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Acute phase proteins and their use in the diagnosis of diseases in cattle: A review

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Abstract
The liver produces acute phase proteins as a reaction to the acute phase response, which occurs during infection, inflammation, or tissue damage. These proteins exhibit minimal significance in healthy animals, but their concentrations rapidly increase during these conditions, making them valuable indicators of inflammation. However, it's important to note that the concentrations and clinical relevance of acute phase proteins differ across various animal species, requiring separate evaluation for each species. While extensive research on acute phase proteins has been conducted in human medicine, their utilization in veterinary medicine has been relatively limited. In this review, we aim to provide the latest information on acute phase proteins specifically relevant to cattle. We will emphasize their potential for early disease diagnosis, differentiation between viral and bacterial infections, guiding therapeutics decisions for diseased animals, and conclusive prognosis. By highlighting the characteristic and prognostic applications of acute phase proteins in cattle, we seek to bridge the gap between human and veterinary medicine. This review aims to raise awareness about the characteristic value of acute phase proteins in bovine health, emphasizing their potential for improving disease management, treatment outcomes, and overall animal welfare.

Keywords: Cattle, acute phase protein, Haptoglobin, serum amyloid a, ceruloplasmin

Introduction
The acute phase response (APR) is a multifaceted physiological reaction triggered by inflammation, tissue injury, infection, cancerous growth, or immunological disorders (Dhama *et al*., 2008) [23]. It encompasses systemic and metabolic shifts, including changes in the level of diverse plasma proteins (Petersen *et al*., 2004) [63]. The primary aim of the APR is to safeguard organs from additional damage, removing infectious agents, eliminating harmful molecules and it helps reestablish balance within the body by initiating the necessary repair mechanism, allowing the organism to return to its usual functioning (Merhan and Bozukluhan, 2022) [57].

The APR is initiated by inflammatory mediators at the site of tissue damage and is described by both local and systemic changes Tothova *et al*., 2014; Merhan and Bozukluhan, 2022) [81, 57]. The APR leads to heightened capillary permeability, movement of white blood cells to the inflammation site, and the release of different chemical messengers (Petersen *et al*., 2004) [63]. Systemic reactions are mediated by cytokines, glucocorticoids, and growth factors. Cytokines, which are soluble signaling molecules with peptide or glycoprotein structure, play a crucial role in the APR (Ramadori and Christ, 1999; Suffredini *et al*., 1999; Ceciliani *et al*., 2002; Gruys *et al*., 2005) [67, 76, 19, 37]. Macrophage, neutrophils, and endothelial cells at the inflammation site secrete pro-inflammatory cytokines like IL-6, IL-1β, TNF-α, interferon γ, IL-8, and macrophage inhibitor protein-1 (Garcia *et al*., 2013) [31]. These cytokines, especially IL-6, stimulate the production of acute phase proteins (APPs), while insulin and okadaic acid inhibit their synthesis (Panichi, 2000) [62].

Cytokines have diverse effects on gene expression, metabolic processes, stimulation of oxidation-reduction potential, and ion flow in cell membranes (Garcia *et al*., 2013) [31]. They stimulate the production of acute-phase proteins, while corticosteroids control the function of cytokines. Inflammatory cytokines such as IL-6 and IL-1 trigger the activation of fibroblast and endothelial cells at the inflamed site, sustaining the release of cytokines (Merhan and Bozukluhan, 2022; Ceciliani *et al*., 2002) [51, 19]. Measurement of APPs has gained popularity due to their ability to provide knowledge about the inflammatory mechnaism and their utility as diagnostic markers for various diseases (Whicher *et al*., 1991) [85].

The availability of rapid and acute measurement methods has further facilitated the widespread use of APP measurement.

Overall, the APR is a multifaceted response triggered by inflammatory mediators, involving local and systemic changes, and culminating in the synthesis of APPs. APPs serve as valuable markers for disease diagnosis and their measurement is increasingly common due to the development of quick and acute detection methods.

Acute Phase Proteins

APPs constitute a cluster of proteins whose blood levels alter as are sponse to inflammation, infection, tissue damage, neoplastic growth, and other pathological situations (Petersen *et al*., 2004; Gruys *et al*., 1994) [63, 35]. It is esteemed to note that the diagnostic significance of APPs varies across different animal species (Murata *et al*., 2004; Gocke, 2009) [57, 32]. It's essential to highlight that the diagnostic importance of APPs differs among various animal. These proteins serve as nonspecific indicators of tissue damage, as their levels are known to fluctuate during infection and inflammation ((Petersen *et al*., 2004; Bazzano *et al*., 2022) [63, 9].

