Acute Phase Proteins: Implications for Animal Disease Prevention and Management

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ABSTRACT

Acute phase proteins (APPs) are biomarkers that are essential for comprehending the dynamic interactions that occur within biological systems in response to infections, physiological processes, or therapeutic interventions. These proteins play a crucial role in illustrating the complex interactions that occur between cytokines, innate immune responses, and changes in serum concentrations during the acute-phase response. Although APPs are widely used in human medicine, their application in Veterinary Sciences is limited. Current research has identified about 40 distinct APPs in different species. The role of APPs in food safety, drug development, and general animal welfare, beyond disease management, calls for identifying APPs in animals. A comprehensive strategy combining biomarker measurements with other diagnostic tools for improved clinical precision is required. The review explores the complex role that APPs, especially C-reactive protein, serum amyloid A, haptoglobin, and alpha-1 acid glycoprotein, play in animal health, emphasizing their importance in prognosis, diagnosis, and therapeutic monitoring and highlights the importance of finding new biomarkers for proactive healthcare management.

Keywords*:* APPs, Biomarkers, C-reactive protein, Cytokines

INTRODUCTION

Biomarkers represent critical indicators of normal physiological functions, infection responses, or reactions to pharmacological interventions within a biological system (Strimbu and Tavel, 2010). They provide valuable insights into the complex interactions between living organisms and various biological, physical, or chemical hazards. The significance of biomarkers lies in their ability to aid in disease diagnosis, study prognosis, monitor overall health, and assess responses to therapeutic interventions. One notable advantage of utilizing biomarkers is their capacity to offer a non-invasive or minimally invasive method for determining the health status of animals, requiring less expertise compared to other diagnostic techniques. Examples of biomarkers encompass diverse indicators such as changes in pulse rate or the analysis of blood and tissue samples. Notably, acute-phase proteins (APPs) are a crucial class of biomarkers, exhibiting substantial variations in concentration in response to injury, trauma, stress, or infection (Figure 1) (Gabay and Kushner, 1999). Defined as conserved plasma proteins, APPs play a pivotal role in maintaining homeostasis (Schrödl *et al.* 2016). APPs, in response to pro-inflammatory cytokines (Kushner, 1993), showing a significant shift of more than 25% in their concentration (Eckersall and Bell, 2010). This intricate interplay between the innate immune response, cytokines, and the subsequent alterations in serum concentrations of APPs underscores the dynamic nature of biomarker responses, forming a foundational aspect of comprehensive health assessment. In this context, this review paper sets the stage for exploring the multifaceted role of biomarkers in understanding and monitoring the health dynamics of animals.

The classification of APPs is essential for understanding their diverse roles in the body's response to various stimuli, such as infection,

trauma, or inflammation. These proteins can be categorized into positive and negative APPs (Jain *et al.,* 2011), based on their respective increase or decrease in concentration (Table I) during the acute-phase response. This classification helps characterize the direction of change in protein levels, providing valuable information about the nature and severity of the underlying condition.

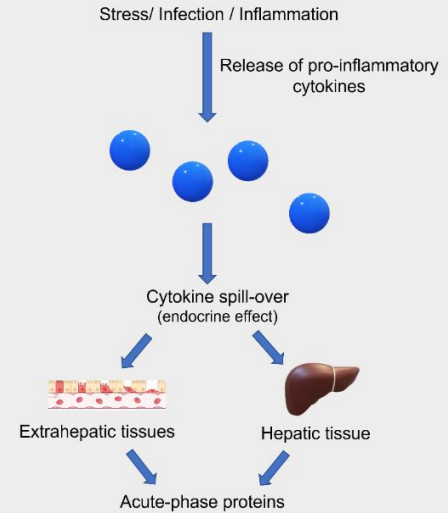

Figure 1: Dynamic response: Acute-phase reaction triggered by injury, trauma, stress, or infection, leading to fluctuations in acute-phase protein concentrations.

Table I: Classification of Acute-Phase Proteins based on changes in concentration (Jain *et al.* 2011)

Type of APP	Response to Stimulus	Examples
Positive APPs	Increase in Concentration	C-reactive protein (CRP), Serum Amyloid A (SAA), Haptoglobin, Fibrinogen, etc.
Negative APPs	Decrease in Concentration	Albumin, Transferrin, Retinol-binding protein, etc.

