC (BPM)		FR (RPM)		ROD NEUTROPHIL(MIL/ML)		TOXIC NEUTROPHIL (THOUSAND/ML)	SURVIVAL
	Dog	Feline	Dog	Feline	Dog	Feline	Dog	Feline	Dog/Feline	Dog/Feline
0 = NORMAL	38,1-39,2	37,8-40	<120	140-225	<20	<40	<300		Absent	Vivo
1= CHANGED	<38,1	<37,8	>120	<140	>20	>40	>300		Present	Death
	>39.2	>40		>225						

After the criteria and scales defined/established, the animals were then analyzed individually; enumerating each variable of the animal according to its clinical and laboratory tests in the table of the Microsoft Excel 2010 program, that is, for each variable analyzed (leukocytes, platelet, urea, creatinine, ALT, Tº, HR, RF, rod neutrophil, toxic neutrophil, survival) a number was released according to the qualitative or quantitative scale.

For statistical analysis, the SigmaPlot 11.0 program was used. The nonparametric Mann-Whitney test compared the score between live animals and deaths, and compared the value of absolute variables with survival. To evaluate the score in the different ages, the Kruskal-Wallis test was used. For the variables grouped into scales, the Chi-square test was used to verify the distribution of cases according to survival. In all tests, a significance level of 5% was considered.

3 RESULTS AND DISCUSSION

During the study period, 127 patients were included; of these, 109 were dogs (63 females and 46 males) and 18 were felines (10 females and 8 males); 16% were puppies (< 1 year), 46% adults (1-7 years) and 38% elderly (> 7 years). Regarding the death rate, only nine animals died, 7 dogs (2 puppies, 1 adult and 4 elderly) and 2 were felines and elderly (Table 4).

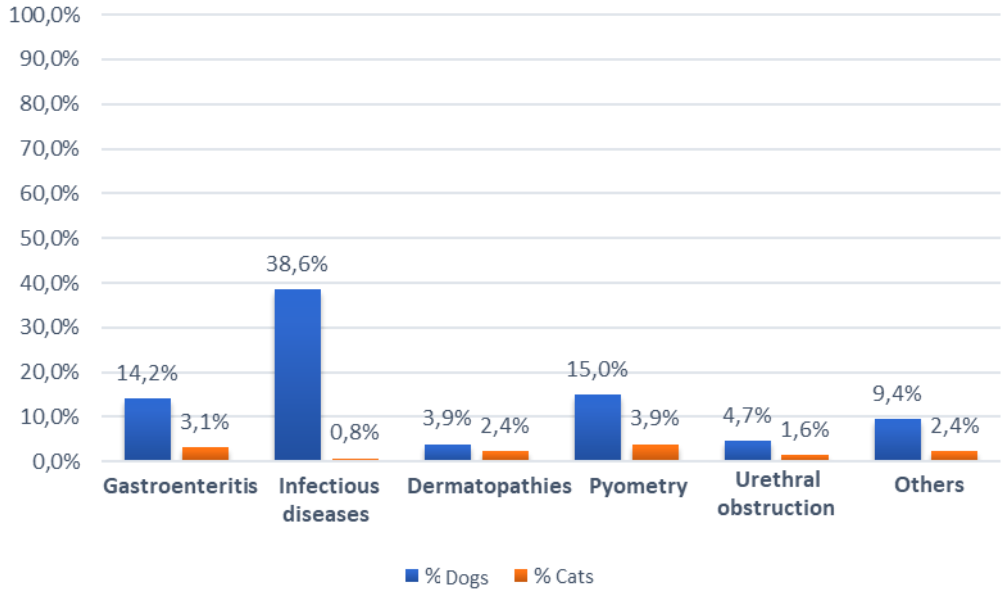
Table 4. Data of the patients attended.

Variables		N (total 127)	%	Median	p=Value
Species					
	Canine	109	86%		
	Feline	18	14%		
Sex					
	Canine	63 ♀; 46 ♂	50%; 36%		
	Feline	10 ♀; 8 ♂	8%; 6%		
Age					0,243
	< 1 year	20	16%	5,5	
	1-7 years	59	46%	6	

	> 7 years old	48	38%	6	
Survival					**0,01**
	Live	118	93%	6	
	Deaths	9	7%	9	

Of the 127 cases registered, 50 cases were of infectious and infectious diseases (39.4%), followed by pyometra with 24 cases (18.9%), gastroenteritis of unknown origin with 22 cases (17.3%), skin diseases and urethral obstruction with 8 cases each (6.3%) and other diseases with 15 cases (11.8%) (Fig. 1).

