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Acute phase proteins and their use in diagnosis of diseases in ruminants

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Abstract
Acute phase response is a group of proteins that respond to tissue damage caused by infections, trauma, neoplasms, inflammation, or stress. Several acute phase proteins (APPs) help to shape the response. APPs are classes of proteins that increase in plasma concentration (positive APP) or decrease in plasma concentration (negative APP). Different animal species have different levels and types of APPs. In cattle, SAA and haptoglobin are the two main APPs. These factors can be measured by various methodologies, some of which are still being developed to make them more specific, sensitive, easy to use, and affordable. The most popular uses for APPs in cattle are to diagnose and track common illnesses like mastitis, metritis, and respiratory diseases in dairy cows and calves. APPs can also be used to improve procedures for better performance, health, and nutrition. There are also other sample types outside of milk and plasma that can be used, like noninvasive sample types and meat.

Keywords: Acute phase proteins (APPs), haptoglobin (Hp), serum amyloid a (SAA)

Introduction
Hepatocytes synthesize the majority of the blood proteins called Acute Phase Proteins (APP) as a part of the acute phase response. The acute phase response can be caused by a wide range of events, including injuries, trauma, infections, stress, inflammation, and neoplasms. The acute phase reaction is a non-deterministic and complicated response. It includes behavioral, physiological, biochemical and dietary changes. The synthesis of a large family of liver proteins called acute phase proteins can significantly.

The use of acute phase proteins (APPs) in human medicine has a long history and has been demonstrated to be useful for the diagnosis and prognosis of a variety of inflammatory and organ diseases, as well as for organ transplantation and for the treatment of cancer (Deans *et al.*, 2005) [8]. APPs may offer an additional approach to the assessment of animal health due to their variable amounts in affected animals. The use of APPs as diagnostic markers in the diagnosis of diseases is a common practice in veterinary clinical practice, particularly in the field of farm animal care. The potential effect of inflammatory conditions on the quantities of APPs is less well understood. The primary objective of this article is to provide an overview of diagnostically useful APPs for ruminants and to discuss how they can be used in the identification and diagnosis of a variety of economically important diseases in ruminants.

Gabay and Kushner (1999) [15] suggest that cytokines initiate a cascade of events that magnifies the onset of certain clinical changes, including fever, weight loss, and anorexia. Furthermore, cytokine receptors on target cells can cause systemic inflammatory reactions, either hormonal or metabolic, which can lead to a variety of biochemical alterations, including an increase in cortisol production, activation of the blood clotting system, a decrease in serum concentrations of calcium and zinc, iron and vitamin A, as well as changes in the concentration of certain plasma proteins (Gruys *et al.*, 2000) [20]. One of the most significant metabolic alterations is the liver's significantly increased production of a group of plasma proteins referred to as the acute phase proteins.

Acute phase proteins (APPs)
Acute phase proteins (APPs) are a wide and diverse class of plasma proteins that are released into the bloodstream in response to a variety of stressors.

To differentiate them from other APPs, all APPs that have been upregulated have been classified as positive APPs (Peterson *et al.,* 2004) [43]. APPs are divided into major, moderate, and minor categories based on their concentration, with major APPs being defined as those that increase 10- to 100-fold; moderate APPs being those that increase two- to ten-fold, and minor APPs being those with only a slight increase in concentration (Ceron *et al.,* 2005) [2].

Major proteins often exhibit a rapid decrease due to their very short half-lives (24 to 48 hours after the triggering event). Depending on the triggering event, intermediate and minor proteins may either decline at a slower rate or persist for longer periods of time depending on the extent of their response to the triggering event (Niewold *et al.,* 2003) [40]. Moderate and small acute phase proteins (APPs) are more likely to be observed when there is an ongoing inflammatory process. In this case, moderate to small acute phase protein (APP) is more likely to be seen. In acute phase responses, there is a very slight decrease in the amount of negative acute phase proteins. (Horadagoda *et al.,* 1999) [26].

