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A comparative study of Procalcitonin with C-reactive Protein, and total Leucocytes count in septic-systemic inflammatory response syndrome in dogs.

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Canine procalcitonin (PCT) is a novel marker which found to be increased dramatically in severe sepsis as well as c-reactive protein (CRP) and total leukocyte count are the most commonly used biomarkers of inflammation in veterinary clinical diagnosis. This study aimed to evaluate the diagnostic value of canine procalcitonin compared with CRP and total leucocyte count in septic-systemic inflammatory response syndrome (SIRS), differential leucocyte count and protein profile. Twenty-four (24) dogs were included in this study (14 male, 10 female), classified into a healthy control group (15 dogs) with mean age 10.66 months and septic-SIRS group (9 dogs) with mean age 9.27 months. All dogs were subjected to a complete physical examination, blood culture, total and differential leukocyte count, protein profile and estimation of serum concentration of PCT and CRP. Physical examination revealed fever, tachycardia, and tachypnea. *Escherichia coli* and *staph. aureus* were the most common isolates in blood culture. The leucogram activity revealed significant leukocytosis ($p \leq 0.05$) associated with a significant increase in both absolute segmented and band neutrophil counts ($p \leq 0.05$).Protein profile showed significant hypoalbuminemia ($p \leq 0.05$). Procalcitonin level showed a highly significant increase ($p \leq 0.001$) in comparison with CRP concentration and leucocyte count which showed a low significant increase ($p \leq 0.05$) in the septic-SIRS group compared to the healthy group. In conclusion, procalcitonin is a superior diagnostic biomarker of inflammation in the septic-SIRS group compared with C- reactive protein and leucocyte count.

Keywords: Procalcitonin, CRP, Leucocyte count, septic-SIRS, dog.

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is an inflammatory state affecting the whole body, mostly a response of the immune system to infection. Systemic inflammatory response syndrome may be the body's response to an infectious or noninfectious insult. Although the definition of SIRS refers to an "inflammatory" response, it actually has pro- and anti-inflammatory components (Tsumura et al., 2004).

Accurate and time for diagnosis of infectious-SIRS remains challenging to the clinician. Clinical signs of systemic inflammation, including changes in body temperature, tachypnea, tachycardia, and leucocytosis are sensitive. However, their use is limited because of their poor specificity for the diagnosis of sepsis (Kofoed et al., 2007).

A positive culture result has a relatively high specificity for infection, but even this finding is not the gold standard, because it lacks sensitivity and the results are only available after 2 to 3 days (Christ-Crain and Müller, 2005).

Delays in identifying the pathogens based on the specimen cultures add to the difficulty in establishing an etiological diagnosis and leads to inappropriate use of antibiotics. In addition, estimation of the severity of bacterial infection is based mainly on the presence of criteria of systemic inflammatory response syndrome, which may not be apparent in the early course of the infection (Hausfater et al., 2007).

In veterinary medicine, there are still no specific biomarkers for sepsis and many studies are in progress to find a reliable diagnostic and prognostic marker of sepsis in various animal species (De Clue et al., 2011).

The acute phase reaction (APR), is a nonspecific response that occurs after infection, inflammation or neoplasia. During the APR, C-reactive protein increase before clinical signs appear which has been used as a marker for the prognosis and diagnosis of several critical illnesses in dogs (Schmidt and Eckersall, 2015).

Procalcitonin (PCT), the precursor of the hormone calcitonin, is produced and secreted by thyroid C cells. During infection and septicemia, there is an increase in PCT circulating levels. Production of PCT is regulated by proinflammatory cytokines produced by extrathyroidal organs such as lung, liver, pancreas, and colon. (Oğuz and Alkım, 2017).

Advantages of PCT as a serum biomarker for sepsis include absence in healthy individuals, rapid induction with the onset of sepsis and a moderately long half-life. Marked elevation in serum PCT is used to distinguish patients with severe bacterial, fungal or parasitic infections from those with severe non-septic SIRS to guide and shorten the course of antimicrobial treatment and to prognosticate outcome (Schuetz et al., 2011).