Figure 1. Sample of care for diseases in canine and feline patients followed at the Veterinary Hospital, in Vila Velha, from August to December 2019.



Among the infectious diseases, ehrlichiosis stands out, which accounted for 62% of the cases in this category, corroborating with several authors about the disease having a high prevalence in Brazil (Sales *et al.,* 2013; Mota *et al.,* 2019). It is a disease caused by *Ehrlichia canis*, a bacterium that causes nonspecific to multisystemic changes depending on its evolution (acute or chronic). This disease is transmitted by the tick *Riphicefalus sanguineus,* due to its vast urban distribution, in addition, Vieira (2017) observed that 50.6% of the animals attended at the HV – UVV had a tick of this species, which justifies the canine monocytic ehrlichiosis being commonplace in the routine.

Although *E. canis* does not lead to acute sepsis, its chronicity can induce spinal cord suppression, coagulation disorders, immunosuppression and predisposition to other diseases of different etiologies such as bacterial, fungal, viral or protozoa, leaving the animal susceptible to developing a septic picture.

The second greatest demand for care related to the course of sepsis was pyometra, which represents 19% of the recorded cases, being more commonly associated with gram-negative bacteria present in the uterus (Trautwein *et al.*, 2018). This disease is of an emergency order, because it leads the animal to a picture of endotoxemia, septic shock and consequently to death if not treated. In a study by Fransson *et al.* (2007) of 53 diagnosed with pyometra, 30 animals (57%) had SIRS and this influenced the increase in hospitalization time.

Gastroenteritis resulting from intoxications, viruses, allergens, infectious agents or parasites accounted for 17% of the recorded visits. This condition has also been cited by Rabelo (2008) as one of the main diseases in emergency care that led animals to hospital admission, being one of the most frequent cases in the clinical care of small animals (Rodrigues *et al.*, 2018). Because it has a multifactorial etiology, the disease affects animals of any age and sex, being seen more frequently in young animals (Decaro *et al*., 2011). It is characterized by causing inflammation and often bleeding in the gastrointestinal tract, causing a bacterial translocation and favoring secondary infections. The clinical signs usually seen are watery to bloody diarrhea, vomiting, prostration, anorexia, and altered body temperature (Isola *et al.,* 2014). One of the consequences of this dysfunction is to lead the animal to generalized inflammatory conditions, and it is essential to evaluate if there is the course of a septic condition, allowing to determine the prognosis, perform a specific treatment and adequate monitoring.

Regarding survival, there was no statistical difference between the groups (live animals x deaths) regarding the variables species, age and sex, that is, sepsis occurred homogeneously among the animals of the study, diverging from the data found in the human literature, where sepsis occurs more frequently in the elderly and men (Adrie, 2007).

The adapted SOFA (Sequential Organ Failure Assessment) scale was different between the groups ($p = 0.01$) (**Table 4),** where the animals belonging to the group of deaths presented higher values in relation to the group of survivors. Corroborating what was found by Singer *et al.* (2016) in his study, in which he states that the SOFA score has a precise relationship with mortality risk. Likewise Rudd *et al.* (2018) noted that patient mortality was related to higher qSOFA (Quick Sequential Organ Failure Assessment) scores. It is worth remembering that the SOFA and qSOFA scales are scores used only in human medicine, and have the objective of verifying if there is organ dysfunction and assessing the risk of death (Castro and Rabelo, 2017), a fact that led us to elaborate a scale for each laboratory variable to obtain an overview of the animal's condition. Associated with this scale we use the criteria of SRIS, which has high sensitivity in the detection of potentially infected animals, being an important tool for screening sepsis (ILAS, 2018).

Another factor that influenced the survival of the animals was the alteration in total leukocytes ($p = 0.042$) (**Table 5),** however, no difference was observed between the absolute values, that is, the

amount of total leukocytes is not the factor that increases the mortality rate in patients with sepsis, but the presence of the alteration, regardless of the value presented in leukocytosis/leukopenia.

Table 5. Association of clinical and laboratory data with animal survival.