Based on the mode of action, these APPs are classified as described in Table II. Despite the well-established use of APPs as biomarkers in human medicine, their animal utilization has been relatively limited. However, ongoing research continues to identify and characterize approximately 40 different APPs in various animal species (Schrödl *et al.* 2016). The primary production site for these proteins is the liver, but in certain instances, tissue-specific responses can lead to their extrahepatic secretion. This focal effect on tissue injury or trauma results in the release of APPs into distal or interstitial fluid, contributing to their systemic impact (Schrödl *et al.* 2016). The most common APPs used as animal biomarkers are C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, and A-1 acid glycoprotein. The normal biological function of these APPs is mentioned in Table III and their activity as biomarkers is described in Table IV in different families of the animal kingdom.

Table II: Classification of APP based on their mode of action (Jain *et al.* 2011)

Protease inhibitors	Alpha 1 antitrypsin, alpha 1 anti-chymotrypsin.
Coagulation proteins	Fibrinogen, prothrombin.
Complement proteins	C2, C3, C4, C5
Transport proteins	Hp, hemopexin.
Other proteins	CRP, SAA, SAP, and acid glycoprotein

Table III: Normal biological function of some selected animal APPs.

Acute phase protein	Biological Functions	Sources
C-reactive protein	Complement activation, Opsonization, Cytokine secretion, Chromatin binding, Binds to Fc receptors	Ballou and Lozanski, 1992; Du Clos, 2000
Serum Amyloid A	Induced cytokine release, Chemoattractant property, Cholesterol transportation, Inhibits oxidative burst in neutrophils, Opsonization, induces migration of phagocytes, Activates NLRP3 inflammasome, Induces calcium mobilization by monocytes	Ye and Sun, 2015; Sack Jr., 2018
Haptoglobin	Binds to Haemoglobin, Antibacterial activity, Antioxidant property, Role in lipid metabolism, Immunomodulatory effect, Inhibition of Nitric Oxide Stimulates angiogenesis	Dobryszycka, 1997; Wassell, 2000
Alpha (1)-acid glycoprotein	Immunomodulatory effect Anti-inflammatory effect	Hochepied *et al.,* 2003; Ceciliani and Lecchi, 2019

Furthermore, APPs may exist in different proteoforms, demonstrating variations in their molecular structure. Separation based on properties such as isoelectric point allows for a more detailed characterization of these proteins, contributing to a comprehensive understanding of their roles in health and disease. Profiles of some common APPs in different groups of animals under diseased conditions are presented in Table IV. Additionally, the kinetics of APP release vary among different species, leading to distinct patterns of APP expression (Cray, 2012; Pradeep, 2014), emphasizing the importance of considering these variations in veterinary and biomedical research.

Table IV: Use of biomarkers for disease identification in different families of animals.

APP	Bovine	Canine	Swine	Feline
CRP	Not a major APP	Babesiosis (Matijatko *et al.,* 2002), Leishmaniosis (Martinez-Subiela *et al.,* 2011), Leptospirosis (Caspi *et al.,* 1987; Yamamoto *et al.,* 1993), Parvovirus infection (Yamamoto *et al.,* 1993), *E.coli* sepsis (Hulton *et al.,* 1985), Trypanosomiasis (Ndung'u *et al.,* 1991), *Ehrlichia canis* infection (Rikihisa *et al.,* 1994)	Not a significant APP	Not a substantial APP for cats
SAA	Bovine respiratory syncytial virus infection (Heegaard *et al.,* 2000), Mastitis (Grönlund *et al.,* 2003; Gerardi *et al.,* 2009), Bovine viral	Familial amyloidosis in Shar-pei dogs (DiBartola *et al.,* 1990), Parvovirus infection (Yule *et al.,* 1997), Leishmaniosis (Martínez-Subiela and	Surgery (Hernandez-Richter *et al.,* 2001)	Marker of inflammatory disorders (Sasaki *et al..* 2003; Hansen *et al.,* 2006), Urinary tract disease (Sasaki *et al.,* 2003), Familial amyloidosis in Siamese and Abyssian cats