This investigation aimed to study the diagnostic value of canine procalcitonin compared with CRP and total leucocyte count and evaluation of differential leucocytic count and protein profile in septic-SIRS in dogs.

MATERIALS AND METHODS

Twenty-four dogs of different breeds (8 *German shepherd,* 4 *Labrador*, 3 *Rottweiler*, 3 *Golden retrievers*, 2 Husky, 2 *Pit-bull*, 1 *Mastiff*, and1 *Griffon*), sexes (14 males, 10 females) and ages ranging from 3 months to 2 years presented at small animal clinic, Faculty of Veterinary Medicine, Cairo University, Egypt between (September 2017 and September 2018).

Study design

Dogs under investigation were exposed to a comprehensive clinical examination and were classified to apparently healthy group (15 dogs, 9M/ 6F with ages ranging from 3 months to 2 years) and septic-SIRS group (9 dogs, 5M/ 4F with ages ranging from 3 months to 2 years) which at least has 2 of the following criteria: hyperthermia, tachycardia, tachypnea, leucocytosis with band cells > 3%. Collected venous blood samples from all examined groups were divided into three portions. The first part was collected on tubes containing ethylene-diamine-tetra-acetic acid (EDTA) for total and differential leukocyte count. The second part was collected in plain tubes for serum separation for canine PCT, CRP and protein profile analyses. The third part was collected on blood culture medium for determination and isolation of bacteria in septic-SIRS in dogs.

Total and differential leukocyte counts were carried out according to the method described by (Feldman et al., 2000). Enriched blood samples were cultured onto sheep blood agar, mannitol salt agar and onto MacConkey agar. Then the plates were incubated for 24-48 hr at 37°C. Colonies were identified as β hemolytic on blood agar, mannitol fermenting (yellow) colonies on mannitol salt agar and lactose fermenting colonies on MacConkey agar. The suspected colonies were picked up and tested for bacterial morphological features and Gram's stain characteristics as described by (Quinn et al., 2011).

Serum total protein and albumin levels were determined spectrophotometrically (total protein and albumin kits; Spectrum Company, Egypt) with a globulin concentration calculation and A/G ratio as described by (Kaneko et al., 2008). Serum CRP concentration was determined by a semi-quantitative method based on a principle of agglutination (Slide test for C- reactive protein kit; VITRO SCIENT, Egypt) according to (Jensen and Kjelgaard-Hansen 2006). Procalcitonin concentrations were measured by using canine-specific procalcitonin ELISA kit (Canine Procalcitonin ELISA Kit, KORAIN BIOTECH CO., LTD, China) as described by (Goggs et al., 2018).

Statistical methodology

The obtained data were analyzed using the SPSS software package for Windows Ver. 20.0 (SPSS Inc., Chicago, IL, USA) and tabulated as mean value ± SE at levels of significance $p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$. The P value of $p \leq$

0.001 was considered highly statistically significant.

RESULTS

The clinical examination results are shown in the table (1) revealed no significant difference was detected in age, sex and breeds between the healthy control group and septic-SIRS group.

Results are shown in the table (1). The most clinical signs observed during physical examination of septic-SIRS group significant hyperthermia (p≤ 0.001), tachycardia (p≤ 0.001) as well as significant tachypnea (p≤ 0.001) compared to healthy control group.

The bacteriological culture showed β hemolytic on blood agar and mannitol fermenting (yellow) colonies on mannitol salt agar specific for coagulase positive *Staphylococci (Staph. aureus*) also, showed lactose fermenting colonies on MacConkey agar specific for isolation of *Escherichia coli (E-coli).*

Direct microscopic examination results of suspected picked colony stained with Gram's stain revealed gram-positive (blue colony) cocci resemble clusters of grapes characteristics for *S. aureus* and gram-negative (pink colony) bacilli reveal *E-coli.*

The leucogram activity of examined dogs revealed significant leucocytosis (p≤ 0.05) associated with significant increase in both absolute segmented and band neutrophil counts (p≤ 0.05) in the septic-SIRS group compared to healthy control group as shown in the table (2).