Variables	**Survival N (%)**		**p=Value**
	Alive	Deaths	
Leukocytes			**0.042**
Normal	15 (11.8%)	0	
Lightweight	67 (52.7%)	3 (2.36%)	
Moderate	27 (21.2%)	3 (2.36%)	
Grave	9 (7.1%)	3 (2.36%)	
Neutrophils Rods			0.703
Normal	103 (81.1%)	8 (6.29%)	
Changed	15 (11.8%)	1 (0.78%)	
Toxic Neutrophils			0.072
Normal	108 (85%)	6 (4.72%)	
Changed	10 (7.87%)	3 (2.36%)	
Urea			**< 0.001**
Normal	90 (70.8%)	4 (3.15%)	
Lightweight	20 (15.7%)	1 (0.78%)	
Moderate	8 (6.3%)	3 (2.6%)	
Grave	0	1 (0.78%)	
Creatinine			**0.003**
Normal	105 (82.6%)	4 (3.15%)	
Lightweight	8 (6.3%)	3 (2.36%)	
Moderate	3 (2.36%)	1 (0.78%)	
Grave	2 (1.57%)	1 (0.78%)	

It is important to consider that the main cell population recruited in the face of an inflammatory response are leukocytes and this may explain the reason for the result found. Isola (2014) demonstrated in his study that the animals that died due to severe sepsis, all had changes in the leukogram (50% leukopenia and 50% leukocytosis) and most deaths had severe leukopenia (<600 leukocytes/uL blood), thus revealing the severity of extreme values in leukocytes. However, in this study, the absolute value of leukocytes did not influence the survival of the animals, in other words, an animal with severe leukocytosis/leukopenia is as severe as an animal with mild leukocytosis/leukopenia. This fact should be considered to evaluate the improvement of the patient, especially of hospitalized patients, because the risk of life is related to the presence of leukocyte alteration as well as the dependence on a competent response of the immune system, as also observed by Rabelo (2008), so it is necessary to keep in mind that hospital discharge is more indicated when the leukocytes are within the normal range,

demonstrating that the immune response was satisfactory and that upon returning to normality there was remission of the condition and the animal is recovered.

One of the essential steps of the blood count is the evaluation of the blood smear, which allows to observe in detail morphological changes of erythrocytes and leukocytes (Allison and Meinkoth, 2007). Through this analysis, it was possible to obtain the data for statistical processing that showed a positive correlation between the number of total leukocytes and segmented neutrophil ($r = 0.974$) and between the number of segmented neutrophil and the number of rods ($r = 0.629$). In sepsis, there is an exacerbated inflammatory response of the body to an infectious stimulus, leading to the production of pro-inflammatory cytokines, tumor necrosis factor-α (TNF) and interleukin 1 (IL-1) (Barbosa *et al.*, 2016). These cytokines induce the release of neutrophils from the medulla that are attracted to the infectious focus in an attempt to control. Therefore, the greater the infection, the greater the demand for neutrophils by the bone marrow, which at a certain time will begin to release immature cells into the bloodstream, as was seen in this study in which neutrophilia leukocytosis with left deviation occurred.

Aroch *et al.* (2005) and Lambert *et al.* (2016) revealed in their studies that the intensity of the left shift and the presence of toxic granulations in neutrophils are the changes that will indicate the severity of the infectious process, so the quantification of these neutrophils will directly influence the survival of the animal. However, there was no statistical difference in the variables rod neutrophils and toxic neutrophils, presenting a $p=0.703$ and $p=0.072$ respectively **(Table 5),** between the groups of animals that died and those that survived. This can be justified by the analysis having been isolated, being the most appropriate to evaluate the variables together, thus being able to verify that when associated, they contribute to the number of deaths, because it raises the level of the animal in the scoring scales. The same was seen by Rabelo (2008), stating that the interpretation of the variables has a more significant value related to the survival rate when analyzed as a whole, and not individually.

Azotemia was also a factor that influenced survival (urea $p<0.001$ and creatinine $p=0.003$) (**Table 5).** This data can be explained because the kidney is one of the organs responsible for the regulation of homeostasis, and in sepsis, the kidney is one of the first organs to suffer an injury due to endotoxins releasing a series of mediators that cause vasodilation, hypovolemia, with hypotension, tissue hypoperfusion and ischemia, decreasing the glomerular filtration rate (Basso *et al.,* 2012) resulting in acute renal failure of prerenal origin (Hirota *et al.,* 2013).