	diarrhoea (Gånheim *et al.,* 2007), *Mannheimia haemolytica* infection (Gånheim *et al.,* 2007) Bovine theileriosis (Nazifi *et al.,* 2009)	Ceron, 2002; Martinez-Subiela *et al.,* 2011)		, *epatozoonfelis* infection(Vilhena *et al.,* 2017)
Hp	*Mannheimia haemolytica* infection (Gånheim *et al.,* 2007), Foot and mouth disease (Höfner *et al.,* 1994), Metritis (Huzzey *et al.,* 2009), Mastitis (Grönlund *et al.,* 2003), *Pasteurella multocida* infection (Dowling *et al.,* 2002), Bovine viral diarrhoea (Gånheim *et al.,* 2007), Bovine respiratory syncytial virus infection (Heegaard *et al.,* 2000), Hepatic lipidosis (Guzelbektes *et al.,* 2010; Singh *et al.,* 2021)	Surgical trauma (Conner *et al.* 1988), Leishmaniosis (Martinez-Subiela *et al.,* 2011), Trypanosomiasis (Ndung'u *et al.,* 1991), Cushing's syndrome (Caldin *et al.,* 2009), Corticosteroid treatment (Arteaga *et al.,* 2010)	Experimental local aseptic inflammation (Lampreave *et al.,* 1994; Eckersall *et al.,* 1996), Intramuscular injection of lipopolysaccharide (*Escherichia coli* serotype 0.55:B5) (Dritz *et al.,* 1996), Surgery (Jacobson *et al.,* 2001), Infection with *Actinobacillus pleuropneumoniae* (serotype 1, 2 and 5) (Hall *et al.,* 1992; Heegaard *et al.,* 1998), Infection with *Toxoplasma gondii* (Jungersen *et al.,* 1999), Infection with *Mycoplasma hyorhinis* (Magnusson *et al.,* 1999), Intranasal inoculation of *Bordetella bronchiseptica* and toxigenic *Pasteurella multocida* type D (Francisco *et al.,* 1996), Infection with Porcine Reproductive and Respiratory Syndrome (PRRS) virus (Asai *et al.,* 1999)	Anemia of inflammatory diseases (Ottenjann *et al.,* 2006), *Hepatozoon felis* and *Babesia vogeli* infection (Vilhena *et al.,* 2017)
AGP	Digestive diseases (dos Santos *et al.,* 2021)	Parvovirus infection (Yule *et al.,* 1997), Babesiosis (Lobetti *et al.,* 2000), *Ehrlichia canis* infection (Rikihisa *et al.,* 1994),Lymphoma (Ogilvie *et al.,* 1993; Hahn *et al.,* 1999), Carcinoma (Ogilvie *et al.,* 1993), Sarcoma (Ogilvie *et al.,* 1993)	Not an effective marker of inflammation in this species	Peritonitis (Duthie *et al.,* 1997; Saverio *et al.,* 2007), Neoplasia (Selting *et al.,* 2000), Chronic enteropathy (Karra *et al.,* 2023), Anemia of inflammatory diseases (Ottenjann *et al.,* 2006), Feline coronavirus infection (non-symptomatic) (Giordano *et al.,* 2004; Paltrinieri *et al.,* 2007), Feline chlamydiosis (TerWee *et al.,* 1998), Feline calicivirus infection (Ter Wee *et al.,* 1997), Feline leukaemia virus (Duthie *et al.,* 1997), Feline immunodeficiency virus

				(Duthie *et al.,* 1997), Gingivostomatitis (Mestrinho *et al.,* 2020)

Quantification of APPs: The quantification of APPs is crucial in understanding the physiological responses associated with various conditions. Several techniques are employed for this purpose, including proteomic profiling and immunoassays such as Enzyme-linked immunosorbent assay (ELISA) (Satoh *et al.,* 1995; Hiss *et al.,* 2003), immunodiffusion (Lampreave *et al.,* 1994), immunoturbidometric tests (Eckersall *et al.,* 1991), and time-resolved immunofluorimetry (Parra *et al.,* 2006), but these methods have certain limitations. One major drawback is their labour-intensive nature, often requiring skilled personnel and extended processing times. Additionally, the costs associated with these techniques can be prohibitive, limiting their widespread application, especially in resource-constrained settings. Moreover, interspecies variation in the expression and response of APPs (Eckersall, 1995) poses a challenge to the uniform application of these tests across different animal species. The diverse range of species involved in veterinary medicine necessitates a more adaptable and standardized approach to ensure accurate and comparable results. Automated assays and serum protein electrophoresis are promising alternatives to address these challenges. Automated assays streamline the quantification process, reducing labour intensity and allowing for faster results. These methods often leverage advanced technologies to enhance precision and accuracy in measurement, making them more suitable for high-throughput applications.