Protein profile analysis showed statistical significant hypoalbuminemia (p≤ 0.05) in the septic-SIRS group compared to healthy control group as shown in the table (3).

The evaluation of inflammatory biomarkers showed a highly significant increase in PCT level (p≤ 0.001) in comparison with CRP and total leucocyte count which revealed low significant increase (p≤ 0.05) in the septic-SIRS group as shown in the table (4)

Table (1).Clinical examination of the septic-SIRS group compared to the healthy control group.

Variables	Control (n=15) Mean± SE	Septic-SIRS (n=9) Mean± SE
Age (months)	10.66 ± 1.90	9.27 ± 2.49
Sex (M/F)	9/6	5/4
Physical examination:		
Temperature(◦C)	38.8 ± 0.13	40.1±0.1[a]
Pulse (bpm)	113.2± 2.5	142.2± 3.5[a]
Respiratory rate (min.)	18.8± 1.53	35.9 ± 2.7[a]

a: p ≤ 0.001 b: p ≤ 0.01 c: p≤0.05

Table (2). Leucogram profile of septic-SIRS group compared to the healthy control group.

Parameters	Control (n = 15) Mean± SE	septic-SIRS (n=9) Mean± SE
WBCS (10^3/mm^3)	7.91 ± 0.68	15.50 ± 2.73 [c]
Absolute Neutrophil count (10^3/mm^3)	5.16 ± 0.56	12.29 ± 2.12 [c]
Neutrophil percent (%)	67.14 ± 1.62 %	80.16 ± 2.32 %
Absolute band Neutrophil count (10^3/mm^3)	0.17 ± 0.03	0.64 ± 0.14[c]
Band percent (%)	2.60 ± 0.50 %	3.25 ± 0.62 %

a: p ≤ 0.001 b: p ≤ 0.01 c: p ≤0.05

Table (3). Protein profile of the septic-SIRS group compared to the healthy control group.

Parameters	Control (n = 15) Mean± SE	septic-SIRS (n=9) Mean± SE
Total protein (g/dl)	5.66 ± 0.33	5.31 ± 0.39
Albumin (g/dl)	2.52 ± 0.05	2.12 ± 0.21[c]
Globulin (g/dl)	3.25 ± 0.27	3.12 ± 0.24
A:G ratio	0.77 ± 0.51	0.68 ± 0.04

a: p ≤ 0.001 b: p ≤ 0.01 c: p ≤0.05

Table (4). PCT in comparison with CRP and total leucocyte count of the septic-SIRS group compared to the healthy control group.

Parameters	Control (n = 15) Mean± SE	Septic-SIRS (n=9) Mean± SE
PCT (ng/ml)	1.15 ± 0.29	3.66 ± 0.47[a]
CRP (mg/l)	6.50 ± 0.50	12.00 ± 4.24[c]
WBCS (10^3/mm^3)	7.91 ± 0.68	15.50 ± 2.73 [c]

a: p ≤ 0.001 b: p ≤ 0.01 c: p ≤0.05

DISCUSSION

Identifying a true ‘‘gold standard’’ for the diagnosis of septic-SIRS in dogs is often problematic as blood culture takes a long time to obtain positive cultures and contamination issues. In addition to the inability of certain bacteria to grow in standard cultures (Mandell et al., 2007).The current study showed no significant difference between healthy control group and septic-SIRS group in age, sex, and breeds which came in accordance to (Andreola et al., 2007; Kocaturk et al., 2010 and El-Azeem et al., 2013).