According to Petersen *et al.,* (2004) [43], APPs' primary functions are to protect the host against pathological damage, to restore homeostasis, and to regulate the various stages of inflammation. Some acute phase APPs (e.g., 1-antitrypsin and 2macroglobulin) show anti-protective activity to minimize damage to healthy tissues. This activity is designed to inhibit the production of proteases generated by phagocytic cells or infections. Other APPs (i.e., haptoglobin, serum amyloid-A, and C reactive protein) bind and scavenge compounds produced from cellular breakdown and have antiprotective activities (Wagener *et al.,* 2002) [57]. Other proteins, such as 1-acid glycoprotein, are characterized by their antibacterial activity and their ability to alter the mode of immune response (Fournier, 2000) [14]. While the acute phase response is homogeneous, there are some variations in acute phase characteristics across animal species (Eckersall and Bell, 2010) [10]. Each important acute phase protein found in one animal species can provide valuable information for diagnostics.

The diagnostic utility of acute phase proteins in veterinary practice

Animals with a wide range of diseases tend to have higher concentrations of acute phase protein. As such, they cannot be used as the primary diagnostic test for a particular disease as they have very low diagnostic specificity in determining the etiology of the disease. However, they are highly sensitive in identifying a range of ailments that affect an animal's health, as well as in identifying inflammation or infections that are not yet manifest (Ceron *et al.,* 2005) [2]. An acute phase response (APP) accurately and promptly detects the presence of inflammatory and infectious disease, but not the underlying cause of the disease. According to the work of (Petersen *et al.,* 2004) [43], APPs also detect the presence of subclinical disease. APPs can be used to predict prognosis and treatment results in the clinical setting. The size and duration of an acute phase response reflect the intensity of infection and the underlying tissue damage. (Heegaard *et al.,* 2000) [22].

There are many acute phase proteins in human medicine that can be used as biomarkers to diagnose a wide variety of diseases and disorders (Samols 2002) [46]. However, only a few of these proteins can be routinely used as biomarkers in ruminants. The two most important acute phase proteins for diagnostic purposes in ruminants are Hp and SAA (Eckersall *et al.,* 2010) [10].

Clinical Value of APP

APPs increase significantly and can be observed the day following stimulation; this is in line with other well-established markers of inflammation. Applications in veterinary medicine have been reported for diagnosing, predicting, and detecting subclinical disease, monitoring stress, and the development of chronic inflammatory diseases.

Acute phase proteins in mastitis: Despite the efforts made on a global scale, mastitis remains the most significant disease affecting dairy cattle in terms of economic impact. As a consequence, the detection and monitoring of mastitis in bovine animals is the most widely used acute phase protein study in cattle (Ceciliciani *et al.,* 2012) [1]. In a study conducted by Conner *et al.,* (1986) [4] they compared the levels of haptoglobin (Hp), ceruloplasm (Ceruloplasm), and 1-antitrypsin in clinically healthy cows and those infected with summer mastitis. Compared to cows without mastitis, all of the affected cows had higher Hp, ceruloplasm, and 1-antitrypsin levels.

Hirvonen *et al.,* (1996) [23] examined pregnant heifers experimentally infected with Actinomyces pyogenes, Fusobacterium necrophorum, and Peptostreptococcus indolicus to determine the utility of APPs in the diagnosis of mastitis. They also assessed the prognostic significance of a few APPs in the infected animals, including haptoglobin, fibrinogen, acid-soluble glycoproteins, and 1-proteinase inhibitor. The aforementioned authors claimed that whereas fibrinogen was a solid signal for spotting bacterial infection, it was ineffective for predicting the prognosis of mastitis. In determining the level of infection and forecasting the course of the disease in heifers with mastitis, they found that HP and acid-soluble glycoproteins were the most useful markers.

In a subsequent study, Hirvonen *et al.,* (1998) [24] observed the changes in a few APPs in cows with acute *E. coli* mastitis and their role in predicting the progression of the disease. All cows in the study had increased serum Hp and serum SAA concentrations due to intra-mammary *E. coli* infection. Furthermore, there was a relationship between SAA concentration and disease severity in cows with clinical mastitis. (Eckersall *et al.,* 2007) [12]. In comparison to healthy cows, cattle with mild or moderate mastitis had significantly higher serum Hp and SAA concentrations. However, the authors found no significant differences between the animals with mild and medium mastitis.