Serum protein electrophoresis, on the other hand, provides a comprehensive view of the protein composition in a sample. This technique allows for separating different protein fractions based on their electrophoretic mobility, enabling the identification and quantification of specific proteins, including APPs (Isaza *et al.,* 2014; Cray, 2021). The advantage of serum protein electrophoresis is its ability to offer a detailed protein profile, which can be particularly valuable in disease diagnosis and monitoring. However, despite the benefits of automated assays and serum protein electrophoresis, there remains an overarching need to introduce methods that are easy to perform, cost-effective, and rapid in measuring APP levels. Efforts to innovate and refine existing techniques, integrating point-of-care technologies or novel detection methodologies, could bridge the gap between the current labour-intensive and costly methods and the practical requirements for broader applicability in diverse veterinary settings. Such advancements would not only enhance the accessibility of APP quantification but also contribute to the timely and efficient monitoring of animal health, ultimately improving the overall management and treatment of diseases in Veterinary Medicine.

Need for Identifying APPs in Animals: The study of APPs as biomarkers holds immense significance in veterinary and biomedical research, with far-reaching implications for animal health, food safety, and disease management (Gånheim *et al.,* 2007). These molecular indicators are invaluable tools in identifying and monitoring various animal health aspects. APPs play a crucial role in detecting chronic inflammation, stress levels, and infections in laboratory animals, providing essential data for research and ethical considerations (Cray *et al.,* 2009). Furthermore, the adaptability of species-specific assays for assessing food safety underscores the practical applications of APPs in ensuring the quality and safety of animal-derived products consumed by humans (Toussaint *et al.,* 1995). The early detection of

animal diseases not only aids in prompt intervention and treatment but also contributes to a more favourable prognosis, benefiting both animal welfare and public health. Additionally, incorporating biomarkers in drug development processes enhances our understanding of pharmaceutical safety and efficacy, facilitating the development of novel therapies (Strimbu and Tavel, 2010). In essence, the safety, exploration and utilization of APPs in Veterinary Sciences are indispensable for advancing our knowledge of animal health, fostering food safety, and improving overall well-being across the human-animal interface.

Limitations of using APPs as Biomarkers for disease Identification: While biomarkers, particularly acute-phase proteins (APPs), offer valuable insights into the physiological responses of organisms, their production primarily by hepatic cells introduces a limitation in their utility for disease identification. Diseases affecting the liver can hinder the production of APPs, as hepatic cells play a central role in this process. As a result, relying solely on biomarkers may not represent a conclusive endpoint in a clinical setup, especially when considering conditions that directly impact hepatic function.

To effectively harness the potential of biomarkers for clinical relevance, it is crucial to recognize that while these may provide an overview of general health, they may not capture the complexity of specific diseases or their underlying mechanisms. APPs as biomarkers necessitate a comprehensive understanding of the physiological processes associated with a particular condition, which is inherently challenging to achieve. Diseases often involve intricate interactions across multiple organ systems, making identifying a singular biomarker as a definitive diagnostic tool difficult. Furthermore, the dynamic nature of biomarker responses adds another layer of complexity. Factors such as variations in individual responses, genetic predispositions, and comorbidities can influence the reliability of APPs as biomarkers in disease identification. Additionally, APPs may lack the specificity required to differentiate between different disease states or may be affected by external factors unrelated to the primary pathology (Jain *et al.,* 2011). To provide precise and tailored treatments for diseases, it becomes imperative to supplement biomarker measurements with appropriate tests that offer a more comprehensive view of the animal's health. This multifaceted approach is essential for overcoming the limitations inherent in relying solely on a single biomarker, ensuring a more accurate and nuanced understanding of the complex landscape of diseases (Gruys *et al.,* 2006). While biomarkers serve as valuable indicators, their application in disease identification requires a judicious integration with a broader spectrum of diagnostic tools to enhance clinical precision and efficacy.

DISCUSSION

Utilizing acute-phase proteins (APPs) as biomarkers in studying animal and human diseases has proven invaluable for scientists, researchers, and physicians. The advantages of employing APPs as biomarkers include precise measurement, objective assessment, and high reliability. Notably, their ability to identify diseases before clinical manifestation is a critical feature, allowing for early intervention and improved prognosis. However, it is crucial to acknowledge the associated disadvantages of using biomarkers in a clinical setup. Challenges such as cost-effectiveness, time-consuming analyses, requisite proper storage conditions, and the inherent potential for laboratory errors underscore the need for a holistic approach in diagnostic practices. Classifying APPs into positive and negative types and awareness of species-specific differences in their expression patterns provides a foundation for unravelling the intricate dynamics of the acute-phase response. This knowledge is pivotal in advancing the use of APPs as diagnostic and