Regarding clinical examination of septic-SIRS in dogs, animals were suffering from fever, tachycardia and tachypnea which consistent to Carcillo et al., (2006) who stated that the earliest clinical sign of clinical infection changes in body temperature. Tachycardia and/or tachypnea are a useful sign of sepsis. Fever may be responsible for tachycardia, as each 1°C increase can result in an increase in heart rate of 10% and possibly respiratory rate. Also, agreed with Kilpatrick et al. (2016) who mentioned that dogs should be considered to have SIRS when they met each of the following criteria: respiratory rate greater than 20 min, heart rate greater than 120 min and rectal temperature less than 38.1°C or greater than 39.2°C.

Bacteriological culture in the septic-SIRS group showed β hemolytic on blood agar and mannitol fermenting (yellow) colonies on mannitol salt agar specific for *Staph. aureus* also, showed lactose fermenting (pink) colonies on MacConkey agar specific for isolation of *E-coli* which came in accordance to Hatherill et al., (1999) who reported that common etiologies of sepsis and septic shock are gram-negative bacteria as *E-coli* and *Enterobacter* spp and gram-positive bacteria as Coagulase-positive *Staphylococcus (Staph. aureus*). The most frequently isolated microorganism was *Staphylococcus aureus* among infectious SIRS Ahmadinejad et al., (2009). Also, agreed with Arora et al., (2016) who listed microbiological isolates encountered in bloodstream infections include *Staph. aureus* and *E-coli* as the most common isolates.

Microscopic examination of picked colony stained with Gram's stain revealed gram-positive (blue colony) cocci resemble clusters of grapes characteristics for *S. aureus* and gram-negative (pink colony) bacilli reveal *E-coli* which agreed with Lappin and Turnwald, (2004).

According to our study, leucogram activity in septic-SIRS in dogs responded by leucocytosis along with an increase in both absolute segmented and band neutrophil counts which agreed with Andonova et al., (2017). Torrente et al., (2015) stated that two important indications of systemic inflammation in dogs include: neutrophilia (>16.0 × 10^6 cells/µL), neutropenia (<6.0×10^6 cells/µL), or left shift in neutrophils

(band cells >3%). Also, Gommeren et al*.,* (2018) recorded that the clinical diagnosis of SIRS is based on defined changes in hematologic parameters: leukocyte counts (>16000 or <5000 $x10^6$ cells/µl) or presence of a left shift (bands >3%). Lovewell et al., (2014) explained leukocytosis by transmigration of these inflammatory cells from the bloodstream to the site of infection is a result of the strong inflammatory response against septic infection. Also, (Aird, 2001; Hack and Zeerleder, 2001) reported that once inflammation had triggered, the response leads to secretion of pro- and anti-inflammatory cytokines, activation and mobilization of leukocytes which lead to leukocytosis.

Protein profile showed significant hypoalbuminemia which came in accordance to Nakamura et al., (2008) who stated that albumin concentration decreases significantly in dogs with experimentally induced inflammation. Also, Tvarijonaviciute et al., (2011) reported that the response to endotoxin in dogs showed decreased concentrations of albumin demonstrating its role in systemic inflammation and behavior as negative acute phase proteins. Throop et al., (2004) mentioned that inflammation is a well-known cause of hypoalbuminemia. During inflammation, cytokines as TNF and IL-1 serve to shunt amino acids towards proteins essential to the inflammatory process (positive acute phase proteins) as C - reactive protein and fibrinogen leading to decrease in negative phase proteins like albumin. In dogs, inflammation showed a mild to moderate decrease in albumin level.

Serum canine PCT significantly increased which came in accordance with Andonova et al., (2017) who mentioned that serum PCT values in infected septic dogs were increased progressively. Joo et al., 2011 and Lika et al., 2013 stated that several animal studies showed an increase in the concentration of PCT during serious infection and induced endotoxemia. Also, Yılmaz et al., (2008) reported that PCT rose as a response to endotoxemia in dogs. Kuzi et al., (2008) mentioned that PCT was used to be a diagnostic and prognostic marker in diseased dogs. Fortunato (2016) stated that PCT concentrations increase at the onset of bacterial infection and correlate with the severity of the infection.