According to Eckersall *et al.,* (2007) [12], the disruption caused by the inflammation induced by mastitis allows most of the serum proteins to leak through the blood-milk barrier. In addition, milk seems to be a better material to sample than serum for the determination of APP levels during mastitis (it is easier and faster to collect milk samples without exposing the animals to stress). Eckersall *et al.,* (2007) [12] found that milk samples from cows with mild and moderate mastitis had considerably greater concentrations of Hp and SAA than milk samples from healthy cows. Additionally, milk samples from cows with moderate mastitis had considerably higher SAA concentrations than milk samples from cows with mild mastitis. In contrast, there were no appreciable changes in the Hp concentrations in the milk between the infected cows. As a result, milk SAA concentrations appear to have a larger potential for utility in detecting the severity of mastitis.

All cows had elevated levels of SAA in milk and plasma, regardless of infection severity. Plasma SAA concentrations increased 12 to 24 hours after inoculation, and milk SAA concentrations increased 6 to 12 hours post-inoculation. Animals with severe mastitis had higher milk SAA concentrations compared to cows with mild or moderate mastitis. Therefore, SAA may be used to determine the degree of tissue damage. According to Pedersen *et al.,* (2003) [42]. SAA may be especially useful for early detection of mastitis due to the rapid increase in milk concentrations following intramammary inoculations of mastitis bacteria. The rapid return to baseline after bacterial clearance suggests that milk SAA measurements could also be used as a measure of treatment effectiveness. Nielsen *et al.,* 2004 [39] similarly found higher serum and milk SAA concentrations in cows with clinical mastitis. Gronlund *et al.,* conducted a study in 2005 [19] to evaluate the levels of Hp and SAA in cows with chronic subclinical mastitis. The milk of cows with chronic subclinical mastitis had elevated levels of both APPs, suggesting that the acute phase response was active in these cows as well. In addition, further studies showed that an extrahepatic variant of Serum Amyloid a (MSAA) was produced (McDonald *et al.,* 2001) [34]. As M-SAA only accumulates in milk during inflammation of the udder, it is considered to be a more sensitive marker for mastitis. A study conducted by (S. Kovac *et al.,* 2007) [31] examined the effectiveness of M-SAA in the diagnosis of both clinical and subclinical mastitis. The results of the study indicated that milk samples from both quarters with clinical abnormalities and quarters without overt mastitis signs but with very positive California Mastitis Test (CMT) results had significantly higher M-SAA concentrations.

The concentrations of M-SAA reported in samples from non-clinical mammary quarters were similarly high, indicating that the non-infected mammary quarters must have either undetectable or extremely low M-SAA levels. These findings suggest that certain regions may be affected by inflammatory processes despite negative CMT results. According to Nazifi *et al.,* (2008) [38], the proportion of quarters that had mastitis had higher concentrations (Hp) and (M-SAA) compared to healthy quarters.

M-SAA and Hp were also associated with lower total protein (TP), casein (C protein), and lactose (Lactose) levels in milk, as well as higher levels of protein-proteolysis activity in milk. These are all markers of poor milk quality.

Disorders of the peripartum reproductive system and acute phase proteins in reproduction

Acute phase protein analysis has also been shown to be useful in the context of several reproductive issues in cattle, particularly in the detection and monitoring of metritis and during the peripartum period. Haptoglobin levels vary significantly during pregnancy and lactation, with cows showing the highest levels at day one postpartum (Gymnich *et al.,* 2003) [21]. Hp concentrations in cows were evaluated in a study conducted by Uchida *et al.,* (1993) [56] which revealed that the levels of Hp were significantly higher during the period immediately prior to and subsequent to parturition. During parturition, two primary acute phase proteins (Hp and SAA) are increased in cows, as shown by Tothova *et. al.,* (2008) [55]. In healthy cows, the SAA concentrations reach their highest levels within 3 days postpartum according to the findings of Chan *et al.,* [3].

Cows with metritis were found to have high HP concentrations according to the study by Skinner *et al.,* 1991[48]. After calving, Chan *et al.,* (2004) [3] compared the postpartum Hp concentrations of clinically ill cows to those of clinically healthy cows to identify which cows had postpartum reproductive problems and which did not. The cows with acute Puerperal Metritis had significantly higher Hp concentrations than those of healthy cows. Low Hp concentrations can be a risk factor or early indicator of metritis. Smith *et al.,* (1998) [49] found low concentrations of acute phase proteins in cows with toxic Puerperal Metritis at day three postpartum. Cows with acute phase Hp concentrations of more than 1 g/l were 6.7-fold more likely to develop mild or severe metritis. Hp concentrations reached their highest point three days after delivery while SAA concentrations reached their highest three to seven days after delivery.