By understanding that sepsis causes prerenal azotemia, the veterinarian is able to perform an early intervention instituting volume replacement and perfusion to stabilize the patient and, thus, increase patient survival. This fact also only reinforces the importance of the therapeutic sequence of sepsis management proposed by Singer *et al.* (2016) in which volume and perfusion replacement is the first stage in the management of patients with sepsis.

4 CONCLUSION

It is observed that the most recurrent diseases in the clinical routine that induced the animals to SIRS/sepsis are: ehrlichiosis, pyometra and gastroenteritis. Sepsis occurs uniformly between dog and feline species; All the variables involved in the assessment of the risk of death should be considered. The minimal laboratory changes in leukocytes, urea and creatinine interfere substantially in the survival of the animal, so the most indicated is the stabilization of the values for the normal ranges as a criterion for medical discharge.

Through the results demonstrated in this study, the importance of the study in the area of sepsis is highlighted, due to the lack of studies in veterinary medicine and the complexity of this condition. It is suggested to include in future research other markers such as serum lactate, hypercoagulability to determine prognosis, as well as protein C dosage as an early marker of inflammation.

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REFERENCES

ADRIE C.; AZOULAY E.; FRANCAIS A. et al. Influence of gender on the outcome of severe sepsis: a reappraisal. *Chest*, v. 132, n. 6, p. 1786-1793. 2007.

AGUIAR, F. G. P. L. *O hemograma no cão e contribuição para a sua caracterização no cão da serra da estrela, variedade de pelo comprido.* 2010. Dissertação (Mestrado em Medicina Veterinária). Universidade Lusófona de Humanidades e Tecnologias. Lisboa, 2010.

ALLISON, R.W.; MEINKOTH, J.H. Hematology without the numbers: in-clinic blood film evaluation**.** *Veterinary Clinics of North America: Small Animal Practice*, v. 37, p. 245-266, 2007.

AROCH, I.; KLEMENT, E.; SEGEV, G. Clinical, biochemical and hematological characteristics, disease prevalence and prognosis of dogs presenting with neutrophil cytoplasmic toxicity. *Journal of Veterinary Internal Medicine*, v.19, p. 64-73, 2005.

BARBOSA, B.C.; ALVES F,S.; BIER S.L. et al. Fisiopatologia e terapia do cão com sepse: revisão. *Publicações em medicina veterinária (PUBVET)***,** v.10, n.1, p. 13-20, 2016.

BASSO, P. C.; MÜLLER, D. C. M.; SERAFINI, G. M. C. Fisiopatologia e manejo da sepse e síndrome da resposta inflamatória sistêmica – revisão de literatura**.** *Medvep - Revista Científica de Medicina Veterinária - Pequenos Animais e Animais de Estimação*, Curitiba/ PR, v. 10, n. 34, p. 430-436, 2012.

CANDIDO, T. D; NETO, F. J. D.; MARUCIO, R. L. et al., Diagnóstico e tratamento de choque séptico em cães. *Medvep - Revista científica de Medicina Veterinária - Pequenos Animais e Animais de Estimação*, Curitiba/ PR, v. 10, n. 32, p. 128-132, 2012.

CASTRO, B. G. A.; RABELO, R. C. Sepsis-3: uma análise aplicada à medicina veterinária. *Journal Laveccs*, v.9, n. 3, nov. 2017.

DECARO, N.; DESARIO, C.; BILLI, M. et al., Western European epidemiological survey for parvovirus and coronavirus infections in dogs. *The Veterinary Journal*, v.187, n. 2, p.195-199, 2011.

FRANSSON B. A.; LAGERSTEDT A.S.; BERGSTROM A. et al., C-reactive protein, tumor necrosis factor α, and interleukin-6 in dogs with pyometra and SRIS. *Journal of Veterinary Emergency and Critical Care*, v.17, p. 373–381, 2007.

HIROTA, I. N.; FRANCO, R. P.; GALVANI, G. D.; SIMÕES, J. G. S. Reposição volêmica em cães portadores de sepse grave: revisão de literatura. *Nucleus Animalium*, v.5, n.1, p.79-90, 2013.