In healthy adults, PCT concentrations generally remain below 0.05ng/ml and increase rapidly within 2–4 hrs in case of systemic bacterial infection (<0.25 to <0.5 ng/ml), sepsis (>0.5 to >2 ng/ml) and severe sepsis (≥2 to ≤ 10ng/ml). Müller et al., (2010) mentioned that PCT was increased significantly in bacteremic patients compared with patients without an identified bacterial pathogen. Besides, Castelli et al., (2006) stated that researches in humans have shown that PCT levels were significantly higher in septic shock and severe infectious diseases compared with noninfectious inflammatory diseases and were diagnostically superior to C-reactive protein.

Regards CRP results showed a low significant increase in the septic-SIRS group as reported by Tvarijonaviciute et al., (2011). Watterson et al., (2009) stated that CRP is one of the major APPs in dogs in which an inflammatory response was monitored. Murata et al., (2004) observed that acute-phase proteins (APPs) are released as a chemical and cellular response to injury as mediators in the inflammatory cascade. CRP increases transiently but long enough to allow detection, thus reflecting a real-time response. Inflammatory biomarkers showed a highly statistically significant increase in PCT level ($p \leq 0.01$) along with low statistical significant increase in CRP and leucocyte count ($p \leq 0.05$) which came in accordance with Vatcheva-Dobrevsky and Ramshev, (2004). They stated that CRP serum level and the leucocyte count associated strongly with bacteremia but lesser degree than PCT. CRP is a very sensitive marker of inflammation, but cannot be used in differentiating bacterial from other inflammation as it shows a significant elevation in such cases as well as in the case of viral infections. Canine procalcitonin is a more specific and sensitive marker of systemic bacterial infection than acute phase protein such as CRP.

Lopez et al., (2003) recorded that both PCT and CRP were found to perform better than leucocyte count in detecting invasive infections; in addition, PCT displayed higher diagnostic accuracy than did CRP. Also, came in accordance with Andreola et al., (2007) who stated that both PCT and CRP are valuable markers in predicting severe bacterial infection and they perform better than Leucocyte count. Latimer et al., (2003) stated that although PCT is expected to be a sensitive marker of inflammation, leucocyte, and neutrophil counts are less sensitive because their numbers may be lower or higher than or within a reference interval, depending on the disease, its stage and severity and other factors (e.g., stress, anxiety, age).

CONCLUSION

In conclusion; Canine procalcitonin measurement displayed higher diagnostic

accuracy than either C-reactive protein or the leucocyte count in detecting septic-SIRS in dogs.

CONFLICT OF INTEREST

The authors declare that the present study has no conflicts of interest or financial ties to disclose.

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AUTHOR CONTRIBUTIONS

The present study was the Ph.D. thesis of AHJ. AHJ collected the samples, performed the analysis and draft the manuscript. AA, GM, and SI were supervisors of the study and participated in its design and coordination, helped to draft the manuscript, interpreted the data, revised and approved the final revision.

REFERENCES

Ahmadinejad Z, et al., 2009. Diagnostic accuracy of procalcitonin in sepsis. Acta Medica Iranica 47(5).

Aird WC, 2001. Vascular bed-specific hemostasis: the role of endothelium in sepsis pathogenesis. Crit Care Med 29: S28–S34; discussion S-5.

Andonova M, Slavov E, Dzhelebov P, Urumova V, Dimitrova D, Lyutskanov M, 2017. Effects of feverfew (*Tanacetum parthenium*) and antibiotic coadministration on blood neutrophil function and serum procalcitonin in dogs with experimental subcutaneous *pseudomonas aeruginosa* infection. The J Anim Plant Sci 27(2): 430-438.

Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L, 2007. Procalcitonin and C-Reactive Protein as Diagnostic Markers of Severe Bacterial Infections in Febrile Infants and Children in the Emergency Department. Pediatr Infect Dis J 26: 672–677.