In cows with retained placentas (either with or without the manual removal of the membrane), according to a study by Huzzey *et al.,* (1999)· Mordak's (2008) [36] observed the effects of APPs on the effectiveness of therapy. Cows with the highest Hp levels were able to get rid of their placentas after 4 days, while cows with the lowest Hp levels could easily get rid of them by hand.

Acute phase proteins in abdominal and cardiac disorders

The importance of measuring acute phase protein concentrations in cattle, particularly fibrinogen levels, has been discussed in relation to the treatment of traumatic pericarditis, including reticuloperitonitis and abomasal displacement. Additionally, postoperative complications have been studied, and the distinction between reticuloperitonitis and other gastrointestinal disorders has been made (Hirvonen and Pyorala 1998 [24]; Jafarzadeh *et al.,* 2004 [29]). Hirvonen & Pyorala (1998) [24] examined the effectiveness of Fbg & Hp in diagnosing reticuloperitonitis in dairy cows. Additionally, they examined whether these indicators could be used to predict the recovery from abdominal illnesses and the effects of abdominal surgery. The results of the study indicated that the preoperative concentrations of Fbg and Hp were significantly higher in cows with traumatic reticuloperitonitis than in those that had abdominal displacement or explorative laparotomy.

Following surgical intervention, plasma Fbg concentrations in cows with traumatic reticuloperitonitis were observed to remain elevated for approximately two days. During the post-surgery phase, Hp concentrations in these cows increased slightly, followed by a gradual decrease. There was a positive relationship between the measured values and the clinical results in the cows with traumatic reticuloperitonitis. The abomasum displacement does not typically cause a significant fibrinogen reaction, as demonstrated by McSherry *et al.,* (1970) [35]. In the study conducted by Jawor *et al.,* (2009) [30], the Fbg concentrations in cows with displaced abomasum were within the normal range.

A study conducted by Nazifi *et al.,* in 2008[38] examined the association of APP levels in dairy cattle with the development of heart diseases (functional murmurs; pathological murmurs; endocarditis; pericarditis). Higher concentrations of Hp and SAA were observed in cases of pericarditis/endocarditis in this study compared to cows with murmur. The concentrations of both measured APPs were also lower in cows with endocarditis compared to pericarditis. This suggests that measuring APPs may be helpful in distinguishing between acute inflammatory conditions such as pericarditis and other cardiac disorders.

Acute phase proteins in hoof diseases and lameness

Kujala *et al.,* (2010) [32] conducted a study to evaluate the significance of acute phase protein (SAA) in the identification of lame cows. The results of the study indicated that lame cows had higher SAA concentrations than those with healthy animals, with an increase in SAA concentrations from day zero to days 7-8. There were no significant differences between healthy and lame cows in the serum Hp concentrations. In a study by (Tothova *et al.,* 2011) [54] they found that heifers suffering from hoof diseases had significantly higher levels of Hp, SAA, and fibrinogen compared to healthy animals. Smith *et al.,* (2010) [54] examined lameness in dairy cows caused by claw abnormalities and the presence of an acute phase response. In addition, they evaluated the effects of the medication on acute phase protein levels, enabling them to evaluate the effectiveness of the treatment. It was found that lame cows with claw-related issues had elevated serum Hp levels. The presence of reduced Hp concentrations between days one and five post-treatment in animals with pododermatitis septica and interdigital necrobacillosis demonstrated the successful treatment of these conditions. High peak concentrations of Hp, SAA and Fbg occurred early in the treatment course. A gradual decrease in acute phase protein concentrations was observed in cows where the treatment went through without complications. At the next blood test, they found an increase in one or two of the APPs in cows that had additional issues (like wound infections or other inflammatory conditions in the legs.

Acute phase proteins in calf diseases

Acute phase protein synthesis in calves has been largely studied in animals with respiratory disorders, as it is one of the primary determinants of disease and mortality in young cattle. Conner *et al.,* (1989) [4] found an increase in the levels of Haptoglobin, 1-antitrypsin, and seromucoid levels in calves following intratracheal aerosol administration of *Mannheimia haemolytica.*

The study also looked at calves that had an intratracheal infection with *M. haemolytica.* The data showed a small increase in Hp concentrations within 10 hours after injection, as reported by Horadagoda and Eckersall (1994) [25]. Tothova *et al.,* (2010) [52] showed that an increase in the production of multiple APPs which is associated with acute as well as chronic respiratory tract infections. In addition, the study showed that calves with severe clinical signs and a poor prognosis were associated with significantly higher Hp and SAAs concentrations.