ILAS. Implementação de protocolo gerenciado de sepse protocolo clínico: Atendimento ao paciente adulto com sepse / choque séptico). São Paulo, 14 p., 2018. Disponível em: <https://ilas.org.br/assets/arquivos/ferramentas/protocolo-de-tratamento.pdf>. Acessado em 29 mai. 2020.

ISOLA, J. G. M. P. *Parâmetros clínicos e laboratoriais relacionados ao prognóstico em cães com gastroenterite hospitalizados*. 2014. Tese (Doutorado) – UNESP/ Jaboticabal, São Paulo, 2014,

ISOLA, J. G. M. P.; SANTANA, A. E.; MORAES, P. C. et al., Estudo da incidência de SIRS, sepse, sepse grave e choque séptico, diagnosticados no atendimento de emergência em cães hospitalizados com gastroenterite. *Revista de Educação Continuada em Medicina Veterinária e Zootecnia do CRMV-SP*, São Paulo, v. 12, n. 2, p. 12 -17, 2014.

KANEKO, J. J.; HARVEY, J. W.; BRUSS M. L. *Clinical Biochemistry of Domestic Animals*. Elsevier, 6 ed., p. 916, 2008.

LAMBERT, J. L.; FERNANDEZ, N. J.; ROY, M. F. Association of Presence of Band Cells and Toxic Neutrophils with Systemic Inflammatory Response Syndrome and Outcome in Horses with Acute Disease. *Journal of Veterinary Internal Medicine,* v.30, p. 1284-1292, 2016.

LEVISKI, D. S.; DUARTE, I. C. B. Família multiespécie: o animal no rompimento das relações afetivas. *(Re)pensando Direito*, Santo Ângelo/RS. v. 09, n. 18, p. 208-223, jul./dez. 2019.

MELLO, W. A.; SILVA, J. O. Sepse – A importância do laboratório clínico no diagnóstico. *Revista Multidisciplinar da saúde*, Piracicaba/SP, n. 2, p. 34-50, 2009.

MEYER, D. J.; HARVEY, J. W. *Veterinary laboratory medicine*. Philadelphia: W.B. Saunders, 2 ed., p. 373, 1998.

MOTA N. M.; RAMALDES F. M.; LEAL D. R. Estudo retrospectivo de casos de erliquiose canina atendidos no centro universitário ICESP de Brasília. *Revista ciência e saúde animal*, v.1, n.1, p. 1-14, 2019.

POWELL L. L. Sepsis/SIRS. Western Veterinary Conference. Disponível em: <http://www.vin.com/Proceedings/Proceedings.plx>. Acessado em 28 mai. 2020.
RABELO, R. C. *Estudio y valor pronóstico de los parâmetros relacionados con supervivência em clínica de urgencias de pequenos animales: estudio multicêntrico.* 2008. Tese (Doutorado) – Universidad Complutense de Madrid, Madrid, 2008.

RODRIGUES, M. D.; ESCAPILATO, P. B.; OLIVEIRA, N. A.; MENOLLI, K. A. P. Gastroenterite canina: principais agentes etiológicos. *Ciência veterinária UniFil*, v.1, n.2, p. 1-12, 2018.

RUDD, K. E.; SEYMOUR, C. W.; ALUISIO, A.R. et al., Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries. *JAMA*, v. 319, n. 21, p. 2202-2211, 2018.

SALES JUNIOR, J. A. L.; DAVID, M. C.; HATUM, R. et al., Sepse Brasil: estudo epidemiológico da sepse em Unidades de Terapia Intensiva brasileiras. *Rev. bras. ter. intensiva*, São Paulo, v. 18, n. 1, p. 9-17, Mar. 2006.

SALES M. R. R. P.; IGNACCHITI M. D. C.; JUNIOR A. F. M. et al., Prevalência de *Ehrlichia canis* pela *Nested*-PCR, correlação com a presença de mórula e trombocitopenia em cães atendidos no Hospital Veterinário da Universidade Federal do Espírito Santo. *Revista Brasileira de Medicina Veterinária,* v. 37, n.1, p. 47-51, 2013.

SILVERSTEIN, D.; SANOTORO-BEER, K. Síndrome da resposta inflamatória sistêmica (SRIS). In: RABELO, R. C. (editor). *Emergências de pequenos animais: condutas clínicas e cirúrgicas no paciente grave.* Rio de Janeiro: Elsevier, 1 ed., cap. 19, p. 444-450, 2012.