The primary role of APPs is to contribute to the body's defense mechanisms against inflammatory agents. They not only help eliminate these agents but also play a role in tissue healing and regeneration. Furthermore, APPs are involved in processes such as restoration of useful molecules, clearance of residues, cholesterol transport, prevention of oxidation, and activation of the complement system (Gruys *et al*., 1994; Grover *et al*., 2016) [35,34]. It is worth mentioning that APPs are specific to each species, and their diagnostic significance can vary accordingly. Therefore, when utilizing APPs as diagnostic markers, it is crucial to consider their species-specific characteristics and interpret the results accordingly. APPs offer valuable insights into the inflammatory response and can provide useful information for understanding and managing various diseases in different animal species.

Important acute Phase Proteins in Cattle

Among the important APPs in cattle, Hp, SAA, Ceruloplasmin, α1-acid glycoprotein, and albumin play significant roles (Petersen *et al*., 2004; Gruys *et al*., 1994; Gul *et al*., 2022) [63, 35, 38].

Haptoglobin

Haptoglobin is a protein that has an approximate molecular weight of 125 kDa that forms a stable complex with hemoglobin, hence its name (Safi, 2012) [69]. In cattle, haptoglobin is found in the form of a polymer with albumin, with a molecular weight ranging from 1000 to 2000 kDa. The reticuloendothelial system system mainly captures it when attached to hemoglobin (Petersen *et al*., 2004; Naryzhny *et al* 2021) [63, 59].

In healthy cattle, Hp is either absent or present at very low levels (<0.1 mg/mL) in the serum (Eckersall *et al*., 1998) [27]. However, its concentration increases significantly, up to 100 times, when the immune system is stimulated due to various reasons (Murata *et al*., 2004; Eckersall *et al*., 2000) [57, 26]. Haptoglobin levels begin to increase within a day of inflammation onset, peak around the 3rd to 5th day and then decline, returning to baseline between the 8th and 21st (Eckersall *et al*., 1998) [27]. In cattle Hp levels, ranging from 0.1 to 1g/L, indicate a positive prognosis, whereas levels over 1g/L suggest a negative prognosis necessitating treatment. Moreover, the concentration of haptoglobin can be used to assess the severity of the disease, with levels of 0.2-0.4 g/L indicating mild infection and levels of 1-2 g/L indicating severe infection (Eckersall *et al*., 1988; Skinner *et al*., 1991) [27, 73].

Haptoglobin has multiple functions, but its main purpose is to prevent iron loss by creating stable complexes with free hemoglobin in the bloodstream (Quaye *et al*., 2008) [66]. By binding to hemoglobin, Hp facilitates its transport to the liver for metabolism. The interaction between Hp and hemoglobin is crucial for the anti-inflammatory properties of Hp(Gabay and Kushner, 1999) [30]. Haptoglobin also hydrolyzes peroxides released by neutrophils in inflamed areas, rendering them harmless. It has been suggested that Hp acts as an immunomodulator, regulating lipid metabolism and lymphocyte functions, making it a potential marker for monitoring immune functions in cattle (Gokce and Bozukluhan, 2009) [32]. However, it is important to note that factors other than the APR can affect the serum concentration of haptoglobin. For example, an increase in free hemoglobin levels in the circulation can lead to decreased circulating haptoglobin, as hemoglobin binds to existing haptoglobin. This is evident in acute hemolysis cases in cattle babesiosis, where haptoglobin is absent from circulation (Petersen *et al*., 2004) [63].

Measurement of APP levels has proven to be an accurate and informative diagnostic tool for inflammatory diseases in ruminants, often providing more clarity compared to hematological findings. Haptoglobin, in particular, has shown diagnostic potential in various conditions in cattle, including neonatal diarrhea (Albayrak *et al*., 2016; Merhan *et al*., 2016; Erkilic *et al*., 2019) [4, 56, 28], omphalitis (Bozukluhan *et al*., 2018; Kurt *et al*., 2019) [14, 48] pneumonia (Bozukluhan *et al*., 2021) [13], ascaridiosis (Bozukluhan *et al*., 2017) [14], besnoitiosis (Gonzalez-Barrio *et al*., 2021) [33], Trypanosoma evansi infection (Alraad *et al*., 2021) [6], anaplasmosis (Nazifi *et al*., 2012; Coskun *et al*., 2012; Bozukluhan *et al*. 2013) [60, 22, 11], hypodermosis (Merhan *et al*., 2017) [54], brucellosis (Bozukluhan *et al*., 2016) [10], tuberculosis (Merhan *et al*., 2017) [54], reticuloperitonitis traumatic (Bozukluhan and Gokie 2007; Alkyuz and Aydin, 2022) [12,2], foot-and-mouth disease (Merhan *et al*., 2017) [54], fatty liver (Nakagawa *et al*., 1997) [58], dystocia (Bayyi and Merhan, 2022) [8], and subclinical ketosis (Merhan *et al*., 2019; Brodzki *et al*., 2021) [55, 17] (Table 1). Research has shown that haptoglobin levels decrease notably in cows with endometritis post-treatment. Additionally, the use of progesterone-releasing intravaginal devices (PRID) boosts haptoglobin and ceruloplasmin levels while reducing albumin levels increases Hp and ceruloplasmin levels but decreases albumin levels (Kaya *et al*., 2021; Kuru *et al*., 2015) [47, 49].