Another disease that can be very expensive for dairy cattle is calf diarrhoea.

When *Salmonella Dublin* virus was experimentally infected, Piercy (1979) [44] looked at the amount of ceruloplasmin produced. After three to four days of infection, acute phase protein levels in infected calves increased significantly; on day seven, they returned to normal.

Responding to an experimental infection with three Salmonella serotype combinations (S. dublin, S. enteritidis, S. heidelberg) in young calves, Deignan *et al.,* (2000) [9] measured serum concentrations of Hp and compared these levels with clinical infection markers.

Following the infection, serum Hp concentrations significantly increased three days post-infection. This increase was statistically linked to other clinical indicators of infection, including fever, diarrhea scores, and mortality ratings. Even though most of the calves were still showing signs of infection on day 5 after infection, all the animals that were analyzed showed that their serum Hp levels had gone back to normal. This suggests that HP levels are a good indicator of how infected the calves are and could help us figure out the prognosis of the infection.

A study conducted by Tothova *et al.,* 2012 [53] examined the effects of omphalophlebitis condition on the levels of key APPs in calves suffering from this condition. SAA concentrations were significantly higher in calves with omphalophlebitis symptoms compared to healthy calves. There were no apparent differences in concentrations of Hp or Fbg between healthy and diseased calves. Tothova *et al*., (2012) [53] observed the opposite pattern in calves with multisystemic diseases (more than one damaged organ, including joints, digestive tract, and respiratory tract), with significantly higher Hp and Fb values compared to healthy calves. The SAA values in this group were only marginally higher.

Acute phase proteins in small ruminants: The acute phase reactions to proteins in small ruminant animals have not been studied as extensively as those found in cattle, however, it appears that they are similar and comparable. While acute phase protein determinations in small ruminants are therapeutically important, little information is available on their use in sheep and goat practice. In these species, Hp and SAA are considered to be the two major acute phase proteins and increase by 80 and 22 fold, respectively, under experimental inflammatory conditions. While albumin concentrations decreased significantly in this study, concentrations of AGP and fibrinogen only increased by two and three and a halffold respectively (Gonzalez *et al.,* 2008 [18]; Lepherd *et al.,* 2009 [33]). Eckersall *et al.,* (2007) [12] evaluated the acute phase protein response in sheep during an experimental caseous lymphadenitis infection to determine their potential usefulness in disease surveillance. Serum Hp, serum SAA and AGP concentrations increased in this setting. An extended AGP response was observed when the infection was changing from acute to chronic phase. Therefore, AGP may be used as a marker for chronic disease in sheep.

A study found higher levels of Hp, SAA, and fibrinogen in ewes that had pregnant toxemia (El-Deeb, 2012) [13]. In addition, acute phase proteins were identified in postpartum sheep with intrauterine bacterial contamination, which were subsequently used as predictors of ovine dystocia (Regassa and Noakes 1999) [45].

Acute-phase proteins were evaluated as markers of subacute ruminant acidosis in goats by Gonzalez *et al.,* 2010[17]. Serum SAA levels remained stable during the induction phase of the study, but serum Hp increased slightly. In a follow-up study, Gonzalez *et al.,* 2010[16] examined the activity of acute phase proteins in fasting induced pregnancy-induced toxemia in goats. However, the amount of Hp, the only acute phase protein they found to have increased significantly. Their findings suggest that an increase in inflammatory indices i.e., Hp prior to parturition may be a contributing factor to the common energy balance problems before kidding.