Arora R, James P, Campbell, Simon G, Sahni N, 2016. Does serum procalcitonin aid in the diagnosis of bloodstream infection regardless of whether patients exhibit the systemic inflammatory response syndrome? Infection 45(3):291-298. DOI 10.1007/s15010-016-0965-0.

Carcillo JA, Planquois JM, Goldstein B, 2006. Early markers of infection and sepsis in newborns and children. Adv Sepsis 5: 118–125.

Castelli GP, Pognani C, Cita M, et al., 2006. Procalcitonin, C-reactive protein, white blood cells and SOFA score in ICU: diagnosis and monitoring of sepsis. Minerva Anestesiol 72: 69–80.

Christ-Crain M, Muller B, 2005. Procalcitonin in bacterial infections – hype, hope, more or less? Swiss Med Wkly 135 (31/31): 451- 460.

De Clue AE, Osterbur K, Bigio A and Sharp CR,2011. Evaluation of serum NT-pCNP as a diagnostic and prognostic biomarker for sepsis in dogs. J Vet Intern Med 25:453-459.

El-Azeem AA, Hamdy G, Saraya M, Fawzy E, Anwar e E, Abdulattif S, 2013. The role of procalcitonin as a guide for the diagnosis, prognosis, and decision of antibiotic therapy for lower respiratory tract infections. Egypt J Chest Dis Tuberc 62: 687–695.

Feldman BF, Zinkl JG, Jain NC, Gasper PE, 2000. Schalm's Veterinary Haematology, 5th Ed., Wiley Blackwell Publishing, Ames, Iowa, USA, pp 504-507.

Fortunato A, 2016. A new sensitive automated assay for procalcitonin detection: LIAISON BRAHMS PCT II GEN. Pract Lab Med 6: 1–7.

Goggs R, Milloway M, Troia R and Giunti M, 2018. Plasma procalcitonin concentrations are increased in dogs with sepsis. Vet Rec Open 5:e000255.

Gommeren K, Desmas I, Garcia A, Bauer N, Moritz A, Roth J, Peeters D, 2018. Inflammatory cytokine and C-reactive protein concentrations in dogs with systemic inflammatory response syndrome. J Vet Emerg Crit Care 28(1): 9–19.

Hack CE, Zeerleder S, 2001. The endothelium in

sepsis: a source of and a target for inflammation. Crit Care Med 29: S21–S27.

Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA, 1999. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. Arch Dis Child 81:417–421.

Hausfater P, Juillien G, Madonna-Py B, Haroche J, Bernard M, Riou B, 2007. Serum procalcitonin measurement as a diagnostic and prognostic marker in febrile adult patients presenting to the emergency department. Crit Care 11(3): R60.

Jensen AL and Kjelgaard-Hansen M, 2006. Method comparison in the clinical laboratory. Vet Clin Pathol 35:276-286.

Joo K, Park W, Lim MJ, Kwon SR, Yoon J, 2011. Serum procalcitonin for differentiating bacterial infection from disease flares in patients with autoimmune diseases. J Korean Med Sci 26: 1151-1147.

Kaneko JJ, Harvey JW and Bruss ML, 2008. Clinical Biochemistry of Domestic Animals, 6thedition, Academic Press, New York, pp 881-888.

Kilpatrick S, Dreistadt M, Frowde P, Powell R, Milne E, Smith S, et al., 2016. Presence of Systemic Inflammatory Response Syndrome Predicts a Poor Clinical Outcome in Dogs with a Primary Hepatitis. PLoS ONE 11(1): e0146560.

Kocaturk M, Martinez S, Eralp O, Tvarijonaviciute A, Cerón JJ, Yilmaz Z, 2010. Prognostic value of serum acute phase proteins in dogs with parvoviral enteritis J Small Anim Pract 51: 478-483.

Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J, et al., 2007. Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study. Crit Care 11(2): R38.

Kuzi S, Aroch I, Peleg K, Karnieli O, Klement E, Dank G, 2008. Canine procalcitonie Messenger RNA expression. J Vet Diagn Invest 20: 629-633.