Table 1: APP protein related studies in Cattle

Diseases	Acute Phase Protein investigated	Findings of the study
Tuberclosis Hypodermosis	HP, albumin	Animals that were infected exhibited elevated haptoglobin levels, accompanied by reduced albumin concentrations.
Pneumonia	HP, SAA, albumin	Animals that were infected exhibited elevated haptoglobin and SAA levels, accompanied by reduced albumin concentrations.
Omphalitis, Ascaridiosis, Anaplasmosis, Brucellosis, Fatty liver Dystocia	Haptoglobin	Haptoglobin was higher.
Reticuloperitonitis traumatica	Haptoglobin, Ceruloplasmin, α1-Acid glycoprotein	Diseased animals displayed increased levels of haptoglobin, ceruloplasmin, and α1-Acid glycoprotein
Subclinical ketosis	Haptoglobin, SAA	Haptoglobin and SAA levels were higher in diseased animals.
Hepatic abscess and *haemolytica*, digestive system disease	α1-Acid glycoprotein	α1- Acid glycoprotein was higher.

Serum amyloid A (SAA)

Serumm amyloid A (SAA) is a protein synthesized by the liver, often bound to lipoprotein, and also locally produced in the udder as "milk SAA" (MAA). In healthy cattle, the typical SAA serum concentration is below 24 µg/mL (Gokce and Bozukluhan, 2009) [32]. SAA is classified as an APP and its levels increase rapidly within 2-5 hours after inflammation and reach a peak within 24 hours (Gruys *et al*., 1994) [34]. It serves as an early diagnostic tool for acute cases, assessing inflammatory presence, disease progression, and treatment effectiveness (Witkowska-Pilaszewicz *et al*., 2019) [86].

SAA serves a range of functions, including transporting cholesterol to hepatocytes, impeding oxidative degradation of neutrophil granulocytes, stimulating calcium mobilization by monocytes, detoxifying endotoxins, restraining lymphocytes and endothelial cell growth, averting platelet aggregation, and aiding T lymphocytes adhesion to extracellular matrix protein (Petersen *et al*., 2004; Murata *et al*., 2004) [63, 57]. The haptoglobin to SAA ratio proves useful in distinguishing between acute and chronic cases for diagnostic purposes (Gruys *et al*., 1994) [34]. In cattle, SAA is considered an important APP that shows increased levels in various conditions. For instance, it has been reported to rise after more than 3 days of non-feeding (Bazzano *et al*., 2022) [9] and in infections like foot-and-mouth diseases (Merhan *et al*., 2017) [52], coryza gangrenosa bovum (Issi *et al*., 2017) [42], hypomagnesemic tetany (Ali *et al*., 2016) [5], enzootic bovine leukosis (Guzel *et al*., 2017) [39], subclinical ketosis (Brodzki *et al*., 2021) [17], postpartum (Varol *et al*., 2022) [84], mastitis (Nazifi *et al*., 2011; Cenesiz *et al*., 2018; Armagan and Emre, 2021) [60,20,7], subclinical endometritis (Salah *et al*., 2021) [71], and pneumonia (Joshi *et al*., 2018; Akgul *et al*., 2019) [44, 1].

Furthermore, SAA levels have been linked to the severity of clinical signs in viral respiratory system disease (Petersen *et al*., 2004) [63]. Interestingly, a study on dual-and single-infected cattle revealed no significant difference in APP levels, including Hp and SAA between the two groups (Sahinduran *et al*., 2017) [70]. However, in cattle with bovine respiratory disease, both Hp and SAA levels are high compared to healthy animals, and these APP levels decreased with treatment (Yilmaz *et al*., 2017) [87].