Table 1: List of APPs by Animal Species

Species	Major APP	Moderate and minor app
Cat	AGP, SAA	FIB, HP
Chicken	-	AGP, CP, FIB, HP, SAA
Cow	HF, SAA	AGP, CP, CRP, FIB
Dog	CRP, SAA	AGP, CP, FIB, HP
Horse	SAA	AGP, CP, FIB, HP
Human	CRP, SAA	AGP, CP, FIB, HP
Pig	HP, MAP, SAA	AGP, CP, CRP, FIB
Sheep	HP, SAA	AGP, CP,CRP, YID
Goat	HP, SAA	AGP, FIB

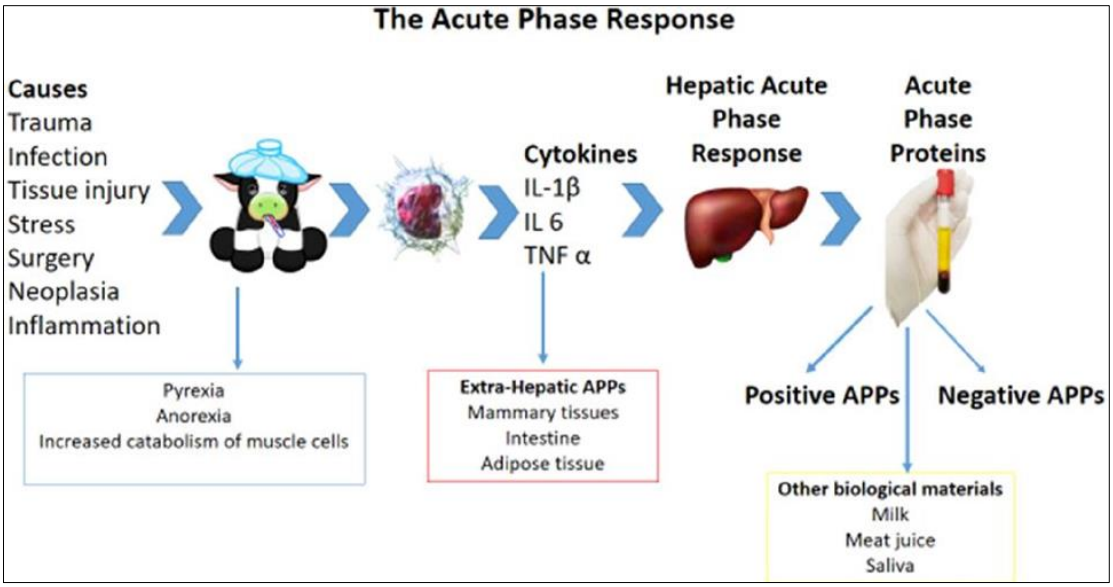

Fig 2: The acute phase response

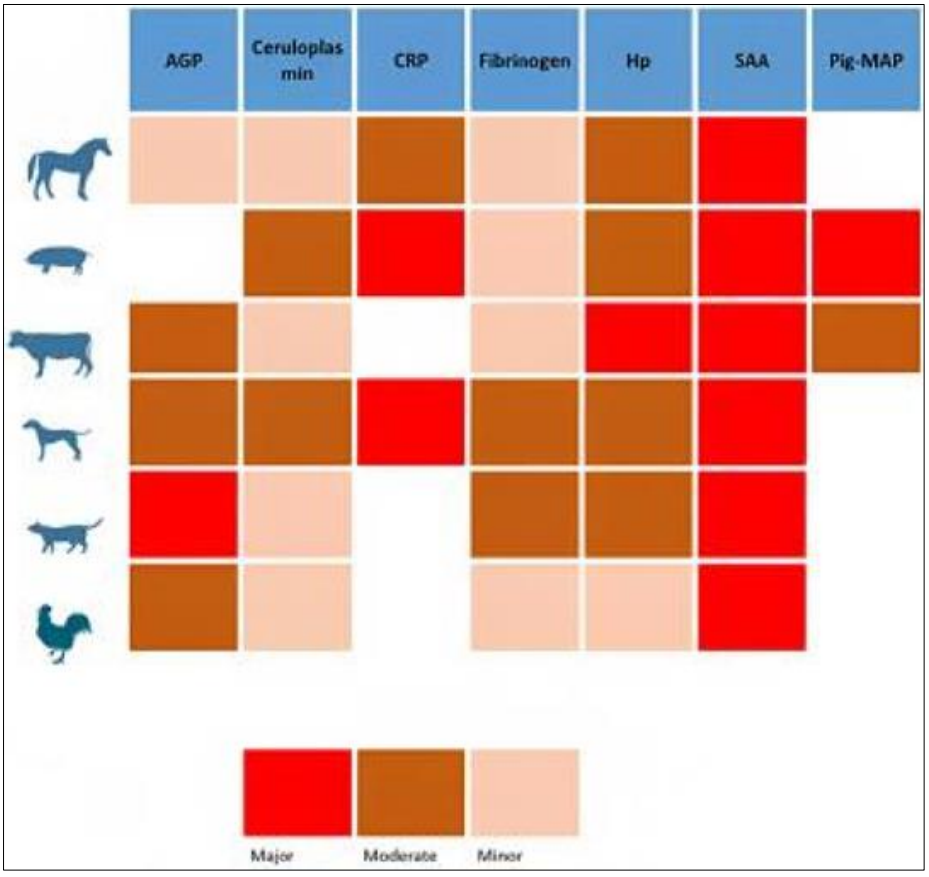

Fig 2: Apps in domestic species adapted from tizard's veterinary immunology (2013)

Table 2: Concentration of different acute phases proteins in different diseases

Virus	Disease	Specie	Health state	SAA	Hp	Cp	Fb	Albumin	Reference
SRLV	Caprine arthritis encephalitis	Goat	Healthy	0.28-27.40	0.21–4.89	NT	NT	NT	Czopowicz et al. (2017)
			Infected	0.31-28.70mg/L	0.22–4.65g/L	NT	NT	NT	
BDV	Border disease	Goat	Healthy	6.06µg/mL	0.056	NT	NT	NT	Balikci et al. (2013)
			Infected	42.13–68.86 µg/mL	0.424–0.866 mg/mL	NT	NT	NT	
PPRV	Peste des petits ruminants	Sheep	Healthy	12.80[A]	1.54[A]	NT	NT	NT	Arslan et al. (2007)
			Infected	32.2[A]	3.13[A]	NT	NT	NT	
BTV	Blue tongue disease	Sheep	Healthy	ND	0.04g/L	41.53	NT	ND	Aytekin et al. (2015)
			Infected		1.58g/L	25.59mg/dL	NT	ND	
BRSV	Bovine Respiratory Syncytial Virus	Cattle	Healthy	<17µg/mL	<18µg/mL	NT	NT	NT	Heegaard et al. (2000)
			Infected	60–80µg/mL	8–10mg/mL	NT	NT	NT	
BVDV	Bovine viral diarrhea	Cattle	Healthy	25.6mg/L	0.13g/L	NT	6.45	NT	Burgstaller et al. (2016)
			Infected	77.7–375mg/L	0.89–1.87g/L	NT	6.5–10g/L	NT	
FMDV	Foot and mouth disease	Cattle	Healthy	4.50–4.86	0.084–0.09	0.06–0.08	0.06	3.43g/dL	Stenfeldt and Arzt (2020)
			Infected	28.8–45.44 µg/mL	0.308–0.41g/L	0.10–0.16 g/L	4.64g/L	2.49–3.39 g/dL	

ND-No Difference, NT-Not Tested, A—No information about units.

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Conclusion