prognostic biomarkers in human medicine and veterinary practice, contributing to enhanced health monitoring and disease management in diverse animal populations. Defining and establishing normal ranges for APPs can be a complex task, further emphasizing the importance of supplementing biomarker measurements with clinical signs and other diagnostic tests. This multifaceted approach enhances sensitivity and specificity, ultimately contributing to developing a specific biosignature for infectious agents. As the current research landscape focuses on identifying new biomarkers, particularly those that can reveal diseases before clinical manifestation, the emphasis remains on improving the overall health status of animals. This endeavour extends beyond the animal kingdom, as they play a vital role in our ecosystem and are integral to human life. Recognizing the interdependence between animal health and human consumption of animal products underscores the importance of preventing diseases in animals to safeguard public health.

The critical need for early disease diagnosis in animals calls for the implementation of advanced techniques to identify additional biomarkers. These advancements will enhance our comprehension of disease dynamics and aid in the creation of improved diagnostic tools and treatments. This will help safeguard animals' health, food chain supply, and the overall ecosystem. In essence, the ongoing exploration of animal biomarkers represents a pivotal step toward proactive healthcare management, aligning with the interconnectedness of all living organisms and reinforcing the significance of early disease detection for preserving both animal and human health.

REFERENCES

Arteaga, A., N.K.Dhand, and T.McCann [2010], Monitoring the response of canine hyperadrenocorticism to trilostane treatment by assessment of acute phase protein concentrations, *J. of Small Anim. Prac.,* **51**: 204-09.

Asai, T., M.Mori and M.Okada [1999], Elevated serum haptoglobin in pigs infected with porcine reproductive and respiratory syndrome virus, *Vet. Imm. and Immunopathology,* **70**: 143-48.

Ballou, S.P. and G.Lozanski [1992], Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein, *Cytokine,* **4**: 361-68.

Boyce, J., S.P.Di Bartola and D.Chew [1984], Familial renal amyloidosis in Abyssinian cats, *Vet. Path.,* **21**: 33-38.

Caldin, M., S.Tasca and E.Carli [2009], Serum acute phase protein concentrations in dogs with hyperadrenocorticism with and without concurrent inflammatory conditions, *Vet. Clin. Path.,* **38**: 63-68.

Caspi, D., F.Snel and R.Batt [1987], C-reactive protein in dogs, *Am. J. Vet. Res.,* **48**: 919-21.

Ceciliani, F. and C.Lecchi [2019], The immune functions of α1 acid glycoprotein, *Current Protein and Peptide Sci.,* **20**: 505-24.

Conner, J., P.Eckersall and J.Ferguson [1988], Acute phase response in the dog following surgical trauma, *Res. in Vet. Sci.,* **45**: 107-10.

Cray, C. [2012], APPs in animals, *Progress in Mol. Bio. and Translational Sci.,* **105**: 113-50.

Cray, C. [2021], Protein electrophoresis of non-traditional species: A review, *Vet. Clin. Path.,* **50**: 478-94.

Cray, C., J.Zaias and N.H.Altman [2009], Acute phase response in animals: a review, *Comp. Med.,* **59**: 517-526.

Di Bartola, S., J.Reiter and J.Cornacoff [1989], Serum amyloid A protein concentration measured by radial immunodiffusion in Abyssinian and non-Abyssinian cats, *American Journal of Veterinary Research,* **50**: 1414-17.

Di Bartola, S., M.Tarr and D.Webb [1990], Familial renal amyloidosis in Chinese Shar Pei dogs, *J. Am. Vet. Med. Asso.,* **197**: 483-87.

Dobryszycka, W. [1997], Biological functions of haptoglobin-new pieces to an old puzzle, *European J. of Clin. Chem. and Clin. Biochem.,* **35**: 647-54.

dos Santos, J.F., R.O.do Rego and J.A.Bastos [2021], Hematologic response and serum and peritoneal fluid proteinogram of cattle affected by intestinal diseases and traumatic reticuloperitonitis, *Semina: Ciências Agrárias (Londrina),* **42**: 209-27.

Dowling, A., J.Hodgson and A.Schock [2002], Experimental induction of pneumonic pasteurellosis in calves by intratracheal infection with Pasteurella multocida biotype A: 3, *Res. in Vet. Sci.* **73**: 37-44.