SINGER, M.; DEUTSCHMAN, C. S.; SEYMOUR, C. W. et al., The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association,* v. 315, n. 8, p. 801-810, 2016.

TRAUTWEIN L. G. C.; SANT´ANNA M. C.; JUSTINO R. C.; MARTINS M. I. M. Guia revisado sobre o diagnóstico e prognóstico da piometra canina. *Revista oficial Colégio Brasileiro de cirurgia e anestesiologia veterinária (CBCAV),* v.17, n.1, p. 16-23, 2018.

VIEIRA, F. T. *Ocorrência de Ehrlichia spp., Anaplasma spp., Babesia spp., Hepatozoon spp., e Rickettsia spp. em cães domiciliados em seis municípios do estado do Espírito Santo, Brasil.* 2017. Tese (Doutorado em doenças infecciosas). Universidade Federal do Espírito Santo (UFES), 2017.

ANNEX I

Altered consciousness	Glasgow Coma Scale < 17 or ADDN less than A
Threatening hypotension	Abrupt drop greater than 40 mmHg in SBP, or a MAP < 65 mmHg or SBP < 90 mmHg in dogs or < 100 mmHg in cats
Oliguria	Urine output < 0.5 mL/kg/h or creatinine >2.0 mg/dL
Respiratory dysfunction	PaO2/FiO2 < 300 or severe signs plus bilateral infiltrate
Coagulation	Thrombocytopenia (<100,000/mm³ or 50% drop in 12h), increased PT/APTT/D-dimer or decrease in fibrinogen
Paralytic ileus	absence of noises on auscultation
Hyperlactatemia	> 3.2 mmol/L in dogs or >2.5 mmol/L in cats
Hyperbilirubinemia	> 0.5 mg/dL

Source: Castro and Rabelo, 2017.

ANNEX II

Table 5. Association of all clinical and laboratory data with animal survival.

Variables	Survival N (%)		p=Value
	Alive	Deaths	
Age			0.694
< 1 year	18 (14.17%)	2 (1.57%)	
1-7 years	56 (44.1%)	3 (2.36%)	
> 7 years	44 (34.64%)	4 (3.15%)	
Temperature			0.863
Normal	75 (59.05%)	6 (4.7%)	
Changed	43 (33.8%)	3 (2.36%)	
FC			
Normal	53 (41.7%)	7 (5.5%)	0.119
Changed	65 (51.2%)	2 (1.6%)	
FRI			0.587
Normal	13 (10.2%)	1 (0.78%)	
Changed	105 (82.6%)	8 (6.3%)	
Leukocytes			**0.042**
Normal	15 (11.8%)	0	
Lightweight	67 (52.7%)	3 (2.36%)	
Moderate	27 (21.2%)	3 (2.36%)	
Grave	9 (7.1%)	3 (2.36%)	
Neutrophils, Segmented			0.850
Normal	43 (33.8%)	4 (3.15%)	
Neutropenia	20 (15.74%)	1 (0.78%)	
Neutrophilia	55 (43.3%)	4 (3.15%)	
Neutrophils Rods			0.703
Normal	103 (81.1%)	8 (6.29%)	
Changed	15 (11.8%)	1 (0.78%)	
Toxic Neutrophils			0.072
Normal	108 (85%)	6 (4.72%)	
Changed	10 (7.87%)	3 (2.36%)	
Platelet			0.502
Normal	53 (41.7%)	4 (3.15%)	
Lightweight	36 (28.3%)	1 (0.78%)	
Moderate	15 (11.8%)	2 (1.57)	
Grave	14 (11%)	2 (1.57%)	
Urea			**< 0.001**

Normal	90 (70.8%)	4 (3.15%)	
Lightweight	20 (15.7%)	1 (0.78%)	
Moderate	8 (6.3%)	3 (2.6%)	
Grave	0	1 (0.78%)	
Creatinine			**0.003**
Normal	105 (82.6%)	4 (3.15%)	
Lightweight	8 (6.3%)	3 (2.36%)	
Moderate	3 (2.36%)	1 (0.78%)	
Grave	2 (1.57%)	1 (0.78%)	
OLD			0.061
Normal	95 (74.8%)	4 (3.15%)	
Lightweight	12 (9.45%)	3 (2.36%)	
Moderate	3 (2.36%)	1 (0.78%)	
Grave	8 (6.3%)	1 (0.78%)	