The utilization of acute-phase protein testing can be beneficial in assessing animal health, the cause of a variety of illnesses, the spread of infection, and the efficacy of treatment, as these proteins are non-specific indicators of inflammation. Additionally, acute phase protein measurements may be used to determine an animal's or herd's objective health status. These biomarkers are reliable and can be used in both diagnostic techniques and research.

In recent years, a considerable amount of scientific research has been published that outlines the potential applications and advantages of acute phase protein testing. However, due to analytical practicalities that limit the scope of their analysis, acute phase protein tests have not been extensively used in clinical animal practice. This is due to the fact that the majority of procedures for evaluating individual acute phase proteins are immunological techniques, which are both time-consuming and costly. It is essential to develop and optimize rapid field tests that allow for the rapid quantification of acute phase protein concentrations, as there are numerous potential applications of acute phase protein based diagnostics for ruminants. Despite the challenges associated with the detection of acute phase proteins, they may be used to diagnose and prognosis disorders in farm animal medicine. Acute-phase proteins provide predictive information about the course of the disease, and have been demonstrated to be particularly useful in the early detection of subclinical disorders or alterations in an animal's health status. Patients may require a more in-depth clinical assessment if changes in serum APP concentrations are observed. Additionally, acute phase proteins can be an effective tool in evaluating the efficacy of treatment.

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