Dritz, S., K.Owen and R.Goodband [1996], Influence of lipopolysaccharide-induced immune challenge and diet complexity on growth performance and acute-phase protein production in segregated early-weaned pigs, *J. of Anim. Sci.,* **74**: 1620-28.

Du Clos, T.W. [2000], Function of C-reactive protein, *Annals of Med.,* **32**: 274-78.

Duthie, S., P.Eckersall and D.Addie [1997], Value of α1-acid glycoprotein in the diagnosis of feline infectious peritonitis, *Vet. Record,* **141**: 299-303.

Eckersall, P. [1995], APPs as markers of inflammatory lesions, *Comp. Haem. Inter.,* **5**: 93-97.

Eckersall, P. and R.Bell [2010], APPs: Biomarkers of infection and inflammation in veterinary medicine, *The Vet. J.,* **185**: 23-27.

Eckersall, P., J.Conner and J.Harvie [1991], An immunoturbidimetric assay for canine C-reactive protein, *Vet. Res. Comm.,* **15**: 17-24.

Eckersall, P., P.Saini and C.McComb [1996], The acute phase response of acid soluble glycoprotein, α1-acid glycoprotein, ceruloplasmin, haptoglobin and C-reactive protein, in the pig, *Vet. Immu. & Immunopath.,* **51**: 377-85.

Francisco, C.J., T.R.Shryock and D.P.Bane [1996], Serum haptoglobin concentration in growing swine after intranasal challenge with Bordetella bronchiseptica and toxigenic Pasteurella multocida type D, *Canadian J. Vet. Res.,* **60**: 222.

Gabay, C. and I.Kushner [1999], Acute-phase proteins and other systemic responses to inflammation, *New England J. Med.,* **340**: 448-54.

Gånheim, C., S.Alenius and K.P.Waller [2007], APPs as indicators of calf herd health, *The Vet. J.,* **173**: 645-51.

Gerardi, G., D.Bernardini and C.A.Elia [2009], Use of serum amyloid A and milk amyloid A in the diagnosis of subclinical mastitis in dairy cows, *J. of Dairy Res.,* **76**: 411-17.

Giordano, A., V.Spagnolo and A.Colombo [2004], Changes in some acute phase protein and immunoglobulin concentrations in cats affected by feline infectious peritonitis or exposed to feline coronavirus infection, *The Vet. J.,* **167**: 38-44.

Grönlund, U., C.Hultén and P.D.Eckersall [2003], Haptoglobin and serum amyloid A in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis, *J. of Dairy Res.* **70**: 379-86.

Gruys, E., M.Toussaint and T.Niewold [2006], Monitoring health by values of APPs. *Acta Histochemica,* **108**: 229-32.

Guzelbektes, H., I.Sen M.Ok [2010], Serum amyloid A, haptoglobin concentrations and liver fat percentage in lactating dairy cows with abomasal displacement, *J. of Vet. Internal Med.,* **24**: 213-19.

Hahn, K.A., K.P.Freeman and M.A.Barnhill [1999], Serum α1-acid glycoprotein concentrations before and after relapse in dogs with lymphoma treated with doxorubicin, *J. Am. Vet. Med. Asso.,* **214**: 1023.

Hall, W.F., T.E.Eurell and R.D.Hansen [1992], Serum haptoglobin concentration in swine naturally or experimentally infected with Actinobacillus pleuropneumoniae, *J. Am. Vet. Med. Asso.,* **201**: 1730-33.

Hansen, A., M.Schaap and M.Kjelgaard-Hansen [2006], Evaluation of a commercially available human serum amyloid A (SAA) turbidimetric immunoassay for determination of feline SAA concentration, *Vet. Res. Communications,* **30**: 863-72.

Heegaard, P.M., D.L.Godson and M.J.Toussaint [2000], The acute phase response of haptoglobin and serum amyloid A (SAA) in cattle undergoing experimental infection with bovine respiratory syncytial virus, *Vet. Immu. and Immunopathology,* **77**: 151-59.

Heegaard, P.M., J.Klausen and J.P.Nielsen [1998], The porcine acute phase response to infection with Actinobacillus pleuropneumoniae. Haptoglobin, C-reactive protein, major acute phase protein and serum amyloid A protein are sensitive indicators of infection, *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology,* **119**: 365-73.

Hernandez-Richter, T., M.Wichmann and W.Schrödl [2001], The acute phase response following implantation of triclosan-bonded vascular prostheses, *Clin. and Exp. Med.,* **1**: 35-41.