Ceruloplasmin

Ceruloplasmin is a type of α-2 globulin that binds to copper, composed of just one polypeptide chain. Its functions include lipid peroxidation, conversion of toxic ferrous iron to a non-toxic ferric form, enhancement of immune function by acting on various enzyme levels, transport of copper to enzymes involved in tissue repair and antioxidant defense, and regulation of phagocytosis and antimicrobial activity (Murata *et al*., 2004; Cerone *et al*., 2000; Hellman and Gitlin, 2002) [57, 21, 40]. Ceruloplasmin is helpful for measurement of the inflammatory process in cattle (Szczubial *et al*., 2008) [77]. Studies have shown increased levels of ceruloplasmin in cattle with conditions such as reticuloperitonitis traumatic (Akyuz *et al*., 2022) [2], endometritis (Kaya *et al*., 2016) [47], subclinical mastitis (Szczubial *et al*., 2012) [78] (Table 1), and foot-and-mouth disease, making it a potential diagnostic marker for these diseases (Merhan *et al*., 2017) [54].

α1-Acid glycoprotein

α1-Acid glycoprotein is a sialoprotein possessed of 180 amino acids and with a molecular weight of 41 kDa, is synthesized by hepatocytes (Albani, 2004) [3]. Its significance lies in two key roles: drug binding and immunomodulation It acts as a natural anti-inflammatory agent by inhibiting neutrophil activation and lymphocyte proliferation (Petersen *et al*., 2004; Murata *et al*., 2004) [63, 57]. α1-Acid glycoprotein is moderately increased in the blood during inflammation, especially in chronic cases. It can be used to measure the inflammatory process in cattle Gruys *et al*., 1994; Safi, 2012) [35, 69]. Studies have reported increased concentrations of α1-acid glycoprotein in cattle with conditions such as hepatic abscess (Gruys *et al*., 1994) [35], leukosis (Eckersall *et al*., 1988) [27], traumatic pericarditis (Bozukluhan *et al*., 2017) [15], Pasteurella haemolytica infection Gruys *et al*., 1994) [35], and digestive system diseases (Santos *et al*., 2021) [72] (Table 1).

Albumin

Albumin is a negative acute-phase protein produced by the liver, with a molecular weight of 67 kDa, comprising 583 amino acids (Jachimska *et al*., 2008; Majorek *et al*., 2012) [43, 50]. It plays a crucial role in maintaining plasma oncotic pressure and membrane integrity (Evans *et al*., 2002; Vande wouw and Joles 2022) [29, 83]. Albumin also functions in binding and transport, as a source of endogenous amino acids, and in maintaining plasma pressure. Decreased albumin levels can indicate liver failure (Don *et al*., 2004) [24] and are associated with various diseases such as liver diseases, anorexia during acute-phase response, kidney and intestinal diseases, and malabsorption syndrome (Gruys *et al*., 2005; Tennant *et al*., 2008) [37, 80]. Studies have shown decreased albumin levels in cattle with conditions like neonatal diarrhea (Merhan *et al*., 2016) [56], pneumonia (Bozukluhan *et al*., 2021) [13], hypodermosis (Merhan *et al*., 2017) [53], tuberculosis (Merhan *et al*., 2017) [53], and foot-and-mouth disease (Merhan *et al*., 2017) [53] (Table 1).

Main methodological techniques For APP quantification in Cattle

The main methodological techniques for quantifying Acute Phase proteins in cattle involve the analysis of a significant number of samples, making automation highly recommended. This is an essential requirement when assessing APPs and other analytical parameters in farm animals (Eckersall, 2019; Canalia *et al*., 2018) [25, 18]. Standardization, particularly through the development of reference materials for calibrating reagents, plays a crucial role in expanding the utilization of Acute Phase Proteins. It is essential for harmonizing various methodologies and disseminating knowledge within the field. Several laboratories have been actively engaged in preparing, optimizing, and validating assays based on immunoturbidimetry and ELISA (Canalias *et al* 2018; Pineriro *et al*., 2018; Saco *et al*., 2010; Young *et al*., 1995; Soler *et al*., 2011; Hussein *et al*., 2019; Soler *et al*., 2019; Pinerio *et al*., 2009; Tecles *et al*., 2007) [18, 65, 68, 88, 74, 41, 74, 65, 79], which can be easily adapted to biochemical analyzers. This availability of reagents and adaptable assays will facilitate the integration of App measurements into routine laboratory testing, thereby enabling the monitoring of large animal health and welfare.

Conclusions

Acute-phase proteins (APPs) are nonspecific markers produced by the liver in response to acute-phase reactions (APR) in cattle. They play a significant role in diagnosing and monitoring diseases, as well as determining the prognosis of affected animals. Measuring APP levels is particularly valuable in distinguishing between bacterial and viral infections and guiding appropriate treatment strategies. By incorporating APP measurement into diagnostic procedures, it enhances the accuracy of diagnosis and provides valuable insights into the prognosis of sick animals.

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