Lappin MR, Turnwald GH, 2004. Microbiology and infectious diseases. In: MD Willard, H Tvedten eds. In: Small animal clinical diagnosis by laboratory methods, 4th ed., Saunders, St. Louis, Missouri, pp 332-355.

Latimer KS, Mahaffey EA, Prasse KW, Duncan JR, 2003. Duncan and Prasse's veterinary laboratory medicine: clinical pathology, 4th ed, Ames (Iowa), Iowa state university press, Ames, LA.

Lika AB, Kasleci AB, Refatlari E, Allıı NH, Barbullushi AJ, Mone I, Mitre A, 2013. Serum procalcitonin levels as an early diagnostic indicator of sepsis. Mat Soc Med 25(1): 23-25.

Lopez FA, Cubells LC, Garcia GJJ, Pou FJ, 2003.Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. Pediatr Infect Dis J 22: 895–903.

Lovewell RR, Patankar YR, Berwin B, 2014. Mechanisms of phagocytosis and host clearance of Pseudomonas aeruginosa. Am J Physiol Lung Cell Mol Physiol 306(7): L591-L603.

Mandell L, Wunderink R, Anzueto A, 2007. Infectious diseases society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44: 27–72.

Müller F, Christ-Crain M, Bregenzer T, et al., 2010. ProHOSP Study group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest 138 (1): 121-129.

Murata H, Shimada N and Yoshioka M, 2004. Current research on acute phase proteins in veterinary diagnosis: an overview. Vet J 168:28–40.

Nakamura M, Takahashi M, et al., 2008. C-reactive protein concentration in dogs with various diseases. J Vet Med Sci 70:127-131.

Oğuz GH, Alkım UP, 2017. Procalcitonin is not a marker of sterile inflammation in dogs after ovariohysterectomy. Acta Vet-Beograd 67 (1):131-136.

Quinn PJ, Markey BK, Leonardo FC, Fitzpatrick ES, Fanning S, Hartigan P, 2011. Veterinary Microbiology and Microbial Disease. 2ndEd., Wiley-Blackwell, pp 143-146.

Schmidt EMS, Eckersall PD, 2015. Acute phase proteins as markers of infectious diseases in small animals. Acta Vet-Beograd 65(2):149-161.

Schuetz P, Albrich WC, Mueller B, 2011.Procalcitonin for diagnosis of infection and guide to antibiotic decisions: Past,

present, and future. BMC Med 9:107-115.
Throop JL, Kerl ME, Cohn LA, 2004. Albumin in health and disease: causes and treatment of hypoalbuminemia. Comp Cont Educ Pract 26 (12): 940-948.
Torrente C, Manzanilla EG, Bosch L, Fresno L, et al., 2015. Iron and other biomarkers in dogs with SIRS. J Vet Emerg Crit Care 25(5): 611–619.
Tsumura H, Ichikawa T, Hiyama E, Murakami Y, Sueda T, 2004. Systemic inflammatory response syndrome (SIRS) as a predictor of strangulated small bowel obstruction. Hepato-gastroenterology 51:1393-6.
Tvarijonaviciute A, Eralp O, Kocaturk M, Yilmaz Z, Cerón JJ, 2011. Adiponectin and IGF-1 are negative acute phase proteins in a dog model of acute endotoxemia. Vet Immunol Immunopathol 140: 147-151.
Vatcheva-Dobrevsky R, Ramshev K, 2004. Application of Procalcitonin (PCT) - Q Test for Early Detection of Bacteremia and Sepsis. Biotechnol Equip 18(2): 177-184.
Watterson C, Lanevschi A, Horner J, Louden C, 2009. A comparative analysis of acute-phase proteins as inflammatory biomarkers in preclinical toxicology studies: Implications for preclinical to clinical translation. Toxicol Pathol 37: 28-33.
Yılmaz Z, Ilcol YO, Ulus IH, 2008. Endotoxin increases plasma leptin and ghrelin levels in dogs. Crit Care Med 36(3): 828-833.