Hiss, S., S.Knura-Deszczka G.Regula [2003], Development of an enzyme immuno assay for the determination of porcine haptoglobin in various body fluids: testing the significance of meat juice measurements for quality monitoring programs, *Vet. Imm. and immunopathology,* **96**: 73-82.

Hochepied, T., F.G.Berger and H.Baumann [2003], α1-Acid glycoprotein: an acute phase protein with inflammatory and immunomodulating properties, *Cytokine and Growth Factor Reviews,* **14**: 25-34.

Höfner, M., M.Fosbery and P.Eckersall [1994], Haptoglobin response of cattle infected with FMD virus, *Res. in Vet. Sci.,* **57**: 125-28.

Hulton, N., D.Johnson and D.Wilmore [1985], Limited effects of prostaglandin inhibitors in E. coli sepsis, *Surgery,* **98**: 291-97.

Huzzey, J. T.Duffield and S.LeBlanc [2009], Haptoglobin as an early indicator of metritis, *J. of Dairy Sci.,* **92**: 621-25.

Isaza, R., E.Wiedner and S.Hiser [2014], Reference intervals for acute phase protein and serum protein electrophoresis values in captive Asian elephants (Elephas maximus), *J. of Vet. Diagnostic Investigation,* **26**: 616-21.

Jacobson, M., J.E.Lindberg and R.Lindberg [2001], Intestinal cannulation: model for study of the midgut of the pig, *Comparative Med.,* **51**: 163-70.

Jain, S., V.Gautam and S.Naseem [2011], Acute-phase proteins: As diagnostic tool, *J. of Pharmacy and Bioallied Sci.,* **3**: 118-27.

Jungersen, G., L.Jensen and U.Riber [1999], Pathogenicity of selected Toxoplasma gondii isolates in young pigs, *International J. for Parasitology,* **29**: 1307-19.

Karra, D.A., C.C.Chadwick and E.M.Stavroulaki [2023], Fecal APPs in cats with chronic enteropathies, *J. of Vet. Internal Med.,* **37**: 1750-59.

Kushner, I. [1993], Regulation of the acute phase response by cytokines, *Perspectives in Biol. and Med.,* **36**: 611-22.

Lampreave, F., N.González-Ramón and S.Martínez-Ayensa [1994], Characterization of the acute phase serum protein response in pigs, *Electrophoresis,* **15**: 672-76.

Lobetti, R., A.Möhr and T.Dippenaar [2000], A preliminary study on the serum protein response in canine babesiosis:

research communication, *J. of the South African Vet. Asso.,***71**: 38-42.

Magnusson, U., B.Wilkie and K.Artursson [1999], Interferon-alpha and haptoglobin in pigs selectively bred for high and low immune response and infected with Mycoplasma hyorhinis, *Vet. Imm. and Immunopathology,* **68**: 131-37.

Martínez-Subiela, S. and J.Ceron [2002], Serum amyloid A levels in canine leishmaniasis, *Vet. Clin. Pathol.,* **31**: 205.

Martinez-Subiela, S., D.Strauss-Ayali and J.J.Cerón [2011], Acute phase protein response in experimental canine leishmaniosis, *Vet. Para.,* **180**: 197-202.

Matijatko, V., N.Kucer and R.Baric-Rafaj [2002], CRP concentration in dogs with uncomplicated babesiosis. In: Proceedings of 3rd European Colloquium on APPs, Doorn, The Netherlands.

Mestrinho, L.A., R.Rosa and P.Ramalho [2020], A pilot study to evaluate the serum Alpha-1 acid glycoprotein response in cats suffering from feline chronic gingivostomatitis, *BMC Vet. Res.,* **16**: 1-9.

Nazifi, S., S.Razavi and Z.Esmailnejad [2009], Study on APPs (haptoglobin, serum amyloid A, fibrinogen, and ceruloplasmin) changes and their diagnostic values in bovine tropical theileriosis, *Parasitology Res.,* **105**: 41-46.

Ndung'u, J., P.Eckersall and F.Jennings [1991], Elevation of the concentration of APPs in dogs infected with Trypanosoma brucei, *Acta Tropica,* **49**: 77-86.

Ogilvie, G.K., L.M.Walters and S.G.Greeley [1993], Concentration of α1-acid glycoprotein in dogs with malignant neoplasia, *J. of the Am. Vet. Med. Asso.,* **203**: 1144-46.

Ottenjann, M., C.Weingart and G.Arndt [2006], Characterization of the anemia of inflammatory disease in cats with abscesses, pyothorax, or fat necrosis, *J. of Vet. Internal Med.,* **20**: 1143-50.

Paltrinieri, S., C.Metzger and M.Battilani [2007], Serum α1-acid glycoprotein (AGP) concentration in non-symptomatic cats with feline coronavirus (FCoV) infection, *J. of Feline Med. and Surgery,* **9**: 271-77.

Parra, M., M.Tuomola and J.Cabezas-Herrera [2006], Analytical and clinical validation of a time-resolved immunofluorometric assay (TR-IFMA) for canine C-reactive protein in serum, *Vet. Res. Communications,* **30**: 113-26.

Pradeep, M. [2014], APPs as biomarkers in modern veterinary practice, *Ind. J. Vet. Anim. Sci. Res.,* **43**: 1-13.

Rikihisa, Y., S.Yamamoto and I.Kwak [1994], C-reactive protein and alpha 1-acid glycoprotein levels in dogs infected with E. canis, *J. of Clin. Microbiology,* **32**: 912-17.

Sack Jr., G.H. [2018], Serum amyloid A–a review, *Mol. Med.,* **24**: 46.

Sasaki, K., Z.Ma and T.S.Khatlani [2003], Evaluation of feline serum amyloid A (SAA) as an inflammatory marker, *J. of Vet. Medi. Sci.,* **65**: 545-48.

Satoh, M., T.Fujinaga and M.Okumura [1995], Sandwich enzyme-linked immunosorbent assay for quantitative measurement of serum amyloid A protein in horses, *Am. J. Vet. Res.,* **56**: 1286-91.

Saverio, P., G.Alessia and T.Vito [2007], Critical assessment of the diagnostic value of feline α1-acid glycoprotein for feline infectious peritonitis using the likelihood ratios approach, *J. of Vet. Diagnostic Investigation,* **19**: 266-72.

Schrödl, W., R.Büchler and S.Wendler [2016], APPs as promising biomarkers: Perspectives and limitations for human and veterinary medicine, *PROTEOMICS–Clinical Applications,* **10**: 1077-92.

Selting, K., G.Ogilvie and S.Lana [2000], Serum alpha 1-acid glycoprotein concentrations in healthy and tumor-bearing cats, *J. of Vet. Internal Med.,* **14**: 503-06.

Singh, R., S.Randhawa and C.Randhawa [2021], Studies on biomarkers of hepatic lipidosis in transition cows with special reference to liver ultrasonograhy, liver specific enzymes and APPs, *Indian J. of Anim. Res.,* **55**: 910-16.

Strimbu, K. and J.A.Tavel [2010], What are biomarkers? *Current Opinion in HIV and AIDS,* **5**: 463.

Ter Wee, J., A.Y.Lauritzen and M.Sabara [1997], Comparison of the primary signs induced by experimental exposure to either a pneumotrophic or a 'limping'strain of feline calicivirus, *Vet. Microbiology,* **56**: 33-45.

Ter Wee, J., M.Sabara and K.Kokjohn [1998], Characterization of the systemic disease and ocular signs induced by experimental infection with Chlamydia psittaci in cats, *Vet. Microbiology,* **59**: 259-81.

Toussaint, M., A.Van Ederen and E.Gruys [1995], Implication of clinical pathology in assessment of animal health and in animal production and meat inspection, *Comp. Haematology International,* **5**: 149-57.

Vilhena, H., A.Tvarijonaviciute and J.J.Cerón [2017], APPs response in cats naturally infected with Hepatozoon felis and Babesia vogeli, *Vet. Cli. Pathology,* **46**: 72-76.

Wassell, J. [2000], Haptoglobin: function and polymorphism, *Clin. Laboratory,* **46**: 547-52.

Yamamoto, S., T.Shida and S.Miyaji [1993], Changes in serum C-reactive protein levels in dogs with various disorders and surgical traumas, *Vet. Res. Communications,* **17**: 85-93.

Ye, R.D. and L.Sun [2015], Emerging functions of serum amyloid A in inflammation, *J. Leucocyte Bio.,* **98**: 923-29.

Yule, T.D., M.B.Roth and K.Dreier [1997], Canine parvovirus vaccine elicits protection from the inflammatory and clinical consequences of the disease, *Vaccine,* **15**: 720-29.